CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS OF SELECTED NEUROMUSCULAR BLOCKING DRUGS

By

J. S. Walker, Dip. Pharm. (N.Z)

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PREFACE

The work described in this thesis was carried out in the Department of Pharmacy, University of Sydney, under the supervision of Dr. Kenneth F. Brown. This thesis has not been submitted for a degree at any other University. Full acknowledgment has been made where the work of others has been cited or used. A list of publications is included in support of this thesis.

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Judith S. Walker

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2. Ramzan, M.I., Somogyi, A.A., Walker, J.S., Shanks, C.A., and Triggs, E.J., Clinical pharmacokinetics of nondepolarizing muscle relaxants. Clin. Pharmacokin., 6, 25-60 (1981).

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PHARMACOKINETIC AND PHARMACODYNAMIC TERMS USED IN THIS THESIS

A_e	The amount of drug in the effect compartment.
AUC_0^∞	Total area under the plasma drug concentration–time curve between zero and time infinity.
AUMC	Total area under the first moment of the plasma concentration (C_p)–time (t) curve, i.e., the area under the curve of t.Cp versus t.
Cl	Total plasma clearance.
$C_{p(t)}$	Plasma drug concentration at time t.
C_{ss}	Plasma drug concentration at steady-state.
$C_{ss(50)}$	The steady-state plasma concentration corresponding to 50 percent maximal effect.
$C_{ss(95)}$	The steady-state plasma concentration corresponding to 95 percent maximal effect.
D	Bolus dose administered.
E	The observed pharmacological effect.
EC_{p50}	The effective plasma concentration corresponding to half maximal (50 percent) effect.
EC_{p95}	The effective plasma concentration corresponding to 95 percent maximal effect.
E_{max}	Maximal effect (paralysis).
ko	Rate of constant intravenous infusion.
k_{12}	First-order mass rate constant associated with movement of drug from compartment 1 to compartment 2.
k_{21}	First-order mass rate constant associated with movement of drug from compartment 2 to compartment 1.
k_{eo}	First-order elimination rate constant from the hypothetical effect compartment.
k_{ne}	First-order transfer rate constant into the hypothetical effect compartment (n=1,2 for a two-compartment mammillary model).
MRT	Mean residence time.
n	Number of compartments in a mammillary model.

N	Number of doses.
s	A power function that confers sigmoidicity to the effect-concentration relationship.
t	Time.
T	Time when infusion is stopped.
$t_{1/2\alpha}$	Distribution half-life.
$t_{1/2\beta}$	Half-life of terminal exponential phase.
$t_{1/2\ k_{eo}}$	Half-life of equilibration between plasma concentration and effect.
V_1	Volume of the central (plasma) compartment.
$V_{d\beta}$	Apparent volume of distribution.
V_n	Volume of the driving (n=1,2) pharmacokinetic compartment.
V_{ss}	Volume of distribution at steady-state, based on measurement of drug in plasma.
Xo	Bolus dose.

Chapter 1

INTRODUCTION

Nondepolarizing neuromuscular blocking agents are used as an integral part of surgical procedure. They are used to facilitate intubation of the trachea and to aid in the control of respiration by paralyzing spontaneous diaphragmatic activity. They also counteract truncal rigidity induced by narcotic analgesics and prevent shivering associated with hypothermia. Principally, these drugs are used to maintain muscle paralysis throughout the intra-operative period and to prevent sudden body or diaphragmatic movements especially during delicate surgical manoeuvres.

The disposition kinetics of the commonly used relaxant drugs, namely d-tubocurarine, gallamine and pancuronium has been extensively investigated previously in both normal surgical patients and patients with various disease states, including renal and hepatic dysfunction. The results of these studies have shown that both the pharmacokinetics and pharmacodynamics of the nondepolarizing muscle relaxants are affected by the presence of renal and hepatic disease and a number of other factors including age, temperature and anaesthetic technique. It has also been demonstrated, with the use of sophisticated pharmacodynamic modelling techniques that a close relationship exists between plasma concentration of the respective muscle relaxants and the intensity of the neuromuscular response they elicit.

The objective of the research for this thesis has been to investigate the pharmacokinetics and where possible the pharmacodynamics of selected nondepolarizing neuromuscular blocking agents. The principal drug studied was alcuronium since only one previous study has examined the disposition of the drug in patients and no pharmacodynamic data were available. Hitherto alcuronium disposition and response was therefore examined in normal surgical patients, patients with cardiac disease

undergoing cardiopulmonary bypass surgery, patients with renal dysfunction, in a patient with biliary obstruction and in a tetanus patient. d-Tubocurarine and gallamine disposition were also investigated in patients undergoing cardiopulmonary bypass surgery. The plasma protein binding of d-tubocurarine was re-examined in plasma from patients with various diseases. Finally, a study in a dog model examined the pharmacodynamics of alcuronium in two separate muscle groups.

In the studies with alcuronium in normal surgical patients a biexponential equation interpreted as a two-compartment open mammillary model adequately described the concentration-time data gathered, using single and multiple i.v. bolus doses and a combined bolus and infusion dosage regimen respectively. Alcuronium kinetic parameters obtained using the three dosage regimens did not differ significantly. Using various mathematical models to characterize the effect-concentration relationship a pharmacodynamic model incorporating a separate effect compartment connected to the central (plasma) compartment was found to be appropriate in characterizing the paralysis-time and alcuronium concentration data.

There have been three previous reports on the use of alcuronium in patients with renal dysfunction. These reports suggested that the duration of the neuromuscular effect of this drug may be prolonged in such patients. However, no prior pharmacokinetic studies had been carried out with alcuronium in patients with renal failure or any other disease. Knowledge of the pharmacokinetics and pharmacodynamics of alcuronium in various disease states may enable a more rational approach to dosage selection and possibly prevent prolonged paralysis. Thus the disposition and effect-concentration relationship of alcuronium was examined in various disease states. Unfortunately, only three patients

with renal dysfunction, one with obstructive biliary disease and one patient with severe tetanus could be studied. The elimination half-life of alcuronium was markedly prolonged in patients with renal dysfunction and the plasma clearance was reduced. In obstructive biliary disease, both the volume of distribution and plasma clearance were increased but half-life was unchanged. Alcuronium disposition in a patient with tetanus appeared unaltered in comparison with normal patients. The effect-concentration relationship for alcuronium was unaltered in patients with renal dysfunction compared to normal patients but there appeared to be increased sensitivity in the patient with biliary obstruction. No quantitative effect-concentration data were available in the patient with tetanus.

For many drugs, it is the unbound drug concentration in plasma that determines the pharmacological effect. There is evidence in the literature of wide inter-individual variation in the clinical response to d-tubocurarine which has been attributed by some workers to differences in the extent of the protein binding in plasma. A study was thus designed to determine the plasma protein binding of d-tubocurarine in several groups of patients, typical of those in whom d-tubocurarine is used and in whom the binding might be altered. To better understand the factors which may influence the protein binding of d-tubocurarine a comprehensive biochemical and clinical profile was obtained for each patient and compared with the binding data. d-Tubocurarine was found to be approximately 50 percent bound in humans and its binding was insensitive to variation in plasma concentration of drug or the presence of renal, hepatic or cardiac disease and was apparently unrelated to plasma concentrations of total protein, albumin, total globulin, total lipids or α_1 acid glycoprotein. The binding in solutions of human

serum albumin was similar to that in plasma suggesting that albumin is the major plasma binding protein for d-tubocurarine.

Although the disposition kinetics of the common neuromuscular blocking agents have been rigorously examined, such studies have not been conducted in patients with cardiac disease. In the present study, therefore the disposition kinetics of alcuronium, gallamine and d-tubocurarine were investigated in three groups of patients undergoing cardiopulmonary bypass surgery. Alcuronium and d-tubocurarine were both administered as bolus and infusion regimens while gallamine was administered as bolus doses. Before cardiopulmonary bypass (CPB) alcuronium plasma concentrations declined in a bi-exponential fashion similar to that noted previously in non-cardiac patients. With the onset of CPB there was a 50 percent increase in alcuronium plasma concentrations but upon completion of CPB and termination of the alcuronium infusion the concentrations again declined biexponentially with time. The mean post-infusion elimination half-life was approximately three times larger than that observed in non-cardiac surgical patients. Similarily the time-averaged plasma clearance was reduced by 40 percent. In the majority of the patients who received gallamine, concentrations in the plasma prior to, during and after CPB were similar to those observed in normal surgical patients, indicating little or no effect of cardiac disease and/or CPB. In the remaining patients, pertubations were not observed before CPB, but with its onset there were varying changes, typically rises in gallamine concentrations ranging from an alteration during the period of CPB only or during the elimination phase to an alteration at all times after starting CPB. Gallamine disposition was only moderately altered in these patients in comparison with control patients. As for alcuronium, d-tubocurarine

plasma concentrations prior to CPB were not different to those observed in normal patients. With the onset of CPB, there was an abrupt discontinuity in the plasma concentration-time profile and plasma, total and free concentrations increased 3-fold during the period of CPB. d-Tubocurarine renal clearance was reduced during CPB and overall there was a reduction in total plasma clearance and a prolongation of the elimination half-life. An increase in d-tubocurarine free fraction in plasma of 27 percent during CPB was associated with haemodilution and was thus attributable to the CPB procedure itself.

The final aspect of this research was aimed at examining, in more detail, the effect-concentration relationship for alcuronium but in an animal model. Clinically muscle activity can coveniently be assessed in peripheral muscles only. However, the muscles of prime interest with respect to recovery from neuromuscular blocking agents are those of the diaphragm. There is some in vivo and in vitro data in the literature suggesting that the muscles of the diaphragm are less sensitive to neuromuscular blocking agents than the limb muscles. However, direct characterization of this difference in terms of relaxant drug plasma concentrations has not been performed. The pharmacodynamics of alcuronium were therefore investigated in dogs employing a constant rate infusion regimen and simultaneous measurement of muscle paralysis in the limb and the diaphragm. During both onset and offset of effect the predicted concentrations at 50 percent effect were lower for the limb muscle than with the diaphragm. An effect model was also used to demonstrate that a higher plasma concentration of alcuronium is needed to elicit an equivalent response in the diaphragm as that in the limb. The half-time for equilibration between plasma concentration and effect was two fold less for the diaphragm and the rate of recovery from paralysis

in the diaphragm was twice that observed in the limb muscles.

It is hoped that the series of investigations described in detail in the subsequent chapters will make a useful contribution to the literature on the clinical pharmacokinetics and pharmacodynamics of the neuromuscular blocking drugs.

Chapter 2

PROPERTIES OF NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

Chapter 2 - PROPERTIES OF NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

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2.1 Muscle Relaxants in Clinical Use

Muscle relaxants are a group of drugs which possess, as their principal pharmacological action, the property of inhibiting the transmission of nervous impulses by acetylcholine (ACh) and blocking transmission across the skeletal neuromuscular junction. These agents are also referred to as neuromuscular blocking agents. d-Tubocurarine (dTc) is the prototype of the group which also includes gallamine (Gl), metocurine (mTc), alcuronium (Alc), pancuronium (Pc), fazadinium (Fz), atracurium (BW 33A) and vecuronium (NC 45).

The alkaloid d-tubocurarine (dTc) was first identified in 1851 (1) as the active principle of the South American arrow poison. However, it was not until 1935, that King (2) isolated the crystalline chloride and in 1940 Bennett (3) introduced the drug to medical practice as an adjunct to electroconvulsive therapy in psychiatry. Subsequently, dTc was introduced to clinical anaesthesia by Griffith and Johnson in 1942 (4). Since dTc is only obtainable from plant sources a search was begun for synthetic neuromuscular blocking drugs.

The first of the synthetic, curare-like drugs, gallamine was synthesized by Bovet and co-workers in 1947 (5), and introduced to clinical anaesthesia in 1949 by Mushin et al. (6). Metocurine (mTc), a trimethyl derivative of dTc has been available since 1948 (7) and recently it was proposed as a good alternative to dTc (8).

While the raw extract, tube curare, yielded the alkaloid dTc on purification, the raw extract calabash or gourd curare yielded the alkaloid toxiferine I. Foldes et al. (9) investigated the pharmacology of toxiferine I and found the compound to be the most potent relaxant to have been tested in humans. It is not used clinically however, because of its protracted action.

Its discovery, however, led to the synthesis of alcuronium (N, N'-Di(2-propenyl)nortoxiferinium; diallylbisnortoxiferine) by Roche Laboratories in 1958 (10). Alcuronium was subsequently introduced into anaesthesia by Frey and Seeger in 1961 (11).

Pancuronium (Pc) was synthesized in the Organon Laboratories (12) and introduced into anaesthetics by Baird and Reid in 1967 (13). It has potent neuromuscular blocking activity in animals and humans (14,15) and is free from hormonal actions. Fazadinium, Fz, (Allen and Hanbury, England), was first introduced by Simpson and co-workers in 1972 (16).

Vecuronium (NC 45) is a monoquarternary analogue of pancuronium which was synthesized by Savage and co-workers (17) and has been undergoing clinical evaluation since 1977 (18).

Atracurium is one of a series of nondepolarizing neuromuscular blocking agents designed to fragment readily in vivo to inactive moieties, partly by esterase hydrolysis and partly by base-catalysed degradation of the quaternary ammonium groups. It was developed by Stenlake (19) and is presently undergoing clinical trials internationally (20).

The eight compounds considered are the principal nondepolarizing muscle relaxant drugs. Their structures are shown in Fig. 2.1. The prominent feature of each compound is the presence of one, two or three (usually two) quaternary nitrogen centres.

d-Tubocurarine is a mono-quaternary compound possessing both a tertiary and quaternary nitrogen function (21). The quaternary nitrogen is located in the tetrahydroisoquinoline ring bearing the free phenolic group and whose asymmetric centre is laevorotatory (-). The tertiary nitrogen is associated with the dextrorotatory (+) centre of asymmetry (Fig. 2.1). Kalow (22) calculated pka values of 8.1 and 9.1 for the 2

hydroxyl groups. Bick and McCleod (23) interpreted the electrometric titration curve for dTc in terms of three pka's of 7.8, 8.85 and 9.75. The lower two values were assigned to the hydroxyl groups in agreement with Kalow (22) while the third was ascribed to the protonated tertiary amino group. At physiological pH, dTc would therefore exist predominantly in the form containing two positively charged nitrogens, the quaternary group, and the protonated tertiary nitrogen.

Gallamine is a benzene derivative and is the simplest of the eight compounds to possess neuromuscular blocking activity.

Alcuronium is derived from toxiferine I which is unstable in aqueous solution undergoing cleavage into two symmetrical monoquaternary compounds (24). Alcuronium is diallylbisnortoxiferine wherein substitution of the methyl groups on the quaternary nitrogen centres has increased chemical stability.

Table 2.1 summarizes some of the important physico-chemical properties of these relaxant drugs.

2.2 Neuromuscular Transmission

2.2.1 Anatomy of the Neuromuscular Junction

The mammalian neuromuscular junction is relatively compact, extending about 10 micrometers above the muscle membrane. It comprises three anatomical divisions: The presynaptic area, also called the endplate or nerve terminal, the postsynaptic area or muscle endplate and the synaptic cleft, the space between (Fig. 2.2).

The motor nerve supply reaches the muscle as a myelinated axon which becomes branched to supply numerous muscle fibres. As the nerve branch approaches the muscle fibre it loses its myelin sheath and subdivides into fine terminations which lie in the grooves on the surface of the muscle endplate (Fig. 2.2). The whole structure lies entirely outside

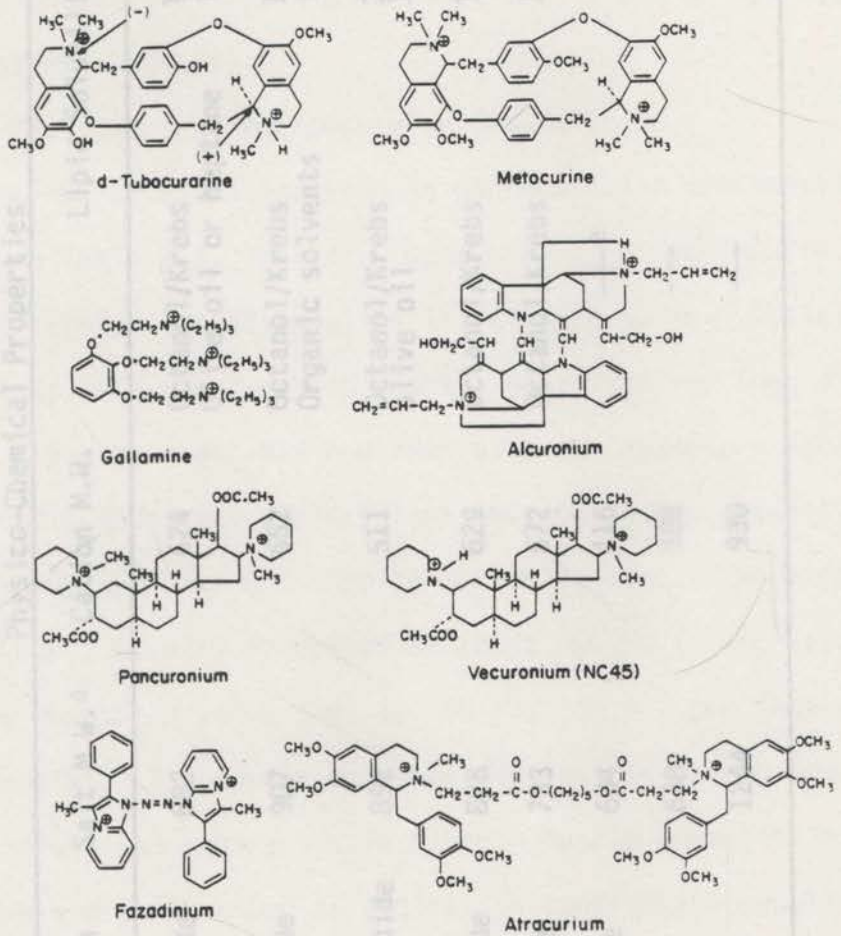


Figure 2.1. Chemical structure of eight nondepolarizing neuromuscular blocking agents of clinical interest.

Table 2.1 Physico-Chemical Properties of Relaxant Drugs

	Physico-Chemical Properties				
Relaxant Drug	Salt Form	Salt M.W.[a]	Cation M.W.	Lipid Solubility[b]	
d-Tubocurarine	dichloride	682	624	Octanol/Krebs Olive oil or heptane	15:85[c] insoluble[d]
Metocurine	dichloride	907	652	Octanol/Krebs Organic solvents	1.99[c] insoluble[c]
Gallamine	triethiodide	892	511	Octanol/Krebs olive oil	3.97[c] 10% soluble[d]
Alcuronium	dichloride	828	629	Octanol/Krebs	1.99[d]
Pancuronium	dibromide	733	572	Octanol/Krebs	1.99[d]
Fazadinium	dibromide	604	416	---[e]	
Vecuronium	bromide	638	588	---	
Atracurium	besylate	1244	930	---	

a M.W. - molecular weight
b Organic solvent/buffer partition ratio
c Meijer and Weitering, 1970 (25)
d Cohen, 1974 (26)
e Data not available

the muscle fibre. The endplate is covered by one or more Schwann cells which insulate the structure from the surrounding fluids. The synaptic cleft or the region between the nerve terminal and the muscle is approximately 20 to 30 nanometers (27). It is filled with either an electrolyte solution similar to extracellular fluid or hydrated basement membrane material (28,29).

2.2.2 Physiology of Neuromuscular Transmission

The sequence of steps involved in neuromuscular transmission are summarized in Table 2.2. Briefly, upon arrival of an impulse at the motor nerve terminal, acetylcholine is released as many vesicles expel their contents into the synaptic cleft. Acetylcholine then diffuses across the synaptic cleft and combines with Ach receptors located on the motor or muscle endplate. This alters the membrane permeability primarily to sodium ions but also to potassium ions. The endplate potential (epp), usually polarized at about -90 mV is increased and it reaches the threshold value (-45 to -60 mV) (30,31) for generation of an action potential. The muscle membrane depolarizes and an impulse propagates along the entire muscle fibre. Muscle contraction is then initiated by a process known as excitation-contraction coupling. The released Ach is immediately removed from the endplate region by diffusion and enzymatic hydrolysis by acetylcholinesterase and the membrane repolarizes (32).

2.2.3 Pharmacology of Neuromuscular Blocking Drugs

From Table 2.2 it is clear that there are numerous stages at which blockade of muscle contraction can occur whereby muscle relaxation could be achieved. The action of a neuromuscular blocking drug such as dTc occurs primarily at the postsynaptic membrane of the neuromuscular junction by competing with Ach for receptor binding sites. If a

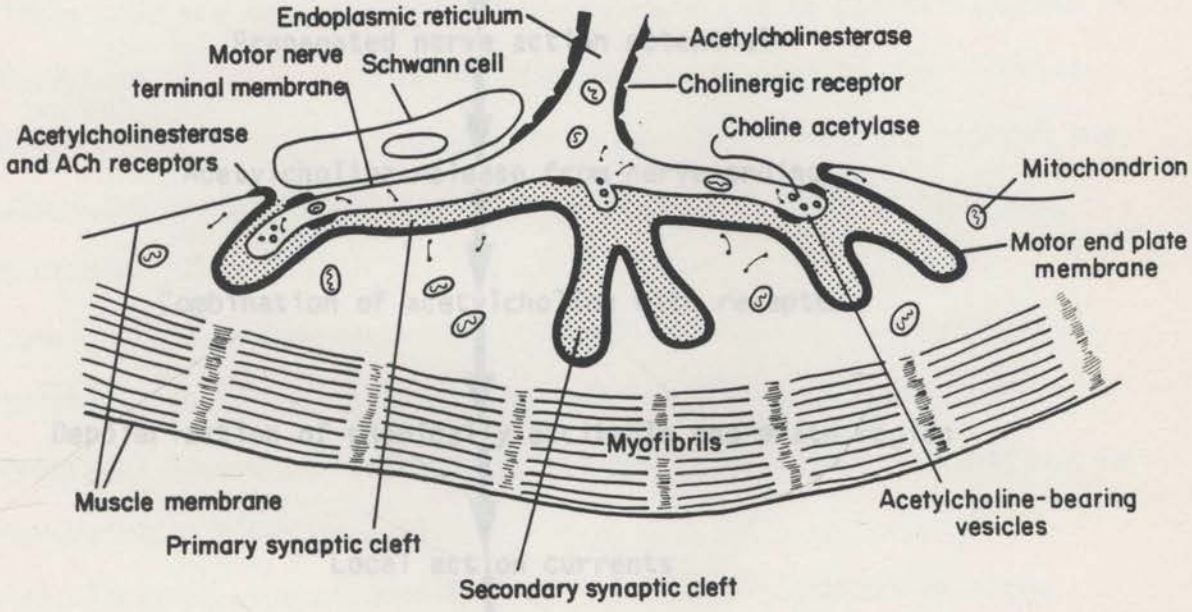
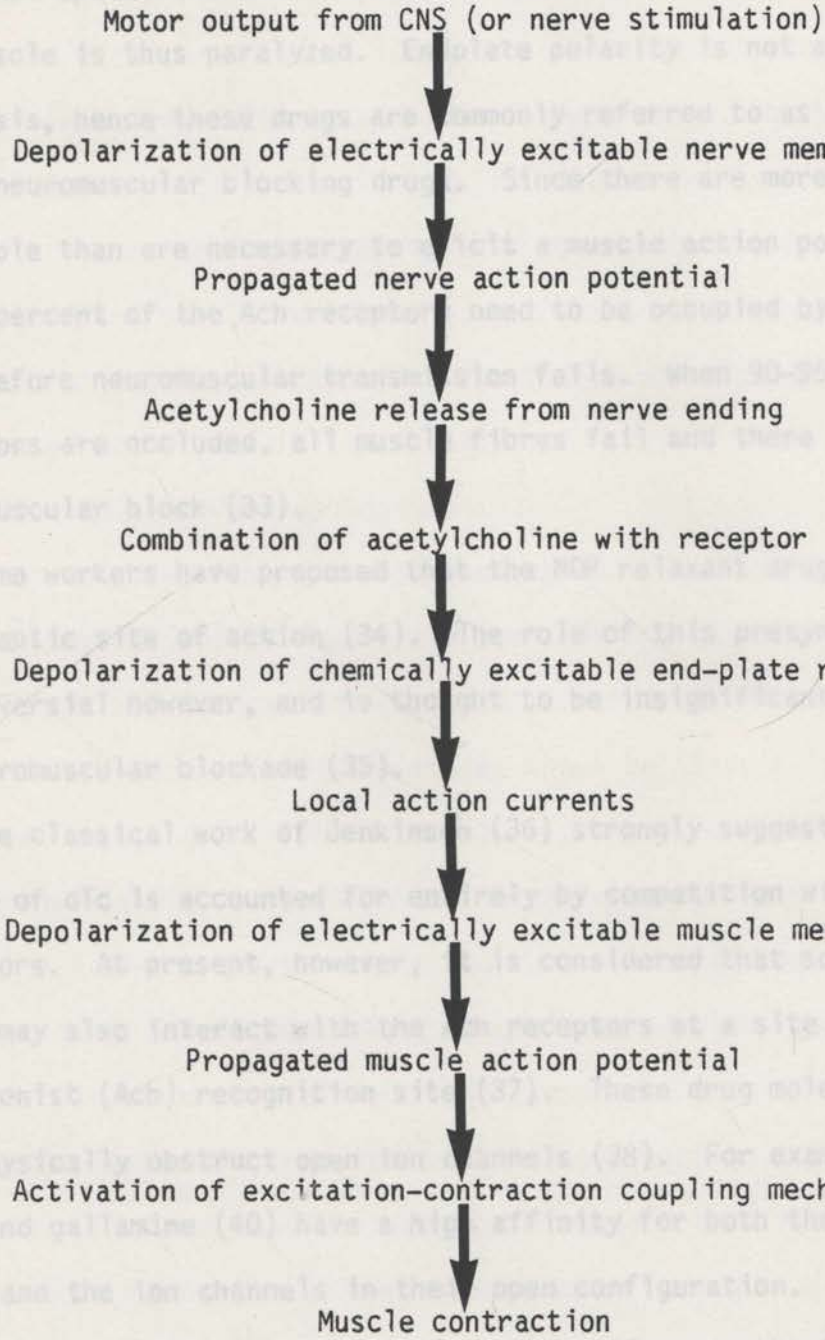


Figure 2.2 A schematic representation of the mammalian neuromuscular junction. Reproduced from Sokoll and Gergis, 1980 (28).

Table 2.2 Steps Involved in Neuromuscular Transmission



From Waud, 1977 (33).

sufficient concentration of the blocking agent is present the receptors are unavailable to Ach. Thus, despite the fact that a nerve impulse may reach the nerve terminal and cause multiple vesicles to rupture into the subneural space, the Ach liberated cannot depolarize the motor endplate. The muscle is thus paralyzed. Endplate polarity is not altered during paralysis, hence these drugs are commonly referred to as nondepolarizing (NDP) neuromuscular blocking drugs. Since there are more receptors available than are necessary to elicit a muscle action potential, some 75 to 80 percent of the Ach receptors need to be occupied by the blocking drug before neuromuscular transmission fails. When 90–95 percent of the receptors are occluded, all muscle fibres fail and there is complete neuromuscular block (33).

Some workers have proposed that the NDP relaxant drugs also have a presynaptic site of action (34). The role of this presynaptic effect is controversial however, and is thought to be insignificant in contributing to neuromuscular blockade (35).

The classical work of Jenkinson (36) strongly suggested that the effect of dTc is accounted for entirely by competition with Ach for the receptors. At present, however, it is considered that some of these drugs may also interact with the Ach receptors at a site distinct from the agonist (Ach) recognition site (37). These drug molecules bind to and physically obstruct open ion channels (38). For example, both dTc (39) and gallamine (40) have a high affinity for both the recognition sites and the ion channels in their open configuration. However, with both these and other curariform drugs the effect on the Ach receptor is still predominantly competition for the agonist recognition sites since normally only relatively few channels are open. In contrast, during tetanic stimulation more channels are open thus channel block by dTc (and

other relaxant drugs) contributes appreciably to neuromuscular blockade, deepening the paralysis.

2.3 Muscle Relaxant Drugs in Clinical Practice

Neuromuscular blocking drugs are used principally to minimize trauma associated with endotracheal intubation and to provide upper abdominal muscle relaxation. Without the aid of these drugs, the high dose of general anaesthetics needed to provide adequate relaxation would be sufficient to cause severe physiologic disturbances. In addition, the nondepolarizing muscle relaxant drugs are also used in the symptomatic treatment of tetanus and the facilitation of ventilation in patients with acute respiratory failure (41,42,43).

2.3.1 Dose and Dosage Regimen

The dose of muscle relaxant required varies of course with each drug but also depends on the nature and duration of the surgical procedure(s); on the anaesthetic technique employed; other drugs given during surgery and on the presence of disease states known to alter relaxant drug pharmacokinetics and/or pharmacodynamics. Under carefully controlled conditions there is wide variation in the response both with respect to the maximal effect and the onset and duration of action to the muscle relaxant drugs (44,45,46). As a result anaesthetists have sought to identify factors which influence the response. Such factors include age, body weight and build, body surface area and sex.

Gray (47) found that the aged need less dTc than the young while Durrans (48) reported that they needed more. Using a dose calculated on the basis of lean body mass, Wulfsohn (49) also observed that the aged needed a larger dTc dose. In contrast, infants were found to require less than older children (50). Dundee (51) however, failed to demonstrate that age of patients is useful in predicting the dosage

requirements of dTc.

Generally dosages are based on total body weight but recommended dosages vary greatly between studies (49). However, many studies (52,53) have failed to demonstrate any relationship between the required dose of relaxant drug and total body weight in adults although a weak relationship has been identified in children (50).

Dundee (49,51) could not demonstrate any relationship between sex and dosage requirement for the relaxant drugs.

There is great variability in the recommended initial doses of the relaxant drugs. For dTc it ranges from a low of 0.1 mg/kg (54) to a high of 1 mg/kg (55). The usual dose for alcuronium is 0.15-0.25 mg/kg (11,56). The recommended dose of gallamine is usually 1.0 mg/kg (57) but doses ranging between 1.4 mg/kg to 6 mg/kg (58-60) have been used without any untoward clinical sequelae in patients with normal renal function.

Muscle relaxant drugs are generally administered intravenously for rapid onset of action either as single (for shorter procedures) or as multiple boluses (for longer operations). Other intravenous regimens include a rapid or loading infusion followed by a slower infusion (61,62) or a combination of a loading bolus and a maintenance infusion. The latter dosage regimens have been designed using average pharmacokinetic and pharmacodynamic parameters and employed successfully with pancuronium (63), dTc (64,65) and gallamine (66). Such regimens produce stable muscle relaxation for the duration of surgery and are easily reversed at the termination. Both the dual infusion regimen and the bolus and concomitant infusion technique afford flexibility enabling individualization of administration since the dosage can be altered continuously during the course of the surgical procedure by simply changing the rate of the maintenance infusion.

There has been some debate in the literature on the relative merits of employing single versus multiple intravenous doses. Feldman (67) believes that the use of large bolus doses is to be preferred since frequently repeated small doses of relaxant drug will result in higher post-operative drug concentrations and residual paralysis. However, recently Ham et al. (68) reported that there was no difference in pharmacokinetics or pharmacodynamics of dTc when it was administered as a single large bolus; repeated small boluses or as a continuous infusion titrated to produce 90 percent depression of twitch height. The fact that recovery from the effects of dTc is independent of the dosage schedule derives from the anticipated relationship between relaxant drug plasma/serum concentrations and effect (see section 2.7.1). Despite this, the use of small multiple doses may have an advantage over the large bolus technique since the required duration of neuromuscular blockade cannot always be estimated at the beginning of surgery and the intensity of neuromuscular blockade can be adjusted more readily with changing surgical needs based on the response to the initial injection. However, the well known cumulative effects of relaxant drugs such as dTc (69) pancuronium (70) and gallamine (71) resulting from their multicompartment pharmacokinetic characteristics (72) needs consideration when selecting the size and time of additional dose(s).

2.3.2 Potency

The degree of neuromuscular blockade produced by a given dose of muscle relaxant drug is determined by the pharmacokinetics of the drug and by the sensitivity of the neuromuscular junction.

A discussion of muscle relaxant pharmacokinetics and pharmacodynamics will be presented in sections 2.5 and 2.7. The present discussion focuses on the clinical estimation of relaxant drug effectiveness and

potency.

A convenient clinical index of relaxant drug potency is the dose eliciting 50 percent effect or paralysis, commonly referred to as the ED_{50} value. The ED_{50} can be determined from a dose-response curve constructed either by the bolus technique, namely administering different bolus doses to different groups of patients and noting the response or by using the cumulative dose response technique (CDR) which involves administering incremental bolus doses to an individual until neuromuscular blockade is essentially complete. A variation on the CDR technique employs a constant-rate infusion regimen which works efficiently provided plasma concentrations are also measured. However, these methods, especially the CDR technique, cannot provide true estimates of the ED_{50} because the pharmacokinetic and pharmacodynamic aspects of the relaxant drug action cannot be separated. It has been shown that the CDR and bolus technique result in similar dose-response curves, and similar estimates of ED_{50}, for the longer acting drugs pancuronium and dTc (73), but not with the shorter acting vecuronium (74). Thus the CDR technique is not recommended for the determination of potency of muscle relaxant drugs of medium and short duration of action (74). This is particularly important when the dose-response (or ED_{50}) characteristics of the various muscle relaxant drugs are to be compared since they all exhibit different pharmacokinetic characteristics.

There have been numerous comparisons of the potencies of muscle relaxant drugs. Table 2.3 summarizes the finding of some recent investigations with dTc, gallamine and alcuronium. It should be emphasized that valid statistical comparison of the potencies of the different relaxant drugs requires uniformity in both study design and technique. Further, differences in molecular weights of the compounds;

Table 2.3 Nondepolarizing Relaxant Drug Clinical Potency in Adult Patients

Drug	ED_{50} (mg/kg)	Relative Potency	Technique	Reference
d-Tubocurarine	0.192		Bolus	Donlon et al. (73)
	0.137	1	CDR	Donlon et al. (73)
	0.154		CDR	Donlon et al. (75)
Gallamine	0.96		CDR	Donlon et al. (76)
	0.767	0.14-0.25	CDR	Donlon et al. (73)
Alcuronium	0.052		CDR	Schuh (77)
	0.042	2.6-4.6	Bolus	Lund and Stovner (78)

the presence of potentially active metabolite(s) and the numerous pharmacokinetic and pharmacodynamic factors need consideration when potency comparisons are made.

2.3.3 Selection of Relaxant Drug: Clinical Considerations

Selection of the agent most suited to a particular surgical procedure and patient involves numerous considerations. A particular agent may be chosen for special characteristics related to onset or duration of action or to the presence of favorable pharmacokinetic characteristics. However, the choice is also influenced by the presence or absence of untoward properties of these agents. The most frequently encountered side effects involve the circulatory system (Table 2.4). For example, dTc produces hypotension (79) while gallamine produces tachycardia (80). Alcuronium also produces hypotension but lacks the histamine releasing properties of dTc (81).

2.4 Assessment of Neuromuscular Blocking Effect

Traditionally, the degree of neuromuscular blockade during and following anaesthesia has been assessed on qualitative criteria such as muscle tone, the occurrence of spontaneous muscular movements, the "feel" of the anaesthetic reservoir bag, the inspiratory force, and the ability to open the eyes and to raise the head. However, these methods have severe limitations. They depend on a subjective interpretation by the anaesthetist and some can be utilized only in the aroused patient. They are also limited by the ability of an individual subject to reproduce a given response. Thus more objective and quantitative methods of assessing the effect of the muscle relaxant drugs are necessary.

Observation of the mechanical or electrical activity of the muscle after stimulation of a peripheral nerve gives a direct measurement of the degree of neuromuscular blockade. Using this information it is possible

Table 2.4 Comparison of the Circulatory Side-Effects of Nondepolarizing Muscle Relaxants

Drug	Ganglion Blocking Action	Anti-Muscarinic Effect	Histamine Release	Blood Pressure	Cardiac Output
d-Tubocurarine	++	0	++	++ ↓	± ↓
Gallamine	0	++	±	+ ↑	++ ↑
Alcuronium	+	±	0	+ ↓	± ↓

0 No change.
± Variable small changes that depend on other factors
\+ Moderate change
++ Large change
↓ Decrease
↑ Increase

Modified from Miller and Savarese, 1982 (35)

to determine a precise, individual dosage requirement for these drugs and their agonists.

2.4.1 Principles of Nerve Stimulation

Under conditions of normal neuromuscular transmission, electrical stimulation of a motor nerve, with sufficient intensity, will result in contraction of the innervated muscles. Following administration of a muscle relaxant drug, the force of muscle contraction will be reduced, in a quantal fashion. Each fibre will contract maximally or not at all. The observed reduction in contraction intensity is related to the proportion of fibres not responding (at an unchanged supramaximal stimulation) and is a manifestation of the degree of neuromuscular blockade. Three types of nerve stimulation are mainly used clinically to assess neuromuscular blockade.

Single Twitch Stimulation

Single supramaximal voltages (150-500V) are applied at a rate of 0.1 to 1 Hz (82). The response to the single twitch stimulus depends on the frequency with which the individual stimuli are applied. A greater "apparent" blockade is observed with more frequent stimulation (83,84). The rate of delivery (~0.1-0.15 Hz) and duration (0.2 msec or less) therefore must be standardized (85,86).

Tetanic Stimulation

With tetanic stimulation, successive stimuli follow at a very rapid rate (30, 50, 100 or 200 Hz). Fifty Hz for 5 sec is commonly used because it stresses the neuromuscular function to the same extent as does a maximal voluntary effort (87). Large amounts of Ach are released at the outset of a tetanic stimulation. The mechanical strength of the muscle response caused by a tetanic stimulation, at say 50 Hz, is however maintained in the presence of normal neuromuscular function since the

released Ach is many times greater than that necessary to evoke a response. In the presence of a neuromuscular blocking drug when surplus receptors are occluded the decrease in the amount of Ach released during tetanic stimulation results in fade or an unsustained response. The degree of fade depends on the extent of blockade, the frequency and duration of the tetanic stimulation and how often the latter is applied (88-90). Tetanic stimulation may also be used in combination with a single stimulus, applied both before and after the tetanus. Thus the post-tetanic twitch response may be facilitated (PTF) or potentiated (PTP) since the mobilization and synthesis of Ach remains elevated for some time after the tetanic stimulation.

Train-of-Four Stimulation

Train-of-four (TOF) stimulation is provided by means of four supramaximal stimuli at intervals of 0.5 sec over a period of 2 sec (2Hz). These are repeated every 10-12 seconds. The amplitude of the fourth response in relation to the first gives the train-of-four ratio. During a nondepolarizing block this ratio is reduced in proportion to the degree of neuromuscular blockade (91).

Comparing the three modes of nerve stimulation, the single twitch is the least sensitive in detecting nondepolarizing blockade; the twitch response is not reduced until 75-80 percent of the cholinergic receptors are blocked. When 90 percent of receptors are blocked the response disappears completely (92). With tetanic stimulation, at 30 Hz for 5 secs, similar sensitivities can be achieved, however, sensitivity is greater at higher frequencies. For example, at 100 Hz (5 sec), fade begins to develop when only 50 percent of the receptors are blocked and at 200 Hz (5 sec) fade is observed at 30 percent receptor blockade (88,92). The train-of-four ratio begins to decrease when more than 70-75

percent of receptors are blocked and is thus more sensitive than the single twitch and has approximately the same sensitivity as tetanic stimulation at 50 Hz. At a ratio of 0.70–0.75, the twitch response is normal and there is no fade in response to stimuli at 50 Hz for 5 sec (82,93,94). See Fig. 2.3 for diagrammatic illustration of the relationship between single twitch and TOF.

2.4.2 Quantification of Extent of Neuromuscular Blockade

A qualitative measure of neuromuscular blockade is made by visual or tactile evaluation of the patient's response to ulnar nerve stimulation. However, to obtain a quantitative measure, the evoked response has to be evaluated either mechanically or by use of electromyography (e.m.g.)(35).

Mechanical Measurement

The hand muscles, especially the adductor pollicis of the thumb, are most commonly used for mechanical measurement. The thumb twitch acts on a force-diplacement transducer whereby the evoked force is transformed into an electrical signal which can be presented on a screen and/or chart recorder, following amplification. The adductor pollicis is the only muscle in the thumb innervated by the ulnar nerve, hence, this measurement approaches the single-muscle precision of the in vitro nerve-muscle preparation. However, to obtain reliable and reproducible measurements it is important, firstly, that the transducer is placed correctly in relation to the muscle in which the measurements are made (95), secondly, that a preload is used and maintained (76) and finally that the transducer used is not overloaded (96).

Electromyographic Measurement

In electromyography (e.m.g.), the evoked compound muscle action potential registered by the muscle (either adductor pollicis or abductor digiti minimi) is detected via two surface or needle electrodes and

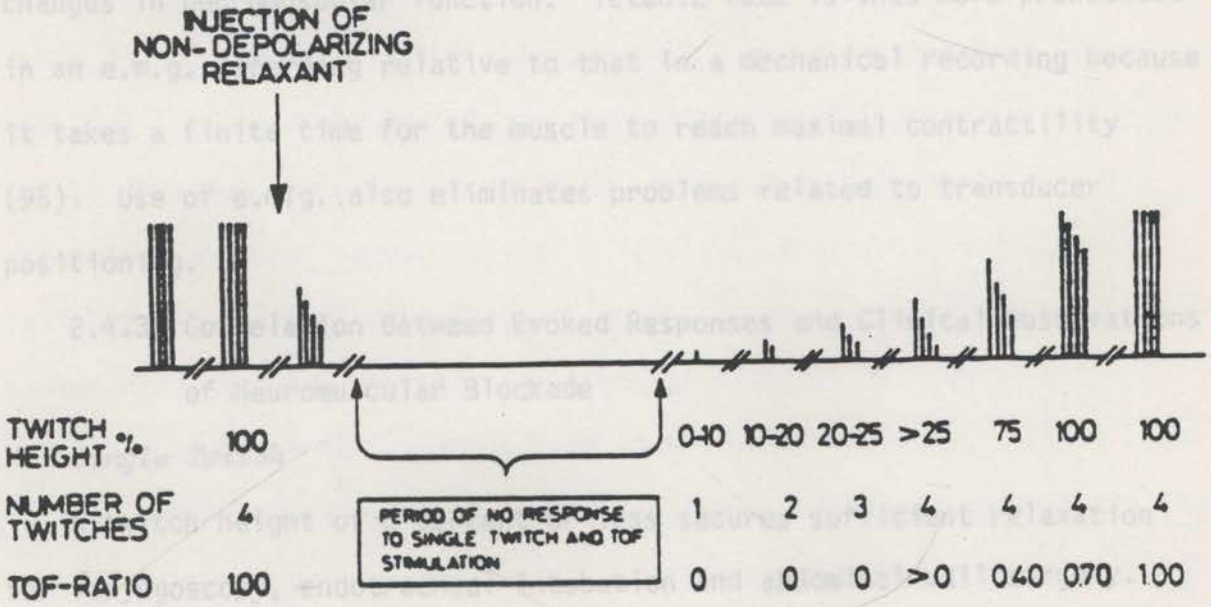


Figure 2.3 Diagrammatic illustration of the relationship between the evoked responses to single twitch (0.1 Hz) and train-of-four (TOF) nerve stimulation during a nondepolarizing neuromuscular blockade. Note the "period of no response" to either of the two forms of stimulation. This period of intense neuromuscular blockade may be evaluated using tetanic and post-tetanic single twitch stimulation. From Viby-Mogensen, 1982 (91).

recorded. In principle the e.m.g. measurement is preferable to the mechanical twitch measurement since the e.m.g. reflects only changes at the endplate whereas the mechanical response depends both on changes at the endplate and on the contractility of the muscle. Further, in contrast to the mechanical response, the e.m.g. can detect very rapid changes in neuromuscular function. Tetanic fade is thus more pronounced in an e.m.g. recording relative to that in a mechanical recording because it takes a finite time for the muscle to reach maximal contractility (95). Use of e.m.g. also eliminates problems related to transducer positioning.

2.4.3 Correlation Between Evoked Responses and Clinical Observations of Neuromuscular Blockade

Single Twitch

A twitch height of 5 percent or less secures sufficient relaxation for laryngoscopy, endotracheal intubation and abdominal wall surgery. The head usually cannot be raised before the twitch height is 90 percent of control (82,94).

TOF Stimulation

A TOF ratio of 0.75 typically enables the patient to open the eyes widely, protrude the tongue, exhibit cough sufficiently and sustain head-lift for at least 5 sec (93,97). At values greater than this, the vital capacity and inspiratory force are normal (98).

Tetanic Stimulation

Tetanus of 50 Hz for 5 sec without fade indicates that the patient is able to maintain a head lift for 5 sec, protrude the tongue, open the eyes, and that vital capacity and maximum voluntary ventilation are at least 90 percent of control (93,99).

2.5 Pharmacokinetics of Nondepolarizing Neuromuscular Blocking Agents

This section will review the pharmacokinetic characteristics of the muscle relaxant drugs with particular emphasis on d-tubocurarine, gallamine and alcuronium, the three relaxant drugs on which this thesis is based.

Following i.v. administration all nondepolarizing muscle relaxant drugs distribute into an initial volume (V_1) of approximately 5-10 ℓ (65,100). Thereafter, the plasma concentration falls in either a bi- or tri-exponential manner. The rapid initial decline in plasma concentration occurs presumably as a result of distribution to highly perfused tissues including lungs, kidneys, liver and heart followed by a slower decline owing to redistribution and elimination. Because the drugs are highly polar, distribution to the poorly perfused tissues such as bone, ligaments and fat is negligible (101). Thus at steady-state the muscle relaxants are largely confined to the extracellular space with a volume of distribution at steady-state of the order of 14-42 ℓ (200-600 ml/kg) (65,102). In the systemic blood circulation relaxant drugs are bound to serum proteins but the extent of this binding is small to moderate, ranging from zero percent bound in the case of gallamine to approximately 50 percent bound in the case of dTc. The relevant data are summarized in Table 2.5.

The characteristic physico-chemical properties of high molecular weight, permanent cationic charge and high water solubility makes it difficult for these compounds to penetrate cell membranes. Thus, they do not enter red blood cells (111), cross the placenta (112), or penetrate the cerebrospinal fluid significantly (113).

The nondepolarizing muscle relaxant drugs are primarily eliminated from the body either essentially unchanged via the kidney as in the cases

Table 2.5 Plasma Protein Binding of the Muscle Relaxant Drugs

Drug	Concentration Range (µg/ml)	Method	Percent Bound to Plasma Proteins[a]	Reference
d-Tubocurarine	1	UF[b]	56 ± 9 (7)	Duvaldestin and Henzel (103)
	0.008	ED[c]	41 (10)	Wood and Wood (104)
	0.2-2	ED	51 ± 3 (5)	Meijer et al. (105)
	4-6	ED	51 ± 8 (5)	Clissold et al. (106)
	5-50	ED	44 ± 7.7 (5)	Ghoneim et al. (107)
	20	ED	33	Cohen et al. (108)
Gallamine	40	ED	0 (1)	Henthorn et al. (109)
Alcuronium	0.1-2.0	ED	40	Raaflaub and Frey (110)

[a] Mean ± S.D. (n) where available

[b] Ultrafiltration

[c] Equilibrium dialysis

of dTc (108), gallamine (114), and alcuronium (110) or in the form of metabolites, as exemplified by pancuronium (115). Although Cohen (116) observed that the renal clearance of ^{3}H-dTc in the dog was essentially the same as that for urea and thus equal to glomerular filtration rate (GFR), Prescott (117) proposed that the relaxant drugs, like other quaternary ammonium bases, are probably actively secreted by the tubular transport system for bases. Although reabsorption and active secretion have been shown to occur with cationic drugs, it has been suggested that these mechanisms do not operate on molecules, like the nondepolarizing muscle relaxant drugs, with two cationic centres (110). Few if any studies have been designed to estimate the renal clearance of the relaxant drugs in humans. For some of the relaxant drugs, biliary secretion is a minor secondary route of elimination as in the case of dTc (108), alcuronium (110) and/or in the form of unidentified metabolites (dTc; 108).

The total plasma clearance of these drugs is low (1 to 3 ml/min/kg or 70-210 ml/min; 83), but they have a short (80-400 min) elimination half-life. The volume of distribution at steady-state (V_{ss}) is also low (118).

d-Tubocurarine

Pharmacokinetic studies with dTc have been conducted by numerous workers (65,105,119-123) and several mathematical models have been formulated to characterize the observed data. Of these models, that formulated by Gibaldi et al. (124) has been most prominent. These workers combined the plasma concentration-time data from four patients (101) with the urinary excretion data from four unanaesthetized volunteers (125) and proposed a three-compartment open model for dTc disposition. This model was used to predict pharmacodynamics (see

section 2.7.1). Wingard and Cook (126) also interpreted previously published data (127,128) in terms of a tri-exponential equation characterizing dTc distribution and elimination and the relationship between concentration and intensity of effect. Subsequently, biexponential equations have been found adequately to characterize dTc pharmacokinetic data following either an i.v. bolus (119); a constant rate infusion (120), dual infusion (121,61) or a bolus and concomitant infusion regimen (65).

Pharmacokinetic parameters for dTc are summarized in Table 2.6. Initial volume (V_1) ranges from 47–200 ml/kg while volume of distribution at steady-state (V_{ss}) ranges from 290–500 ml/kg, which is higher than that found for the other relaxant drugs (118). The rapid distribution half-life is 2–20 min while the slower distributional phase ranges from 24–120 min. Elimination half-life was reported to lie between 120 min and 350 min when plasma/serum was sampled for 6 to 12 hours (105,119–121,124). However, Matteo et al. (123) have reported a prolonged elimination half-life of 20–40 hours in humans when sampling was carried out for 96 hours. Similar findings were observed in rats, where dTc could be detected in tissues for up to a week following a single dose (129). This prolonged half-life, which has been attributed to storage in and slow release from connective tissues and mucopolysaccharide (130,131) storage depots, has, however, little clinical significance. The total plasma clearance of dTc is low, ranging from 1–3 ml/min/kg (70–210 ml/min) and represents mainly excretion of the unchanged drug via the renal route. Biliary elimination is a secondary route of elimination which accounts for about 12 percent of the administered dose over 24 hours in humans (105) and animals (108). Although no biliary metabolites have been detected in humans (105) and

Table 2.6 Pharmacokinetic Parameters of dTc in Humans

Dosage Regimen	Parameter[a] $t_{1/2\beta}$ (min)	Cl (ml/min/kg)	V_{ss} (ml/kg)	Reference
Bolus	462	0.45[b]	300	Buzello and Agoston, 1978 (122)
Infusion	275 ± 89	1.81 ± 0.49	565 ± 82	Shanks et al., 1979 (120)
Bolus and Infusion	172 ± 80	2.69 ± 1.02	455 ± 173	Ramzan et al., 1980 (65)
Bolus	122 ± 28	3.89 ± 0.42	480 ± 104	Ramzan, 1980 (132)
Double Infusion	119 ± 66	2.25 ± 0.7	297 ± 105	Stanski et al., 1979 (121)
Bolus	346 ± 17.3	0.94[b]	387 ± 54	Meijer et al., 1979 (105)
Bolus	166 ± 10 40.1 ± 2.7[c]	1.8 ± 0.1	420 ± 20[d]	Matteo et al., 1980 (123)

a Mean ± S.D. where possible.
b Calculated from author's data.
c Hours
d Vd_{β}

rats (25), there is evidence to suggest that an N-dealkylated metabolite (<1 percent of administered dose) is formed and excreted in the bile in dogs (108).

Gallamine

Gallamine disposition in humans, like that of dTc, has been characterized by both triexponential (122,114,66) and biexponential equations (58,59,133,134) the latter being most commonly used. In the dose (2 to 6 mg/kg) ranging studies performed by Ramzan et al. (58,59), no major dose dependent pharmacokinetic differences could be demonstrated. Gallamine thus displays linear pharmacokinetics. The total plasma clearance is low (1-2 ml/min/kg or 70-140 ml/min). There is no evidence of significant metabolism of gallamine which has the largest fraction excreted renally of all the muscle relaxants. Thus a wide proportion (53 to 95 percent) of the administered dose has been recovered in the urine within 24 to 30 hrs and less than 0.4 percent is recovered from bile (133). Gallamine pharmacokinetic parameters are presented in Table 2.7.

Alcuronium

Other than this work only one previous study by Raaflaub and Frey (110) has been concerned with the pharmacokinetic characterization of alcuronium in humans. This study involved the administration of a single dose of ^{3}H-alcuronium to six patients after which plasma was sampled for 12 hrs and in three patients, urine was sampled for 24 hrs. These data were analysed graphically according to a bi-exponential relationship. The mean (± S.D.) V_1 was 165 (± 29) ml/kg, V_{ss} was 324 (± 38) ml/kg (approximately 32 percent of body weight) and total plasma clearance was 1.3 (± 0.27) ml/min/kg. The mean elimination half-life was 3.3 hrs (200 min). The distribution half-life (presented in one patient

Table 2.7 Pharmacokinetic Parameters of Gallamine

Dosage Regimen	Parameters[a] $t_{1/2\beta}$ (min)	Cl (ml/min/kg)	V_{ss} (ml/kg)	Reference
Bolus	128 ± 24	1.26[b]	---[c]	Duvaldestin et al. 1977 (133)
Single and Multiple Bolus (low dose)	135 ± 33	1.20 ± 0.32	210 ± 50	Ramzan et al. 1980 (58)
Single Bolus (high doses)	150 ± 28	1.51 ± 0.33	272 ± 50	Ramzan et al. 1980 (59)
Infusion	174 ± 42	1.15 ± 0.28	279 ± 31	Ramzan et al. 1980 (134)
Bolus and Infusion	247 ± 45	1.0 ± 0.19	291 ± 65	Shanks et al. 1982 (66)

a Mean ± S.D.
b Calculated from author's data.
c Not available

only) was 17 min. Eighty-three percent of the administered radioactivity was recovered from the urine within 24 hrs and thin-layer chromatography of urine samples indicated that all radioactivity was in the form of unchanged alcuronium. It was concluded that the plasma (and renal) clearance of alcuronium was entirely consistent with renal glomerular filtration of the unchanged drug without reabsorption or secretion. In this study Raaflaub and Frey (110) also administered ^{3}H alcuronium to rats. Seventy-five to eighty percent of the dose was recovered from the urine within 24 hrs and an additional 15-20 percent was recovered from the bile. The secondary, biliary route of elimination for alcuronium has also been noted in cats (135) and dogs (110).

Contrary to the observation by Raaflaub and Frey (110) that alcuronium is not metabolized, a recent report (136) describing a new liquid chromatographic assay for alcuronium has indicated that two minor metabolites (<1 percent of administered dose) of alcuronium are detectable in the urine of patients. The structures of these metabolites remain to be elucidated.

2.6 Determinants of Muscle Relaxant Pharmacokinetics

2.6.1 Age

The pharmacokinetics of the nondepolarizing muscle relaxant drugs appear to be altered as a result of ageing. Reduced plasma clearance and prolonged elimination half-life have been reported for pancuronium (137,138) and d-tubocurarine (139) in the elderly but not for metocurine (140). However, the volumes of distribution of pancuronium and dTc were reported to be either unchanged (137,138) or decreased (139). Most authors attribute reduced plasma clearance to the fact that renal function in elderly patients is also diminished. Renal perfusion decreases 1.5 percent per year after maturity such that renal blood flow

in a 65-year old patient is half that of a younger patient. This decrease is reflected in the corresponding decreases in glomerular filtration rate and clearance of urea. Drug metabolism (which may contribute significantly to the elimination of pancuronium) may also be decreased in the elderly patient as a result either of reduced hepatic enzyme activity or perfusion (141).

At the reverse end of the ageing scale, muscle relaxant drug pharmacokinetics are also altered. It has been reported that d-tubocurarine clearance is elevated and elimination half-life reduced in infants and children relative to young adults (142). Apparent volume of distribution was unchanged. In contrast Fisher et al. (143) observed lower dTc clearance and longer elimination half-lives in both neonates and infants. In this work a significantly larger apparent volume of distribution at steady-state was observed both in neonates and infants. The pharmacokinetics of dTc in children were found to be unaltered relative to adults. Fisher and co-worker's findings with dTc (143) were recently confirmed by Matteo et al. (144) who attribute the increased volume in neonates and infants to the relatively larger volume of extracellular fluid in these patients. The reduced clearance and prolonged elimination half-life were attributed to the fact that the glomerular filtration rate and renal plasma flow in the newborn is 30-40 percent (based on body surface area) of the adults (145,146).

2.6.2 Temperature

In cats, temperature reductions from 39°C to 34°C and 28°C respectively have been shown to reduce the total plasma clearance and the renal and biliary excretion of both pancuronium (147) and d-tubocurarine (148). For pancuronium, both the volume of the central compartment and the volume of distribution at steady-state (V_{ss}) were reduced at 28°C

and 24° relative to those at 39°C. Furthermore, it was found that there was decreased formation and excretion of the 3-hydroxy and 17-hydroxy metabolites at the lower temperatures. For d-tubocurarine no alteration in V_{ss} as a result of hypothermia was observed. Recently, however, Ham and colleagues (149) reported that hypothermia has little effect on the pharmacokinetics of dTc in humans, but only used temperatures ranging from 31.8° to 35.8°C.

2.6.3 Inhalation Anaesthetics

In studies designed to evaluate the effect of different anaesthetic agents on dTc-induced neuromuscular blockade and pharmacokinetics, Stanski et al. (62,121) were unable to detect any differences in dTc pharmacokinetics between patients anaesthetized with combinations of either halothane and nitrous-oxide, enflurane and nitrous oxide or morphine-diazepam and nitrous oxide. Thus the differing dosage requirements of dTc in these groups of patients probably relate to pharmacodynamic influences of the inhalation anaesthetics (141).

2.6.4 Renal Disease

The majority of the nondepolarizing muscle relaxant drugs are largely eliminated via the kidney. Thus, the presence of renal disease or failure is expected to alter markedly, their disposition kinetics. The degree of such alteration is expected to vary with the extent to which the particular drug is eliminated via the kidney.

Miller et al. (150) administered d-tubocurarine to a group of five patients in renal failure and nine control patients. The dTc elimination half-lives of 231 and 330 min respectively in patients with and without renal function calculated from the pharmacokinetic model of Gibaldi et al. (124) were consistent with the dTc plasma concentrations observed in their study. In a recent review, Stanski (102), from a consideration

of the raw data of Sheiner et al. (61), also reported a marked reduction in dTc plasma clearance and an increased elimination half-life in renal disease patients. Apparent volume of distribution was unaltered. Similar findings have been reported for gallamine with respect to elimination half-life and clearance but volume of distribution ($V_{d\beta}$ and V_{ss}) were significantly higher in renal failure (151).

Alcuronium disposition was examined in a single anephric patient by Raaflaub and Frey (110). Alcuronium elimination half-life in this patient was approximately 16 hrs relative to about three hrs in healthy patients.

2.6.5 Liver Disease

Patients with liver dysfunction may be expected to exhibit diminished elimination of those muscle relaxant drugs which are predominantly metabolized by the liver. Agents eliminated via other organs, particularly the kidney, are expected to be affected less significantly by hepatic dysfunction. The pharmacokinetics of d-tubocurarine or alcuronium have not been examined in patients with liver disease. Gallamine disposition in patients with total biliary obstruction has been examined by Ramzan et al. (152) and Westra et al. (153). Apart from a minor change in V_{ss} in the former study, gallamine pharmacokinetics were largely unaffected by the presence of biliary obstruction in both these studies. This finding is not unexpected since gallamine is eliminated almost exclusively via the kidneys (114).

2.7 Pharmacodynamics of the Nondepolarizing Muscle Relaxants

2.7.1 Plasma Concentration - Pharmacologic Effect Relationships

That the action of dTc and presumably other curariform drugs is related to the concentration of drug in the blood and not that in tissues was believed as early as the 1950s. This view was based on observations

that the relaxant drug concentration in tissues is maximal several hours following an intravenous bolus dose whereas both maximum paralysis and peak plasma concentrations are attained rapidly. Early attempts to relate plasma dTc concentrations to the degree of neuromusclar blockade in humans proved unsuccessful, however, because the methods employed to quantify both relaxant drug concentrations and neuromuscular effect were insensitive (154).

The first major advance in characterizing muscle relaxant pharmacodynamics was made by Gibaldi and co-authors in 1972 (124). Using a three compartment pharmacokinetic model for dTc disposition these workers were able to demonstrate that the neuromuscular blocking effect of dTc was related to the theoretical amount and hence concentration in the central compartment. Based on this hypothesis they were able to predict the duration of action and effect of different doses of dTc. However, their predictions deviated slightly from the observed pharmacologic effect data of Walts and Dillon (69) especially after small doses of dTc and when effect measurements were made soon after drug administration. It was concluded nonetheless that the 'effector site' of dTc was pharmacokinetically indistinguishable from the central compartment.

In 1974 Matteo et al. (128) attempted to demonstrate a relationship between serum concentration and pharmacologic effect of dTc in 48 surgical patients. Response to dTc was determined by twitch measurement while dTc serum concentrations were monitored by radioimmunoassay. Matteo and co-authors were able to demonstrate a linear correlation ($r=0.71$) between serum dTc concentration and percent recovery of twitch. The mean (± S.E.M.) serum concentration at 50 percent recovery was 0.45 ± 0.13 µg/ml and complete recovery was observed at 0.20 ±

0.13 µg/ml. The observed correlation was independent of dTc dose at 0.3 and 0.6 mg/kg and the anaesthetic agents employed.

The classic observations of Matteo et al. (128) have been confirmed by numerous subsequent studies with dTc (61,120), pancuronium (155,156), metocurine (157), gallamine (58,59), fazadinium (158) and vecuronium (159). However, in the original report by Matteo et al. (128), and in the majority of later studies the relationship between relaxant serum or plasma concentration and neuromuscular effect was demonstrated using data gathered during the post-distribution phase of relaxant disposition. Whether such a relationship also exists at earlier times and indeed whether the serum or plasma concentration of a relaxant drug is the sole determinant of recovery from neuromuscular blockade will be discussed later (section 2.7.4).

2.7.2 Relationship Between Dose, Duration of Action and Rate of Recovery

Drugs having single compartment pharmacokinetics exhibit a linear relationship between duration of effect and the logarithm of the dose and consequently exhibit a dose-independent rate of recovery (160,161). This linear relationship is independent of the shape of the dose-response curve or the endpoint used to estimate duration of effect. The theoretical basis for this was established by Levy (160) and tested using effect data for several drugs, including the depolarizing muscle relaxant succinylcholine (162).

No such direct relationship applies however, to drugs which exhibit multicompartment characteristics (72). For such drugs the qualitative relationship between duration (and rate of recovery) and dose depends on the site of drug action (72). The relationship between the duration of action and the size of the dose of dTc and gallamine was investigated by

Walts and Dillon (163), who observed a nonlinear, disproportionately larger increase in duration of action with increasing (log) dose.

Gibaldi et al. (124) were able to explain the disproportionate increase in duration of action of dTc by means of their three compartment model for dTc disposition on the assumption that dTc acts at a site within the central or sampling compartment.

Nonlinear relationships between duration of action and dose have also been observed for d-tubocurarine (164), pancuronium (70,77,164), fazadinium (77) and alcuronium (77,164). This dose-dependency is a direct consequence of the poly-exponential pharmacokinetics of the relaxant drugs.

2.7.3 Relationship Between the Number and Frequency of Doses and Duration of Action

It is well recognized that a more prolonged effect is obtained when a second (or additional) dose of a neuromuscular blocking drug is given after partial recovery from the first dose. Walts and Dillon (69) determined the duration of effect of second doses of dTc administered after recovery from the effect of first dose and expressed their findings as 'cumulation ratios' calculated as the duration of action of the second dose divided by the duration of action of the first dose. They showed that a second dose of dTc is cumulative and that this cumulation can be reduced by administering the additional dose after a more complete recovery from the first dose.

Using their three compartment model for dTc disposition, Gibaldi et al. (124) calculated that the duration of action increases with each successive dose but that the cumulation ratio is dose-dependent, decreasing with increasing dose. The duration of action has also been shown to be cumulative for gallamine (71).

2.7.4 Factors Controlling Duration of Action and Rate of Recovery

As indicated in section 2.7.1 (p. 42) the existence of a close relationship between the serum or plasma concentration of a nondepolarizing neuromuscular blocking drug and the intensity of the response elicited, has been widely demonstrated, at least during the recovery phase. Notwithstanding this, there has been considerable argument in the literature over the validity of the claim that the serum or plasma concentration is the principal determinant of the intensity of effect and hence the duration of action and rate of recovery from paralysis. Feldman (166) is the major disputant against this claim. His view arises from observations with the depolarizing relaxant decamethonium and dTc and gallamine, given i.v. into an arm, isolated by a tourniquet, from the central circulation. Upon release of the tourniquet, presumably resulting in a sudden reduction in plasma concentration, the duration of action and rate of recovery after dTc and gallamine was substantially longer than with decamethonium. Feldman argued that if the effects of dTc and gallamine were plasma concentration related then recovery should have occurred more rapidly from these two drugs than from decamethonium. He thus proposed a different mechanism of action, namely that recovery is governed, not by the plasma concentration but by the strength of the drug-receptor association. His proposal was supported by Agoston et al. (166) and by Goat et al. (167), and Heneghan et al. (168) who showed that recovery was unrelated to muscle blood flow. However, from considerations of muscle blood flow and relaxant-receptor dissociation constants, Waud (169) concluded that the results of Matteo et al. (128) and subsequent researchers who have observed a relationship between plasma concentration and response were in fact not in disagreement with those of Feldman and Tyrrell (165) or with

the conventional views of neuromuscular physiology and pharmacology. Stanski and Sheiner (170) agreed with Waud's conclusion. Thus it is now considered that there is a competitive interaction between the nondepolarizing relaxant drug and acetylcholine for the receptor and that the rate of decline of plasma concentration determines the rate of recovery from paralysis. This has been demonstrated recently with pancuronium (156).

2.7.5 Simultaneous Modelling of Muscle Relaxant Drug Pharmacokinetics and Pharmacodynamics

It is widely recognized that there is a weak correlation between neuromuscular effect and drug plasma concentration immediately following an i.v. bolus dose. Furthermore, the relationship between plasma concentration and effect during onset via an i.v. infusion regimen is different from that observed during offset of action following cessation of the infusion. To reconcile these differences and to characterize the relationship between concentration and effect throughout the time course of relaxant effect, several models have been developed. These approaches are novel in that the pharmacokinetic and pharmacodynamic data are integrated and simultaneously modelled.

Hull et al. (171) developed the earliest such model for pancuronium to account for their observation that the concentration of pancuronium in each compartment of a two compartment open mammillary model did not quite parallel the onset of neuromuscular paralysis. They postulated a hypothetical third "biophase" compartment which was envisaged to contain the fraction of pancuronium which equilibrates with the endplate receptors. Hull et al. reasoned that as soon as the drug reaches the biophase it needs only to occupy the receptor to exert an immediate pharmacologic response. Thus the biophase concentration should relate to

the intensity of effect at all times. Further, it was assumed that the concentration in the biophase undergoes reversible exchange with the plasma concentration by first-order kinetics. Assuming that the same response intensity elicited by any particular drug concentration during either the onset phase or the recovery phase is constant, they postulated that there is a unique rate constant, relating plasma concentration and biophase concentration which has these characteristics. Hence, putative biophase drug concentrations may be calculated. Using this approach an excellent agreement was demonstrated between the hypothetical biophase pancuronium concentration and twitch depression during both onset of paralysis and during recovery. The model of Hull et al. (171) is presented in Figure 2.4a.

Sheiner et al. (61) developed a very similar pharmacodynamic model to characterize the behaviour of dTc. If plasma and pharmacological effect data are gathered under non steady-state conditions there occurs a 'disequilibrium' between the concentration of drug in the plasma and the site of action resulting in a plasma concentration-pharmacologic effect disequilibrium. Sheiner's model adjusts for this temporal disequilibrium and permits calculation of the expected effect-concentration relationships at steady-state without the need to achieve steady-state conditions. In this model (Figure 2.4b), a first-order rate constant, k_{eo}, essentially analogous to that used by Hull et al. (171), characterizes the rate at which the drug at the effect site equilibrates with plasma concentration. Again a 'hypothetical' effect compartment is postulated, the dynamics of which are adjusted by the rate constant k_{eo}. The amount of drug in the effect compartment, Ae is related to the observed effect by the use of the Hill equation (172) that characterizes a sigmoidal effect-concentration relationship. Sheiner

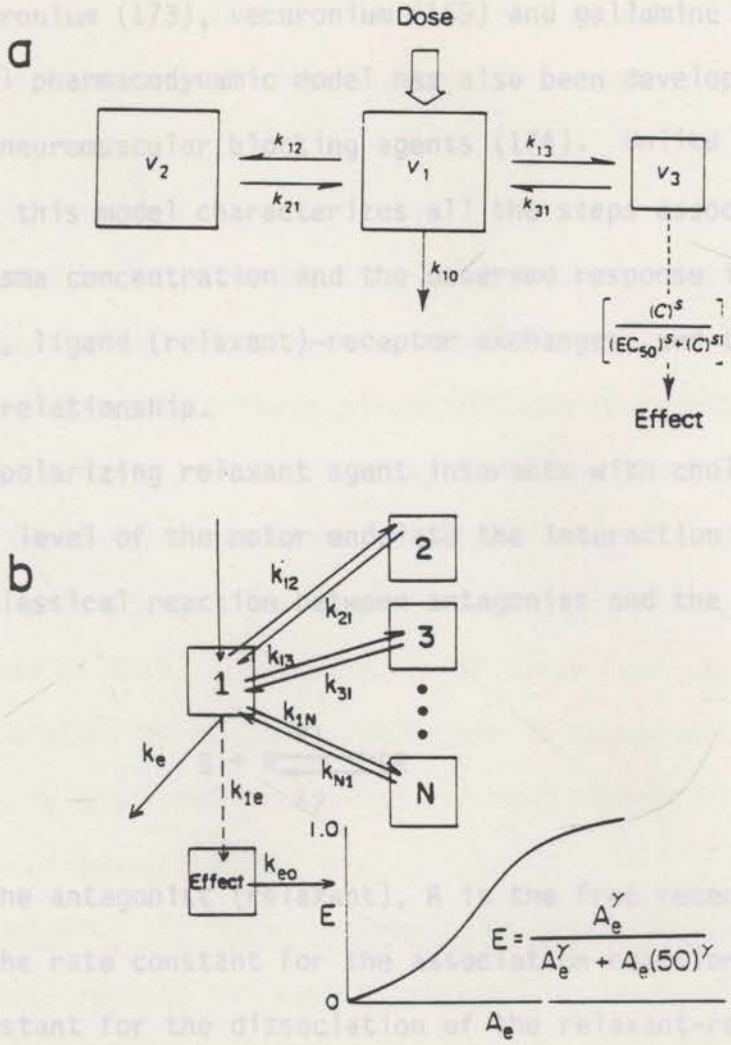


Figure 2.4. Diagrammatic representation of the pharmacokinetic and pharmacodynamic models as proposed by Hull et al. (a) and Sheiner et al. (b) when viewed as a 3 or N compartment mammillary model respectively. In a) compartment 3 represents the biophase compartment while in b), Ae represents the amount of drug in the hypothetical effect compartment and E is the fraction of maximal response. See text (pg. 46) for additional details. Adapted from references 171 and 61 respectively.

et al. (61) tested the utility of their model using plasma concentration-effect data for dTc. The model since has been successfully applied to pancuronium (173), vecuronium (159) and gallamine (134).

An analytical pharmacodynamic model has also been developed for the nondepolarizing neuromuscular blocking agents (174). Unlike the two previous models, this model characterizes all the steps associated with the changing plasma concentration and the observed response including pharmacokinetics, ligand (relaxant)-receptor exchanges, and the receptor-effect relationship.

When a nondepolarizing relaxant agent interacts with cholinergic receptors at the level of the motor endplate the interaction can be described as a classical reaction between antagonist and the free receptor, thus,

$$B + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} BR \qquad \text{Eq. 2.1}$$

Where B is the antagonist (relaxant), R is the free receptor, k_1 designates the rate constant for the association reaction and k_2 the rate constant for the dissociation of the relaxant-receptor (BR) complex.

Occupation of the receptors by the relaxant drug inhibits muscle response to nerve stimulation, as measured by a decrease in twitch height. The relationship between receptor occupation and the observed twitch height can be described by equation 2.2

$$TH = 1 - \frac{[BR/R_0]^P}{[BR/R_0]^P + [BR_{50}/R_0]^P} \qquad \text{Eq. 2.2}$$

Where TH is the twitch height and its initial value, recorded with no

paralysis, in the absence of relaxant, is assigned a value of unity. BR_{50}/R_0 is the receptor occupation ratio which produces 50 percent response, i.e., TH = 0.5 and P is the parameter that describes the steepness of the twitch height-receptor occupation curve.

The model therefore includes an input function, namely, the plasma relaxant concentration dynamics, and an output function, the TH dynamics. The relationship between plasma concentration and postsynaptic receptor occupation ratio are described by two parameters k_2 and k_1. The equilibrium constant of the reaction between drug and receptor, k_D is given by the ratio k_2/k_1. The parameters, BR_{50}/R_0 and P, define TH in terms of BR/R_0. By iteration of these four parameters, the model can characterize how BR/R_0, R/R_0 and TH change with time. The utility of this model has been elegantly demonstrated with fazadinium, dTc and pancuronium (174).

2.8 Factors Modulating the Pharmacodynamics of Muscle Relaxant Drugs

The dosage requirements for muscle relaxants is reportedly increased in patients with liver disease (175) and patients with severe thermal burns (176). In contrast, increased sensitivity and thus, diminished dosage requirements, has been noted in hypothermia (177), in neonates and infants (143). However, in relatively few studies has it been established whether there is a pharmacokinetic or pharmacodynamic basis for these differences. In the present discussion only the factors which influence muscle relaxant effect-concentration relationships will be discussed.

2.8.1 Age

Infants are variously reported to be sensitive (178), resistant (179)

or indistinguishable from adults (180). Fisher et al. (143) investigated the pharmacokinetics and pharmacodynamics of dTc in infants, children and adults in an attempt to resolve these differences. It was found that $C_{ss(50)}$ increased with age, but $t_{1/2}\ k_{eo}$ was unaltered. They therefore concluded that infants have increased sensitivity to dTc but resolved that dosage adjustment is not necessary because in infants, the distribution volume of dTc is increased.

In the elderly (≥77 yr), pancuronium concentrations corresponding to a particular degree of paralysis, during the recovery phase, were similar to those in controls (25–60 yr). However, the duration of action was prolonged and the rate of recovery slower, owing to altered pharmacokinetics, namely a slower rate of decline of plasma concentration (138).

2.8.2 Temperature

Zaimis et al. (181), were the first researchers to report the reduced degree of dTc blockade in humans during hypothermia. The magnitude of the blockade was reduced at 30° relative to that at 35°C. The pharmacodynamics of both dTc (148) and pancuronium (147) appear to be altered by temperature in cats also. The plasma concentration of dTc (148) associated with a given degree of paralysis is greater at lower temperatures. The reverse is true for pancuronium (147). Furthermore, the time periods to onset of peak paralysis are prolonged during hypothermia for both compounds. This effect may be attributed to diminished perfusion of the neuromuscular junction at lower temperatures. However, recently, work on dTc in humans (149), indicates that $C_{ss(50)}$ was not different during hypothermia at 32°C ($C_{ss(50)}$ 0.46 ± 0.07 µg/ml) relative to normothermia ($C_{ss(50)}$ 0.57 ± 0.07 µg/ml) nor was the $t_{1/2}\ k_{eo}$ different between the two groups. However, in

four of the nine hypothermia patients, $t_{1/2\ k_{eo}}$ was greater than ten minutes. It was thus suggested that hypothermia reduces blood flow to the neuromuscular junction delaying onset of paralysis.

2.8.3 Anaesthetic Agents

The dose requirement of nondepolarizing muscle relaxants during surgery varies with the anaesthetic agent employed and the depth of anaesthesia (82,182). Relaxant dosage requirement is lower when volatile anaesthetics are used as compared with i.v. anaesthetic agents, the relaxant dose being governed by the minimum alveolar concentration with each of the volatile agents (183).

The ability of inhalation anaesthetic agents to augment the neuromuscular blockade by nondepolarizing relaxant drugs appears to have a pharmacodynamic basis since $C_{ss(50)}$ of dTc is reduced in the presence of inhalational anaesthetics relative to nitrous oxide-narcotic procedures (62,121) while the different agents have different quantitative effects. For example, it has been shown that the $C_{ss(50)}$ for dTc is higher during enflurane anaesthesia than during halothane anaesthesia (62). Furthermore, during halothane anaesthesia $C_{ss(50)}$ remains constant for the duration of anaesthesia while with enflurane there is a time-dependent decrease. This increased sensitivity of the neuromuscular junction with enflurane appears to be constant, at least for the first two to three hours of anaesthesia, with depression of the force of thumb adduction increasing at approximately nine percent per hour. These differences between halothane and enflurane are thought to be related to the difference between the effects of these two agents on the muscle fibre itself (62).

2.8.4 Thermal Burns

Martyn et al. (176) have demonstrated that both the dose and plasma

concentration of dTc necessary to produce a given degree of paralysis is significantly greater in patients who have sustained thermal burns in excess of 25 to 50 percent of their bodies. Plasma concentrations of 2.3 and 3.3 μg/ml are necessary to cause 50 and 95 percent paralysis respectively in burn patients compared to 0.4 and 0.7 μg/ml respectively in normal patients. Plasma protein binding alterations in burn patients are moderate (184), and thus cannot account for the burn related hyposensitivity to dTc. Martyn et al. thus suggested that, more fundamental changes at target tissues may be responsible for the elevated demand for dTc. It was suggested that an increase in the number of acetylcholine receptors at the neuromuscular junction may occur or that the affinity of these receptors for dTc, may be altered. A similar burn related hyposensitivity has also been reported by these workers for metocurine (185-187).

2.8.5 Renal Failure and Liver Disease

Miller et al. (150) have reported that neuromuscular junction sensitivity to dTc is unchanged in the presence of renal failure in humans. However, Sheiner et al. (61) found k_{eo} may be increased in renal failure patients over that in normal subjects. Further statistical evaluation indicated that both k_{eo} and $C_{ss(50)}$ may be increased in renal disease.

The pharmacodynamics of metocurine have also been examined in renal failure (188). The serum concentration of metocurine at 10 percent recovery was 1.05 ± 0.26 μg/ml in patients with renal failure and 0.46 ± 0.11 μg/ml in patients with normal renal function. However, these results were obtained after an i.v. bolus injection and the pharmacologic endpoint was attained before distribution was complete. Disease-related differences in drug distribution kinetics and protein binding, and in

particular possible interference in the assay by metabolite(s) accumulating in renal failure may have influenced these results also.

Although several authors (175,189) have reported an increased dosage requirement of dTc in patients with liver disease these have only been anecdotal clinical reports and need to be substantiated in controlled studies. The pharmacodynamics of vecuronium, only has been evaluated in liver cirrhosis (190). In this study of vecuronium, Duvaldestin et al. (190) were unable to demonstrate any difference in $C_{ss(50)}$ between cirrhotic and control patients. The observed increase in recovery time in the cirrhotic patients with vecuronium could be attributed entirely to a reduced rate of decline of the plasma concentration as indicated by the increase in elimination half-life in cirrhotics.

Chapter 3

GENERAL METHODOLOGY

Chapter 3 - GENERAL METHODOLOGY

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Presented here is a general outline of the procedures used. Specific details are presented in the appropriate chapters.

3.1 Patients and Subjects

The clinical studies described in this thesis were approved by the Ethics committee of the Royal Prince Alfred Hospital, Sydney and were supported by the National Health and Medical Research Council of Australia. The patients chosen for study were those requiring muscle relaxation during anaesthesia for elective surgery; were free of known or suspected neuromuscular disease, and were not receiving drugs known to affect neuromuscular function. All patients gave informed consent prior to participating in these studies.

Investigations involving greyhound dogs were conducted in the Gordon Craig Laboratories, Department of Surgery, University of Sydney.

3.2 Surgical and Anaesthetic Techniques

3.2.1 Patients

In general patients were premedicated with a narcotic analgesic (morphine or pethidine) about an hour prior to commencement of anaesthesia. Anaesthesia was induced with droperidol 5-10 mg, phenoperidine 0.5 mg, and thiopentone 150-300 mg. Endotracheal intubation was facilitated by use of topical lignocaine (4 percent) applied to the pharynx and larynx. Ventilation with 70 percent nitrous-oxide in oxygen was adjusted to maintain an end-expired carbon-dioxide (CO_2) of 5 percent. Barbiturate-nitrous oxide-narcotic anaesthesia was maintained with further increments of thiopentone or phenoperidine as required. Deep body and limb temperatures were maintained above 36°C and 34°C respectively by conservation of body heat, by surface insulation. During the course of the surgical procedure all patients received replacement intravenous isotonic (normal) saline and/or

whole blood.

3.2.2 Subjects

Anaesthesia was induced in unpremedicated, fasting animal by intravenous sodium pentobarbitone 30 mg/kg, injected into a foreleg vein. Additional amounts were infused at this site when required to ensure unconciousness. The animals were intubated and ventilated mechanically with a mixture of air and oxygen to maintain an end-expired CO_2 level at 5 percent. This was monitored continuously with an Infrared analyzer[a] to eliminate the possibility of neuromusclar blockade related to CO_2 retention (191,192). A femoral artery was cannulated to monitor blood pressure, blood gases and for blood sampling. Continous monitoring of the gas flow in the airway, electrocardiogram and arterial blood pressure were performed by means of a multichannel recorder[b]. Dextran (6 percent) in isotonic saline[c] was infused via the foreleg vein throughout the experiment to help maintain arterial pressure and urinary flow. The temperature of the lower oesophageal and anterior tibialis muscles was maintained between 37°C and 39°C by means of water-circulating heating/cooling blankets[d].

3.3 Muscle Relaxant Drug Dosage

3.3.1 Patients and Subjects

Intravenous bolus doses were administered over 3 to 5 sec via an established intravenous infusion line in the arm (limb) contralateral to the blood sampling site. When a constant-rate infusion regimen was

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a Datex CD-101

b Sanborn 350

c Macrodex

d Gaymar, U.S.A.

employed, a calibrated volumetric infusion pump[a] was utilized to control the infusion rate. Commercial dose forms of alcuronium (Alloferin^{R})[b], gallamine (Flaxedil^{R})[c], and d-tubocurarine (Tubarine^{R})[d] were used.

3.4 Quantification of Neuromuscular Blockade

Degree of neuromuscular blockade was assessed in all patients and animals except in those patients undergoing cardiac surgery where the complexity of the surgical procedure precluded assessment of pharmacologic effect.

In patients, the ulnar nerve was stimulated supramaximally at the elbow every 10 sec (0.1 Hz), using impulses of 0.1-0.15 msec duration, at a nomimal voltage output of up to 500V delivered via surface (silver-silver chloride) electrodes. The mechanical twitch response was recorded from an immobilized upper arm, using a linear force displacement transducer applied perpendicular to the thumb with a preload of approximately 200g. Compound muscle action potentials (e.m.g.) were also obtained from the small muscles of the first interspace of the same hand via surface electrodes placed dorsally. The gated e.m.g. response was processed, analog-to-digital conversion[e] enabling simultaneous mechanical and e.m.g. responses to be traced on the chart recorder.

In greyhounds, both the phrenic and sciatic nerves were stimulated simultaneously and the e.m.g. response from each nerve were recorded simultaneously.

The intensity of paralysis was assessed from the depression of the

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[a] McGraw, Australia

[b] Hoffman La Roche, Switzerland

[c] May and Baker, Australia

[d] Wellcome, Australia

[e] Digitmer, Herts

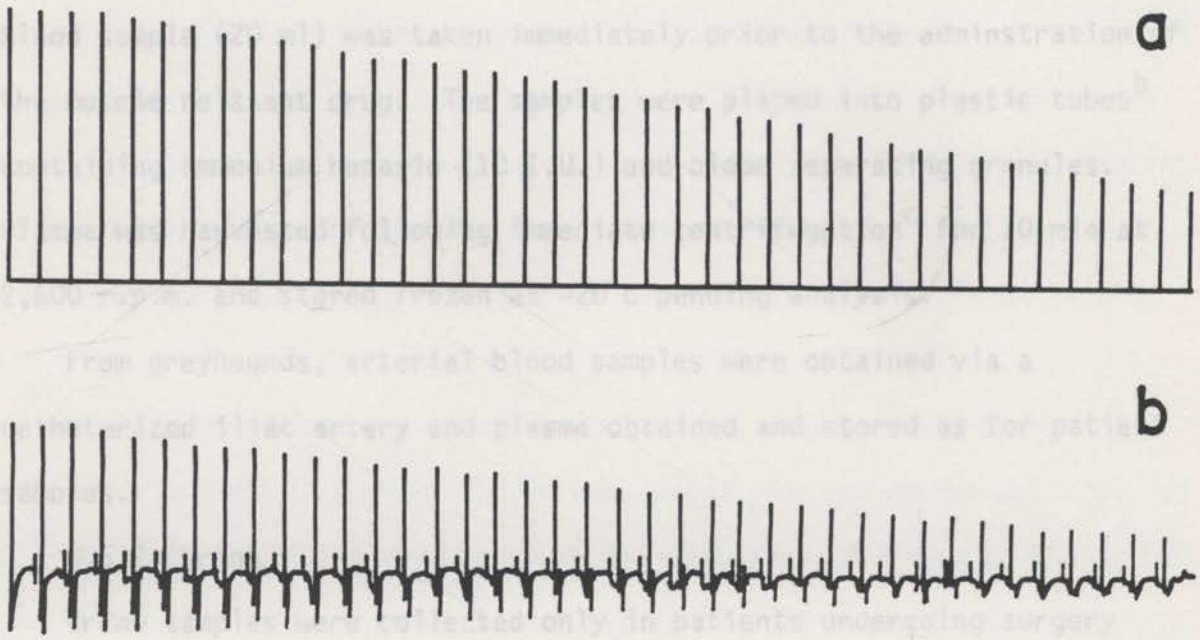

Figure 3.1 Portion of a typical tracing in a patient exhibiting progressive depression of simultaneously recorded mechanical twitch (A) and electrical or e.m.g. (B) responses during constant-rate (10 µg/kg/min) infusion of alcuronium.

mechanical twitch response and the e.m.g. amplitude relative to their respective control heights. Relaxant drug effect was quantified by the degree of paralysis; with zero percent (the control value) representing no paralysis and 100 percent respresenting complete paralysis. Typical mechanical twitch and e.m.g. recordings are illustrated in Fig. 3.1.

3.5 Biological Sample Collection and Handling

3.5.1 Blood

Throughout the investigation either venous or arterial blood samples (5–10 ml) were collected into plastic syringes[a] via a nonheparinized central venous or arterial catheter respectively. A blank (drug-free) blood sample (20 ml) was taken immediately prior to the adminstration of the muscle relaxant drug. The samples were placed into plastic tubes[b] containing ammonium heparin (10 I.U.) and blood separating granules. Plasma was harvested following immediate centrifugation[c] for 10 min at 2,500 r.p.m. and stored frozen at -20°C pending analysis.

From greyhounds, arterial blood samples were obtained via a catheterized iliac artery and plasma obtained and stored as for patient samples.

3.5.2 Urine

Urine samples were collected only in patients undergoing surgery involving cardiopulmonary bypass. Samples were collected via uretheral catheters, the volumes were recorded and an aliquot stored in plain plastic tubes[d] at -20°C until analyzed.

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[a] Monoject, Australia

[b] Disposable Products, Australia

[c] Clements GS 200 Centrifuge

[d] Becton Dickinson

3.6 Muscle Relaxant Drug Analysis in Plasma and Urine

The three muscle relaxant drugs, alcuronium, gallamine and d-tubocurarine, were analyzed in plasma and/or urine using the general dye binding technique developed for dTc by Cohen (193) and successfully modified for pancuronium (194), d-tubocurarine (65) and gallamine (195). These methods all involve complexation of the relaxant drug moiety with fluorescent dye (either rose bengal[a] or xylene red B[b]) directly in plasma or urine, extraction of the complex into an organic solvent and fluorescence detection. The major disadvantages of this technique is that it does not differentiate between the unchanged drug and possible metabolite(s) unless prior separation is achieved. However, gallamine is not metabolized (114) and only two minor metabolites of alcuronium have been reported in urine only which together constitute less than 1 percent of the dose (136). d-Tubocurarine is also believed to be metabolized to a neligible extent. Only a very minor metabolite has been detected in the bile of dogs (108).

All determinations were made in triplicate using an appropriate aliquot or plasma (1 ml for alcuronium, 0.1 ml for gallamine and 1 ml for dTc) or urine (0.1 ml for alcuronium and gallamine, 0.5 ml for dTc). For each batch of unknown plasma (or urine) samples, a reagent blank and a known standard (3 µg/ml for alcuronium, 75 µg/ml for gallamine and 3 µg/ml for d-tubocurarine) were also analysed.

3.6.1 Alcuronium

One millilitre samples of plasma were placed in separate glass centrifuge tubes[c] and to each tube was added an alcuronium standard

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[a] George T. Gurr, Australia

[b] Sandoz, Australia

[c] Bakelite Screwtop with teflon liner, Soveril, France

solution (0.1 to 3.0 µg/ml). Phosphate buffer (pH 7.8, 1 ml) was added and each tube mixed[a] for 10 seconds. One ml of a solution containing rose bengal purified according to Cohen et al. (196), containing 1 mg/ml in 0.45 M K_2HPO_4, was then added and mixed for 30 sec to form the relaxant dye complex. After mixing, 5 ml of a chloroform solution containing phenol (2.5 percent) and ethanol (5 percent) was added and the sealed tubes were rotated on a roller mixer at 12 r.p.m. for 30 minutes to extract the alcuronium - rose bengal complex. After mixing, the tubes were centrifuged[b] for 10 min (2,500 r.p.m.) and the aqueous phase was removed by aspiration. The fluorescence intensity of the organic phase was determined in 1 cm quartz cells at the excitation wavelength of 550 nm and emission wavelength of 570 nm (uncorrected)[c].

Fluorescence intensity was linear over the concentration range 0.1 to 3.0 µg/ml of alcuronium. Using 1.0 ml of plasma the minimum reliably detectable concentration of alcuronium was 0.05 µg/ml. The inter-batch coefficient of variation was 5.0 percent at 3.0 µg/ml and 10.0 percent at 0.05 µg/ml.

Urine was diluted so that the concentrations of alcuronium were in the linear portion of the standard curve. Best results were obtained using 0.1 ml urine, a rose bengal concentration of 0.1 mg/ml, 1 ml of 0.2 M sodium- bicarbonate-carbonate buffer (pH 10.5) and extracting the drug-dye complex into 5 ml of chloroform-ethanol (5 percent v/v) without added phenol. The coefficient of variation of the assay in the range 0.1 to 3.0 µg/ml was ±7.5 percent.

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[a] Vortex genie, Scientific Industries, Inc. U.S.A.

[b] Clements GS 200 Centrifuge

[c] Perkin Elmer Model 204 Fluorescence Spectrometer

3.6.2 Gallamine

Gallamine in plasma was determined as for plasma alcuronium with the modification that 0.1 ml of plasma was used in place of 1 ml. Fluorescence intensity was linear between 0.05 µg/ml and 80 µg/ml. The interbatch coefficient of variation was 5 percent at 80 µg/ml and 10 percent at 0.05 µg/ml.

Total gallamine concentrations in urine were analyzed using the procedure for alcuronium determination in urine. Calibration curves in the range 5 to 40 µg/ml were prepared for the urine samples. For urine samples containing higher concentrations samples were diluted with water such that concentrations would fall within the range of the standard curve. The interbatch coefficient of variation was ±7.5 percent for the concentration range 5 to 40 µg/ml.

3.6.3 d-Tubocurarine

d-Tubocurarine was analyzed in plasma as for alcuronium (plasma) except that 1 ml of xylene red B solution (2 mg/ml in 0.45 M K_2HPO_4) was used rather than rose bengal. A calibration curve was prepared over the concentration range 0.1 to 5 µg/ml and the interbatch coefficient of variation was between 10 and 5 percent over this concentration range.

d-Tubocurarine concentrations in urine were analyzed in a similar manner to those in plasma except that 0.5 ml of urine and a 10 µg/ml solution of xylene red B were used. Calibration curves for dTc in urine were linear over the range 0.5 to 25 µg/ml with the interbatch coefficient of variation being 10 to 15 percent over this concentration range.

Plasma and urine calibration curve data for alcuronium, gallamine and d-tubocurarine are presented in Table 3.1.

Table 3.1 Calibration Curve Data for the Relaxant Drugs in Plasma and Urine

Drug	Plasma	Urine
Alcuronium	$y = 59.09x - 0.39$	$y = 49.74x - 2.24$
	$R^2 = 0.9996$	$R^2 = 0.9982$
Gallamine	$y = 10.75x - 0.55$	$y = 13.11x + 3.11$
	$R^2 = 0.9988$	$R^2 = 0.9976$
d-Tubocurarine	$y = 18.30x + 1.14$	$y = 10.84x - 0.95$
	$R^2 = 0.9994$	$R^2 = 0.9998$

3.7 Biochemical Profiles

As part of the routine in the hospital care, a routine biochemical profile of each patient was prepared using standard methods on a SMAC Autoanalyzer[a]. Clinical laboratory data included serum and urinary creatinine; serum urea; uric acid; total serum bilirubin; serum alkaline phosphatase activity; serum aminotransferase (AST and ALT) activity, serum total proteins (including albumin by electrophoresis and total globulins by difference) and serum cholesterol and triglycerides.

Serum alpha$_1$ acid glycoprotein (AAG) concentrations were determined in selected patients by radial immunodiffusion (197) using a commercially available kit[b].

3.7.1 Free Fatty Acids

Non-esterified free fatty acid (NEFA) concentrations in plasma from cardiac patients receiving d-tubocurarine (Chapter 7, p. 205) were determined by the method of Sampson and Hensley (198) with the following modifications. The methyl esters of the free fatty acids were prepared by adding 100 µl of boron trichloride in methanol (10 percent w/v) and heating for 15 min at 80°C. Following evaporation of the organic solvent under a gentle stream of nitrogen at room temperature the residue was dissolved in 100 µl of chloroform-n-heptane-methanol, 28:21:1 v/v. Myristic (C14:0)[c], palmitic (C16:0), palmitoleic (C16:1), stearic

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a Technicon Instruments Corp., New York, U.S.A.

b M-Partigen, Behringwerke AG

c The number of carbon atoms and the degree of unsaturation is presented in the parenthesis

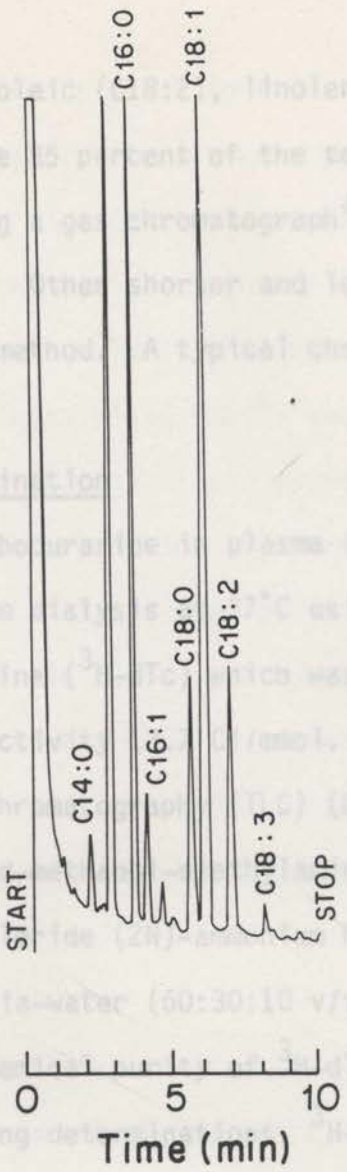

Figure 3.2. A typical gas chromatogram of the methyl esters of plasma free fatty acids from a cardiac patient. C14:0=myristic; C16:0=palmitic, C16:1=palmitoleic, C18:0=stearic; C18:1=oleic; C18:2=linoleic; C18:3=linolenic acids respectively. The stationary phase was 10 percent SP216-PS and the chromatographic conditions were as follows: isothermal column temperature, 200°C; injection port temperature, 220°C; detector temperature 220°C; carrier gas (nitrogen) flow, 25 ml/min; air flow, 400 ml/min; hydrogen flow, 40 ml/min; sensitivity setting, 1.10^{-9}A.

(C18:0), oleic (C18:1), linoleic (C18:2), linolenic (C18:3) acids respectively, which comprise 85 percent of the total free fatty acids (199) were quantified, using a gas chromatograph[a] equipped with an autosampler and integrater. Other shorter and longer chain acids could not be detected using this method. A typical chromatogram is shown in Figure 3.2.

3.8 Protein Binding Determination

Protein binding of d-tubocurarine in plasma and/or serum was determined using equilibrium dialysis at 37°C using radioactive drug. Tritium labeled d-tubocurarine (^{3}H-dTc) which was obtained from New England Nuclear, specific activity 13.7 Ci/mmol. The purity was established by thin layer chromatography (TLC) (200) using three separate solvent systems; acetic acid-methanol-diethylamine (77.5:17.5:5 v/v, rf 0.38); methanol-ammonium chloride (2N)-ammonium hydroxide (70:30:1 v/v, rf 0.24) and methanol-ammonia-water (60:30:10 v/v, rf 0.55). Using these solvent systems the radiochemical purity of ^{3}H-dTc was determined to be >95 percent. For the binding determinations, ^{3}H-dTc was diluted with unlabeled dTc to a specific activity of 93.5 mCi/mmole.

Binding was determined in duplicate or triplicate using a Dianorm[b] equilibrium dialysis unit as described by Weder et al. (201). One ml of plasma and/or serum was dialysed across a cellulose membrane (Spectrapor 2, MW cut-off 12,000 daltons[b]) against 1 ml phosphate buffer[c] containing ^{3}H-dTc. Equilibrium was achieved within 3 hours. There was no detectable leakage of protein across the dialysis membrane (no protein

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a Hewlett Packard Model 5880A

b Spectrum Medical Industries, U.S.A.

c Sorensen's Phosphate Buffer, pH 7.4, 0.067M

could be detected on the buffer side using trichloroacetic acid). Volume shifts were shown to be neligible (less than 5 percent volume change) by measuring the volume on each side of the membrane at the completion of the dialysis procedure. After dialysis, 100 µl aliquots were transferred from the solutions from both sides of the membrane to plastic vials[a] containing 10 ml of scintillaton fluid (ACS[b]) and 1 ml of water. Radioactivity was determined using a liquid scintillation spectrometer[c] using automatic external standardization of quench correction. Thin layer chromatography of post dialysis samples indicated that no decomposition of ^{3}H-dTc occurred during the dialysis procedure.

The fraction of unbound (free) drug in plasma was calculated as the ratio of the disintegration rates in buffer to that in plasma (or serum). The binding methodology was reproducible (CV=4 percent, n=10).

3.9 Data Treatment

3.9.1 Pharmacokinetics

Model-Independent Methods

The major pharmacokinetic parameters calculated throughout this thesis are total plasma clearance (Cl), plasma elimination half-life ($t_{1/2\beta}$), and the apparent volume of distribution at steady-state (V_{ss}). Although these parameters are model-independent, they are calculated assuming that there were no time-dependent changes occurring as a result of the surgical procedure(s) and that drug was eliminated solely from the central (or sampling) compartment. Clearance was obtained by dividing the total dose by the area under the total plasma

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[a] Packard Instruments, Australia

[b] Amersham Laboratories, Australia

[c] Packard Model 3255

concentration-time curve (AUC) extrapolated to infinity (202). The $t_{1/2\beta}$ was calculated as $\ln 2/\beta$, where β was estimated using a least squares regression analysis of the terminal (elimination) plasma concentration-time points.

Volume at steady-state was determined by the method of Benet and Galeazzi (203) by dividing the product of the dose and the first moment of the area under the plasma concentration-time curve with respect to the time axis (AUMC) from zero to infinity by $(AUC)^2$ extrapolated to infinity, corrected where necessary (bolus and infusion regimens) for input via an infusion (204). Both AUC and AUMC were calculated using the La Grange approximation (205).

For computer fitting and simulation it was necessary to assume a pharmacokinetic model for alcuronium, gallamine and d-tubocurarine respectively. A two-compartment open mammillary model was chosen for gallamine and d-tubocurarine on the basis of previous experience from this laboratory (58,119). For alcuronium, the most appropriate model was determined by fitting the data obtained after single bolus doses (Chapter 4, p. 77) to bi-and tri-exponential macroparameter equations (206) respectively and using the criteria of Boxembaum et al. (207).

3.9.2 Pharmacodynamics

Where sufficient plasma concentration-paralysis and time data were available during onset and/or offset of paralysis two approaches were used to model the pharmacodynamic data for alcuronium:

a) Plasma concentration-paralysis data obtained during the offset of paralysis (following a bolus dose or after cessation of a maintenance infusion) were fitted to the nonlinear form of the Hill equation (Eq. 3.1).

$$E = \frac{E_{max} \cdot Cp^s}{EC_{p50}{}^s + Cp^s} \qquad \text{Eq. 3.1}$$

Where E_{max} is the maximum effect (100 percent paralysis), Cp is the plasma concentration corresponding to a particular degree of effect (E); EC_{p50} is the effective plasma concentration corresponding to half maximum effect (50 percent) and s is a power factor which confers sigmoidicity to the effect-concentration relationship.

To fit offset data to the above equation, the input values were the plasma concentration data and the corresponding degrees of paralysis and the computer generated estimates and variability (S.D. and 95 percent confidence intervals) of the two pharmacodynamic parameters, EC_{p50} and s were obtained. Similar fitting of onset or 'steady-state' data alone to the Hill equation was not possible owing to the limited number of response data points available during these time periods.

b) An effect model (61) was used to characterize the combined alcuronium onset and offset data following bolus doses and the entire effect data obtained during onset, apparent steady-state and offset of paralysis using the bolus and infusion regimen.

Plasma concentration-time data were fitted to a biexponential pharmacokinetic equation (Chapter 4, p. 82) and the resulting pharmacokinetic parameters (α, β, k_{21} and V_1) for each individual patient were then used to calculate the amount of alcuronium in the effect compartment with the alternative assumptions that the effect compartment is driven by either central or the peripheral compartment (208). Simultaneously, the measured pharmacological effect (percent paralysis and time data) was related to the amount of drug in the effect compartment by use of Eq. 3.2.

$$E = \frac{(k_{eo}\ Ae/k_{ne}\ V_n)^s}{(k_{eo}\ Ae/k_{ne}\ V_n)^s + C_{ss(50)}{}^s} \qquad \text{Eq. 3.2}$$

Where E is the observed pharmacological effect (percent paralysis); kne is the transfer rate constant into the effect compartment (n = 1,2 for a two compartment mammillary model where k1e and k2e are the rate constants for the central and peripheral effect models respectively); Vn is the volume of the driving (n = 1,2) pharmacokinetic compartment; $C_{ss(50)}$ is the steady-state plasma concentration causing half-maximal effect and s is a power factor defined previously (p. 68).

The estimates and variability (S.D. and 95 percent confidence intervals) of the three pharmacodynamic parameters ($C_{ss(50)}$, k_{eo} and s) were obtained by computer methods. The half-time of equilibration of the effect with the driving compartment ($t_{1/2}\ k_{eo}$) was calculated as the quotient of ln2 and k_{eo}.

Pharmacokinetic modelling was performed with each plasma concentration (C_p) being weighted using the weighting factor $1/Cp^2$ normalized for the total number of data points (209), while unweighted response (percent paralysis) data were used in the pharmacodynamic modelling. All pharmacokinetic and pharmacodynamic modelling was done using the iterative nonlinear least squares regression program NONLIN (210) on a digital computer.

The rate of recovery from paralysis during offset of action in the linear (80-20 percent paralysis range) was determined by linear regression analysis of the effect-time data.

3.9.3 Statistics

Statistical comparisons between any two groups of patients were made using either the non-parametric Mann Whitney U Test or a paired t-test

(211), (when paired data were compared). For comparisons between more than two groups of patients, a one-way (one variable) or a two-way (two variable) analysis of variance was used. Bivariate linear regression analysis was used to examine the relationship between any two variables when an error in only the dependent variable was suspected while a linear regression program BOTHERR (212) was used when both variables were subject to error. Significance of the correlation coefficient from such regression analysis was determined using either the t-test or the F-test (211). Statistical significance was accepted at $p < 0.05$.

Chapter 4

ALCURONIUM DISPOSITION AND PHARMACODYNAMICS IN HEALTHY PATIENTS UNDERGOING ELECTIVE SURGERY

A. SINGLE AND MULTIPLE INTRAVENOUS DOSES

B. COMBINED INTRAVENOUS BOLUS AND INFUSION REGIMEN

ABSTRACT

The pharmacokinetics and pharmacodynamics of alcuronium were investigated in nineteen patients who received either single or multiple bolus doses and in twelve patients who received bolus and infusion regimens. A biexponential equation interpreted as a two-compartment open mammillary model was found to describe the observed plasma concentration-time data using each of the three dosage regimens, and alcuronium pharmacokinetic parameters did not differ between the various groups of patients. In nine patients for whom sufficient alcuronium concentration-time and response data were available over the 0 to 100 percent response range, various mathematical models were used to characterize the effect-concentration relationship. A pharmacodynamic model incorporating a separate effect compartment connected to the central compartment was found to characterize the pharmacodynamic data most appropriately.

A. SINGLE AND MULTIPLE INTRAVENOUS DOSES

INTRODUCTION

The low concentrations of alcuronium in plasma following doses required to produce neuromuscular blockade has made quantitative studies difficult. Consequently, previous studies of alcuronium disposition in humans have been performed using either radiolabeled drug (110) or a bioassay technique (213). Further, alcuronium disposition has only been examined in surgical patients following a single intravenous bolus dose of the drug and no reference was made to the degree of muscle relaxation.

The development of a fluorimetric technique for the quantitation of pancuronium bromide in biological fluids (194) which, with modification can be applied to other relaxant drugs (65,195) makes it possible to conduct a more rigorous study with alcuronium. The purpose of this study was thus to re-examine the pharmacokinetics of alcuronium following both single and multiple dose administration in patients undergoing elective surgery. In addition, the degree of neuromuscular blockade was evaluated.

METHODS

Nineteen healthy adult patients were studied during intra-abdominal surgical procedures. They were not known to have renal or hepatic disease. Relevant patient details are presented in Tables 4.1 and 4.2.

Approximately 20 min following induction of anaesthesia, an intravenous bolus dose of alcuronium was administered. The initial bolus dose was 0.25 mg/kg as recommended by the manufacturer[a], and used by others previously (56). When this dose produced neuromuscular blockade of insufficient duration for the completion of surgery, further doses corresponding to half the initial (0.125 mg/kg) were administered when neuromuscular blockade had recovered to approximately 70 percent paralysis (Table 4.3). Following each dose of alcuronium, venous blood samples were taken at approximately 5 min intervals until 20 min, then at 30, 45, 60 and 90 min. Further samples were obtained at 120 min and thereafter at 1 to 2 hr intervals for 6 to 8 hr following administration of the final dose.

Pharmacokinetic Analysis

Data from the single dose patients were fitted to a bi- (n=2) and a tri-exponential (n=3) forms of Eq. 4.1.

$$C_p = \sum_{i=1}^{n} C_i e^{-\lambda_i t} \qquad \text{Eq. 4.1}$$

Where C_p represents the plasma concentration, t is the time, C_i is the ith coefficient and λ_1 is the exponent of the ith exponential term.

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[a] Hoffman La Roche, Sydney, Australia

Table 4.1 Clinical Details of the Healthy Surgical Patients who Received a Single Intravenous Bolus Dose of Alcuronium (0.25 mg/kg)

Patient Code	Sex	Age (yr)	Weight (kg)	BSA[a] (m^2)	Total Dose (mg)	(mg/kg)	Surgery
HK	F	34	54	1.50	13.5	0.250	Cholecystectomy
SH	F	39	70	1.82	17.5	0.250	Cholecystectomy
AS	M	56	83	1.81	21.0	0.254	Closure of colostomy
DA	F	20	64	1.76	16.0	0.252	Cervical rib resection
AD	M	78	64	1.63	16.0	0.251	Haemorrhaphy
TE	F	54	63	1.73	16.5	0.263	Vagotomy and antrectomy
MA	F	38	64	1.79	17.0	0.265	Cholecystectomy
KB	F	32	67	1.87	16.5	0.246	Epigastricherniorrhaphy
CA	M	51	65	1.64	16.0	0.246	Carotid endartectomy
WK	M	68	76	1.93	19.0	0.250	Sympathectomy
FO	M	62	80	1.85	20.0	0.250	Cholecystectomy

[a] Body Surface Area

Table 4.2 Clinical Details for the Healthy Surgical Patients who Received Alcuronium as Multiple Bolus Doses

Patient Code	Sex	Age (yr)	Weight (kg)	BSA[a] (m^2)	Surgery
DJ	F	19	57	1.65	Cholecystectomy
PL	F	60	62	1.46	Cholecystectomy
GC	M	37	69	1.79	Cholecystectomy
RW	M	80	63	1.73	Abdomino-perineal resection
AB	F	51	66	1.63	Cholecystectomy
LC	F	70	48	1.43	Aorto-bifemoral anastomosis
TP	F	25	104	2.06	Gastric bypass
PS	M	50	63	1.76	Aorto-bifemoral anastomosis

[a] Body surface area

Data from the multiple dose patients were fitted to a biexponential equation of the form:

$$Cp^N = \left[\frac{(k_{21}-\alpha)}{(\beta-\alpha)} . D . V_1 . e^{-\alpha t} + \frac{(k_{21}-\beta)}{(\alpha-\beta)} . D . V_1 . e^{-\beta t} \right]^N \quad \text{Eq. 4.2}$$

Where k_{21} represents an intercompartmental transfer rate constant, V_1 is the reciprocal of the volume of the central or sampling compartment, α and β represent the usual hybrid rate constants; N is the number of doses administered and D represents each individal dose.

In identifying the simplest pharmacokinetic model consistent with alcuronium plasma concentration-time data, a comparison was made of the fits to two compartment and three compartment open models respectively, using the three criteria suggested by Boxembaum et al. (207). These included examination of a) the weighted squared deviations of the fitted equations, b) the randomness of residual plots and c) goodness of fit of the observed and theoretical curves.

In addition to the pharmacokinetic parameters (Cl, $t_{1/2\beta}$, V_{ss}) mentioned earlier (Ch. 3, p. 69), the distribution half life ($t_{1/2\alpha}$), initial dilution (or central compartment) volume (V_1) were also calculated in these patients, according to methods described by Gibaldi and Perrier (214).

Pharmacodynamics

In patients where response (paralysis)-plasma concentration and time data were available both during onset and offset of paralysis, an effect model was used to characterize the pharmacodynamic data. In brief, the plasma concentraton-time data were fitted first to a microparameter

Table 4.3 Dosage Details for Healthy Surgical Patients who Required Additional Doses of Alcuronium

Patient Code	Number of Doses	Total Dose (mg)	Total Dose (mg/kg)	Initial Dose (mg)	Initial Dose (mg/kg)	2nd Dose (mg)	2nd Dose (mg/kg)	Time of 2nd Dose (min)	3rd Dose (mg)	3rd Dose (mg/kg)	Time of 3rd Dose (min)
DJ	2	21.0	0.368	14.0	0.246	7.0	0.123	62.5	--	--	--
PL	2	23.5	0.379	15.0	0.242	8.0	0.129	80.0	--	--	--
GC	2	25.7	0.372	17.2	0.249	8.5	0.123	44.0	---	--	--
RW	2	23.8	0.376	15.8	0.250	8.0	0.127	11.0	--	--	--
AB	3	32.5	0.492	16.5	0.250	8.0	0.121	71.0	8	0.121	141.0
LC	3	24.0	0.500	12.0	0.250	6.0	0.125	32.0	6	0.125	93.0
TP	2	34.0	0.327	21.0	0.202	13.0	0.125	86.0	--	--	--
PS	2	23.3	0.370	15.5	0.247	7.8	0.123	53.0	--	--	--

biexponential pharmacokinetic Eq. 4.3:

$$C_p = \frac{Xo\ (k_{21} - \alpha)}{V_1\ (\beta - \alpha)} .e^{-\alpha t} + \frac{Xo\ (k_{21} - \beta)}{V_1\ (\alpha - \beta)} .e^{-\beta t} \qquad \text{Eq. 4.3}$$

Where C_p is the plasma concentration, V_1 is the volume of the central (sampling) compartment, Xo is the dose administered and α and β are as defined previously.

This was followed by calculation of the amount of drug in the effect compartment (A_e) assuming that it was either driven by the central (Eq. 4.4) or the peripheral (Eq. 4.5) compartment.

$$A_e = k_{1e}.Xo \left[\frac{(k_{21} - \alpha)}{(\beta - \alpha)(k_{eo} - \alpha)} .e^{-\alpha t} + \frac{(k_{21} - \beta)}{(\alpha - \beta)(k_{eo} - \beta)} .e^{-\beta t} + \frac{(k_{21} - k_{eo})}{(\alpha - k_{eo})(\beta - k_{eo})} .e^{-k_{eo} t} \right] \qquad \text{Eq. 4.4}$$

Where k_{1e} is the transfer rate constant from central to the hypothetical effect compartment, k_{eo} is the elimination rate constant from the hypothetical effect compartment, and other terms are as previously defined.

$$A_e = \frac{k_{2e}.k_{12}.Xo}{(\beta - \alpha)(k_{eo} - \alpha)} .e^{-\alpha t} + \frac{k_{2e}.k_{12}.Xo}{(\alpha - \beta)(k_{eo} - \beta)} .e^{-\beta t} + \frac{k_{2e}.k_{12}.Xo}{(\alpha - k_{eo})(\beta - k_{eo})} .e^{-k_{eo} t} \qquad \text{Eq. 4.5}$$

Where k_{2e} is the transfer rate constant from peripheral to the hypothetical effect compartment and k_{12} is the transfer rate constant from central to peripheral compartment.

The amount of drug in the hypothetical effect compartment was then related to the degree of neuromuscular blockade by application of the Hill equation as described earlier (Ch. 3, p. 72). Offset data alone were fitted to the Hill equation without the additional effect compartment (Ch. 3, p. 71).

RESULTS

Table 4.4 compares the weighted sums of squared residuals (WSSR) for fits of bi- and tri-exponential equations to plasma concentration-time data obtained in patients who received a single bolus dose. In two cases (CA and SH) where the F-ratio test was applied there was a significant reduction ($p < 0.05$) in the sums of weighted squared deviations by using the more complex tri-exponential equation. However, in the tri-exponential fit to the data for patient SH, the computed estimate of β was unrealistically high being of the order 10^5 with a correspondingly high standard deviation. Thus, according to the F-ratio test, the tri-exponential equation gave a better fit only for the data of patient CA.

The WSSR of the observed plasma concentration-time data about the predicted curves for each patient were obtained for each model fit and were plotted as a function of time. Plots of these weighted residuals for patient CA are shown in Fig. 4.1. There was less systematic skewing of the weighted residuals with the tri-exponential equation than with the simpler bi-exponential equation. This was not the case for the other patients, where, generally, systematic deviations were apparent in the tri-exponential fits while the corresponding plots for the bi-exponential fit showed roughly random distribution in most cases. Visual inspection of the fit of the experimental plasma concentration-time data to the predicted curve for patient CA (Fig. 4.1) showed no marked improvement with the tri-exponential equation. Similarly, examination of the corresponding plots for the other patients also indicated that overall visual fits with both models appeared to differ insignificantly. Inspection of the curves for all patients receiving multiple doses of alcuronium also revealed excellent agreement between the observed and

Table 4.4 Statistical Comparison of Fits of the Bi- and Tri-Exponential Equations Used to Describe Alcuronium Plasma Levels with Time Following a Single Bolus Dose of 0.25 mg/kg Administered to Healthy Surgical Patients

	Bi-Exponential		Tri-Exponential			
Patient Code	$WSSR_2$ [a] ($\times 10^2$)	DF_2 [b]	$WSSR_3$ [a] ($\times 10^2$)	DF_3 [b]	F[c]	Critical Value of F ($p=0.05$)[d]
HK	0.4801	7	0.3490	5	0.94	5.79
SH	0.9986	8	0.2338	6	9.81	5.14
CA	0.3441	7	0.0745	5	9.03	5.79
AS	0.2525	9	0.1561	7	2.16	4.74
DA	0.1658	11	0.1772	9	[e]	4.26
AD	0.6614	10	0.8759	8	[e]	4.46
TE	0.7128	11	0.5272	9	1.58	2.26
MA	0.3512	8	0.2220	6	2.32	4.46
KB	0.1803	9	0.0868	7	3.76	4.74
WK	0.5035	9	0.4785	7	0.18	4.74
FO	0.4035	10	0.2629	8	2.14	4.10

a WSSR - weighted sums of squared residuals
b DF - degrees of freedom
c Calculated according to Boxembaum et al. (207)
d Critical values of F were obtained from Davies and Goldsmith (215)
e F-ratio test not performed as there was no minimization of WSSR using the tri-exponential equation.

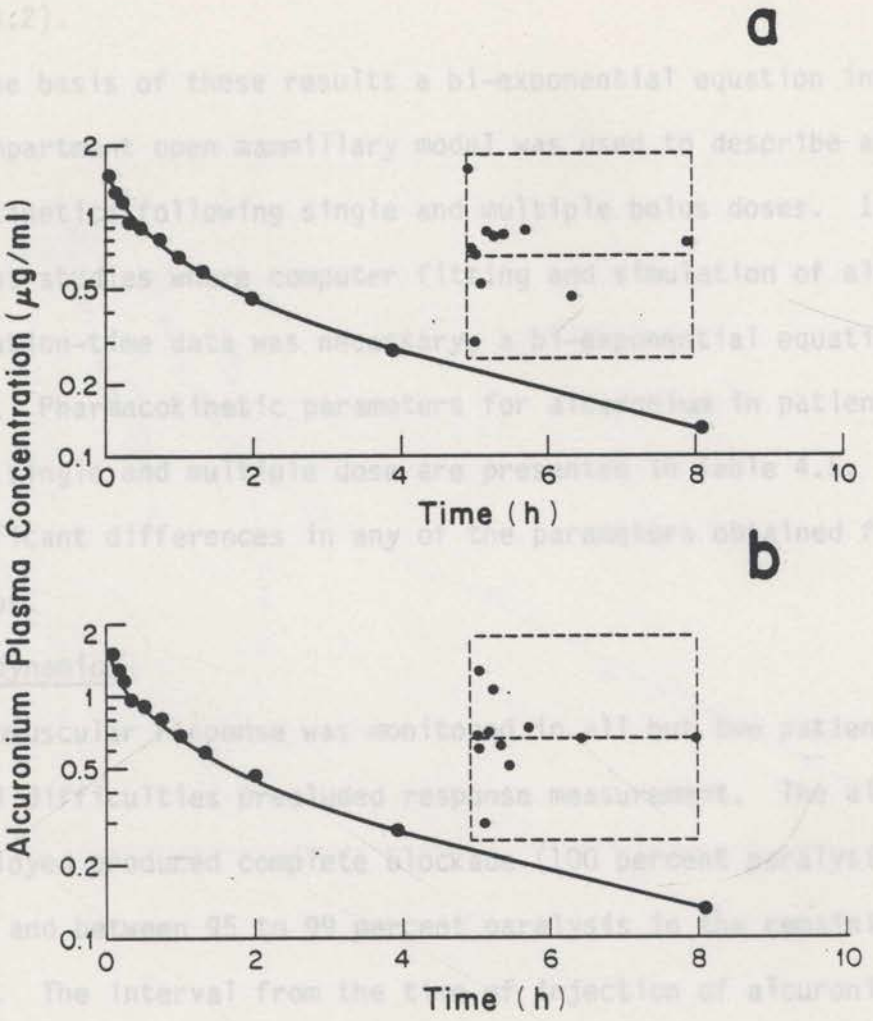

Figure 4.1 Representative, semi-logarithmic plot of alcuronium plasma concentrations versus time for a patient (CA) after a single intravenous bolus dose of 0.25 mg/kg. Experimental data (●) were fitted to a two-compartment (a) and a three-compartment (b) open model. The computer fitted curves are shown by the solid lines, and the insets contain the corresponding plots of the weighted residuals versus time obtained from each fit.

fitted plasma concentration using a bi-exponential equation (example shown in Fig. 4.2).

On the basis of these results a bi-exponential equation interpreted as a two compartment open mammillary model was used to describe alcuronium pharmacokinetics following single and multiple bolus doses. In all subsequent studies where computer fitting and simulation of alcuronium concentration-time data was necessary, a bi-exponential equation was utilized. Pharmacokinetic parameters for alcuronium in patients receiving both the single and multiple dose are presented in Table 4.5. There were no significant differences in any of the parameters obtained from these two groups.

Pharmacodynamics

Neuromuscular response was monitored in all but two patients, where technical difficulties precluded response measurement. The alcuronium dose employed produced complete blockade (100 percent paralysis) in nine patients and between 95 to 99 percent paralysis in the remaining eight patients. The interval from the time of injection of alcuronium until the time of peak effect (maximum paralysis) was taken to be the time for onset of action. Onset times and the corresponding plasma concentrations at these times are summarized in Table 4.6. The time (3-30 min) for maximum (95 to 100 percent) blockade and the corresponding alcuronium concentrations (0.74 to 2.17 μg/ml) varied considerably and there was no apparent relationship between these parameters.

In patients receiving more than one dose of alcuronium the intensity of paralysis induced by subsequent doses was compared to that produced by the initial dose (Table 4.7). Where the size of the subsequent dose(s) was half the original, the degree of blockade was either similar or marginally higher than that noted after the first dose in all but one (RW)

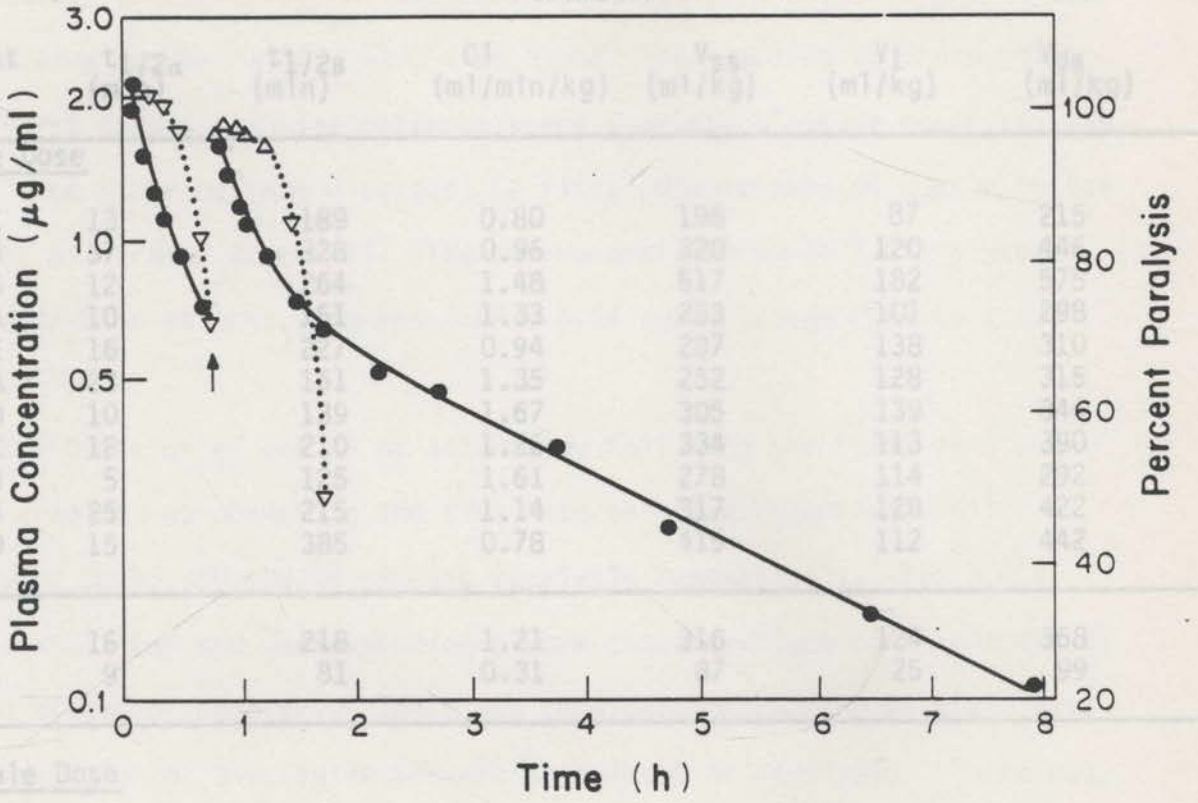

Figure 4.2 Semi-logarithmic plot of alcuronium plasma concentrations versus time for patient GC receiving an initial intravenous bolus dose of 0.25 mg/kg followed by an additional dose of 0.125 mg/kg at a time indicated by the arrow. Experimental data are shown as solid circles and the computer fitted two compartment fit as a solid line. Associated degrees of neuromuscular paralysis appear as solid triangles joined by visual fit.

Table 4.5 Pharmacokinetic Parameters for Alcuronium After Single and Multiple Doses

Patient Code	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	Cl (ml/min/kg)	V_{ss} (ml/kg)	V_1 (ml/kg)	$V_{d\beta}$ (ml/kg)
			Parameter			
Single Dose						
HK	13	189	0.80	198	87	215
SH	37	328	0.96	320	120	446
AS	12	264	1.48	517	182	575
DA	10	151	1.33	253	101	298
TE	16	227	0.94	287	138	310
MA	23	161	1.35	252	128	315
FO	10	139	1.67	305	139	344
WK	12	210	1.26	334	113	390
KB	5	125	1.61	278	114	292
CA	25	215	1.14	317	128	422
AD	15	385	0.78	419	112	442
Mean	16	218	1.21	316	124	368
± S.D.	9	81	0.31	87	25	99
Multiple Dose						
DL	8	166	1.79	378	126	427
PL	16	127	1.44	210	99	264
GC	13	143	1.54	259	105	317
RW	9	316	0.95	404	122	434
AB	11	163	1.48	299	109	349
LC	8	207	1.77	488	165	531
TP	10	114	1.06	153	119	174
PS	23	161	1.81	327	164	421
Mean	12	175	1.48	315	126	365
± S.D.	5	64	0.33	109	25	113
Pooled Data						
Mean	14	200	1.32	316	125	367
± S.D.	8	76	0.34	94	25	102

patient. In this patient, the initial dose produced insufficient blockade (63 percent paralysis) necessitating a second dose almost immediately (within 11 min). Generally, if a more pronounced neuromuscular paralysis followed the second dose relative to the first, the plasma concentrations were also higher (as compared to those after the first dose). In nine patients where complete blockade occurred, the mean time (from maximum blockade) to first reappearance of muscle twitch was 32 min (range 20 to 45). The corresponding mean (± S.D.) plasma concentration at this time was 0.87 ± 0.14 μg/ml (range 0.59 to 1.03 μg/ml).

The duration of action of alcuronium following the first dose was also examined by observing the time interval from injection until recovery to 95, 90 and 80 percent paralysis respectively. Table 4.8 shows the times and corresponding plasma concentrations of alcuronium at these stages of recovery. There was considerable overlap in the plasma concentration of alcuronium between each level of paralysis. There was, however, a tendency for the mean concentration to be greater at the higher level of paralysis. Examination of the plasma concentration-time profiles from these patients also revealed that recovery to 95, 90 and 80 percent paralysis was completed prior to, or just after pseudodistribution equilibrium had been attained in all but two (TP and TE) patients. Thus, with 0.25 mg/kg alcuronium dose, recovery begins in the distributive (α) phase and is completed during the elimination (β) phase.

In three patients (AD, FO and DA) who received single doses of alcuronium the central effect model characterized the pharmacodynamic data more adequately than the peripheral effect model. Alcuronium pharmacodynamic parameters derived using this model are compared to the parameters obtained by fitting the offset data alone to the Hill equation

Table 4.6 Time to Onset of Maximum Neuromuscular Blockade and the Associated Alcuronium Plasma Concentration for Healthy Surgical Patients Receiving Single and Multiple Intravenous Bolus Doses.

Patient Code	Time to Maximum Paralysis (min)	Maximum Paralysis (percent)	Alcuronium Plasma Concentration (µg/ml)
HK	10	100	1.98
CA	5	95	1.49
DA	15	99	1.25
AD	15	95	1.38
TE	10	100	1.53
MA	5	100	1.89
KB	10	97	1.02
WK	10	98	1.34
FO	30	95	0.74
DJ	10	98	0.79
PL	15	100	1.41
GC	3	100	2.17
RW	10	100	1.27
AB	10	100	1.43
LC	10	100	0.95
TP	0	100	2.25
PS	5	99	1.32
Mean ± S.D.	10 ± 6	98 ± 2	1.42 ± 0.44

Table 4.7 Time to Onset of Maximum Blockade and the Associated Alcuronium Plasma Concentration Following Each Dose in Healthy Surgical Patients Receiving Multiple Intravenous Bolus Doses of Alcuronium

Dose Number	Parameters	Patient Code						
		PL	GC	RW	AB	LC	TP	PS
1	Time to Max. Block (min)	15	3	10	10	15	0	30
	Maximum Paralysis (percent)	100	100	63	100	91	100	93
	Concentration (µg/ml)	1.41	2.17	1.16	1.43	0.66	2.25	0.78
2	Time to Max. Block (min)	0	10	10	5	5	0	5
	Maximum Paralysis (percent)	100	98	100	99	97	100	99
	Concentration (µg/ml)	1.84	1.61	1.49	1.19	1.06	2.29	1.32
3	Time to Max. Block (min)	---	---	---	5	10	---	---
	Maximum Paralysis (percent)	---	---	---	99	100	---	---
	Concentration (µg/ml)	---	---	---	1.79	1.05	---	---

Table 4.8 Plasma Concentration and Duration of Action (Time) in Healthy Surgical Patients Administered Single and Multiple Bolus Doses of Alcuronium at Various Stages of Neuromuscular Recovery

	Patient Code																Mean ± S.D.
	AD	CA	HK	DA	TE	MA	KB	WK	FO	DJ	PL	GC	RW	AB	LC	TP	PS	
Paralysis 95 Percent																	
Time (min)	--[a]	30	--[b]	40	60	45	22	35	--[a]	40	62	33	42	47	45	75	48	44.6 ± 13.8
Concentration (µg/ml)	--	0.90	--	0.76	0.68	0.86	0.78	0.75	--	0.62	0.66	0.9	0.73	0.63	0.73	0.78	0.60	0.74 ± 0.09
Paralysis 90 Percent																	
Time (min)	--	50	--	60	77	61	30	--[a]	49	57	66	39	51	56	50	85	61	55.2 ± 14.5
Concentration (µg/ml)	--	0.76	--	0.60	0.66	0.72	0.69	--	0.57	0.57	0.63	0.81	0.71	0.54	0.69	0.72	0.55	0.66 ± 0.08
Paralysis 80 Percent																	
Time (min)	--	80	--	77	102	72	40	--	65	78	76	47	66	68	66	111	71	71.3 ± 18.0
Concentration (µg/ml)	--	0.58	--	0.51	0.58	0.65	0.62	--	0.48	0.53	0.55	0.71	0.69	0.45	0.64	0.58	0.50	0.58 ± 0.08

[a] Data not available at these levels of paralysis

[b] Reversal before 95 percent paralysis

Table 4.9 Pharmacodynamic Parameter Estimates in Patients Receiving Single Bolus Doses of Alcuronium

	Parameters						
	Offset Data			Effect Model			
Patient Code	s	EC_{p50} (µg/ml)	EC_{p95} (µg/ml)	k_{eo} (min^{-1})	s	$C_{ss(50)}$ (µg/ml)	$C_{ss(95)}$ (µg/ml)
AD	8.8	0.49	0.68	0.07	3.5	0.50	1.16
FO[a]	---	---	---	0.77	6.9	0.28	0.43
DA	5.5	0.51	0.87	3.15	3.5	0.50	1.16
Mean	7.2	0.50	0.78	1.33	4.6	0.43	0.92
± S.D.	2.3	0.01	0.13	1.6	2.0	0.13	0.42

a Insufficient data to fit offset data alone to Hill equation

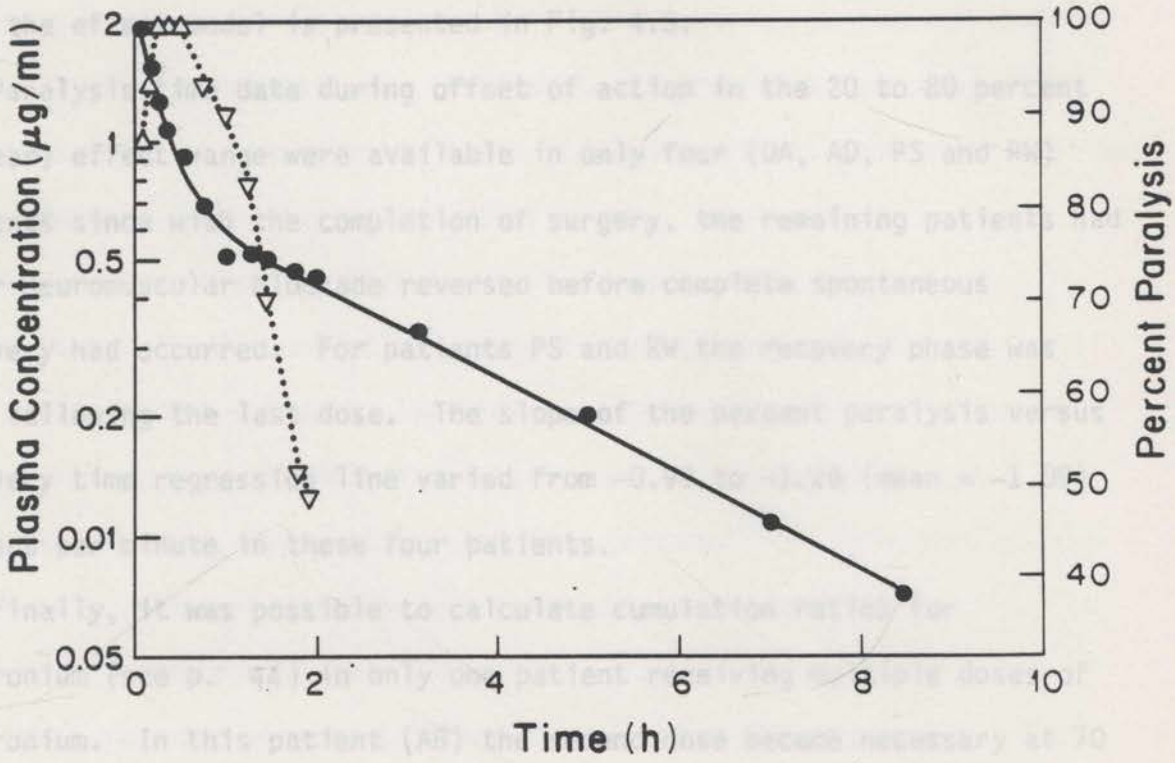

Figure 4.3 Semi-logarithmic plot of alcuronium plasma concentrations versus time for patient DA following a single intravenous bolus dose of 0.25 mg/kg. Experimental data appear as solid circles and the computer predicted two compartment fit as a solid line. Associated degrees of neuromuscular paralysis appear as solid triangles while the curve joining these points was generated by means of the effect model.

in Table 4.9. Included in this table are the calculated concentrations $C_{ss(95)}$ and EC_{p95}, respectively corresponding to 95 percent paralysis. These are more relevant clinically. An example of the good characterization of paralysis-time data during onset and offset of action with the effect model is presented in Fig. 4.3.

Paralysis-time data during offset of action in the 20 to 80 percent (linear) effect range were available in only four (DA, AD, PS and RW) patients since with the completion of surgery, the remaining patients had their neuromuscular blockade reversed before complete spontaneous recovery had occurred. For patients PS and RW the recovery phase was that following the last dose. The slope of the percent paralysis versus recovery time regression line varied from -0.99 to -1.26 (mean = -1.09) percent per minute in these four patients.

Finally, it was possible to calculate cumulation ratios for alcuronium (see p. 44) in only one patient receiving multiple doses of alcuronium. In this patient (AB) the second dose became necessary at 70 min after the initial dose when neuromuscular blockade had decreased to 79 percent paralysis. Following two subsequent (0.125 mg/kg) doses, a similar degree of recovery occurred at 68 to 70 min after administration of each dose, thus giving cumulation ratios of approximately 0.97 and 1.0 for the second and third doses respectively. The plasma concentrations of alcuronium at these levels of paralysis following each dose were also similar (range 0.47 to 0.64 μg/ml).

DISCUSSION

In this preliminary study using single and multiple doses of alcuronium a bi-exponential equation interpreted as a two-compartment open mammillary model was found to be the simplest polyexponential equation which described appropriately the plasma concentration-time data, in all but one patient. Raaflaub and Frey (110) used a similar equation model to characterize their alcuronium plasma concentration-time data obtained after single i.v. bolus doses.

Alcuronium volume of distribution at steady-state (V_{ss}) is approximately 20 percent of body weight and is similar in magnitude to the volume of the extracellular fluid suggesting that distribution of this relaxant drug is limited and tissue uptake is not extensive. This is to be expected, since alcuronium is a permanent cationic species and unlikely to penetrate tissue cell membranes readily (Ch. 2, p. 31). It is rapidly eliminated from the body ($t_{1/2\beta}$ approximately 3 hr), with the total plasma clearance (after correction for plasma binding) of the same order of magnitude as glomerular filtration rate.

The model-independent pharmacokinetic parameters obtained here are in excellent agreement with those reported by Raaflaub and Frey (110); Table 4.10. Alcuronium pharmacokinetic parameters are also generally similar to those reported previously for gallamine (58,59), d-tubocurarine (65) and pancuronium (63,216) from this laboratory (Table 4.11). However, the striking difference between these drugs is the two-fold larger V_{ss} and Cl for d-tubocurarine relative to the other relaxant drugs. The higher V_{ss} is unlikely to be due to differences in plasma protein binding because d-tubocurarine is more highly bound than the other relaxant drugs (see Table 2.5, p. 32). It more likely results from the greater lipophilicity of d-tubocurarine (25) compared with the other agents.

Table 4.10 Comparison of Model-Independent Pharmacokinetic Parameters of Alcuronium

Study	Parameter		
	$t_{1/2\beta}$ (min)	Cl (ml/min/kg)	V_{ss} (ml/kg)
Present (n=19)	197 ± 33[a]	1.29 ± 0.27	324 ± 38
Raaflaub and Frey[b] (n=6)	200 ± 76	1.32 ± 0.34	316 ± 94

a Mean ± S.D.
b Reference 110

Table 4.11 Comparison of the Model-Independent Pharmacokinetic Parameters for Alcuronium, Gallamine, d-Tubocurarine and Pancuronium

Relaxant Drug	Parameter[a] $t_{1/2\beta}$ (min)	Cl (ml/min/kg)	V_{ss} (ml/kg)
Alcuronium (n=19)[b]	200 ± 76	1.32 ± 0.34	316 ± 94
Gallamine (n=14)[c]	150 ± 27	1.59 ± 0.28	290 ± 54
d-Tubocurarine (n=7)[d]	124 ± 31	3.89 ± 0.42	480 ± 104
Pancuronium (n=7)[e]	133 ± 25	1.85 ± 0.53	260 ± 40

a Mean ± S.D.
b Present study
c Data from Ramzan et al. (59)
d Data from Ramzan et al. (132)
e Data from Somogyi et al. (216)

Differences in tissue binding may also play a role but such data are not available. The disposition of alcuronium more closely resembles that of gallamine and pancuronium. That alcuronium and gallamine are similar, from a pharmacokinetic view, is not unexpected, since for both these drugs renal excretion is the predominant route of elimination. Pancuronium on the other hand, undergoes metabolic, biliary and urinary routes of elimination but no study has examined the disposition of unchanged pancuronium. It is thus difficult to make quantitative comparisons between alcuronium and pancuronium.

The initial bolus dose (0.25 mg/kg) of alcuronium employed in this study provided adequate intubating conditions in all patients. This observation agrees with Lund and Stovner (56) who also found that an average dose of 0.25 mg/kg produced satisfactory conditions for intubation of the trachea. Other workers (217,218) have similarly reported that doses between 0.2-0.4 mg/kg were satisfactory for intubation.

No relationship was found between the degree of peak or maximum blockade and the corresponding plasma concentration of alcuronium. This is not unexpected since these plasma concentrations are measured when distribution is continuing; there is a disequilibrium between plasma concentration and effect, hence plasma concentration and effect are out of phase.

Using the pharmacodynamic effect model as previously proposed for d-tubocurarine (61)(Ch. 2, p. 47) it was possible to investigate whether an effect compartment driven by the central or the peripheral compartment of a conventional two-compartment open mammillary model was most appropriate to characterize alcuronium response data. When response was modelled with the effect compartment adjacent to and thus driven by the

central compartment, a good fit was obtained between observed and predicted effect data (Fig. 4.3). Estimates for the pharmacodynamic parameter, k_{eo} were, however, highly variable, possibly due to the limited number of data points available. When the effect compartment was adjacent to the tissue (peripheral) compartment, response did not parallel the calculated alcuronium concentrations in the theoretical tissue compartment and there was a marked discrepancy between predicted and observed paralysis data. In two patients, the response data gathered during offset of paralysis were also adequately characterized using the Hill equation without the effect compartment. Using these two approaches, there were no significant differences in the EC_{p50} and $C_{ss(50)}$ estimates and the exponent, s, values were also similar between the two fits. Further the calculated EC_{p95} (0.78 µg/ml) and $C_{ss(95)}$ (0.92 µg/ml) were of the same order of magnitude and similar to the mean observed plasma concentration (0.74 µg/ml) corresponding to 95 percent paralysis during offset of action. Thus, although response data over a wide range were available in only three patients, the results indicate the appropriateness of a sigmoid effect-plasma concentration relationship for alcuronium

The mean rate of recovery (1.1 percent min^{-1}) from paralysis with alcuronium in the linear range is similar to 1-2 percent min^{-1} noted with d-tubocurarine (65); 0.73 percent min^{-1} with gallamine (58) and 1 percent min^{-1} with pancuronium (219).

B. COMBINED INTRAVENOUS BOLUS AND INFUSION REGIMEN

INTRODUCTION

From the limited pharmacodynamic data on alcuronium presented in the last section, it appears that the response elicited is related to alcuronium plasma concentration, at least during onset and offset of action. As yet, however, steady-state plasma concentration and response data are not available with alcuronium.

Clinically it is desirable to provide continuous, uninterrupted neuromuscular blockade during prolonged surgery and prompt recovery of muscle contractility in the post-operative period. Infusion of a neuromuscular blocking agent at an appropriate rate following an initial loading dose can satisfy these requirements. Such a dosage regimen has been designed for alcuronium based on previously (p. 89) reported pharmacokinetic data. Since the body weight of the patient is not always available prior to surgery, the regimen was designed for adult patients without regard to their weight, ideal, or otherwise. The pharmacokinetic and pharmacodynamic results obtained using such a bolus and infusion regimen for alcuronium are described in this section.

METHODS

Twelve adults with normal hepatic and renal function were studied during intra-abdominal surgery (Table 4.12).

Dosage

The dosage regimen was calculated by a method developed by Mitenko and Ogilvie for theophylline (220), where the loading bolus dose is calculated as the product of the apparent volume of distribution ($V_{d\beta}$) and the desired steady-state relaxant concentration (C_{ss}) in plasma and the maintenance infusion rate is equal to the product of the total plasma clearance (Cl) and C_{ss}. Using this method, the initial concentration of relaxant in plasma will be higher than the desired 'steady-state' level but will decrease with time to the desired 'steady-state' plasma concentration (221). Alcuronium Cl and $V_{d\beta}$ estimates were taken from the preliminary study presented in the previous section (A). The desired steady-state concentration (C_{ss}) selected was 0.74 µg/ml corresponding to 95 percent paralysis (C_{p95}) during offset of action following the single and multiple doses (Table 4.8, p. 93). This dosage calculation resulted in an i.v. bolus dose of 18.0 mg of alcuronium and a constant infusion rate of 4.25 mg/hr. The alcuronium infusion was commenced at the time of the bolus injection and was continued for 58 to 165 min in the twelve patients who received between 22-31 mg (mean 27) total alcuronium (Table 4.12).

Arterial blood samples were collected at -5 (drug-free), 5, 10, 15, 20, 30 and 45 min after the alcuronium bolus and commencement of the infusion and then at 15 min intervals until the end of the infusion. Following cessation of the infusion, the same sampling protocol was repeated for up to 60 min post infusion. Subsequently blood samples were obtained at 90, 120, 180 and 240 min and thereafter at two hourly

Table 4.12 Clinical Characteristics of Patients who Received a Combined Intravenous Bolus and Infusion Regimen

Patient Code	Sex	Age (yr)	Weight (kg)	BSA[a] (m^2)	Duration of Infusion (min)	Total Alcuronium Dose (mg)	Surgical Procedure
KJ	M	38	62	1.71	135	28	Cholecystectomy
OG	F	56	59	1.67	165	30	Gastrectomy
EE	F	29	146	2.27	141	28	Gastric Bypass
CJ	M	57	74	1.84	150	29	Subphrenic Hydatid Excision
LM	F	30	115	2.02	180	31	Gastric Bypass
DC	F	59	69	1.76	152	29	Cholecystectomy/Cholangiogram
CM	F	29	49	1.44	93	25	Cholecystectomy/Cholangiogram
JB	M	38	43	1.59	60	25	Ilio-femoral Bypass
SS	F	17	58	1.56	70	23	Cholecystectomy
AM	F	63	63	1.68	58	22	Cholecystectomy
JR	M	41	77	1.91	104	25	Laparotomy/Splenectomy
GH	F	60	52	1.53	75	23	Gastrectomy

[a] BSA - Body surface area

intervals for a twelve hour period.

Pharmacokinetic and Pharmacodynamic Analysis

On the basis of the results obtained in the previous section (A) a bi-exponential macroparameter equation (Eq. 4.6) was used to describe alcuronium plasma concentration time data in all patients.

$$C_{p(t)} = \left[\frac{A^*.ko\ (e^{\alpha T} - 1)}{\alpha} + A^*.Xo \right] e^{-\alpha t} + \left[\frac{B^*\ ko\ (e^{\beta T} - 1)}{\beta} + B^*.Xo \right] e^{-\beta t} \qquad \text{Eq. 4.6}$$

In this equation ko is the infusion rate, Xo is the loading bolus dose, t is the real time, T is the infusion time and A*, B*, α and β are constants.

This equation describes the entire plasma concentration time data for a drug administered by constant-rate infusion together with a loading i.v. bolus dose.

From the computer estimates of A*, B*, α and β, standard methods (214) were used to calculate the volume terms V_1, V_2 and $V_{d\beta}$ and the micro-constants k_{12} and k_{21}. Alcuronium plasma concentrations were assumed to be at 'steady-state' when the drug concentration had reached an apparent plateau since the slope of the plasma concentration versus-time curve was close to zero and the 95 percent confidence band of the slope included zero.

Plasma concentration-time-paralysis data for the pharmacodynamic modelling was available in only six patients. Two approaches were again used to model the pharmacodynamic data in these patients: a) plasma concentration-paralysis data obtained during the offset of paralysis, after cessation of the maintenance infusion, were fitted to the nonlinear

form of the Hill equation (Eq. 3.2, p. 72) and b) the entire plasma concentration-time data were fitted to the pharmacokinetic Eq. 4.6 and the resulting parameters for each individual patient were then used to calculate the amount of alcuronium in the effect compartment (A_e) assuming it to be driven by either the central (Eq. 4.7) or peripheral (Eq. 4.8) compartment. Simultaneously, the measured neuromuscular paralysis observed during onset, at steady state and during offset was related to the amount of drug in the effect compartment by use of Eq. 3.2 (Ch. 3, p. 72) and estimates of the pharmacodynamic parameters obtained.

$$A_e = k_{1e}.Xo\left[\frac{(k_{21}-\alpha)}{(\beta-\alpha)(k_{eo}-\alpha)}.e^{-\alpha t} + \frac{(k_{21}-\beta)}{(\alpha-\beta)(k_{eo}-\beta)}.e^{-\beta t} + \frac{(k_{21}-k_{eo})}{(\alpha-k_{eo})(\beta-k_{eo})}.e^{-k_{eo}t}\right]$$

$$+ k_{1e}.ko.\left[\frac{(k_{21}-\alpha)(1-e^{\alpha T})}{\alpha(\alpha-\beta)(k_{eo}-\alpha)}.e^{-\alpha t} + \frac{(\beta-k_{21})(1-e^{\beta T})}{\beta(\alpha-\beta)(k_{eo}-\beta)}.e^{-\beta t} + \frac{(k_{eo}-k_{21})(1-e^{k_{eo}T})}{k_{eo}\ (\alpha-k_{eo})(\beta-k_{eo})}.e^{-k_{eo}t}\right]$$

Eq. 4.7

$$Ae = k_{12}.Xo\left[\frac{k_{2e}}{(\beta-\alpha)(k_{eo}-\alpha)}.e^{-\alpha t} + \frac{k_{2e}}{(\alpha-\beta)(k_{eo}-\beta)}.e^{-\beta t} + \frac{k_{2e}}{(\alpha-k_{eo})(\beta-k_{eo})}.e^{-k_{eo}t}\right]$$

$$+k_{2e}.k_{12}.ko\left[\frac{(1-e^{\alpha T})}{\alpha(\alpha-\beta)(k_{eo}-\alpha)}.e^{-\alpha t} + \frac{(1-e^{\beta T})}{\beta(\beta-\alpha)(k_{eo}-\beta)}.e^{-\beta t} + \frac{(1-e^{k_{eo}T})}{ko(\alpha-k_{eo})(k_{eo}-\beta)}.e^{-k_{eo}t}\right]$$

Eq. 4.8

Where ko is the infusion rate; X_o is the bolus dose; k_{eo} is the elimination rate constant from the effect compartment; k_{1e} and k_{2e} are the transfer rate constants from the central and peripheral compartments to the hypothetical effect compartment respectively; k_{12} and k_{21} are intercompartmental transfer rate constants and α, β, t and T are as defined previously (p.105).

RESULTS

Representative plasma concentration-time curves for alcuronium following the bolus and infusion regimen are shown in Figure 4.4. Figure 4.4a is the profile in a typical patient where 'steady-state' concentrations of alcuronium were attained during the maintenance infusion and Figure 4.4b illustrates similar data for a typical patient in whom the infusion time was insufficient to allow attainment of 'steady-state'. Thus the patients in this study could be divided into two groups on the basis of whether 'steady-state' alcuronium concentrations were attained or not. In the first group (n = 6), alcuronium plasma concentrations fell to a mean (± S.D.) apparent 'steady-state' level of 0.80 ± 0.23 μg/ml some 90 to 100 minutes following the initiation of the maintenance infusion. This value is similar to that (0.74 μg/ml) used to calculate the bolus plus infusion regimen. In the remaining patients in whom a 'steady-state' was not reached, the mean (± S.D.) plasma concentration at the end of the infusion was 0.91 ± 0.39 μg/ml.

The mean kinetic parameters obtained in the twelve patients are summarized in Table 4.13. None of the parameters from the group of patients who attained 'steady-state' were different from those in the group who did not.

In Figure 4.5, the pharmacokinetic parameters derived using single and multiple bolus doses are compared to those obtained using the bolus and infusion regimen. No differences between the two studies were noted in any parameter.

In the twelve patients, peak effect (paralysis) varied between 93 and 100 percent (mean ± S.D. = 98 ± 3 percent) and was observed between (mean ± S.D. = 9 ± 4) 5 to 15 min. The concurrently measured alcuronium

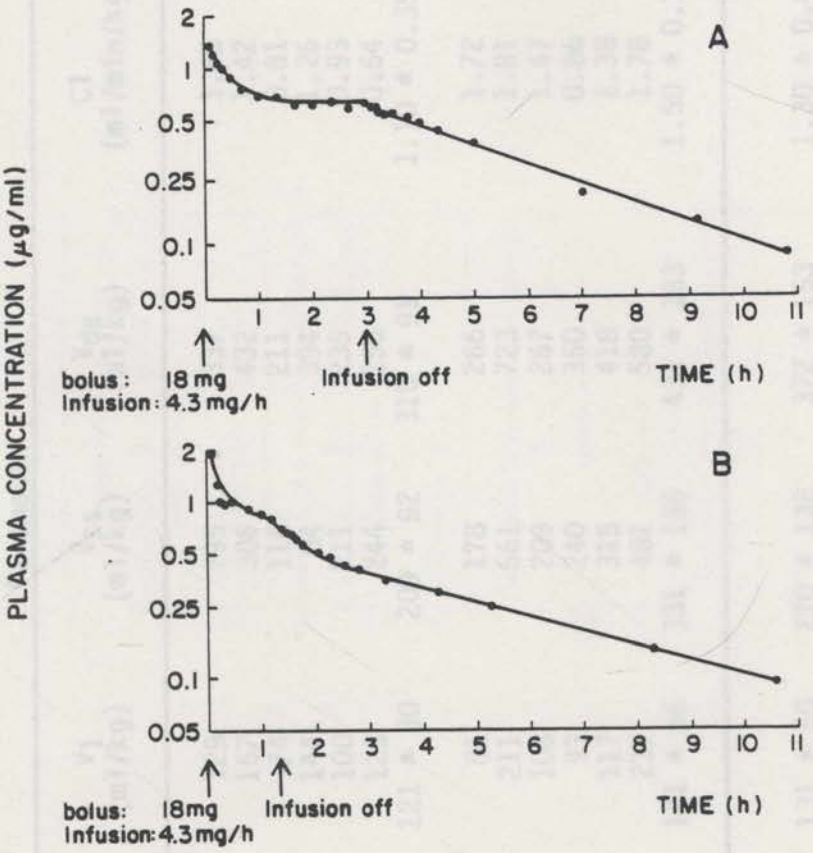

Figure 4.4. Representative concentration-time profiles for alcuronium following the loading bolus and maintenance infusion regimen. A represents a profile in a typical patient where 'steady-state' concentrations were attained and B illustrates similar data in a patient in whom the infusion was terminated before 'steady-state' was reached. The solid circles are the measured plasma concentrations while the line is that generated by the computer.

Table 4.13 Model-Independent Pharmacokinetic Parameters in Patients Receiving a Combined i.v. Bolus and Infusion Regimen

Patient Code	Parameter					
	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_1 (ml/kg)	V_{ss} (ml/kg)	$V_{d\beta}$ (ml/kg)	Cl (ml/min/kg)
KJ[a]	17	156	129	295	337	1.48
OG	35	210	157	306	432	1.42
EE	19	180	74	116	211	0.81
CJ	20	217	144	84	394	1.26
LM	14	175	100	211	235	0.93
DC	16	273	123	244	250	0.64
Mean ± SD	20 ± 8	202 ± 42	121 ± 30	209 ± 92	310 ± 91	1.10 ± 0.35
CM[b]	15	103	81	178	266	1.72
JB	15	277	211	561	723	1.81
SS	18	126	108	209	267	1.47
AM	19	233	93	240	350	0.86
JR	19	210	117	315	418	1.38
GH	25	225	237	481	580	1.78
Mean ± SD	19 ± 4	196 ± 67	141 ± 66	331 ± 156	434 ± 183	1.50 ± 0.36
Pooled Data Mean ± SD	19 ± 6	199 ± 53	131 ± 50	270 ± 138	372 ± 153	1.30 ± 0.40

a 'Steady-state' achieved
b 'Steady-state' not achieved

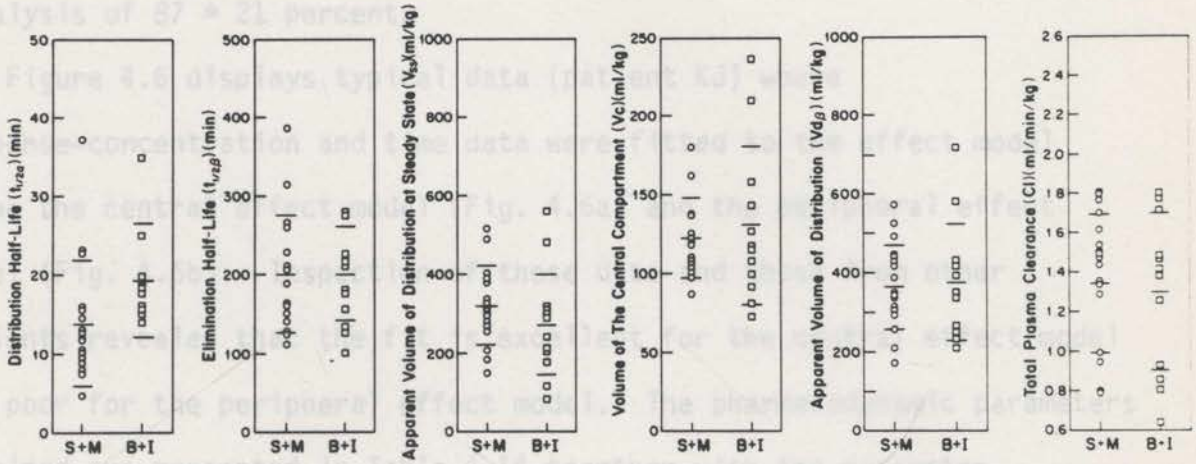

Figure 4.5 Kinetic parameters obtained for alcuronium following single and multiple i.v. bolus doses (S+M) and following the bolus plus infusion regimen (B+I). The horizontal bars represent the mean ± 1 standard deviation.

plasma concentrations ranged from 0.62 to 2.46 μg/ml (mean ± S.D. = 1.60 ± 0.50 μg/ml).

In the patients in whom a 'steady-state' was attained, the mean alcuronium 'steady state' plasma concentration of 0.80 μg/ml was associated with a mean (± S.D.) paralysis of 95 ± 4 percent. In the remaining patients, the mean alcuronium concentration of 0.91 μg/ml at the termination of the infusion was associated with a mean (± S.D.) paralysis of 87 ± 21 percent.

Figure 4.6 displays typical data (patient KJ) where response-concentration and time data were fitted to the effect model using the central effect model (Fig. 4.6a) and the peripheral effect model (Fig. 4.6b). Inspection of these data and those from other patients revealed that the fit is excellent for the central effect model and poor for the peripheral effect model. The pharmacodynamic parameters obtained are presented in Table 4.14 together with the parameter estimates obtained using the offset data and the calculated $C_{ss(95)}$ and EC_{p95} (corresponding to 95 percent paralysis) values respectively. The mean parameter estimates of s, EC_{p50}, EC_{p95} from the offset data did not differ ($p < 0.05$) from the mean parameter estimates of s, $C_{ss(50)}$, and $C_{ss(95)}$ generated using the effect model (Table 4.14). However, the mean (± S.D.) EC_{p95} (0.76 ± 0.13 μg/ml) was closer than the mean $C_{ss(95)}$ (0.91 ± 0.35 μg/ml), to both the concentration (0.74 μg/ml) used to devise the bolus and infusion regimen of alcuronium and the actual mean 'steady-state' alcuronium concentration (0.80 ± 0.23 μg/ml) observed in this study.

Mean $t_{1/2}\ k_{eo}$, the half-time for equilibration between the driving (plasma) compartment and effect; from the six patients where the effect model was used, was 3.6 ± 2.0 min, about one-third the time (9 ± 4 min)

before maximum neuromuscular blockade was attained using the bolus and infusion regimen.

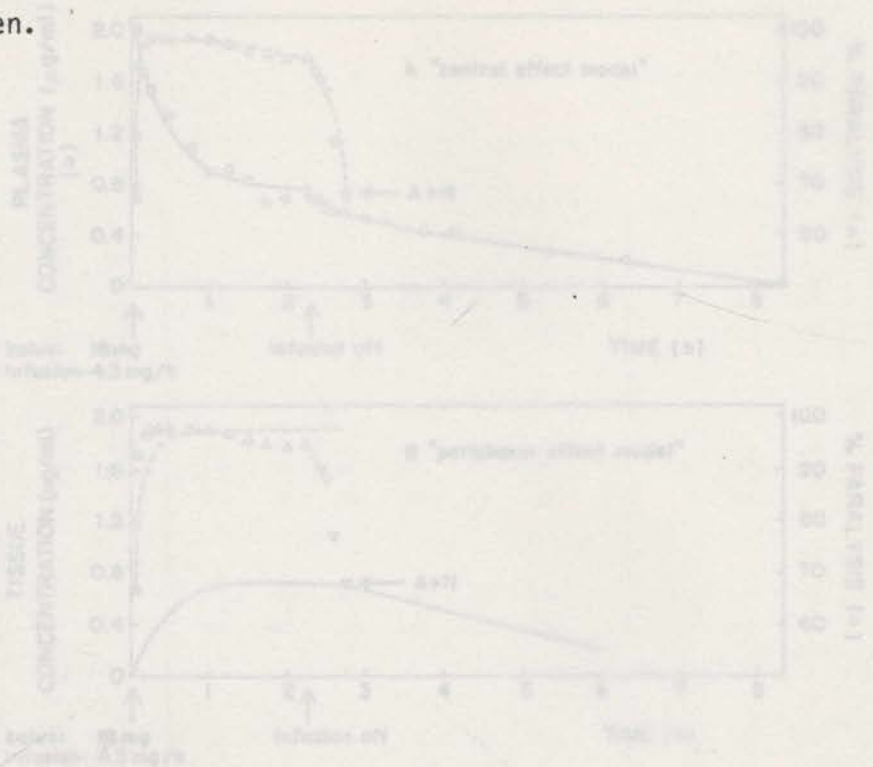

Figure 4.6. Relationship between alcuronium concentration in plasma and neuromuscular blocking effect for one patient where A represents the resultant profile utilizing the 'central effect' model and B a similar profile for the 'peripheral effect' model. The open circles show the measured plasma concentrations while the open triangles represent the corresponding degrees of muscle paralysis. The curves joining the paralysis and plasma concentration data respectively are those generated by the computer while in B the lower curve shows the theoretical tissue concentrations. The arrows indicate either the time where the reversal agents, atropine, and neostigmine (A+N) were administered or the time at which the alcuronium infusion was terminated.

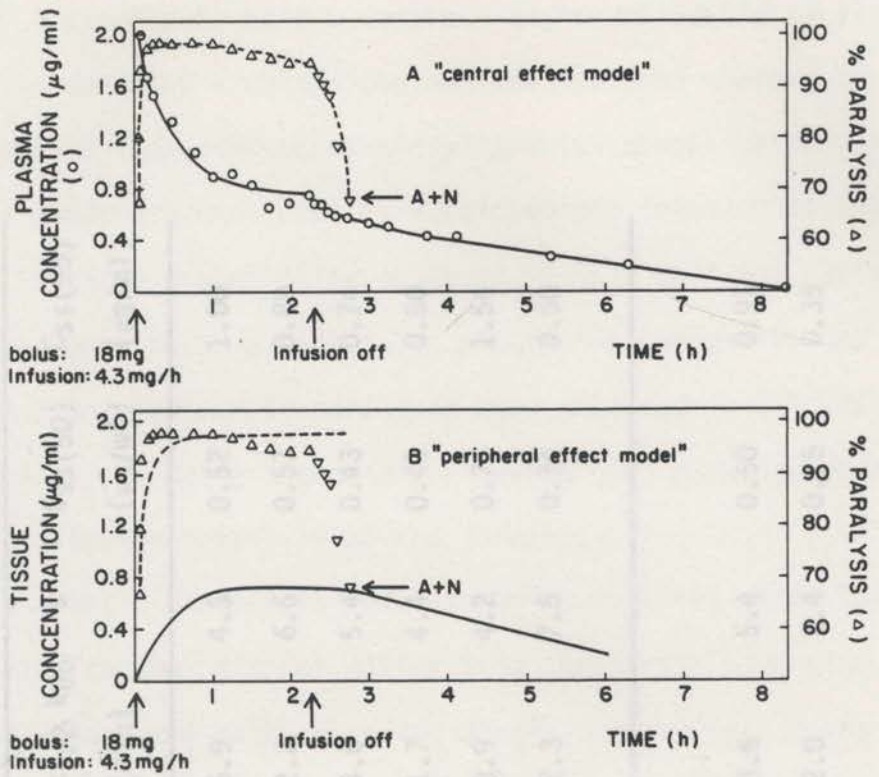

Figure 4.6. Relationship between alcuronium concentration in plasma and neuromuscular blocking effect for one patient where A represents the resultant profile utilizing the 'central effect' model and B a similar profile for the 'peripheral effect' model. The open circles show the measured plasma concentrations while the open triangles represent the corresponding degrees of muscle paralysis. The curves joining the paralysis and plasma concentration data respectively are those generated by the computer while in B the lower curve shows the theoretical tissue concentrations. The arrows indicate either the time where the reversal agents, atropine, and neostigmine (A+N) were administered or the time at which the alcuronium infusion was terminated.

Table 4.14 Pharmacodynamic Parameter Estimates for Alcuronium in Patients Receiving a Combined i.v. Bolus and Infusion Regimen

	Offset Data			Effect Model				
Patient Code	s	EC_{p50} (μg/ml)	EC_{p95} (μg/ml)	k_{eo} (min^{-1})	$t_{1/2}$ k_{eo} (min)	s	$C_{ss(50)}$ (μg/ml)	$C_{ss(95)}$ (μg/ml)
KJ	5.2	0.47	0.83	0.10	6.9	4.5	0.52	1.00
OG	5.2	0.49	0.86	0.31	2.2	6.6	0.57	0.89
EE	7.7	0.43	0.63	0.15	4.6	5.4	0.43	0.74
CJ	5.1	0.43	0.77	0.40	1.7	4.4	0.41	0.80
JR	7.2	0.60	0.90	0.18	3.9	4.2	0.76	1.54
SH	3.5	0.25	0.58	0.30	2.3	7.5	0.34	0.50
Mean	5.7	0.45	0.76	0.24	3.6	5.4	0.50	0.91
± S.D.	1.5	0.11	0.13	0.11	2.0	1.4	0.15	0.35

DISCUSSION

Since it is desirable to have a constant degree of muscle paralysis during surgical procedures a dosage regimen was designed whereby an initial loading dose is administered and alcuronium concentrations are maintained at a predetermined level by a maintenance infusion of the drug. Despite 'steady- state' being achieved in only half the patients, this regimen was found to be successful. Alcuronium concentrations adequate to maintain good muscle paralysis were attained in all patients, with residual paralysis being adequately reversed with neostigmine at the end of surgery following cessation of the infusion.

The pharmacokinetic parameters for alcuronium obtained using the bolus and infusion regimen did not differ from those used to design this dosage regimen, which were gathered using single and multiple doses of alcuronium. These results confirm previous findings (Section A, p. 89; reference 110) and those of others that the pharmacokinetic parameters of alcuronium are reasonably constant regardless of the dose and mode of administration.

Pharmacodynamically, the success of the present dosage regimen is substantiated by the observation that complete (100 percent) paralysis was attained in all patients following the loading bolus dose and that in patients in whom an apparent 'steady-state' was attained, the degree of neuromuscular blockade was at least 95 percent. There was, however, a definite latency to peak effect, in that the maximum blockade was somewhat delayed in relation to the time of peak drug concentrations. This lag preceding the appearance of maximum effect has also been observed with d-tubocurarine (dTc) and led to the development of a pharmacodynamic effect model for dTc (61). In the present study, a similar effect model has been successfully employed to account for the

disequilibrium between alcuronium concentration and effect. Further, it was possible to investigate whether an effect compartment driven by the central or the peripheral compartment of a conventional two compartment mammillary model was most appropriate. When response was modelled with the effect compartment adjacent to, and thus driven by the central compartment, a good fit was obtained between observed and predicted effect data. When the effect compartment was envisaged to be adjacent to the tissue (peripheral) compartment, response data did not parallel the predicted alcuronium concentrations in the theoretical tissue compartment and there was a marked discrepancy between predicted and observed paralysis data. Thus, the central effect model as also utilized with dTc (61) was more appropriate in explaining the response-time-alcuronium concentration data as well as the disequilibrium between concentration and effect.

Although the effect model was the more appropriate in adjusting for the disequilibrium between concentration and effect, response data, gathered during offset of paralysis, were adequately characterized using the Hill equation without invoking the additional effect compartment. This is not unexpected because during offset a pseudo-distribution equilibrium exists between drug in plasma and tissues and the disequilibrium between concentration and effect is minimal and negligible. However, the effect model is considerably more versatile in that it is able to characterize, simultaneously, response data gathered during onset, offset and at 'steady-state'. Further, the effect model is able to characterize the concentration effect relationship both in terms of a temporal (k_{eo}) and a sensitivity ($C_{ss(50)}$) component. As a result it has a predictive capability in that the model can generate a 'steady-state' concentration using data gathered during the distributive

phase or other non steady-state conditions.

The mean value of k_{eo} for alcuronium of 0.24 ± 0.11 min^{-1} is similar in magnitude to that (0.15 min^{-1}) noted for dTc (61). Thus the calculated $t_{1/2}$ k_{eo} is also similar (3.6 min for alcuronium versus 4.7 min (121) and 5.4 min (61) for dTc. Since the major determinants of k_{eo} (and thus $t_{1/2}$ k_{eo}) are muscle perfusion and the blood to muscle partition coefficients of these drugs (61), the similarity of alcuronium and dTc $t_{1/2}$ k_{eo} may be a reflection of the likely similarity of the partition coefficients of these two quaternary ammonium compounds.

In conclusion, the bolus and infusion regimen designed for alcuronium proved very useful in maintaining a constant degree of neuromuscular paralysis in patients and in enabling the collection of pharmacodynamic data, which were then used to characterize the plasma concentration-effect relationship for alcuronium.

Chapter 5

ALCURONIUM PHARMACOKINETICS AND PLASMA CONCENTRATION EFFECT RELATIONSHIP IN DISEASE

ABSTRACT

Pharmacokinetics and pharmacodynamics of alcuronium were assessed in three patients with renal dysfunction, one patient with biliary obstruction and a patient with tetanus. The elimination half-life was prolonged in patients with renal dysfunction and the plasma clearance was reduced. In the patient with cholestasis there was no change in half-life but the steady-state volume of distribution and plasma clearance were both increased by 50 percent as compared to normal patients. Alcuronium pharmacokinetic parameters in the tetanus patient were identical to those observed in healthy surgical patients. The concentration-effect relationship of alcuronium was unaltered as a result of renal dysfunction but there appeared to be increased sensitivity to alcuronium in biliary obstruction. Although alcuronium neuromuscular effect was not quantified in the patient with tetanus, clinical assessment of its effect detected no alteration in sensitivity.

INTRODUCTION

It might be expected that any impairment in the function of the kidneys and possibly the liver would alter the disposition and/or pharmacodynamics of alcuronium since it is excreted predominantly in the urine via the kidneys. In the clinical situation where the drug is used over prolonged periods the possibility that accumulation may occur with attendant untoward effects is a matter of concern. Thus knowledge of the pharmacokinetics of alcuronium in various disease states may enable more rational dose selection and hopefully prevent prolonged paralysis.

There have been three previous reports on the use of alcuronium in patients with renal dysfunction. Raaflaub and Frey (110) reported a prolongation of the elimination half-life of alcuronium (16 hr vs 3-4 hr in normals) in one case of complete anuria after a 20 mg dose of ^{3}H-alcuronium. Havill et al. (222) administered alcuronium (42 mg) to a patient undergoing renal transplant surgery and found that the patient required assisted ventilation for 48 hr post-operatively owing to residual paralysis. After 48 hr alcuronium effect was successfully reversed in this patient with atropine and neostigmine. Höfer et al. (223) also administered ^{3}H-alcuronium to patients undergoing kidney transplantation. These workers advocated the use of alcuronium in such patients provided post-operative ventilation is maintained for 12 to 24 hrs until adequate diuresis resumes to facilitate elimination of alcuronium.

Alcuronium use and/or disposition in patients with liver dysfunction or in patients with tetanus requiring prolonged muscle relaxation in intensive care units has not been described previously.

In this study, an opportunity arose to examine the disposition and concentration-effect relationship of alcuronium in a very limited number

of patients with various disease states. These included three patients with chronic renal failure, one patient with extrahepatic cholestasis (resulting from carcinoma of the pancreas) and a patient with tetanus requiring prolonged paralysis in an intensive care unit.

METHODS

Patient characteristics, alcuronium dosage and biochemical parameters for these patients are presented in Table 5.1. Only in the patients with renal failure and cholestasis was neuromuscular function monitored. Clinical criteria, including muscle spasm and breathing pattern were used to assess alcuronium effect in the tetanus patient.

Renal and Liver Dysfunction Patients

In these patients alcuronium plasma concentrations were determined as described previously for healthy patients (Ch. 4, p. 77) and Cl, V_{ss} and $t_{1/2\beta}$ were determined.

Alcuronium pharmacodynamic parameters were obained using both the Hill equation fit to the offset data (Ch. 3, p. 71) and using an effect model (Ch. 3, p. 72).

Tetanus Patient

This patient had received intermittent bolus doses of d-tubocurarine (2 days) and an alcuronium bolus plus infusion regimen for 6 days followed by a 4 day washout period prior to enrollment into this study. Unfortunately blood samples were not taken prior to the initial bolus dose. However, it appears reasonable to assume that neligible residual amounts of alcuronium persisted from the first infusion since 4 days, equivalent to approximately 20 half-lives in normal subjects, had elapsed since the termination of the previous infusion of alcuronium.

Following the initial bolus dose and during the course of the alcuronium infusion, blood samples were taken by venipuncture at 8 hourly intervals for 9 days. Following termination of the infusion on the ninth day, further samples were taken at 5, 15, 20, 30, 45, 60, 90 and 130 min then at 240, 360, 540, 600 and 840 min post-infusion.

The pharmacokinetic parameters calculated were $t_{1/2\beta}$, $V_{d\beta}$ and Cl,

Table 5.1. Clinical Characteristics of Patients with Various Diseases who Received Alcuronium

Patient Group	Code	Sex	Age (yr)	Weight (kg)	BSA (m^2)	Total Dose (mg)	Total Dose (mg/kg)	Serum Creatinine (μmol/ℓ)	ALT IU/ℓ	AST IU/ℓ	Total Bilirubin (μmol/ℓ)	Serum Urea Nitrogen (μmol/ℓ)	Surgery
Renal	LA[a]	F	35	60	1.68	18	0.30	120	--	--	--	--	Renal transplantation
	VL[b]	F	49	80	1.85	20	0.25	--	--	--	--	--	Saphenous vein loop to right forearm
	SP[c]	M	66	54	1.62	21	0.38	1620	73	25	7	36.3	Renal transplantation
Liver	MC	F	76	44	1.49	11	0.25	70	110	71	420	4.4	Choledochojejunostomy/ liver biospy
Tetanus	MS[d]	F	48	--[e]	--	1793[f]	--						
		Day 1						80	60	23	4	6	Tracheostomy/prolonged paralysis
		Day 8						60	58	34	7	6	

ALT - Alanine Transferase
AST - Aspartate Transferase

a Dialysed immediately prior to surgery
b Dialysed 12 hr prior to surgery
c This patient received two doses of alcuronium, 0.25 mg/kg + 0.125 mg/kg, (13.5 + 7 mg). The second dose was given at 26 min
d This patient was not weighed
e Not determined
f Dosage details are presented in Fig. 5.4

where the latter was obtained using two methods. Firstly, from the maintenance infusion data, when plasma concentrations were at steady-state, as $Cl = ko/C_{ss}$, where ko was the maintenance infusion rate and C_{ss} the steady-state alcuronium plasma concentration, and secondly as $Cl = Dose/AUC_{\infty}^{\circ}$ (Ch. 3, p. 69). The volume term, $V_{d\beta}$ was calculated rather than volume of distribution at steady-state (V_{ss}) becasue the model-independent method for calculating V_{ss} (Eq. 5.1) requires calculation of a corrected MRT when the drug is administered by infusion, such that:

$$V_{ss} = dose\ [MRT\ (inf) - T/2]/AUC \qquad \text{Eq. 5.1}$$

$$MRT\ (inf) = MRT\ (bolus) + (T/2) \qquad \text{Eq. 5.2}$$

Where MRT is the mean residence time of a drug in the body, T is the infusion time and AUC is as defined previously (Ch. 3, p. 70).

In this patient, the infusion was continued for approximately 200 hrs and such a correction for MRT (and thus V_{ss}) was considered inappropriate. The patient weight was not available, hence the pharmacokinetic parameters from this patient were not corrected for body weight.

RESULTS

Plasma concentration-time profiles of alcuronium in the two (LA and VL) renal patients who received single doses are presented in Fig. 5.1 while the similar profile for patient SP, who received two doses, is presented in Fig. 5.2. Figures 5.3 and 5.4 are the concentration-time profiles for each of the biliary and tetanus patients respectively.

In renal disease patients, alcuronium plasma concentrations are higher than those for healthy patients and declined more slowly. In the renal patient who received two doses, alcuronium concentrations were essentially constant for 40 min after the second dose but there was a sudden decline in alcuronium concentrations as the newly transplanted kidney was revascularized.

In the patient with biliary disease alcuronium plasma concentrations initially tended to be lower than the mean concentrations observed in normal patients but declined at the same rate during the elimination phase.

In the tetanus patient, alcuronium plasma concentrations which were about 2.5 μg/ml after the bolus dose declined over a period of two days to a mean steady-state concentration of 1.42 μg/ml (± 0.15) during the period when the infusion rate was constant at 9 mg/hr. During the maintenance infusion the concentrations remained reasonably constant, with minor fluctuations occurring when the infusion rate was altered. Once the infusion was terminated (on day 9), alcuronium plasma concentrations declined in typical biexponential fashion, at a rate similar to that noted in normal patients.

The pharmacokinetic parameters from these patients are presented in Table 5.2 and are compared with those from normal patient group. There were no differences in V_{ss} between patients with renal disease and normal patients, but V_{ss} was substantially higher than normal in the patient with liver disease.

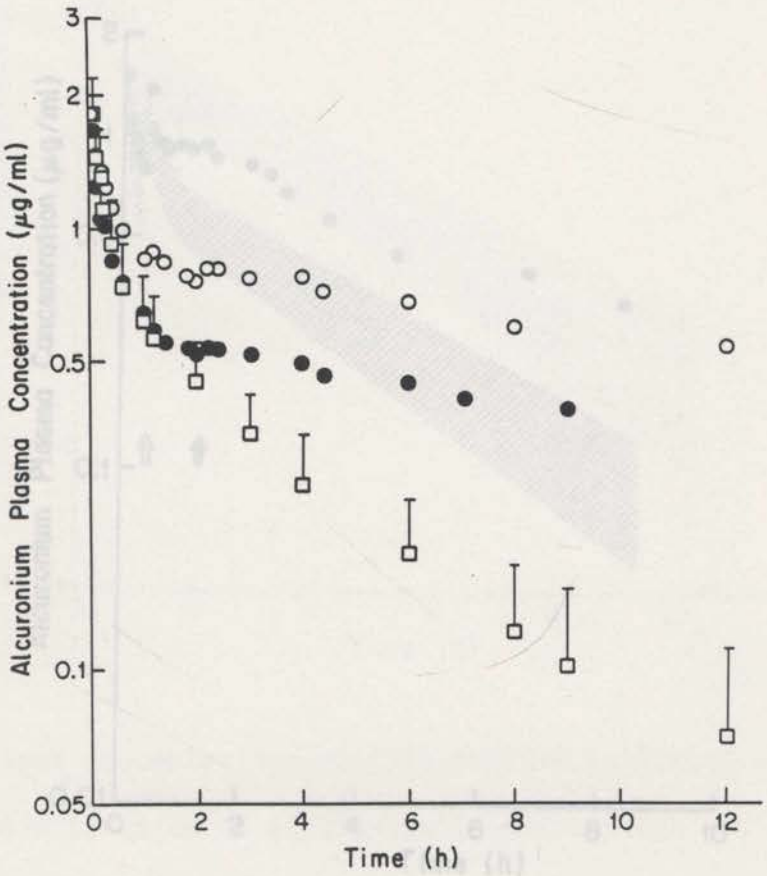

Figure 5.1. Plasma concentrations of alcuronium following intravenous administration (0.25 mg/kg) in two (○=LA; ●=VL) patients with renal disease. Mean (± S.D.) alcuronium concentrations (□) from normal patients are also presented for comparison.

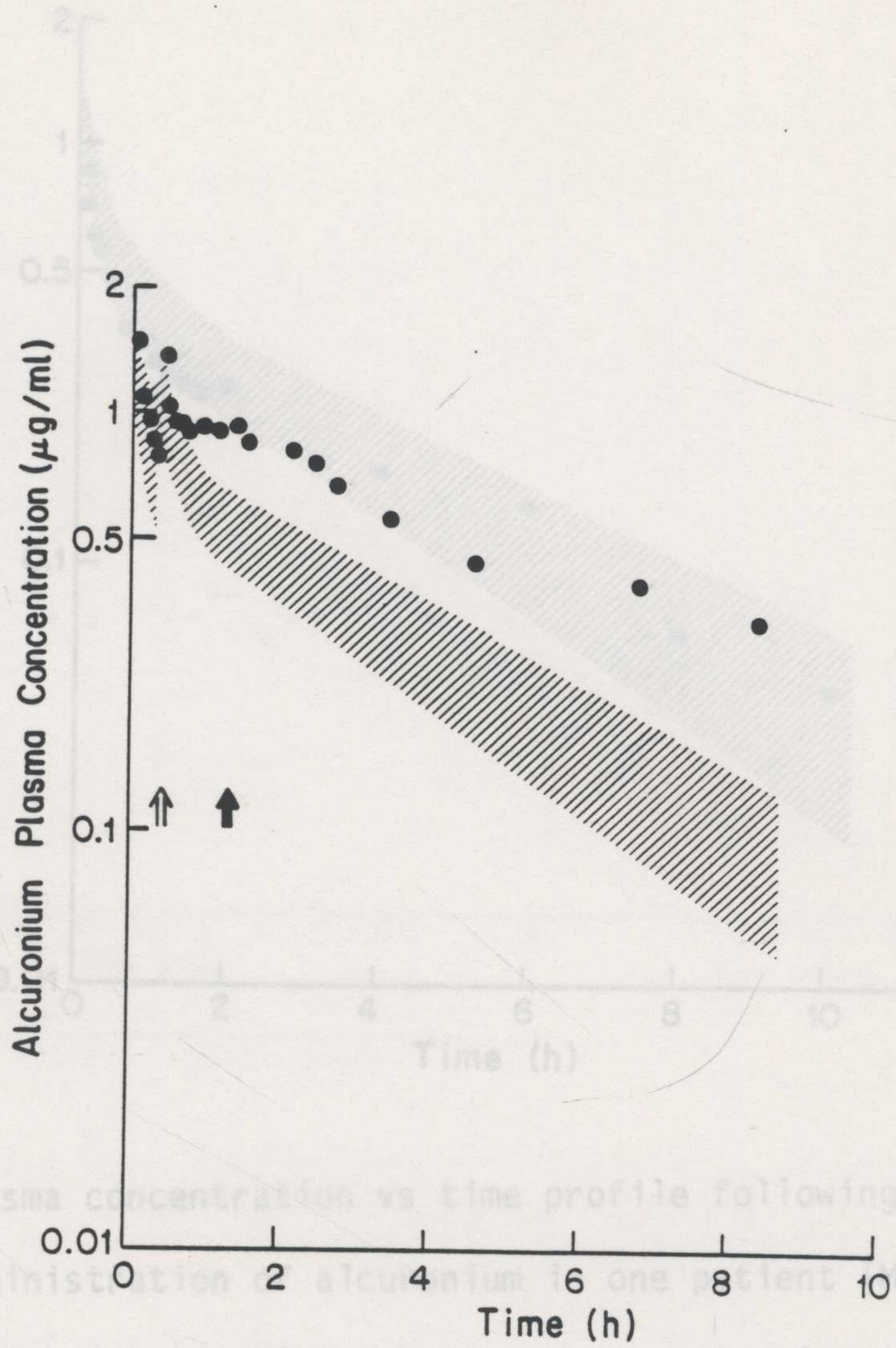

Figure 5.2. Plasma concentration vs time profile of alcuronium in patient SP undergoing renal transplantation who received an initial dose of 0.25 mg/kg alcuronium followed by an additional dose (0.125 mg/kg at 26 min; open arrow). The closed arrow represents the time at which the transplanted kidney was revascularized. Measured concentrations are shown as solid circles while the shaded area represents the mean (± 1 S.D.) concentrations noted in normal patients who received a similar dosage regimen (Ch. 4, p. 79).

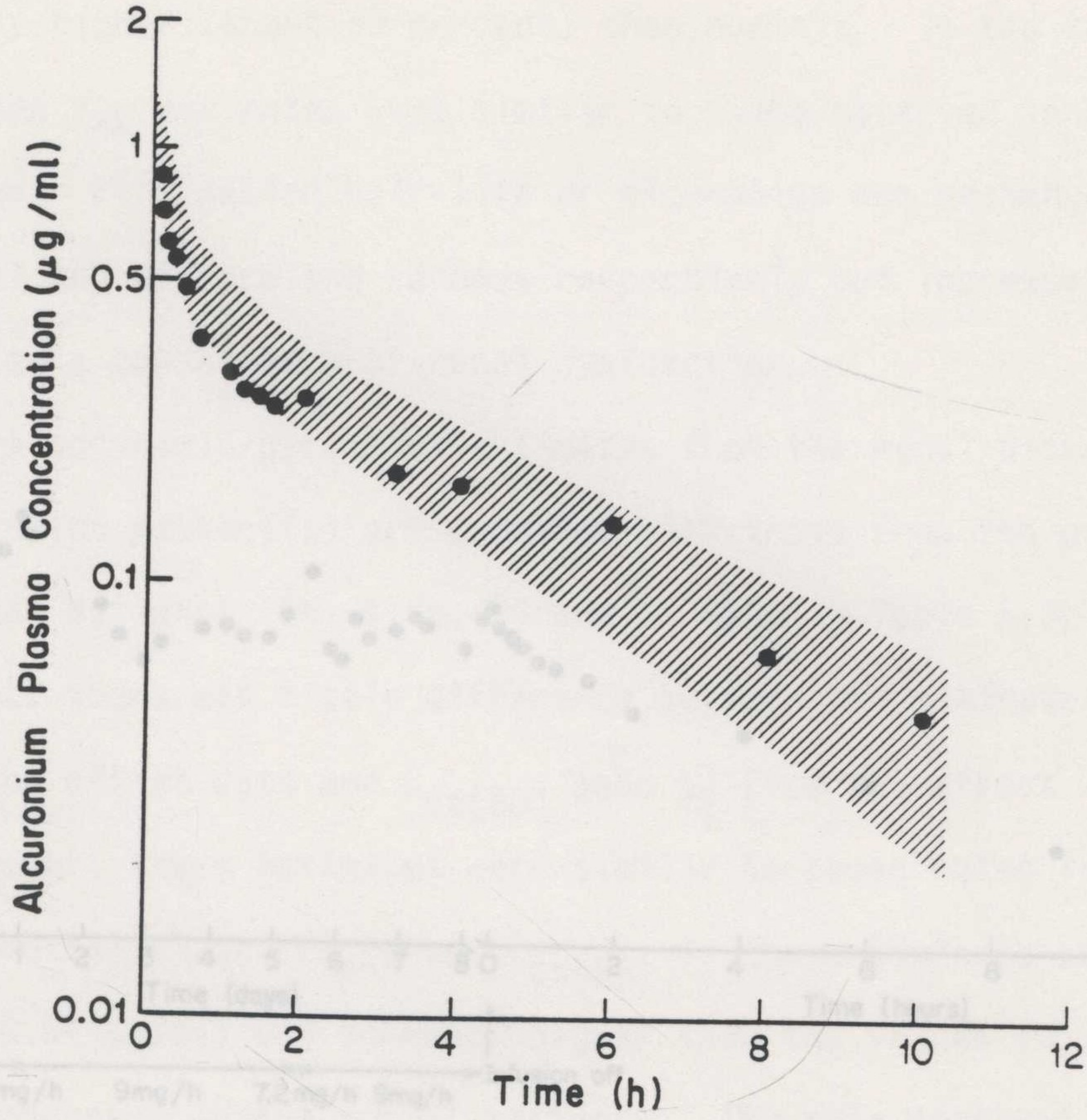

Figure 5.3. Plasma concentration vs time profile following bolus (0.25 mg/kg) administration of alcuronium in one patient (MC) with total biliary obstruction. Measured concentrations are shown as solid circles while the shaded area represents the mean ± 1 S.D. concentrations observed in normal patients. Concentrations in the normal patients are normalized to the same total dose (11 mg) administered to the patient with liver disease.

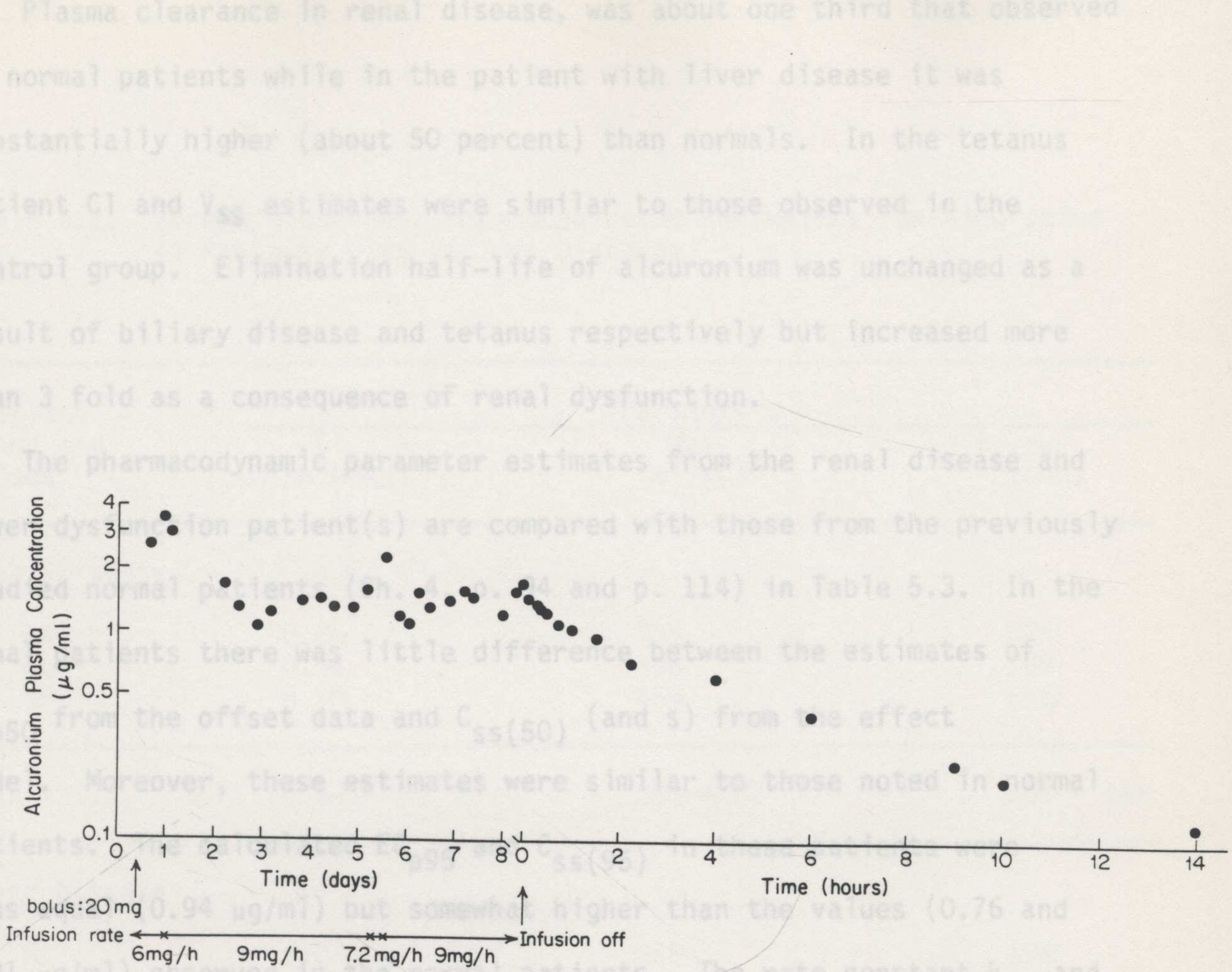

Figure 5.4. Plasma concentration-time profile of alcuronium in a patient with tetanus who received an initial bolus (20 mg) dose followed by a maintenance infusion of alcuronium for 8 days. Post-infusion concentrations were observed for 14 hr after the infusion was terminated. Note the change in time scale at 8 days.

Plasma clearance in renal disease, was about one third that observed in normal patients while in the patient with liver disease it was substantially higher (about 50 percent) than normals. In the tetanus patient Cl and V_{ss} estimates were similar to those observed in the control group. Elimination half-life of alcuronium was unchanged as a result of biliary disease and tetanus respectively but increased more than 3 fold as a consequence of renal dysfunction.

The pharmacodynamic parameter estimates from the renal disease and liver dysfunction patient(s) are compared with those from the previously studied normal patients (Ch. 4, p. 94 and p. 114) in Table 5.3. In the renal patients there was little difference between the estimates of EC_{p50} from the offset data and $C_{ss(50)}$ (and s) from the effect model. Moreover, these estimates were similar to those noted in normal patients. The calculated EC_{p95} and $C_{ss(95)}$ in these patients were thus equal (0.94 µg/ml) but somewhat higher than the values (0.76 and 0.91 µg/ml) observed in the normal patients. The rate constant k_{eo} and $t_{1/2\ k_{eo}}$ estimates were similar to normal patients. In the biliary disease patient the parameters from the offset data and the effect models were similar but EC_{p50} and $C_{ss(50)}$ and thus EC_{p95} and $C_{ss(95)}$ were substantially lower than the mean parameter estimates in the normal patients. However, k_{eo} (and $t_{1/2\ k_{eo}}$) estimates were not different.

The neuromuscular response was not monitored in the tetanus patient but the infusion rate had to be increased several times to prevent spontaneous muscular activity until a rate of 9 mg/hr was found to be satisfactory.

Table 5.2. Model-Independent Pharmacokinetic Parameters for Alcuronium in Patients with Various Diseases

Patient Group and Code	Parameters		
	Cl (ml/min/kg)	V_{ss} (ml/kg)	$t_{1/2\beta}$ (min)
Renal Disease			
LA	0.26	295	824
VL	0.35	390	788
SP	0.70	459	516
Mean ± S.D.	0.44 ± 23	381 ± 82	709 ± 168
Liver Disease			
MC	2.0	518	196
Normal Patients[a]	1.32 ± 0.34	316 ± 94	200 ± 76
	Cl (ml/min)	V_{ss} (ℓ)	$t_{1/2\beta}$ (min)
Tetanus			
MT	96[b] 106[c]	31	231
Normal Patients[a]	94 ± 29	27 ± 11.0	200 ± 76

a Single and multiple doses of alcuronium (Ch. 4, p. 89; n=19)
b Cl - Dose/AUC_{∞}
c Cl - ko/C_{ss}

Table 5.3. Pharmacodynamic Parameter Estimates for Alcuronium in Patients with Renal and Liver Dysfunction

Patient Code	Parameters: Offset Data s	EC_{p50} (μg/ml)	EC_{p95} (μg/ml)	Effect Model k_{eo} (min^{-1})	s	$C_{ss(50)}$ (μg/ml)	$C_{ss(95)}$ (μg/ml)	$t_{1/2\ k_{eo}}$ (min)
LA	10.4 ± 1.8[a]	0.67 ± 0.02	0.89	0.14 ± 0.01	9.4 ± 0.8	0.62 ± 0.01	0.84	5.0
VL	3.4 ± 0.40	0.36 ± 0.02	0.86	0.13 ± 0.02	3.6 ± 0.5	0.38 ± 0.03	0.86	5.3
SP[b]	5.6 ± 0.8	0.64 ± 0.02	1.08	0.10 ± 0.01	9.7 ± 2.0	0.82 ± 0.02	1.11	6.9
Mean	6.5	0.56	0.94	0.12	7.6	0.61	0.94	5.7
± S.D.	3.6	0.17	0.12	0.02	3.4	0.22	0.15	1.0
Liver Disease								
MC	7.4 ± 0.8	0.25 ± 0.003	0.37	0.12 ± 0.2	4.4 ± 0.4	0.19 ± 0.003	0.37	5.8
Normal Patients[c]								
Mean	5.7	0.45	0.76	0.24	5.4	0.50	0.91	3.6
± S.D.	1.5	0.11	0.13	0.11	1.4	0.15	0.35	2.0

a Estimate ± S.D.
b Generated using data from second dose
c Receiving bolus and infusion regimen; n=6

DISCUSSION

In the absence of renal function a significantly lower plasma clearance and prolonged $t_{1/2\beta}$ have been noted previously with both d-tubocurarine (150) and gallamine (151). Data from the present study indicates a similar significant alteration in alcuronium pharmacokinetics in patients with renal disease. These results agree with those of Raaflaub and Frey (110) who also observed a significant prolongation in the elimination half-life of alcuronium in a single anephric patient. Miller et al. (150) found that a newly transplanted kidney is capable of excreting d-tubocurarine at a rate similar to that of two normal kidneys. In the two patients who underwent renal transplantation, alcuronium plasma clearance was substantially lower than that observed in normal patients but in one of these patients (SP), the newly transplanted kidney was able to eliminate alcuronium almost immediately as indicated by the abrupt decline in alcuronium concentrations. Unfortunately, plasma concentrations were only monitored for 9 hrs and it was not possible to predict whether the newly transplanted kidney was as efficient as a pair of normal kidneys.

In the patient with total biliary obstruction, alcuronium plasma concentrations declined in biexponential fashion similar to that observed in normal patients. However in this patient, both the plasma clearance and volume of distribution of alcuronium were elevated in comparison to healthy surgical patients. It is unwise to speculate on the likely reasons for these changes from data in only one patient, however, it is possible that the free fraction increased as a result of decreased total serum proteins (55 g/ℓ) and serum albumin (35 g/ℓ).

The pharmacodynamic parameters for alcuronium in patients with renal dysfunction are similar to results obtained in normal patients. These

findings suggest that the plasma concentration-effect relationship of alcuronium is unaltered in renal disease and that the prolonged paralysis noted with alcuronium previously (110,222) can be explained entirely on a pharmacokinetic basis. In the patient with biliary disease, however, it appears that the plasma concentration required for 95 percent paralysis is reduced by approximately half. This, together with the fact that the plasma clearance of alcuronium is about 50 percent higher in this patient, suggests that alcuronium dosage adjustments may not be necessary in patients with extrahepatic cholestasis.

In a study involving the use of pancuronium in tetanus patients no evidence of accumulation of pancuronium was detected over a period of 8 to 24 days (224). The data presented here with alcuronium, albeit in only one patient, are in agreement with these previous results. In the present study a maintenance infusion of 9 mg/hr of alcuronium was titrated to eliminate spasms in all muscle groups, including the diaphragm. This infusion rate produced a mean steady-state plasma concentration of 1.42 µg/ml. In contrast, normal surgical patients receiving a bolus and infusion regimen of alcuronium displayed a mean (± S.D.) plasma concentration of alcuronium, corresponding to 95 percent paralysis of the peripheral hand muscle, equal to 0.80 ± 0.23 µg/ml during a maintenance infusion at a rate of 4.3 mg/hr. Although the plasma concentration of alcuronium in the tetanus patient was approximately twice that required in normal patients; it is unlikely that the concentration-effect relationship of alcuronium was altered in this patient. The concentration of relaxant drugs needed to block the diaphragm is approximately twice that needed to block peripheral muscles (225).

In summary, from the limited number of cases described herein, it

would seem that alcuronium pharmacokinetics are altered markedly in patients with renal disease, moderately in extrahepatic liver disease and unaltered in tetanus. Further, no change in the concentration-effect relationship of alcuronium was noted in renal disease or in tetanus. However, the patient with extrahepatic cholestasis appeared to more sensitive to the neuromuscular blocking activity of alcuronium than healthy surgical patients.

ABSTRACT

d-Tubocurarine protein binding was determined in plasma from "normal" surgical patients; patients with renal dysfunction; patients with alcoholic cirrhosis and patients scheduled for coronary artery surgery and was compared with binding determined in solutions of isolated human serum albumin (HSA). The free fraction of d-tubocurarine was independent of plasma drug concentration throughout the range 0.1 to 5.0 μg/ml which spans the clinical plasma dTc concentration range. The free fraction of d-tubocurarine in renal disease (0.44 ± 0.05; n=15), liver disease (0.53 ± 0.05; n=8), and cardiac disease (0.49 ± 0.05; n=15) were not significantly different from that in normal subjects (0.48 ± 0.04; n=22). The free fraction of d-tubocurarine (0.55 ± 0.02, n = 7) in solutions of HSA (0.58 mM; 4 percent) was similar to that observed in plasma. Albumin, therefore, appears to be the major plasma binding protein for d-tubocurarine. The variation in free fraction of d-tubocurarine was unrelated to plasma concentrations of total protein, total globulin, albumin, total lipids, or α_1-acid glycoprotein in the four patient groups. d-Tubocurarine was found to be approximately 50 percent bound in humans and its free fraction was not influenced by plasma concentration or any of the three disease states. Thus, plasma protein binding variations do not explain the reported variation in clinical response to d-tubocurarine.

Chapter 6

d-TUBOCURARINE PLASMA PROTEIN BINDING IN HEALTH AND DISEASE

ABSTRACT

d-Tubocurarine protein binding was determined in plasma from "normal" surgical patients; patients with renal dysfunction; patients with alcoholic cirrhosis and patients scheduled for coronary artery surgery and was compared with binding determined in solutions of isolated human serum albumin (HSA). The free fraction of d-tubocurarine was independent of plasma drug concentration throughout the range 0.1 to 5.0 µg/ml which spans the clinical plasma dTc concentration range. The free fraction of d-tubocurarine in renal disease (0.44 ± 0.05; n=15), liver disease (0.53 ± 0.05; n=8), and cardiac disease (0.49 ± 0.05; n=15) were not significantly different from that in normal patients (0.50 ± 0.04; n=22). The free fraction of d-tubocurarine (0.55 ± 0.02, n = 7) in solutions of HSA (0.58 mM; 4 percent) was similar to that observed in plasma. Albumin, therefore, appears to be the major plasma binding protein for d-tubocurarine. The variation in free fraction of d-tubocurarine was unrelated to plasma concentrations of total protein, total globulin, albumin, total lipids, or α_1-acid glycoprotein in the four patient groups. d-Tubocurarine was found to be approximately 50 percent bound in humans and its free fraction was not influenced by plasma concentration or any of the three disease states. Thus, plasma protein binding variations do not explain the reported variation in clinical response to d-tubocurarine.

INTRODUCTION

Although dTc activity has been shown to be related to its total plasma concentration (128; Ch. 2, p. 42), it is probably the unbound drug in plasma that crosses cell membranes and reaches the postsynaptic membrane, at the neuromuscular junction to produce a response. Hence knowledge of the extent of interindividual variation in plasma protein binding of dTc is of interest to the anaesthesiologist since it may account for the wide interindividual variation in response encountered clinically with this relaxant drug.

The extent of plasma protein binding of d-tubocurarine (dTc) has been studied in healthy volunteers (105), post-surgical patients (107,226), in patients with various diseases including renal failure (106,107) and cirrhosis (103,107), in mothers and infants (104) and in individuals who had suffered severe burns (184). In these cases, the extent of binding ranged from 37 to 71 percent (see Table 2.5, Ch. 2). d-Tubocurarine has been shown to bind to both albumin and gamma globulins (226,228). Although originally the binding was considered to occur primarily to the plasma gamma globulins, it has recently been suggested that albumin is the major binding protein (103).

The aim of this study was to determine the plasma protein binding of dTc in several groups of patients, typical of those in whom dTc is used and in whom the binding might be altered. They included normal surgical patients, patients with hepatic cirrhosis, patients undergoing coronary artery bypass surgery and patients with varying degrees of renal dysfunction. To better understand the factors which might influence the protein binding of dTc a comprehensive biochemical and clinical profile was obtained for each patient and compared with the binding data. The protein binding of dTc was also determined in solutions of purified human serum albumin.

METHODS

The binding methodology is described in Chapter 3 (p. 68).

Subjects

The subjects included twenty-two patients in normal health between the ages of 17 and 83 years and scheduled for elective surgery, usually an intra-abdominal procedure. Twelve were female but were not taking oral contraceptive agents. Fifteen patients aged from 29 to 63 years (7 females and 8 males), twelve with chronic renal failure, one undergoing haemodialysis and three with acute renal failure. These patients, 12 of whom were scheduled for surgery, had blood urea nitrogen concentrations higher than 15 mmol/ℓ and serum creatinine concentrations ranging from 0.17 to 1.25 mmol/ℓ. They had no clinical or laboratory evidence of respiratory and/or cardiac insufficiency. Eight patients (7 males and 1 female) were aged from 41 to 72 years with confirmed laboratory diagnosis of alcoholic liver cirrhosis with total bilirubin concentrations ranging from 6 to 540 μmol/ℓ and with elevated liver enzymes (ALT range: 1-57 I.U./ℓ; AST range 16-18 I.U./ℓ). These patients were not scheduled for surgery. Fifteen patients scheduled for coronary artery bypass surgery ranged in age from 41 to 70 years (14 males and 1 female).

Blood Sampling

At the time blood was drawn for the plasma protein binding determination all patients undergoing surgery had received premedication, usually comprising of a narcotic (either papaveretum or pethidine) and atropine or scopolamine. All other drugs routinely taken by these patients were discontinued 36 hours prior to surgery. Four patients with cirrhosis had received no medication prior to blood sampling while the remaining four were in intensive care, receiving replacement intravenous fluids, usually containing water soluble vitamins and other nutritional

supplements. Three patients with renal dysfunction were also in intensive care. Two of these patients were receiving intravenous lipids[a] as a nutritional supplement. All patients with renal failure were receiving diuretics. In normal patients, those with renal dysfunction and in those with cirrhosis, blood samples were collected by venipuncture. In patients with coronary artery disease (CAD) samples were drawn from an indwelling radial arterial catheter. All samples were collected into plastic syringes[b] and transferred to either plain plastic tubes[c] (for serum) or tubes[c] containing ammonium heparin, 10 IU/ml, for plasma. To obtain serum samples, blood was immediately centrifuged to separate the cells and was again centrifuged after clot formation. Plasma samples were obtained by immediate centrifugation. Vacutainers were not used for blood collection since these have been shown to reduce the binding of dTc (184).

Since it has been shown with other drugs (227) that the method of blood collection; handling procedures and storage conditions can cause artifactual changes in free fraction it was necessary to examine whether the plasma and/or serum protein binding of dTc was stable under certain experimental conditions. Preliminary experiments were therefore carried out to determine a) the effect of storage conditions; b) the effect of dTc concentrations; c) the effect of using plasma or serum; and d) the effect of other drugs.

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[a] Intralipid

[b] Monoject

[c] Becton Dickinson

Effect of Storage Conditions

For this study, a large (100 ml) sample of blood from a healthy volunteer was collected via venipuncture. Immediately upon collection, one half was transferred to tubes containing ammonium heparin (10 IU) while the remaining half was transferred to plain plastic tubes. Plasma and serum, respectively were then harvested and spiked with dTc, 2 µg/ml, which is within the clinical range. The free fraction of dTc was then determined in aliquots (approximately 3 ml) of both serum and plasma after the following times and storage conditions: 1) immediately after collection; 2) after storage for 6 hr at 37°C; 3) after storage at 4°C for 24 hr; and 4) after storage for 1 month at -20°C.

Plasma Versus Serum dTc Binding

Another study was carried out in six healthy patients to determine the free fraction of dTc in both plasma and serum samples. Binding was determined after storage of the plasma and serum samples respectively at -20°C. Samples were thawed only once and spiked with dTc, 2 µg/ml for the binding determination. On the basis of the results obtained in these preliminary studies, all subsequent comparative studies between the four patient groups were carried out in plasma only.

Influence of d-Tubocurarine Concentrations

Initially, the protein binding of ^{3}H-dTc was determined in plasma samples from each patient group over the therapeutic concentration range 0.1 to 5.0 µg/ml. All subsequent determinations were carried out at a total concentration of 2 µg/ml.

Influence of Other Drugs

To rule out the possibility that dTc may be displaced from the plasma protein binding sites by other drugs, the plasma protein binding of ^{3}H-dTc (2 µg/ml) was determined after *in vitro* addition of typical

therapeutic plasma concentrations of adrenaline (0.2 ng/ml), protamine plus heparin (0.42 mg/ml + 10 IU/ml), propranolol (2.7 ng/ml), furosemide (1.0 ng/ml), digoxin (2.5 ng/ml), morphine (2.5 µg/ml), heparin (10 IU/ml), neostigmine (0.5 µg/ml), protamine (0.42 mg/ml), atropine (3 µg/ml), promethazine (5 µg/ml), isoprenaline (8 ng/ml), cephalothin (600 µg/ml), droperidol (1.25 µg/ml), meperidine (0.6 µg/ml) and diazepam (0.5 µg/ml).

d-Tubocurarine binding was also determined in 0.58 mM (4 percent) human serum albumin[a] (HSA) solution in phosphate buffer. The total dTc concentration range for this study was 0.1 to 5.0 µg/ml.

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[a] Sigma Laboratories, containing 1-2 percent free fatty acids.

RESULTS

The free fraction of dTc in the healthy volunteer was essentially unchanged whether binding was determined immediately, after storage at 4°C for 24 hr or after storage at -20°C for one month. Further there were no differences in the protein binding in serum or plasma (Table 6.1). d-Tubocurarine binding in normal surgical patients was similar to that noted in the healthy volunteer and again serum and plasma binding were not different (Table 6.2).

Duplicate plasma samples were examined at each of several dTc concentrations ranging from 0.1 to 5 μg/ml in both normal patients and patients with various diseases. The binding of dTc was essentially similar at each concentration in normal surgical patients, patients with renal dysfunction, cirrhosis and coronary artery disease (CAD), independent of the dTc concentration (Table 6.3).

As a result of this concentration independent dTc binding, the binding characteristics of dTc were determined at a representative therapeutic concentration of 2 μg/ml in a larger group of subjects. The free fraction of dTc ranged from 0.41 to 0.57 in 22 normal surgical patients with the mean (± S.D.) being 0.50 ± 0.04. In the ten male subjects, the free fraction of dTc was 0.50 ± 0.04 and in the twelve female subjects the free fraction was 0.49 ± 0.04. In patients (n=15) with ages between 17-59 years the free fraction was 0.50 ± 0.04 and was not different to that (0.49 ± 0.05) noted in patients (n=7) between 60 and 83 years of age.

The mean free fraction of dTc determined at a total concentration of 2 μg/ml was 0.44 ± 0.05 (n=15), 0.53 ± 0.05 (n=8) and 0.49 ± 0.05 (n=15) in patients with renal failure, cirrhosis and coronary artery disease respectively (Fig. 6.1). The plasma binding of dTc in the three disease

Table 6.1. Effect of Storage Conditions on dTc Free Fraction in Serum and Plasma Taken from a Healthy Volunteer

Storage Conditions	dTc Free Fraction	
	Serum	Plasma
Immediate	0.49[a]	0.50
6 hr at 37°C	0.52	0.55
24 hr at 4°C	0.51	0.51
1 month at -20°C	0.50	0.50

[a] Mean of duplicate determinations

Table 6.2. Comparison of d-Tubocurarine Free Fraction Values in Plasma and Serum Samples Taken from Normal Surgical Patients

Patient Code	Plasma	Serum
HF	0.47[a]	0.49
HK	0.47	0.49
LT	0.48	0.48
CS	0.45	0.46
CH	0.44	0.41
KB	0.48	0.47
Mean ± S.D.	0.47 ± 0.02	0.47 ± 0.03

[a] Mean of duplicate determinations

Table 6.3. Plasma Free Fraction of dTc as a Function of Concentration in Normal Surgical Patients and in Patients with Various Diseases

Plasma Concentration	Free Fraction[a]			
	Normal Patients (n=6)	Renal Failure (n=8)	Cirrhosis (n=5)	Coronary Artery Disease (n=15)
0.1	0.47 ± 0.09	0.46 ± 0.06	0.52 ± 0.02	0.48 ± 0.05
0.5	0.47 ± 0.05	0.46 ± 0.06	0.50 ± 0.03	0.50 ± 0.05
1.0	0.47 ± 0.08	0.46 ± 0.05	0.53 ± 0.04	-----
1.5	0.46 ± 0.08	-----	0.54 ± 0.04	-----
2.0	0.46 ± 0.08	0.46 ± 0.05	0.54 ± 0.04	0.48 ± 0.05
2.5	-----[b]	------	0.54 ± 0.04	-----
3.0	0.47 ± 0.08	0.46 ± 0.06	0.54 ± 0.04	0.48 ± 0.05
5.0	-----	-----	0.51 ± 0.02	0.47 ± 0.04

[a] Mean ± S.D.

[b] Not determined.

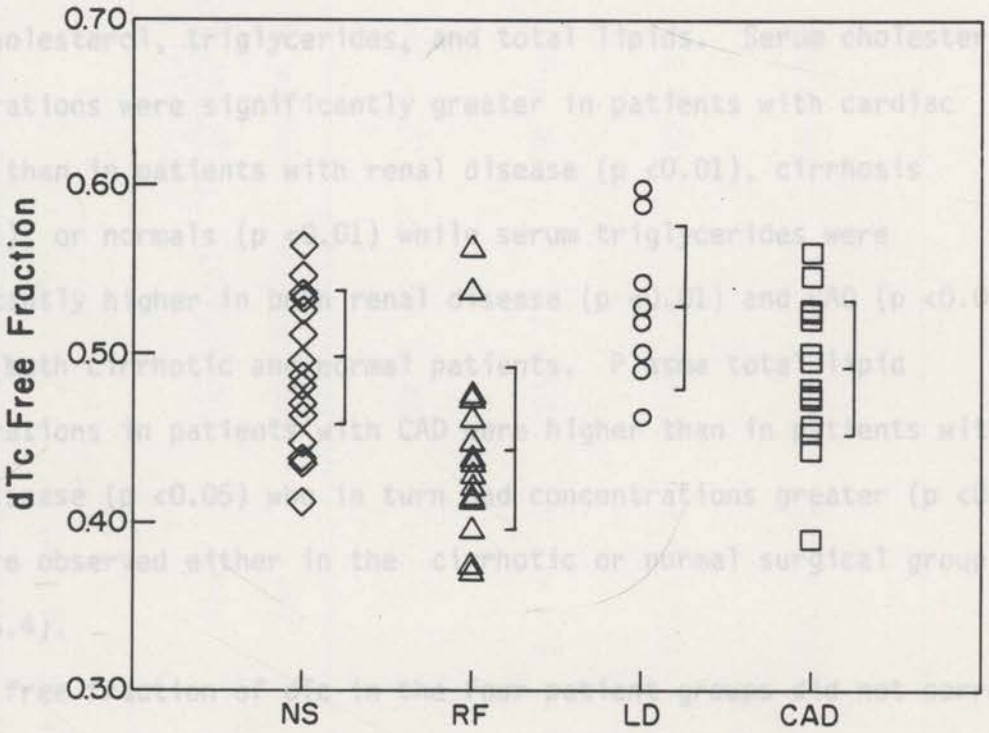

Figure 6.1. d-Tubocurarine free fraction in plasma of normal surgical patients (NS), ◇; patients with renal disease (RF), △; cirrhosis (LD), ○; and coronary artery disease (CAD), □. Means and standard deviations are indicated.

states did not differ significantly from that in the normal surgical patients but the binding in patients with renal failure was significantly greater ($p < 0.01$) than the binding in the cirrhotic patients. No differences were detected in the biochemical profile of patients in each of the four groups with respect to total protein, albumin, total globulins and AAG (Table 6.4). Differences were noted with respect to serum cholesterol, triglycerides, and total lipids. Serum cholesterol concentrations were significantly greater in patients with cardiac disease than in patients with renal disease ($p < 0.01$), cirrhosis ($p < 0.01$), or normals ($p < 0.01$) while serum triglycerides were significantly higher in both renal disease ($p < 0.01$) and CAD ($p < 0.01$) than in both cirrhotic and normal patients. Plasma total lipid concentrations in patients with CAD were higher than in patients with renal disease ($p < 0.05$) who in turn had concentrations greater ($p < 0.01$) than were observed either in the cirrhotic or normal surgical group (Table 6.4).

The free fraction of dTc in the four patient groups did not correlate significantly with either sex, age ($r = -0.28$), total protein ($r = -0.06$), albumin ($r = 0.14$), or any other protein fraction, nor did it correlate with any of the other biochemical parameters measured (Table 6.5 and Fig. 6.2).

When the binding of dTc to purified human serum albumin (HSA) (containing 1 to 2 percent non-esterified fatty acids, NEFA) was investigated, free fraction values (0.55 ± 0.02, $n = 7$) were of the same order as those in plasma. This similarity in the binding of dTc between HSA and human plasma suggests that albumin is probably the major binding protein for dTc.

The free fraction of dTc was not altered in the presence of

Table 6.4 d-Tubocurarine Free Fraction and Biochemical Parameters in Normal Patients, Patients with Renal Failure, Cirrhosis, and Coronary Artery Disease

Patient Group	Age[a] (yr)	Biochemical Profile[a]							d-Tubocurarine[a] Free Fraction
		Total Protein (g/l)	Albumin (g/l)	Total Globulin (g/l)	AAG[b] (g/l)	Lipids: Cholesterol (mg/100 ml)	Lipids: Triglycerides (mg/100 ml)	Lipids: Total (mg/100 ml)	
Normal Patients (n=22)	44 ± 19	67 ± 8	39 ± 5	28 ± 5	---[c]	204 ± 39	82 ± 39	288 ± 43	0.50 ± 0.04
Renal Disease (n=15)	50 ± 11	60 ± 12	32 ± 8	28 ± 6	1.4 ± 1.0	203 ± 62	196 ± 87	399 ± 115	0.44 ± 0.05
Liver Disease (n=8)	53 ± 9	65 ± 7	35 ± 7	29 ± 7	0.6 ± 0.3	158 ± 76	82 ± 53	240 ± 110	0.53 ± 0.05
Coronary Artery Disease (n=15)	56 ± 7	74 ± 8	42 ± 3	32 ± 6	1.0 ± 0.3	251 ± 31	192 ± 110	447 ± 101	0.49 ± 0.05

a Mean ± S.D.
b α_1-acid glycoprotein
c Not determined

Table 6.5 Correlation Coefficients for Regression Between d-Tubocurarine Free Fraction and Plasma Protein Concentrations

Patient Group	Correlation Coefficients Total Protein	Albumin	Total Globulin	AAG[a]
Normal	-0.16	-0.34	-0.02	---[b]
Renal Disease	-0.52	-0.28	-0.61	-0.39
Liver Disease	0.003	-0.04	-0.80	-0.15
Cardiac Disease	-0.46	-0.48	0.37	-0.06
Pooled Data	-0.06	0.14	-0.03	-0.36

[a] α_1-acid glycoprotein

[b] Not determined since AAG concentrations were unavailable because of insufficent plasma volume

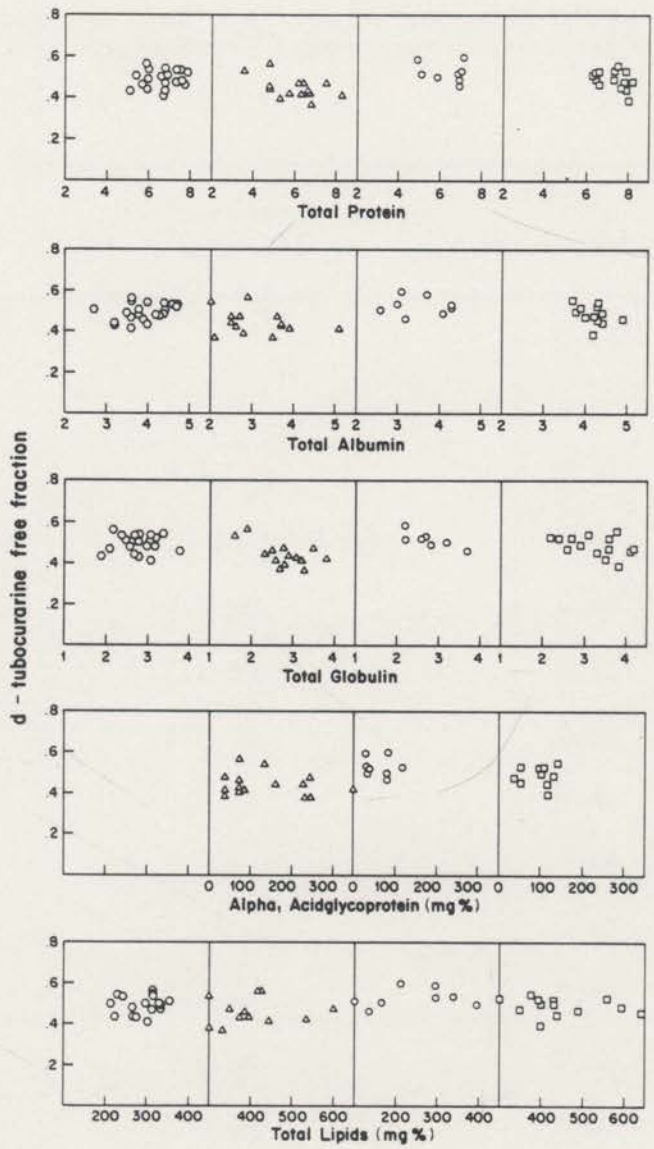

Figure 6.2. Relationship between d-tubocurarine free fraction and plasma protein fractions and total plasma lipids in normal patients (⬡), and patients with renal (△), liver (○) and cardiac (□) disease.

therapeutic concentrations of any of the fourteen drugs tested (Table 6.6).

Table 6.6 d-Tubocurarine Free Fraction Values Determined in the Presence of Therapeutic Concentrations of Various Drugs

Drug	Concentration (per ml)	dTc Free Fraction
Control Plasma		0.49 - 0.53[a]
Heparin	10 IU	0.50[b]
Protamine	0.42 mg	0.47
Heparin + Protamine	10 IU + 42 mg	0.49
Neostigmine	0.5 µg	0.49
Propranolol	2.7 ng	0.51
Atropine	3.0 µg	0.51
Adrenaline	0.2 ng	0.48
Promethazine	5 µg	0.49
Droperidol	1.25 µg	0.50
Diazepam	0.5 µg	0.49
Morphine	2.5 µg	0.51
Cephalothin	600 µg	0.52
Digoxin	2.5 ng	0.51
Isoprenaline	8 ng	0.52

[a] Range in control plasma

[b] Mean of duplicate determinations

DISCUSSION

The results presented support previous findings (103-108,184,226,228) that dTc is approximately 50 percent (free fraction range 0.41 - 0.57) bound to plasma proteins in healthy adults. Despite large differences in binding methodology and experimental conditions, the free fraction values reported here for dTc are remarkably similar to those reported previously by other workers (range 0.49 to 0.63). In the therapeutic concentration range between 0.1 to 5 μg/ml there is no concentration dependency of the plasma protein binding of dTc and the major binding protein is most probably albumin.

The *in vitro* binding of dTc in plasma taken from patients with renal failure, cirrhosis, and coronary artery disease was also determined in the present study. Patients with liver disease had dTc free fractions significantly higher ($p < 0.01$) than in the patients with renal failure in contrast to the findings of Ghoneim and co-workers (107), who noted no difference in the binding of dTc in uraemic and cirrhotic patients (free fractions 0.59 and 0.63 respectively). The difference in dTc binding between these two groups in the present study remains unexplained since only serum triglycerides and total lipid concentrations were different between them. The contribution of either serum triglycerides or total lipids to the binding of dTc remains to be evaluated.

In the past, several workers (175,189,229) have reported a resistance to the action of dTc in patients with liver dysfunction and this has been attributed (189) to excessive binding of dTc to gamma globulins since inversion of the albumin/globulin ratio is common in the chronic active state of liver disease. In the present study, in the patients with cirrhosis, dTc binding actually tended to be lower than in normals, although not significantly. Further, there were no differences in the

total protein, serum albumin, or globulin concentrations of the two patient groups, nor was there inversion of the albumin/globulin ratio in patients with cirrhosis. These results are in agreement with those of two previous reports (107,109) that there is no significant difference in the dTc binding to plasma proteins of healthy patients compared to patients with cirrhotic liver disease. Thus, it would appear that altered protein binding does not account for the anecdotal reports of clinical resistance to the action of dTc in liver disease.

Previous studies have shown that protein fractions of plasma may be altered in individuals requiring cardiac surgery (230). For example, AAG has been reported to increase in conditions of inflammation and stress in cardiac disease, especially following myocardial infarction (231). Furthermore, cardiac patients have been shown to have elevated plasma concentrations of cholesterol and triglycerides, reflecting elevated plasma lipoproteins, which have been implicated in alterations of binding of basic drugs (232). It might, therefore, be expected that cardiac disease could lead to altered plasma binding of such drugs. In the present study, samples for dTc binding were taken from patients immediately prior to coronary artery bypass surgery. As expected, these patients had concentrations of serum triglycerides, cholesterol, and total lipids which were significantly higher than in normal patients. Despite these differences, the free fraction of dTc in the cardiac patients was similar to that in normal patients and was unrelated to the concentration of serum lipids. Thus, it would appear that dTc binding is unimpaired as a result of coronary artery disease provided that concentrations of albumin are within normal limits.

In the four groups of patients, the free fraction of dTc was not significantly correlated with any of the biochemical parameters

monitored. This lack of correlation between dTc free fraction and even the concentration of the major binding protein, albumin, may in part be due to the relative constancy of all the individual plasma protein fractions in these patients. Thus, it appears that, unless major changes occur in the measured biochemical parameters, these are poor predictors of any possible disease-induced changes in dTc binding.

There is wide individual variation in the clinical response to the relaxant drugs (65,176,226; and Ch. 2, p. 19) which has been attributed by some workers (118,226) to differences in the extent of their protein binding in plasma. Results obtained here show that variations in protein binding of dTc are slight in patients with different diseases. Variation in plasma protein binding cannot explain the variation in clinical response.

Chapter 7

MUSCLE RELAXANT DRUG DISPOSITION DURING CARDIAC SURGERY INVOLVING CARDIOPULMONARY BYPASS

A. ALCURONIUM

B. GALLAMINE

C. d-TUBOCURARINE

ABSTRACT

The pharmacokinetics of three neuromuscular blocking drugs alcuronium, gallamine and d-tubocurarine were examined in patients undergoing surgery involving cardiopulmonary bypass (CPB). Ten patients received a combined bolus dose of 0.27 mg/kg and an infusion of alcuronium at 1 μg/min/kg approximately 60 min prior to the start of CPB. Before CPB alcuronium plasma concentrations declined in bi-exponential fashion similar to that noted previously in non-cardiac patients. With the onset of CPB there was a 50 percent increase in alcuronium plasma concentrations but upon completion of CPB and termination of the alcuronium infusion the concentrations again declined bi-exponentially with time. The mean post-infusion elimination half-life was 532 min, approximately three times longer than that observed in non-cardiac surgical patients. Similarly, the time averaged clearance was reduced by 40 percent in comparison with normal patients (0.80 vs 1.32 ml/min/kg).

Twenty-two patients received gallamine. Eleven patients received 480 mg gallamine i.v., the other eleven patients received an initial dose of 240 mg i.v. followed by another 240 mg through the pump priming fluid at the start of CPB. In 14 patients the time course of gallamine concentrations in the plasma prior to, during and after CPB was similar to that observed in normal surgical patients, indicating little or no effect of cardiac disease and/or CPB. In the remaining patients, perturbations were not observed before CPB, but with its onset there were varying changes, typically, rises in gallamine concentrations, ranging from an alteration during the period of CPB only or during the elimination phase, to an alteration at all times after starting CPB. Gallamine disposition was only moderately altered in these patients in

comparison with control patients.

Thirteen patients received an intravenous bolus of 0.6 mg/kg and a maintenance infusion of 3 µg/kg/min of d-tubocurarine, again 60 min before CPB. Prior to CPB, d-tubocurarine plasma concentration-time data were not different to those observed previously in normal surgical patients. With the onset of CPB, these was an abrupt discontinuity in the plasma concentration-time profile and plasma, total and free, concentrations increased three-fold during the period of CPB. d-Tubocurarine renal clearance was reduced during CPB and overall there was a reduction in total plasma clearance and a prolongation of the elimination half-life. A 27 percent increase in d-tubocurarine free fraction in plasma during CPB could be attributed to the CPB procedure itself resulting from haemodilution.

Although the mechanism for the observed rise in relaxant drug plasma concentrations during and after CPB is not known, computer simulations suggest that it is due to a contraction in blood volume and/or decreased tissue perfusion during the period of extracorporeal circulation. From a pharmacokinetic viewpoint, gallamine use is not contra-indicated in CPB surgery provided that renal function is not impaired. However, lower doses of alcuronium and d-tubocurarine will need to be used in these patients unless the concentration-effect relationship for alcuronium and dTc is also altered such that higher concentrations are needed to elicit the same response as in normal patients.

GENERAL INTRODUCTION

Cardiopulmonary bypass involves the use of a prosthetic device to totally replace temporarily the function of the heart and the lungs. Properly used, it allows the function of the other organs of the body to remain unchanged. However, an artificial heart cannot precisely mimic the action of a normal heart. Thus a number of factors may alter drug disposition during this procedure. These include: (1) hypothermia which is employed for myocardial preservation. Topical hypothermia is utilized to bring the body temperature to 28°C then cold cardioplegic solutions are infused to keep the myocardial temperature between 10° and 20°C thus producing a still, bloodless field for the surgeon; (2) haemodilution is utilized in combination with low flow techniques and is used primarily to decrease blood viscosity and hence reduce systemic vascular resistance; (3) metabolic changes including acidosis, which develops as a result of hypoxia caused by inadequate flow rates, and/or respiratory alkalosis resulting from hyperventilation; (4) low pump flow rates are employed to reduce blood damage and are compensated for by haemodilution but are effectively analogous to a decrease in cardiac output. Thus there is a homeostatic redistribtuion of blood flow, more to the brain and heart, less to skin and muscle; (5) blood damage results from contact with the heart lung machine. Red cells become more fragile with increased susceptibility to haemolysis and denaturation of platelet membranes causing platelet aggregation; and (6) organ damage results from the moderate to low blood flow. For example, liver disease, in the form of mild jaundice, occurs in 10 percent of cases and acute renal failure occurs in 1-2 percent of cases.

Many drugs are administered during cardiopulmonary bypass (CPB) surgery, but despite the frequency of these operations, relatively few

studies have been undertaken to examine the effect of CPB surgery on the disposition of such drugs. In the present study, the disposition of the three muscle relaxant drugs, alcuronium, gallamine and d-tubocurarine which are frequently used during CPB, has been examined. The use of these three agents is based on their autonomic effects. For example, alcuronium may be desirable since it affords cardiovascular stability (233); gallamine causes tachycardia (80) which may be desirable in the patient with bradycardia due to residual propranolol and the hypotensive response to d-tubocurarine (79) may be helpful in the hypertensive patient.

GENERAL METHODS

Patients and Anaesthetic Techniques

The patients were usually undergoing surgery for valve replacement or coronary artery bypass grafting. Routine biochemical investigations revealed normal renal and hepatic function. All patients were receiving beta blocking drugs and nitrates for the control of angina pectoris and some patients were receiving digoxin and diuretics routinely. Generally, medication was discontinued 12 hrs prior to surgery with the exception of nitroglycerin paste.

The anaesthetic technique in these patients differed from that described previously (Ch. 3, p. 57) in that it was not controlled and these patients received halothane (0.5 to 4.0 percent) for maintenance of anaesthesia and control of blood pressure.

CPB Equipment and Procedure

A Bentley Bos 10 or Cobe-optiflow II oxygenator equipped with a Sarns 5000 extracorporeal pump and heat exchanger was used for cardiopulmonary bypass. Fig. 7.1 is a photograph of the pump oxygenator assembly.

The pump was primed with a solution consisting of: Hartmann's solution[a] (1 ℓ), a plasma substitute[b] (0.5 ℓ - 1.0 ℓ) and whole blood (0.3 ℓ - 0.5 ℓ), containing 10,000 I.U. of heparin. Additional solutions and/or whole blood were added during CPB as required. Additional heparin (300 IU/kg body weight) was administered before insertion of the caval

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[a] Ringer lactate solution containing NaCl, KCl, $CaCl_2$, $MgCl_2$ and sodium lactate.

[b] Haemaccel - a 3.5 percent colloidal infusion solution consisting of 35 g degraded gelatine polypeptides (equivalent to 6.3 g nitrogen), NaCl 8.5 g, KCl 0.38 g, calcium 0.25 g and water to 1 .

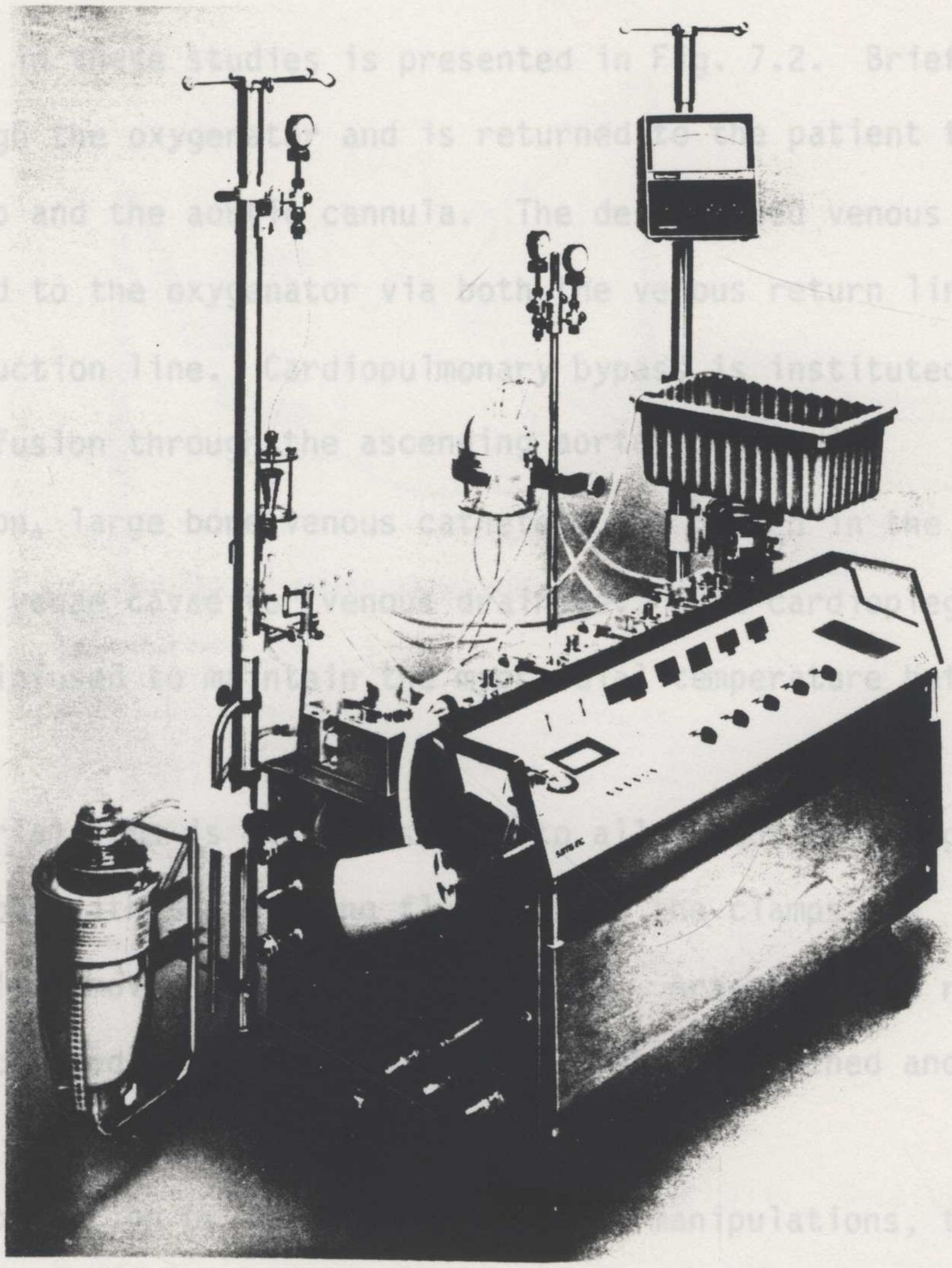

Figure 7.1 Sarns pump assembly with Bentley Spiraflo Bos-10 oxygenator. The oxygenator has a built-in heat exchanger and a Sarns bubble trap is placed in the arterial line. Note the ice bucket for cardioplegia solution container and on-line PO_2 monitor mounted near top of pole at right.

Reproduced from Kulesza and White, 1982 (234).

and aortic cannulae. Cardiopulmonary bypass involved hypothermia to 28°C, pump flow rates of 2.2 ℓ/min/m^2 and haemodilution to a haematocrit of 25 percent. A schematic represenation of the bypass circuit used in these studies is presented in Fig. 7.2. Briefly, blood passes through the oxygenator and is returned to the patient through the arterial pump and the aortic cannula. The desaturated venous blood is then returned to the oxygenator via both the venous return line and the cardiotomy suction line. Cardiopulmonary bypass is instituted by arterial perfusion through the ascending aorta. Following heparinization, large bore venous catheters are placed in the superior and inferior venae cavae for venous drainage. Cold cardioplegia[a] solution is infused to maintain the myocardial temperature between 10 and 20°C.

The arterial pump is started slowly to allow gentle mixing of the patient's blood with the priming fluid, while the clamps are simultaneously removed from the venous lines. Arterial flow rate is gradually increased until the desired flow rate is reached and bypass begins.

At the completion of the cardiac surgical manipulations, the heart is perfused with warmed, oxygenated blood from the pump-oxygenator. After an extended period of cold ischaemia, warmed perfusion is allowed for approximately 40 min before imposing a significant load on the heart. When the patient's body temperature returns to 37°C and a functional cardiac rhythm established, the lungs are again ventilated and the return line from the venae cavae to the venous resevoir is gradually occluded.

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[a] Contains $MgCl_2.6H_2O$ 16 mmol, KCl, 16 mmol and Procaine HCl, 1 mmol in 20 ml.

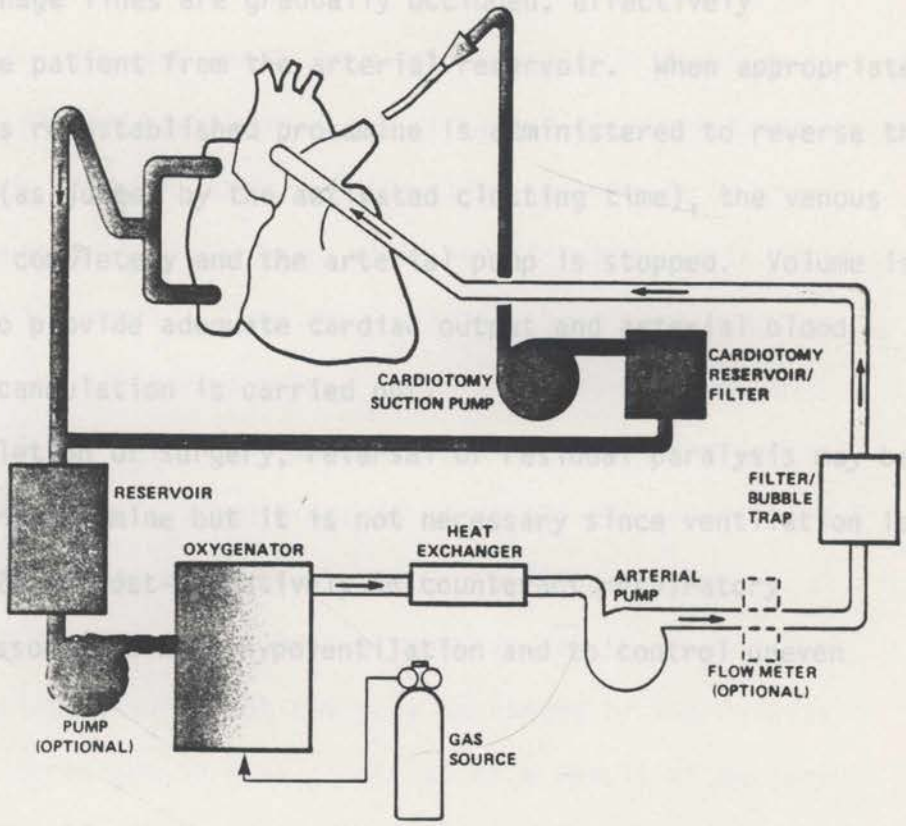


Figure 7.2. The basic extracorporeal bypass circuit. Desaturated (venous) blood is returned to the oxygenator via both the venous return lines and the cardiotomy suction line (shaded areas). Blood is oxygenated in the oxygenator and returned to the patient through the arterial pump and the aortic cannula.
Reproduced from Calkins and Conahan, 1982 (235).

As the volume retained by the patient increases, venous pressure rises, and the ventricles begin to pump blood. Arterial flow from the pump to patient is gradually reduced (over a period of 1 to 5 min). Likewise, the venous drainage lines are gradually occluded, effectively transferring the patient from the arterial reservoir. When appropriate fluid balance is re-established protamine is administered to reverse the heparin effect (as judged by the activated clotting time), the venous line is clamped completely and the arterial pump is stopped. Volume is then adjusted to provide adequate cardiac output and arterial blood pressure and decannulation is carried out.

At the completion of surgery, reversal of residual paralysis may be attempted with neostigmine but it is not necessary since ventilation is controlled for 24 hr post-operatively to counteract respiratory insufficiency associated with hypoventilation and to control uneven ventilation.

A. ALCURONIUM KINETICS IN PATIENTS UNDERGOING CARDIOPULMONARY BYPASS SURGERY

INTRODUCTION

A non-depolarizing neuromuscular blocking agent is usually administered to patients undergoing CPB surgery. Alcuronium may be chosen to produce skeletal muscular relaxation, particularly when avoidance of hypertension and tachycardia is desirable, as in patients with myocardial ischaemia. Alcuronium kinetics have been reported in patients undergoing elective surgery, usually in intra-abdominal procedures (Ch. 4, p. 89, ref. 110). In these studies, the initial volume of distribution (V_1) was found to be relatively small hence alteration in the plasma or blood volume may influence drug concentrations during CPB. Further, alcuronium has previously been reported to be eliminated almost entirely unchanged by the kidneys (110). Thus, alterations in renal function as a result of surgery involving CPB may affect the disposition kinetics of alcuronium.

The purpose of this study was to examine the effects of cardiac surgery and CPB on the distribution and elimination of alcuronium administered by a loading bolus plus concomitant infusion regimen.

METHODS

The study involved ten adult patients undergoing coronary artery bypass grafting. They are described in Table 7.1. Each patient received an intravenous bolus dose of 0.27 mg/kg alcuronium, administered simultaneously with the commencement of an infusion of 1 μg/min/kg body weight. These dosages were calculated using previous alcuronium kinetic data and a desired 'steady-state' plasma concentration of 0.74 μg/ml, a concentration usually associated with about 95 percent depression of the evoked twitch response (Ch. 4, p. 93).

Arterial blood samples were obtained immediately prior to alcuronium administration and then at 5, 10, 15, 20 and 30 min after the commencement of the infusion and thereafter at 15 min intervals. Further blood samples were obtained immediately prior to CPB and 10 min after the commencement of bypass. Upon termination of the infusion the blood samples were collected at 5, 10, 15, 20, 30, 45, 60, 90 and 120 min, thereafter at hourly intervals for 6 hrs, two hourly intervals for 12 hrs and four hourly intervals for 24 hrs. During the period of alcuronium infusion, urine samples were also collected via a catheter at 30 min intervals.

Pharmacokinetics

Total body clearance (Cl), the apparent volume of distribution at steady-state (V_{ss}) and the elimination half life ($t_{1/2\beta}$) were calculated on the assumption that there were no time-dependent changes occurring as a result of the CPB procedure.

Visual inspection of the data in all patients indicated a discontinuity in the plasma concentration-time profile consistent with a decrease in the apparent volume of distribution at the commencement of CPB. An estimate of β was obtained from the post-infusion alcuronium

Table 7.1 Characteristics of Patients Undergoing Surgery Involving Cardiopulmonary Bypass (CPB) who Received Alcuronium as a Bolus and Infusion Regimen

Patient Code	Sex	Age	Wt (kg)	BSA[a] (m^2)	Baseline Serum Creatinine[b] (μmol/ℓ)	Total Alcuronium Dose (mg)	Duration of Infusion (min)	Time Prior to CPB[c] (min)	Time Rewarming Commenced[d] (min)	Duration of CPB (min)
DF	M	53	80	1.90	90	38.6	214	57	56	146
AG	F	56	62	1.67	70	31.1	243	52	--[e]	101
LF	M	61	86	1.97	90	42.2	218	53	--	138
DB	M	73	64	1.65	85	30.4	210	54	--	113
FB	M	68	48	1.48	60	20.1	157	52	34	82
HW	M	60	80	1.90	80	39.3	211	94	35	73
AD	M	42	68	1.74	75	31.0	205	48	38	127
TM	M	61	83	1.95	102	44.0	257	84	35	146
MM	F	56	84	1.72	70	38.6	180	56	36	98
HR	M	65	86	1.96	90	39.8	195	60	40	110
Mean		60	74	1.79	81	35.5	205	61	39	113
± S.D.		8.6	12.9	0.17	13	7.3	26	15	8	26

a Body surface area
b Measured one day prior to surgery
c Time after alcuronium dose
d Time prior to end of CPB
e Not available

concentrations and the plasma concentration-time data up to the start of CPB were then fitted (using this predetermined value of β) to a biexponential microparameter equation (7.1) for input via a bolus plus infusion regimen (with α, k_{21} and V_1 as unknowns).

$$Cp = \left[\frac{Xo \cdot (k_{21} - \alpha)}{V_1 \cdot (\alpha - \beta)} + \frac{ko(k_{21} - \alpha)(1 - e^{\alpha T})}{V_1 (\alpha - \beta)} \right] .e^{-\alpha t} + \left[\frac{Xo \cdot (k_{21} - \beta)}{V_1 \cdot (\alpha - \beta)} + \frac{ko (\beta - k_{21})(1 - e^{\beta T})}{V_1 (\alpha - \beta)} \right] .e^{-\beta t} \quad \text{Eq. 7.1}$$

Where the individual parameters are as defined previously (Ch. 4, p. 80, 82 105).

Concentration-time data gathered after the start of CPB were fitted using iterated estimates of α, k_{21} and V_1 but reducing the estimated V_1 appropriately to enable optimal characterization of the data.

Alcuronium renal clearance was determined by dividing the total amount of alcuronium excreted unchanged into the urine during the collection interval by the AUC for that interval. Endogenous creatinine clearance was calculated based on the concentration of creatinine in the urine and the plasma concentration of creatinine at the mid-point of the urine collection period. The clearance ratio was then determined from the ratio of alcuronium renal clearance and endogenous creatinine clearance.

RESULTS

The mean plasma concentrations of alcuronium in ten patients undergoing CPB surgery are shown in Figure 7.3. An individual curve for a typical patient is shown in Figure 7.4. Also shown in Figure 7.4 is a simulated curve, using previous pharmacokinetic parameters (Ch. 4, p. 109), depicting the concentrations that would have occurred without CPB surgery.

After administration of the intravenous bolus dose and concomitant infusion, alcuronium plasma concentrations were initially about 1.1 µg/ml and during the first 20 min fell rapidly to a mean concentration of 0.55 µg/ml immediately before the initiation of extracorporeal circulation (Table 7.2). In all but one patient (HW), CPB was instituted before an apparent steady-state was attained. That patient did, however, achieve the desired alcuronium concentration of 0.74 µg/ml. Upon institution of CPB the alcuronium plasma concentration increased and a plateau or apparent steady-state was reached at a mean alcuronium concentration of 1.02 (± 0.13 SD) µg/ml. Immediately following CPB, mean plasma concentrations were generally somewhat higher than those reached during CPB (1.13 ± 0.24 µg/ml). Individual alcuronium concentrations are shown in Table 7.2.

The individual and mean pharmacokinetic parameters are presented in Table 7.3 and are compared with those from the previous i.v. bolus study with alcuronium in patients not undergoing CPB surgery (Ch. 4, p. 89). There were no differences in V_{ss} between these two groups, however, the $t_{1/2\beta}$ was 532 ± 217 min, approximately three times longer than in the control group (200 ± 76 min). The time-averaged Cl in the CPB group was significantly lower than that observed in the group of control patients (0.80 ± 0.21 vs 1.32 ± 0.34 ml/min/kg). It should be noted however that

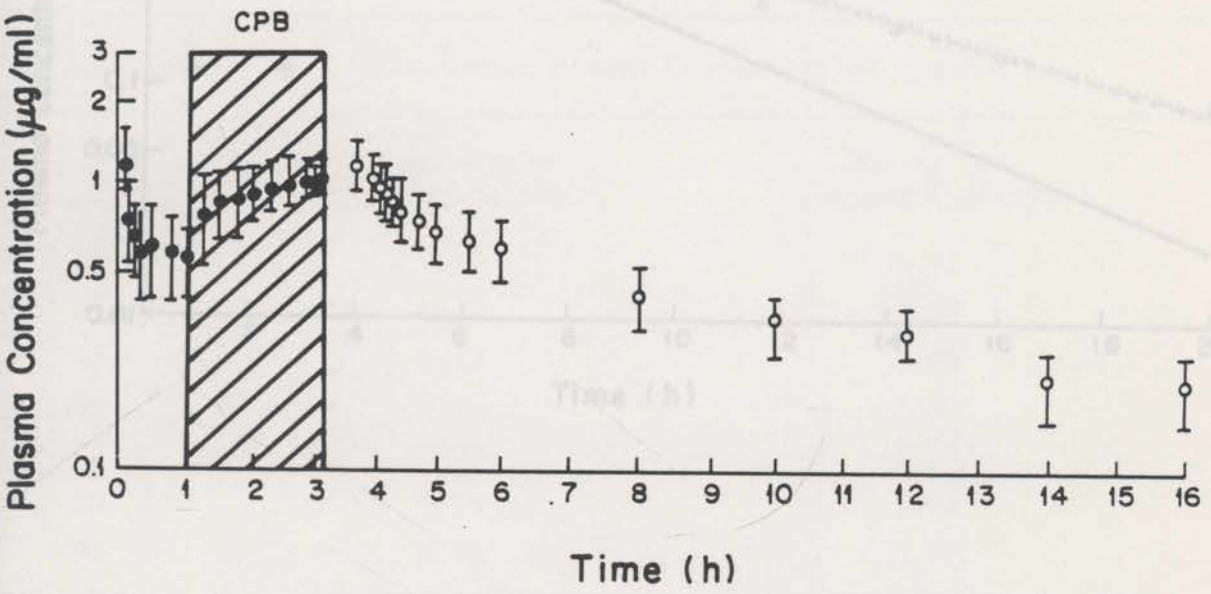


Figure 7.3. Alcuronium plasma concentration-time profile in ten patients undergoing surgery involving cardiopulmonary bypass (CPB). The closed circles represent plasma concentrations during the infusion of alcuronium while the post-infusion plasma concentrations are represented by open circles. All data are means ± S.D.

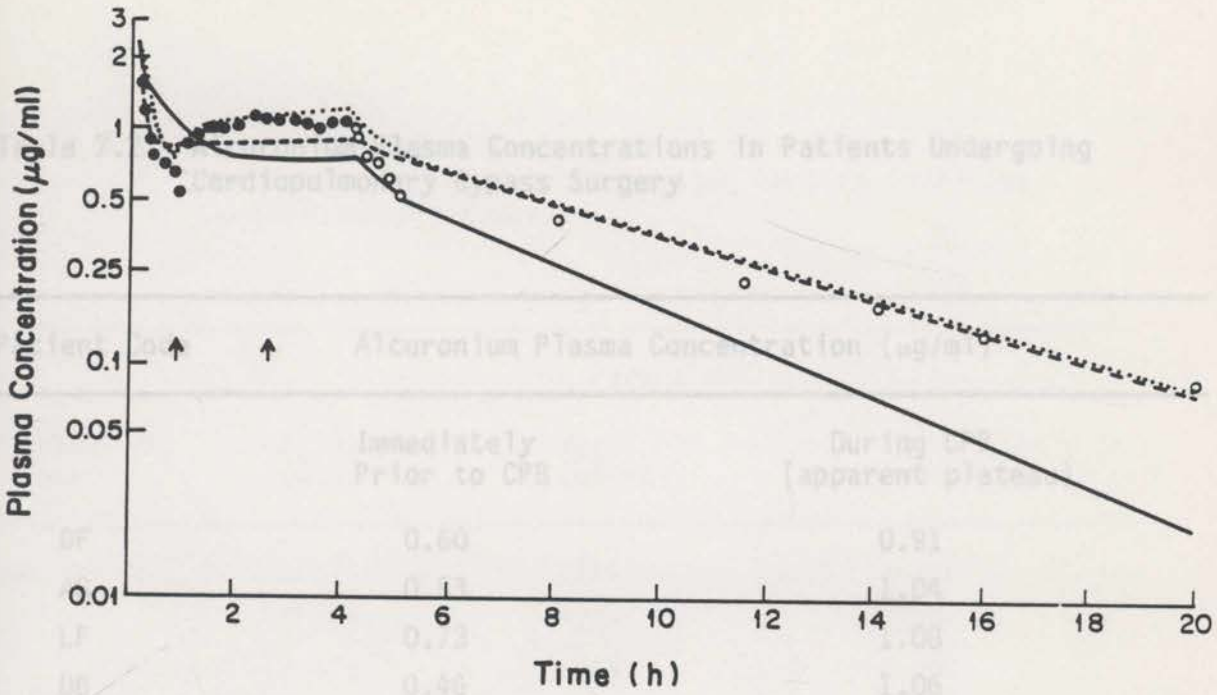


Figure 7.4. Representative plasma concentration-time profile for one individual undergoing surgery involving cardiopulmonary bypass (CPB). The closed circles represent plasma concentrations during the infusion of alcuronium while the post-infusion plasma concentrations are represented by open circles. The first arrow indicates the initiation of CPB while the second arrow shows the time at which CPB was terminated. The solid curve shows a computer simulation of predicted alcuronium concentrations from normal patients (Ch. 4, p. 78). Also shown are the simulated plasma concentration-time profiles for this patient in the absence of CPB (---) and the predicted time course if a time-dependent change in the volume of the central compartment (V_1) is incorporated during CPB (...). The average value of V_1 (8 ℓ) from the normal patients was used for the simulation of pre-bypass and post-infusion concentrations while during CPB this volume was assigned a value equal to estimated plasma volume (4 percent of body weight).

Table 7.2. Alcuronium Plasma Concentrations in Patients Undergoing Cardiopulmonary Bypass Surgery

Patient Code	Alcuronium Plasma Concentration (µg/ml)	
	Immediately Prior to CPB	During CPB (apparent plateau)
DF	0.60	0.91
AG	0.53	1.04
LF	0.73	1.08
DB	0.46	1.06
FB	0.53	1.04
HW	0.74	1.03
AD	0.36	0.71
TM	0.29	1.10
MM	0.63	1.21
HR	0.60	1.02
Mean	0.55	1.02
± S.D.	0.15	0.13

Table 7.3. Model-Independent Pharmacokinetic Parameters of Alcuronium in Patients Undergoing Surgery Involving Cardiopulmonary Bypass.

Patient Code	Parameters		
	$t_{1/2\beta}$ (min)	V_{ss} (ml/kg)	Cl (ml/min/kg)
DF	375	214	0.90
AG	301	259	0.89
LF	475	348	0.64
DB	806	491	0.66
FB	396	477	1.14
HW	433	372	1.00
AD	513	509	0.84
TM	365	142	0.87
MM	963	158	0.47
HR	693	322	0.56
Mean ± S.D.	532 ± 217[a]	329 ± 135	0.80 ± 0.21[a]
Normal Group[b]			
Mean ± S.D.	200 ± 76	316 ± 94	1.32 ± 0.34

a Significantly different from normal group, $p < 0.001$
b Ch. 4, p. 89 using bolus alcuronium doses.

this control group were generally younger and lighter and did not recieve halothane as part of their anaesthetic.

Figure 7.5 compares the individual pharmacokinetic parameters from the CPB patients with those from normal surgical patients (Ch. 4, p. 109) who also received a bolus plus infusion regimen of alcuronium. Clearance was significantly reduced ($p<0.001$) and $t_{1/2\beta}$ markedly prolonged ($p<0.001$) in the CPB patients. Volume of distribution at steady-state was unaltered.

Serum creatinine concentrations prior to CPB were in the normal range (mean ± S.D., 79 ± 9 μmol/ℓ; Table 7.1) and remained within this same range throughout the study period. Creatinine clearance was not determined pre-operatively but during the period of CPB the creatinine clearance was within the range of 52 to 69 ml/min. The measured renal clearance of alcuronium during CPB was in the range of 14 to 34 ml/min (mean ± S.D., 27 ± 6 ml/min) and the total urinary recovery of alcuronium during this same period (mean time = 205 min) averaged 5.7 mg, i.e., 13 percent of the total dose administered. Using the creatinine clearance as a measure of glomerular filtration rate (GFR), the clearance ratio was found to have a mean value (± S.D.) of 0.44 ± 0.13 during the period of CPB (Table 7.4). There was no apparent relationship between the clearance ratio and serum creatinine or creatinine clearance.

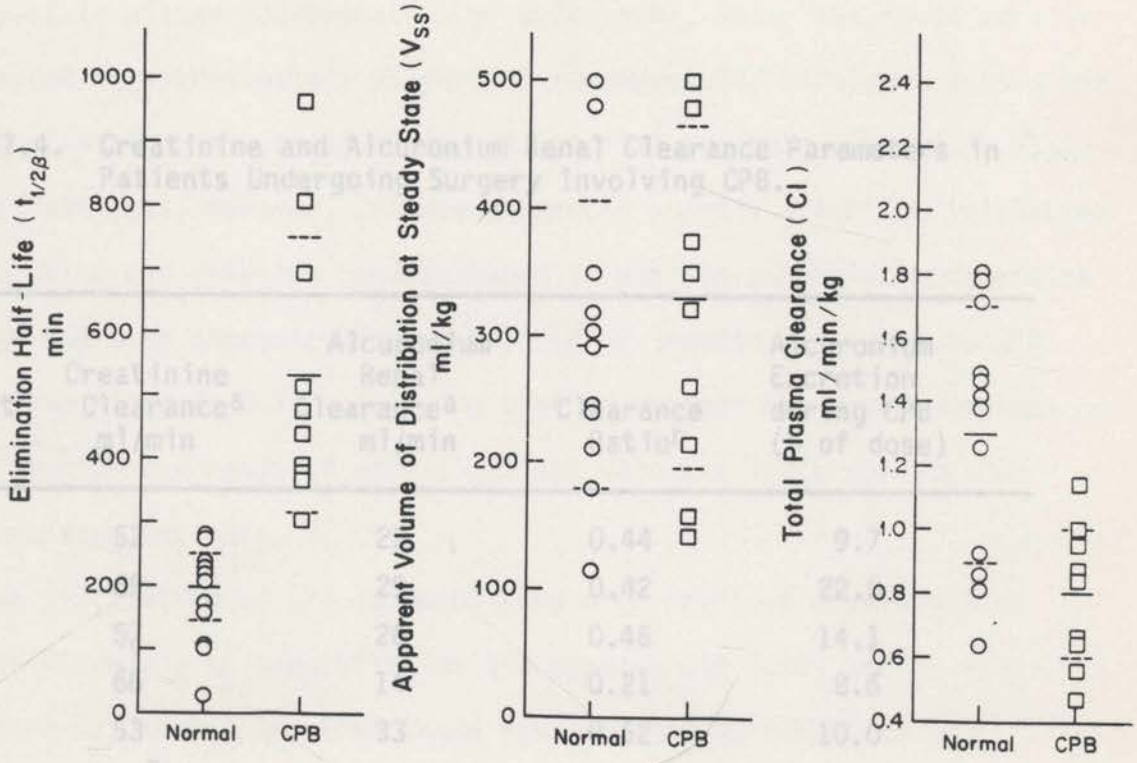


Figure 7.5. Comparison of alcuronium pharmacokinetic parameters in normal patients (Ch. 4, p. 109) and in patients undergoing cardiopulmonary bypass (CPB) surgery. Both groups of patients received a bolus plus infusion regimen of alcuronium. The horizontal bars represent the mean ± S.D.

Table 7.4. Creatinine and Alcuronium Renal Clearance Parameters in Patients Undergoing Surgery Involving CPB.

Patient Code	Creatinine Clearance[a] ml/min	Alcuronium Renal Clearance[a] ml/min	Clearance Ratio[b]	Alcuronium Excretion during CPB (% of dose)
DF	52	23	0.44	9.7
AG	69	29	0.42	22.0
LF	57	26	0.46	14.1
DB	66	14	0.21	8.6
FB	53	33	0.62	10.0
HW	--[c]	--	----	13.4
AD	66	29	0.44	11.6
TM	66	34	0.52	15.6
MM	--	--	----	16.8
HR	--	--	----	6.2
Mean	61	27	0.44	12.8
± S.D.	7	7	0.12	4.6

a During CPB procedure.

b = $\frac{\text{Alcuronium renal clearance}}{\text{Creatinine clearance}}$

c Data not available

DISCUSSION

The combined bolus and infusion regimen chosen for use in these cardiac patients was designed to achieve, in 90 to 120 min, a steady-state plasma concentration of 0.74 µg/ml, which was found to correspond to approximately 95 percent neuromuscular paralysis during the offset of action in a group of normal surgical patients (Ch. 4, p. 93). In most patients, however, CPB was commenced shortly after the initiation of the bolus and infusion regimen hence it was not possible to determine whether the mean concentration of 0.55 µg/ml immediately prior to CPB would have risen to 0.74 µg/ml with time or whether the dosage regimen calculated on the basis of normal patient data was inappropriate for these cardiac patients.

The institution of CPB is associated with profound physiological changes secondary to haemodilution and hypothermia (236) and it is therefore not surprising that there was a marked perturbation in alcuronium concentrations. Immediately following establishment of CPB, the mean plasma concentration of alcuronium rose and stabilized at a concentration approximately twice as high as that immediately prior to CPB. These results with alcuronium are similar to those reported for cephalothin (237) and propranolol (238,239) but are in disagreement with results for cephazolin (240), fentanyl (241), and a more recent study with propranolol (242); where a decrease or no change in plasma concentration was observed with the onset of CPB. Several hypotheses including distributional changes secondary to decreased protein binding (239) and/or a reduction in metabolic clearance secondary to hypothermia (238) have been proposed to explain the elevations in plasma concentration during CPB. Haemodilution, as a result of the added volume of the pump prime, seems to be the most widely postulated explanation for

the fall in plasma concentrations.

There are several reasons which might account for the increase in alcuronium concentrations including: a progressive rise in concentrations as a result of the continuing infusion and not a direct effect of the CPB procedure per se; contraction of blood volume and/or decreased tissue perfusion. The first possibility seems unlikely since simulations (Fig. 7.4) show that, although concentrations of alcuronium do in fact rise over a period of time, in the absence of CPB, this rise is still much lower and not as pronounced as that noted during CPB. Thus, the rise in plasma concentrations of alcuronium during CPB would not appear to be due to the continuing infusion of alcuronium progressing towards a true steady-state, but would appear to be a result of the CPB procedure itself.

The most plausible explanation for the sudden increase in plasma concentrations is a contraction in blood volume during CPB. In spite of haemodilution, effective circulating blood volume during CPB is significantly lower than the sum total of initial blood volume plus priming fluid volume (243). Thus, it may be expected that alcuronium which distributes into a small initial volume (V_1) of approximately 8 ℓ in non-cardiac surgical patients, distributes into an even smaller space during CPB. Assuming that the size of this space before and after CPB is the same as V_1 but that it contracts to a volume equivalent to plasma volume, approximately 4 percent of body weight, (244), during CPB, computer simulations (Figure 7.4) demonstrate a good agreement between the observed and predicted concentrations of alcuronium in these cardiac patients during the period of CPB. Thus the elevation in plasma concentrations of alcuronium are consistent with a contraction in the volume of the central compartment either owing to a reduction in blood volume per se or to a reduction in alcuronium distribution to the highly

perfused tissues which are assumed to be part of the central compartment. The latter possibility seems more likely especially in the light of data which suggest that large amounts of alcuronium are sequestered by the lungs following intravenous doses (135). Therefore with the onset of CPB, which excludes the lungs from the general circulation, the immediate effect would be an increase in plasma concentrations (since input into the body is still continuing), which will remain high until the drug is able to diffuse out of the blood/plasma and redistribute to the lungs and other tissues.

During the period of CPB, numerous urine collections permitted the measurement of creatinine clearance, alcuronium renal clearance and alcuronium renal excretion. Although creatinine determinations are usually carried out over 24 hrs, it has been shown that a one hour urine collection gives comparable results provided bladder emptying is complete (245). Creatinine clearance values were similar to those noted by Porter et al. (246) in patients undergoing CPB, but lower than the value of 87 ml/min predicted by Hull et al. (247) in patients with good (serum creatinine <120 μmol/ℓ) renal function. The mean renal clearance of alcuronium during this same period was found to be 27 ± 6 ml/min, considerably lower than that (82 ml/min) predicted by Raaflaub and Frey (110) in three normal surgical patients. The lower renal clearance was also reflected in a diminished urinary recovery of alcuronium during CPB which was one third to one half that (13 ± 5 vs 36 ± 16 percent) noted previously (110) for a similar time interval (205 min). The mechanism of this reduction in alcuronium renal clearance is unclear but may be related to the diminished renal function (as judged by diminished creatinine clearance) observed in these patients.

The predominant mechanism by which a drug is cleared by the kidneys

can be ascertained from the ratio of renal clearance of drug to that of creatinine. In this study the clearance ratio was 0.44. Although the free fraction of alcuronium was not measured here, the clearance ratio, corrected for plasma protein binding, was 0.73 assuming the free fraction value to be 0.6 as reported previously (110). That the clearance ratio is less than unity may perhaps be attributable to altered plasma binding of alcuronium during CPB since tubular reabsorption and secretion (active) apparently do not occur with molecules such as alcuronium having two cationic centres (110).

Immediately following cessation of CPB, the restoration of cardiac activity was associated with a transient rise in alcuronium concentrations but upon termination of the infusion alcuronium concentrations declined in the usual biexponential fashion. It is common practice in pharmacokinetics to computer-fit post-infusion concentration-time data to various multi-exponential equations corresponding to a chosen compartmental model. However, the validity of this approach depends on the constancy of the physiological factors that modulate the disposition of the drug. In the present study, during the infusion of alcuronium, intervention of CPB severly disrupted the plasma concentration-time profile of the drug. These disruptions in the alcuronium plasma concentrations cast doubt on the usefulness of computer analysis in generating meaningful pharmacokinetic parameters. Hence analysis of post-infusion concentration-time data according to classical methods (248) were not used and $t_{1/2\beta}$, Cl and V_{ss} were calculated model-independently. The elimination half-life of alcuronium was on the average, some three times longer than that noted in the healthy surgical patients (Ch. 4, p. 89) and the time-averaged total plasma clearance was reduced by 40 percent. The increase in $t_{1/2\beta}$ after CPB could be due to

several haemodynamic changes, secondary to hypothermia (27°C) during CPB, which has been reported to cause a reduction in clearance and prolongation of $t_{1/2\beta}$ of d-tubocurarine (148) and pancuronium (147).

In conclusion, the combined bolus and infusion regimen employed in this present study produced plateau concentrations which were some 50 percent higher than those achieved in non-cardiac patients. Further the elimination of alcuronium was also impaired in these cardiac patients. In view of these findings and the fact that the plasma concentration-effect relationship of alcuronium might be different during the period of CPB, a closer monitoring of neuromuscular function in cardiac patients undergoing CPB may be necessary.

B. GALLAMINE KINETICS IN PATIENTS UNDERGOING CARDIOPULMONARY BYPASS SURGERY

INTRODUCTION

Neuromuscular blocking agents are an integral part of the anaesthetic management in cardiac surgery involving cardiopulmonary bypass (CPB), allowing the use of smaller amounts of major anaesthetics. Pancuronium is widely used despite the tachycardia that may accompany its administration, since the use of the traditional alternative (d-tubocurarine) may induce hypotension. Gallamine which is a vagolytic and also induces tachycardia but without a significant change in stroke volume (80) is used less frequently.

The disposition of gallamine has been studied extensively (Ch. 2, p. 37) in normal surgical patients (58,59), patients with renal dysfunction (151), and those undergoing correction of extrahepatic cholestasis (152,153). Although the use of gallamine in patients undergoing cardiopulmonary bypass has been reported (249), no pharmacokinetic data for gallamine are available in patients with cardiac disorders.

The objectives of this study were to determine (1) the effect, if any, of cardiac disease and cardiopulmonary bypass procedure on the disposition kinetics of gallamine and (2) the influence of injection mode (peripheral venous line and pump priming fluid) on the delivery of the gallamine dose or gallamine pharmacokinetics.

METHODS

The subjects were 22 adult patients scheduled for elective surgery requiring cardiopulmonary bypass (Table 7.5).

Patients were randomly assigned to one of two groups for the use of gallamine; group I patients (n=11) received an intravenous bolus dose of gallamine triethiodide 480 mg, and those in group II (n=11) received an intravenous bolus dose of 240 mg with an additional 240 mg being added to the pump prime immediately before the bypass procedure.

Assigning the time of intravenous gallamine dosing as time zero, arterial blood samples were obtained at -5 (drug-free), 5, 10, 15, 20, 30, 45 and 60 min and immediately (1 min) before the initiation of CPB in both groups of patients. Further samples were obtained at 10, 20, 30, 40, 50 and 60 min in group I patients and in group II patients at 5, 10, 15, 20, 30, 45, 60 min after CPB was started and then at 15 minute intervals in both groups until completion of CPB. In addition, an aliquot (10 ml) was withdrawn from the priming fluid immediately after the addition of gallamine and before CPB was instituted, in group II patients. Following completion of CPB, further samples were taken in both groups of patients at 120, 180, 240, 360, 480, 600, and 720 min after the initial bolus dose of gallamine.

For the determination of creatinine clearance, and gallamine renal clearance, urine samples were collected, via a catheter, at 30 minute intervals until 720 minutes and then at 12 hour intervals until 24 hrs and where possible 48 hours.

Pharmacokinetics

Total plasma clearance, V_{ss} and $t_{1/2\beta}$ were calculated as for alcuronium patients again with the limiting assumption that there were no pertubations in the gallamine concentration-time data as a result of the

CPB procedure.

In some patients, visual inspection of the data indicated a discontinuity in the plasma concentration-time profile consistent with a decrease in the apparent volume of distribution at the start of CPB. In these patients the plasma concentrations were simulated using a microparameter i.v. bolus equation (Ch. 4, p. 82 , Eq. 4.3) to obtain optimal characterization of the observed concentrations as described for alcuronium patients (Section A to this chapter).

Plasma concentration-time data from group II patients were fitted to a biexponential microparameter equation adapted for a multiple dosing regimen as utilized previously (Ch. 4, p. 80 , Eq. 4.2).

Table 7.5 Clinical Characteristics of Patients Undergoing Surgery Involving Cardiopulmonary Bypass Who Received Gallamine

Patient Code	Sex	Age (yr)	Wt (kg)	BSA[a] (m^2)	Baseline Serum Creatinine[b] (μmol/ℓ)	Time from Initial Gallamine Dose to start of CPB (min)	Time Rewarming Commenced[c] (min)	Duration of CPB (min)	Surgery
Group I									
RS	M	64	83	1.97	120	71	23	62	CAG[d]
TD	M	45	71	1.82	68	74	—	68	AVR[e]
RD	M	53	91	1.70	85	76	—	80	CAG
MM	F	43	54	1.50	80	49	—	120	CAG
BA	F	30	56	1.59	73	49	15	31	MVR[f]
ID	M	36	58	1.74	70	65	24	62	MVR
EC	M	56	77	1.90	97	58	30	70	MVR
LB	M	54	68	1.82	88	54	16	38	CAG
DF	M	62	55	1.54	75	46	25	67	CAG
BL	M	51	87	2.05	85	52	—	181	CAG
BK	M	40	69	1.78	85	51	33	84	MVR
Mean		49	70	1.76	84	59	24	79	
± S.D.		11	13	0.17	15	11	7	41	
Group II									
FI	M	47	77	1.91	85	66	35	166	AVR + MVR
PK	M	56	90	2.08	125	62	57	133	CAG
NB	M	45	88	2.00	70	61	60	104	CAG
DM	M	47	96	2.15	83	46	—	103	CAG
JC	M	18	63	1.68	90	59	22	51	WPWS[g]
NC	F	55	63	1.72	82	51	43	37	ASD[h]
AK	M	66	64	1.77	80	58	19	120	MVR
ML	F	70	53	----	70	40	—	78	AVR
HC	M	57	80	1.87	85	60	60	128	CAG
RR	M	39	65	1.80	70	54	30	45	CAG
KD	M	64	60	1.58	100	26	57	73	CAG
Mean		51	73	1.86	85	53	48	99	
± S.D.		15	14	0.18	16	12	27	39	

[a] Body surface area.
[b] Measured one day before surgery
[c] Time prior to end of CPB.
--- Data not available

[d] Coronary artery grafting
[e] Aortic valve replacement
[f] Mitral valve replacement
[g] Wolf Parkinson White syndrome
[h] Atrial septal defect

RESULTS

In most of the 22 patients in this study the CPB procedure was completed without unusual problems and without untoward clinical sequelae in the post-operative period. Two patients (AK and PK) developed post-operative renal failure, with serum creatinine levels reaching 235 and 139 μmol/ℓ respectively. In all other subjects serum creatinine concentrations were within normal limits for the duration of the study period.

The twenty patients who had normal post-operative renal function exhibited differing plasma concentration-time profiles before, during and after CPB. In 14 patients gallamine plasma concentrations were within one standard deviation of those observed previously (59) in a control group of 14 normal surgical patients. Data from two (TD and HC)of the 14 CPB subjects are shown in Fig. 7.6a and d. Three patients (JC, DF and BL) had higher plasma concentrations than the control group, during and after CPB. Data for one (BL) of these subjects is indicated in Fig. 7.6b. Two patients (RS and ML; Fig. 7.6c and f) had higher than control plasma concentrations only during the terminal phase and one patient (JC; Fig. 7.6e) had elevated gallamine plasma concentrations only during the period of extracorporeal circulation. The two patients (AK and PK) who developed post-operative renal failure also had markedly elevated plasma concentrations during the elimination phase (curves not shown).

Comparison of the pharmacokinetic parameters from the present study with those from a previous study from this laboratory involving normal surgical patients (59) receiving bolus 4 and 6 mg/kg doses are shown in Fig. 7.7. The $t_{1/2\beta}$ was longer ($p<0.05$) and the V_{ss} and Cl lower ($p<0.05$ and $p<0.01$ respectively) in the cardiac patients. However no differences in any of the kinetic parameters could be demonstrated

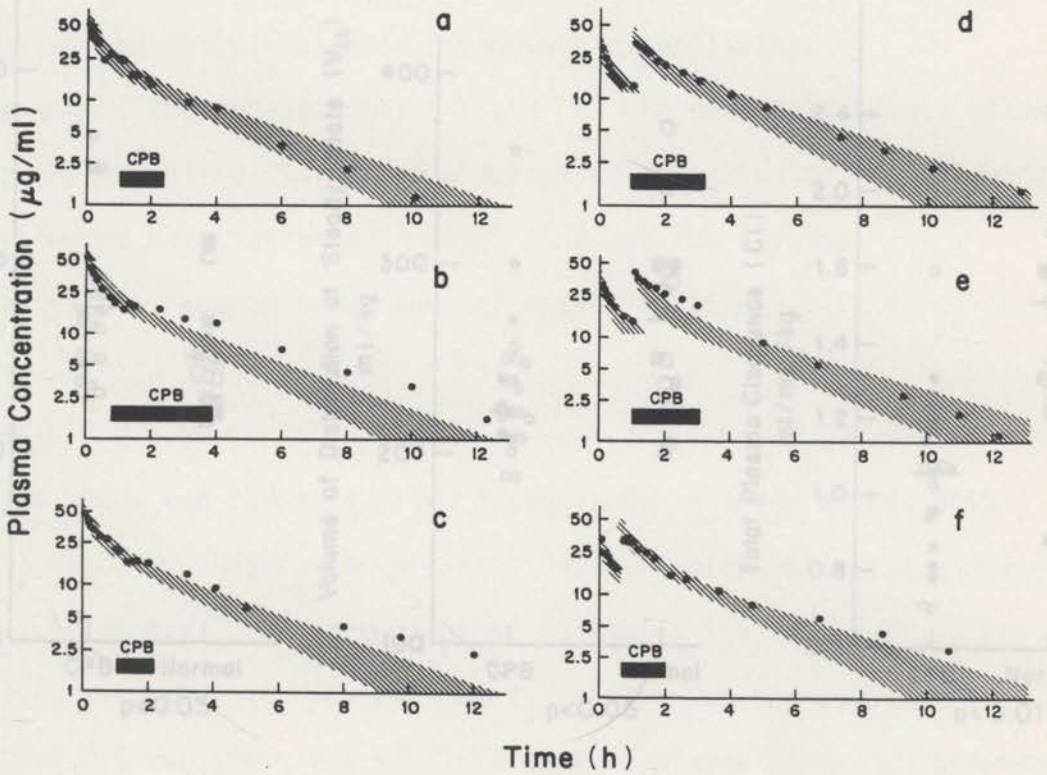


Figure 7.6. Plasma concentration-time profiles of gallamine in six (TD,BL, RS, HC, JC, ML) patients, represented as a to e respectively who received either a single i.v. bolus dose of 480 mg (a,b,c) or an initial bolus dose of 240 mg plus 240 mg in the priming fluid (d,e,f) and were undergoing surgery involving cardiopulmonary bypass (CPB). The measured plasma concentrations are represented as solid circles while the shaded area represents the mean ± 1 S.D. of the concentrations predicted based on the pharmacokinetic data from normal surgical patients who received either 4 or 6 mg/kg of gallamine.

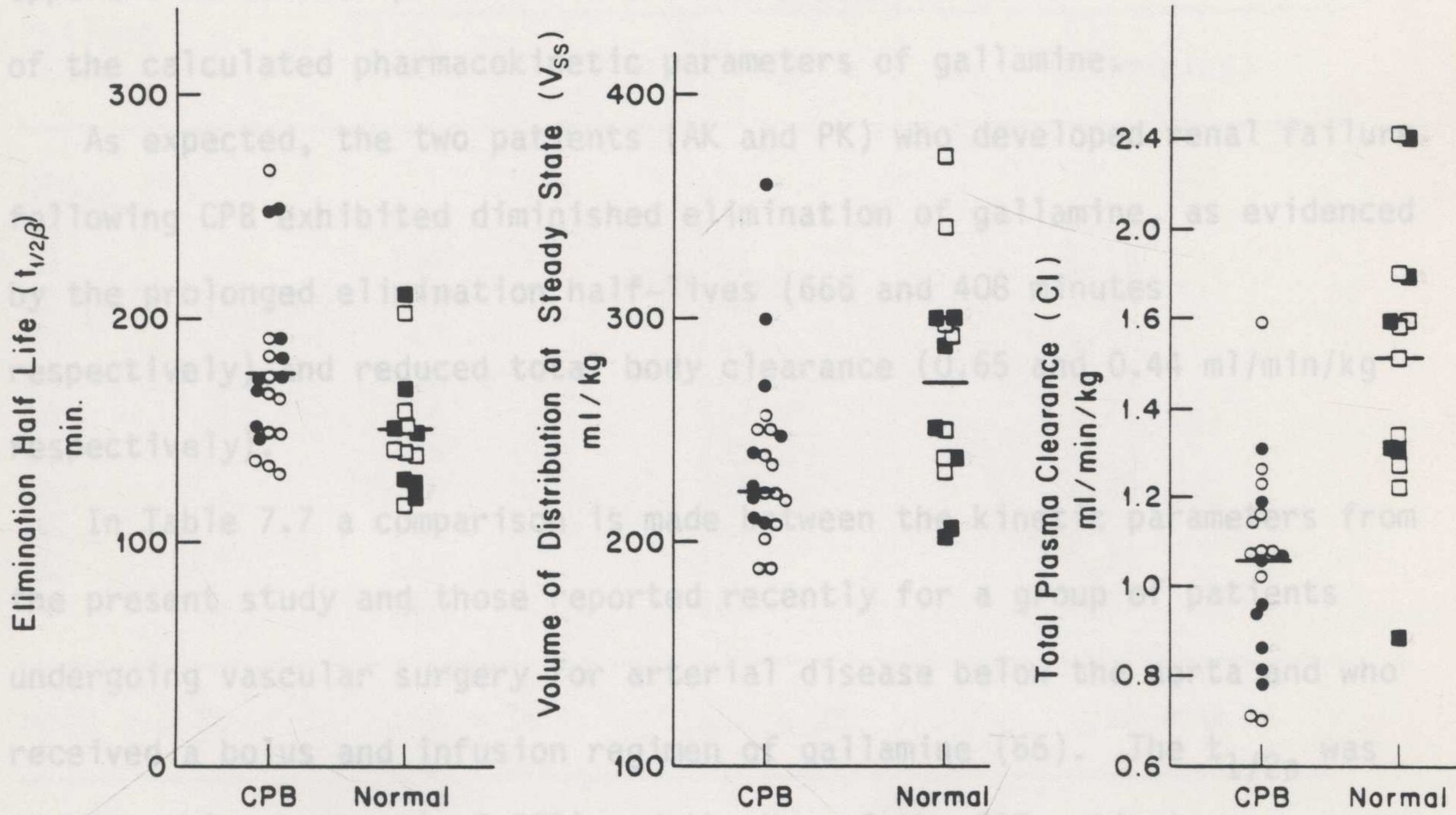


Figure 7.7. Comparison of the pharmacokinetic parameters for gallamine in cardiac patients undergoing cardiopulmonary bypass (CPB) surgery and in normal patients undergoing elective surgery (59). Group I CPB patient data are represented as open circles while the closed circles represent data from Group II patients. In the normal group the open squares represent data from patients who received 4 mg/kg while the closed squares represent data from patients who were administered 6 mg/kg of gallamine. Mean data are indicated as horizontal bars.

between group I and group II patients in the present study (Table 7.6), or between the four subgroups of patients who exhibited the different plasma concentration-time profiles (Fig. 7.6). Furthermore there was no apparent relationship between the duration of the CPB procedure and any of the calculated pharmacokinetic parameters of gallamine.

As expected, the two patients (AK and PK) who developed renal failure following CPB exhibited diminished elimination of gallamine, as evidenced by the prolonged elimination half-lives (666 and 408 minutes respectively) and reduced total body clearance (0.65 and 0.44 ml/min/kg respectively).

In Table 7.7 a comparison is made between the kinetic parameters from the present study and those reported recently for a group of patients undergoing vascular surgery for arterial disease below the aorta and who received a bolus and infusion regimen of gallamine (66). The $t_{1/2\beta}$ was considerably shorter ($p<0.001$) and the V_{ss} of the CPB patients was smaller ($p<0.01$) but there was no difference in plasma clearance between the present CPB group who underwent vascular surgery involving cardiac vessels and those undergoing vascular surgery not involving cardiac vessels.

Mean urinary excretion of gallamine during the entire surgical period (approximately 4 hr) was 16 ± 7 percent after a dose of 480 mg. The renal clearance of gallamine during CPB was 18 ± 9 ml/min as compared to 32 ± 12 ml/min determined after CPB. Creatinine clearance was also reduced during the period of CPB (48 ± 24 vs 112 ± 41 ml/min before CPB) with a gradual recovery to 67 ± 27 ml/min in the first 12 hr after CPB (Table 7.8).

In group II patients half of the total dose (240 mg) of gallamine was added to the pump priming fluid. Analysis of the prime fluid for

Table 7.6. Model-Independent Pharmacokinetic Parameters of Gallamine in Patients Undergoing Surgery Involving Cardiopulmonary Bypass

Patient Code	Parameters $t_{1/2\beta}$ (min)	V_{ss} (ml/kg)	Cl (ml/min/kg)
Group I[a]			
RS	266	239	0.70
TD	134	201	1.16
RD	149	207	1.08
MM	167	222	1.07
BA	130	222	1.59
ID	174	257	1.23
EC	136	235	1.14
LB	164	251	1.26
DF	191	251	1.04
BL	184	187	0.72
BK	148	188	1.07
Mean ± S.D.	168 ± 39	224 ± 25	1.10 ± 0.24
Group II[b]			
FI	174	208	0.83
PK[c]	408	249	0.44
NB	168	219	0.86
DM	175	218	0.96
JC	146	211	0.94
NC	152	240	1.06
AK[c]	666	492	0.65
ML	248	358	1.19
HC	192	224	1.06
RR	172	300	1.31
KD	250	270	0.78
Mean ± S.D.	186 ± 38[d] 250 ± 157[e]	250 ± 51 272 ± 86	1.0 ± 0.17 0.92 ± 0.25
Pooled Data			
Mean ± S.D.	176 ± 38[d] 209 ± 119[e]	235 ± 40 248 ± 67	1.05 ± 0.22 1.0 ± 0.26

[a] Dose = 480 mg
[b] Dose = 240 + 240 mg in pump prime
[c] Patients who developed post-operative renal failure
[d] Excluding patient PK and AK
[e] Mean ± S.D. including patient PK and AK.

Table 7.7 Comparison of Gallamine Pharmacokinetic Parameters

Parameters	CPB Patients n = 22	Non CPB Patients[a] n = 11	P
$t_{1/2\beta}$ (min)	180 ± 39[b]	247 ± 45	<0.01
V_{ss} (ml/kg)	248 ± 56	291 ± 65	<0.05
Cl (ml/min/kg)	1.05 ± 0.22	1.0 ± 0.19	NS

a From reference (66) consisting of 11 patients aged between 50 and 76 yr undergoing vascular surgery for arterial disease below the aorta.
b Mean ± S.D.

Table 7.8 Creatinine and Gallamine Renal Clearance Parameters in Patients Undergoing Surgery Involving CPB.

Patient Code	Renal Clearance (ml/min) Before CPB Creatinine	Before CPB Gallamine	During CPB Creatinine	During CPB Gallamine	After CPB[a] Creatinine	After CPB[a] Gallamine	Gallamine Excretion[b] During Surgery (% of dose)
Group I							
RS	50	—[c]	—	10	66	17	8
TD	128		25	22	103	25	18
RD	43		—	—	77	—	—
MM	61		34	24	36	18	28
BA	151		74	17	93	27	—
ID	133		33	11	50	23	9
EC	67		25	27	37	47	17
LB	111		52	34	39	37	22
DF	131		24	11	48	20	9
BL	134		52	22	53	22	—
BK	—		25	11	77	—	8
Group II							
FI	154		55	9	64	53	10
PK	—		—	12	—	15	12
NB	—		53	3	42	35	22
DM	166		112	34	94	52	28
WC	138		—	23	71	39	21
JC	146		60	22	137	45	15
AK	69		64	21	85	—	22
ML	79		33	8	30	—	6
HC	—		66	24	76	41	25
RP	142		—	25	85	35	17
KD	—		27	10	48	31	14
Mean ± S.D.	112 ± 41		48 ± 24	18 ± 9	67 ± 27	32 ± 12	16 ± 7

a Determined during first 12 hrs after CPB
b Mean time of surgery = 230 min
c Not determined

gallamine gave concentrations which were consistent with the dose added and the prime volume, indicating that no relaxant was lost because of binding and/or adsorption to the components of the CPB machine. It also appears that all of the additional dose was delivered rapidly to the patient when the CPB procedure was started. Computer fitting of the concentration-time data from each patient (example shown in Fig. 7.8), assuming that a 240 mg dose was injected as a bolus at the start of CPB, gave a very close agreement between the observed concentrations and those estimated by the computer.

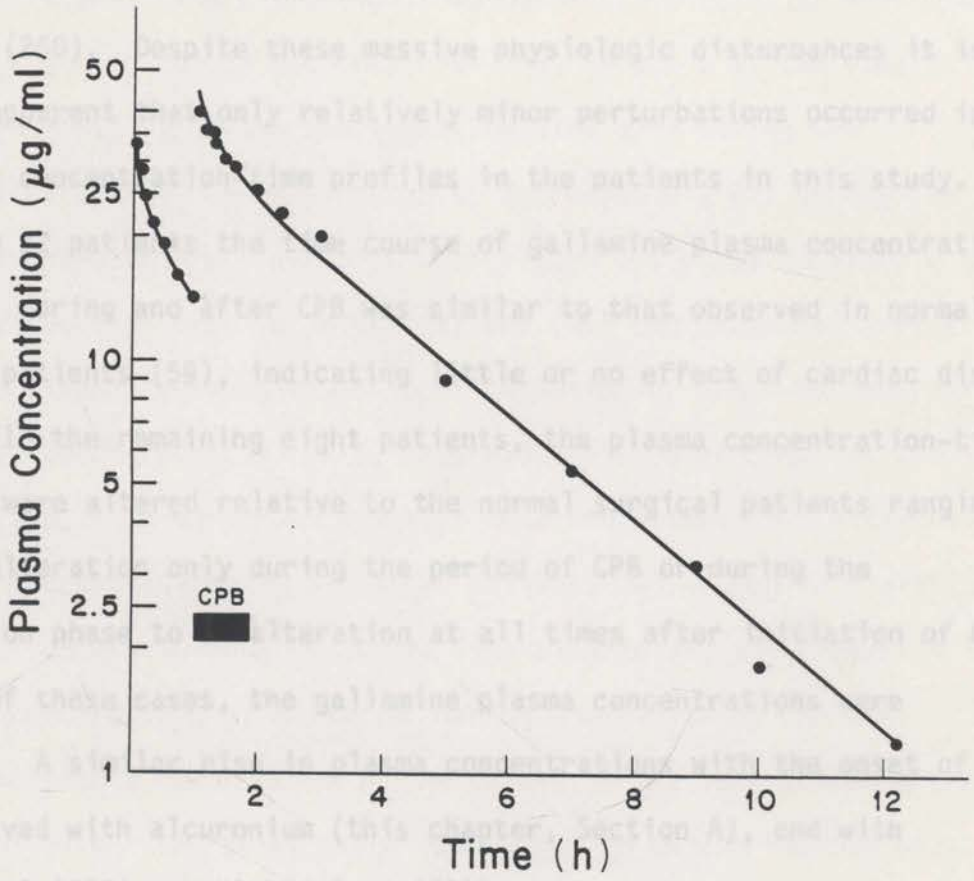


Figure 7.8. Gallamine plasma concentration-time profile in a patient (JC) from Group II undergoing cardiopulmonary bypass (CPB) surgery. Observed plasma concentrations are represented as closed circles while the solid line represents the best fit of the observed data using a bi-exponential equation and assuming that all the dose in the pump prime fluid was delivered to the patient as a bolus at the initiation of CPB.

DISCUSSION

Drug disposition during CPB may be influenced by various factors including haemodilution, hypotension, hypothermia and diminished renal function (250). Despite these massive physiologic disturbances it is readily apparent that only relatively minor perturbations occurred in the gallamine concentration-time profiles in the patients in this study. In 14 of the 22 patients the time course of gallamine plasma concentrations prior to, during and after CPB was similar to that observed in normal surgical patients (59), indicating little or no effect of cardiac disease or CPB. In the remaining eight patients, the plasma concentration-time profiles were altered relative to the normal surgical patients ranging from an alteration only during the period of CPB or during the elimination phase to an alteration at all times after initiation of CPB. In most of these cases, the gallamine plasma concentrations were elevated. A similar rise in plasma concentrations with the onset of CPB was observed with alcuronium (this chapter, Section A), and with propranolol (238) and alphaxalone (251).

As for alcuronium the elevation in drug concentrations may be explained by (1) a decreased gallamine distribution volume as a consequence of the contraction in blood volume and diminished tissue perfusion resulting from reduction in cardiac output and hypothermia (246), and (2) reduced plasma clearance. The former appears to be the most acceptable explanation since the effective circulating blood volume during CPB is significantly smaller than the sum of the initial blood volume plus priming fluid (243). Thus the net effect may be to elevate concentrations during (and possibly following) CPB. To test the hypothesis that a change in gallamine distribution occurs with the onset of CPB, concentration-time profiles of gallamine were simulated in those

patients who exhibited a rise in plasma concentrations. To characterize the data in these patients, the volume of the central compartment (V_1) had to be reduced from a pre-bypass value of 7.5 ℓ (similar to the mean value of 7.2 ℓ in normal patients; ref. 59) to 5.5 ℓ at the completion of CPB. Perturbations in the concentration-time data during CPB necessitated that V_1 be constrained at approximately 6 ℓ during the period of extracorporeal circulation. Figure 7.9 shows an example of the concentration-time profile in one patient (BL) who exhibited a rise in gallamine plasma concentrations upon initiation of CPB. By incorporating a time-dependent reduction in V_1 (approximately 30 percent) at the start of CPB, good agreement was also observed between the simulated and observed concentrations in all other patients who showed an elevation in gallamine concentrations. Thus, as with alcuronium, the elevation in plasma concentrations of gallamine during and following CPB are consistent with a contraction in the volume of the central compartment because of either decreased blood volume per se and/or reduced drug distribution to highly perfused tissues (see Section A., p. 180). Large amounts of gallamine are also sequestered by the lungs following intravenous doses (252). During CPB, gallamine plasma concentrations would therefore rise and remain high until normal equilibrium between the lungs and the blood is re-established.

In patients undergoing CPB lower plasma clearances, longer elimination half-lives and smaller apparent volumes of distribution at steady-state were noted as compared to a group of control patients (59). A comparison between the kinetic parameters from the present study and those from a group of patients undergoing vascular surgery not involving CPB (66) also revealed some differences. The elimination half-life and the apparent volume of distribution differed significantly but the

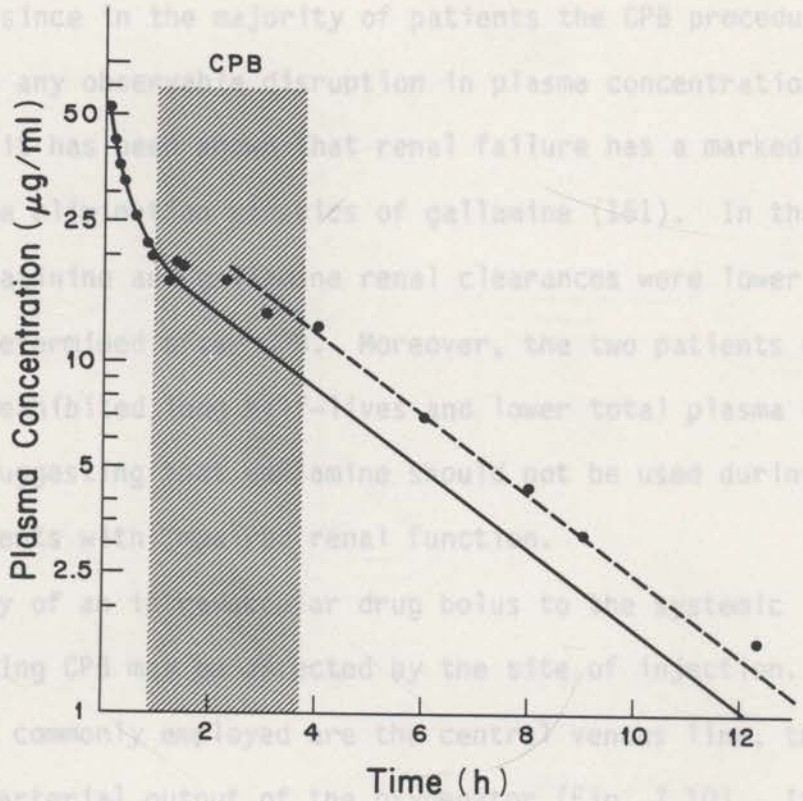
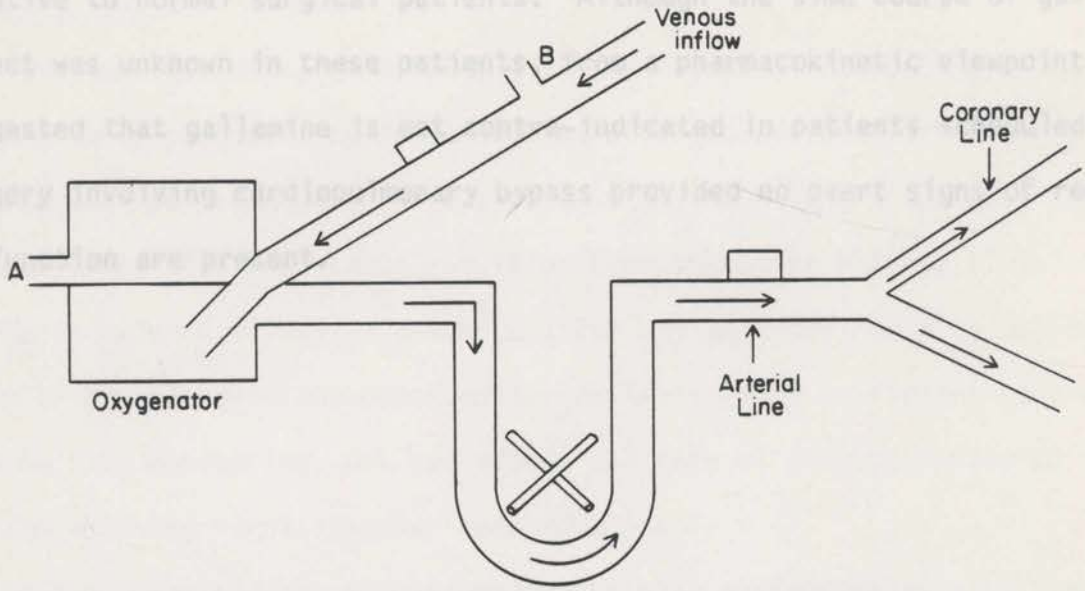


Figure 7.9 Plasma concentrations of gallamine in patient (BL) prior to, during and after cardiopulmonary bypass (CPB) surgery. The closed circles represent the measured concentrations while the solid line represents the simulated concentration-time curve using a value of 7.5 ℓ for the volume of central compartment. The stippled line represents the profile if the volume of the central compartment is changed to 5.5 ℓ during and after CPB.

clearance values were the same (Table 7.7). These comparisons between the cardiac patients undergoing CPB and the normal patient groups (59,66) demonstrates that gallamine disposition is altered as a result of cardiac disease per se since in the majority of patients the CPB procedure itself did not produce any observable disruption in plasma concentrations.

Previously it has been shown that renal failure has a marked influence on the elimination kinetics of gallamine (151). In the present study, both creatinine and gallamine renal clearances were lower during CPB than that determined after CPB. Moreover, the two patients with poor renal function exhibited long half-lives and lower total plasma clearance of gallamine, suggesting that gallamine should not be used during CPB surgery in patients with impaired renal function.

The delivery of an intravascular drug bolus to the systemic circulation during CPB may be affected by the site of injection. The injection sites commonly employed are the central venous line, the venous inflow and the arterial output of the oxygenator (Fig. 7.10). It is logical to assume that drugs injected into the arterial output of the oxygenator should exert their effects most rapidly because this site is the closest to the systemic circulation. Although delivery from the other two injection sites is governed not only by distance but also by the flow rate and the pattern of flow through the oxygenator it has been demonstrated, using a radioactive indicator (^{99m}Te), that the venous inflow of the oxygenator is the most efficient site of injection during CPB (253). In the group II patients from the present study half of the total dose of gallamine was added to the pump prime fluid. The concentrations determined in the priming fluid and the good agreement between the observed and predicted plasma concentrations of gallamine (Fig. 7.8) demonstrate that the pump priming fluid may be a convenient



Injection Site A Arterial Reservoir
B Venous inflow
C Central Venous Line

Figure 7.10 A schematic representation of the cardiopulmonary bypass circuit showing the common injection sites (the central venous line of the patient is not shown).
Adapted from Kamath et al., 1980 (253).

mode of administration of additional drug during CPB.

In conclusion, this study demonstrates that gallamine disposition in cardiac patients undergoing cardiopulmonary bypass is only moderately altered relative to normal surgical patients. Although the time course of gallamine effect was unknown in these patients, from a pharmacokinetic viewpoint it is suggested that gallamine is not contra-indicated in patients scheduled for surgery involving cardiopulmonary bypass provided no overt signs of renal dysfunction are present.

C. d-TUBOCURARINE KINETICS IN PATIENTS UNDERGOING CARDIOPULMONARY BYPASS SURGERY

INTRODUCTION

The haemodynamic side effects of the neuromuscular blocking drugs are particularly pertinent during anaesthesia for cardiovascular surgery. d-Tubocurarine produces dose-related hypotension giving a decrease in the systemic vascular resistance resulting from histamine release (79). Although such an effect of d-tubocurarine may be undesirable it can be used to advantage in the hypertensive patient. With sufficient care and appropriate monitoring, one can adjust the dose of d-tubocurarine to attain balanced cardiovascular haemodynamics.

d-Tubocurarine, the oldest nondepolarizing neuromuscular blocking drug in clinical use has been studied extensively (Ch. 2, p. 33). It's disposition kinetics have been examined in normal surgical patients (65,119), patients with renal disease (150) and in patients with extensive burns (186). However, to date no information is available on its pharmacokinetics in cardiac patients.

The present study was thus designed to examine the disposition kinetics of d-tubocurarine in patients undergoing cardiac surgery who required cardiopulmonary bypass. Since plasma protein binding methodology for d-tubocurarine was available, both free and total d-tubocurarine plasma concentrations were measured to ascertain if the effects (if any) of the cardiopulmonary bypass procedure could be interpreted in terms of binding alterations.

METHODS

The subjects were 13 patients scheduled for coronary artery bypass grafting and requiring cardiopulmonary bypass. Relevant patient characteristics are summarized in Table 7.9.

Each patient received an intravenous bolus dose of 0.6 mg/kg dTc administered simultaneously with the commencement of an infusion of dTc at a rate of 3 µg/min/kg. These dosages were calculated using previous (65) dTc kinetic data obtained from a study involving subjects undergoing elective surgery ('normal group') utilizing a bolus and infusion regimen and a desired 'steady-state' plasma concentration of 1.09 µg/ml which is usually associated with about 95 percent depression of the evoked twitch response (65).

Arterial blood samples were obtained immediately prior to dTc administration (drug-free) and then at 5, 10, 15, 20 and 30 min after the commencement of the infusion and thereafter at 15 min intervals. Further blood samples were obtained immediately prior to CPB and 10 min after the commencement of bypass. Upon termination of the dTc infusion the blood samples were collected at 5, 10, 15, 20, 30, 45, 60, 90 and 120 min and thereafter at hourly intervals for 24 hrs.

During the period of dTc infusion urine samples were collected through a catheter at 30 min intervals for urinary creatinine and dTc measurement.

The plasma protein binding of dTc was determined in all plasma samples as described earlier (Ch. 3, p. 68) except that the dialysis buffer contained ^{3}H-dTc equivalent to only 0.1 (rather than 2) µg/ml dTc.

Using a method similar to that described previously for propranolol (239), an *in vitro* experiment was carried out to simulate the effects of haemodilution due to the pump prime on the free fraction of dTc. An

Table 7.9 Clinical Characteristics of Patients Undergoing Surgery Involving Cardiopulmonary Bypass Who Received d-Tubocurarine

Patient Code	Sex	Age (yr)	Wt (kg)	BSA[a] (m^2)	Baseline Serum Creatinine[b] (µmol/ℓ)	Time from d-Tubocurarine Bolus till Start of CPB (min)	Duration of CPB (min)	Duration of dTc Infusion (min)	Total Dose of d-Tubocurarine (mg)
GB	M	63	81	1.93	65	63	120	227	104
MW	M	53	96	2.15	92	62	155	267	135
TQ	M	41	82	2.04	90	62	74	166	91
JT	M	59	93	2.08	82	60	129	222	118
KL	M	78	60	1.86	110	38	98	163	86
ME	M	70	81	2.00	105	61	158	255	110
TK	M	65	78	1.93	80	52	66	180	89
AM	F	55	69	1.63	66	57	99	194	80
RW	M	58	62	1.68	65	49	94	180	71
FD	M	50	92	2.00	85	60	65	150	96
TT	M	52	67	1.87	71	57	84	183	77
BC	M	47	90	2.00	75	60	120	199	108
ER	M	53	67	1.75	75	60	83	180	76
Mean		57	78	1.92	82	57	104	197	96
± S.D.		10	12	0.16	14	7	31	36	19

[a] Body surface area
[b] Determined one day prior to surgery.

average total blood volume of 5 ℓ was assumed in these patients and the effect on dTc plasma protein binding of diluting this volume of blood with (1) a pump prime consisting of Hartmann's solution (0.5 ℓ) and Haemaccel[a] (either 0.5, 1.0 or 1.5 ℓ) and (2) Haemaccel (1 ℓ) and Hartmann's solution (either 1.0 or 2.0 ℓ) determined. For the in vitro experiment all volumes were decreased two hundred fold. The free fraction of dTc in plasma and the haematocrit were determined before and after these dilutions. In addition dTc binding was measured (at a total concentration of 1 and 4 μg/ml) to other constituents alone, namely Haemaccel and Hartmann's solution with either Haemaccel or Hartmann's solution being substituted for plasma inside the dialysis cell.

Nonesterified-free fatty acid (NEFA) concentrations were determined (Ch. 3, p. 66) in three plasma samples (immediately prior to, 5 min after heparin administration before commencement of CPB and 12 or 24 hrs following CPB) from each patient immediately following in vitro dTc binding determination using equilibrium dialysis. In a few plasma samples NEFA concentrations were determined before and after equilibrium dialysis.

$Alpha_1$ acid glycoprotein (AGP) concentrations were determined (Ch. 3, p. 66) in samples taken immediately before (day 0) and 24 hr (day 1) and 48 hr (day 2) after CPB surgery.

Pharmacokinetics

Calculation of dTc pharmacokinetic parameters and renal clearance and simulation of total dTc plasma concentration-time profiles in these

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[a] a 3.5 percent colloidal solution containing 35 g degraded gelatine polypeptides (equivalent to 6.3 g nitrogen), NaCl 8.5 g, KCl 0.38 g, calcium 0.25 g and water to 1 ℓ.

patients was carried out as described for alcuronium patients (Section A, p. 168).

RESULTS

Total (bound + unbound) and free (unbound) plasma concentration-time profiles from a typical patient (KL) are shown in Figure 7.11a. Depicted in Figure 7.11b are the mean (± S.D.) of the total dTc concentrations obtained in these patients together with the range of concentrations anticipated on the basis of normal patient results (65).

In all patients the dTc bolus plus infusion regimen calculated to maintain a plasma concentration of 1.1 μg/ml led to peak total dTc concentrations ranging from 2.79 to 5.94 (mean ± S.D., 4.31 ± 1.11) μg/ml which fell rapidly during the first 57 min of surgery to a mean (± S.D.) of 2.04 ± 0.35 (range 1.38 to 2.66) μg/ml immediately before the start of extracorporeal circulation. On an equivalent dose to body weight basis, these dTc concentrations were not significantly different to those observed previously (65) in a normal patient group (Fig. 7.11b). Immediately upon institution of CPB, dTc total plasma concentrations rose and an apparent plateau (3.98 ± 0.59 μg/ml) some three time higher than anticipated was attained (Table 7.10). d-Tubocurarine infusion was terminated approximately 40 min after completion of CPB and the plasma concentrations appeared to decline in a bi-exponential fashion in all patients.

dTc individual (presented in Table 7.11) and mean pharmacokinetic parameters from the CPB group are compared with those from the normal group in Fig. 7.12. Clearance was significantly lower in the CPB patients (0.61 ± 0.19 vs 2.7 ± 1.0 ml/min/kg, $p < 0.005$). V_{ss} was unaltered as a result of CPB (405 ± 98 vs 455 ± 173 ml/kg) while $t_{1/2\beta}$ (590 ± 104 vs 172 ± 80 min, $p < 0.005$) was increased in the CPB group.

Mean 4 hr urinary excretion of dTc, determined during the period of dTc infusion was 10 ± 5 percent after a dose of 96 (± 18) mg. The renal

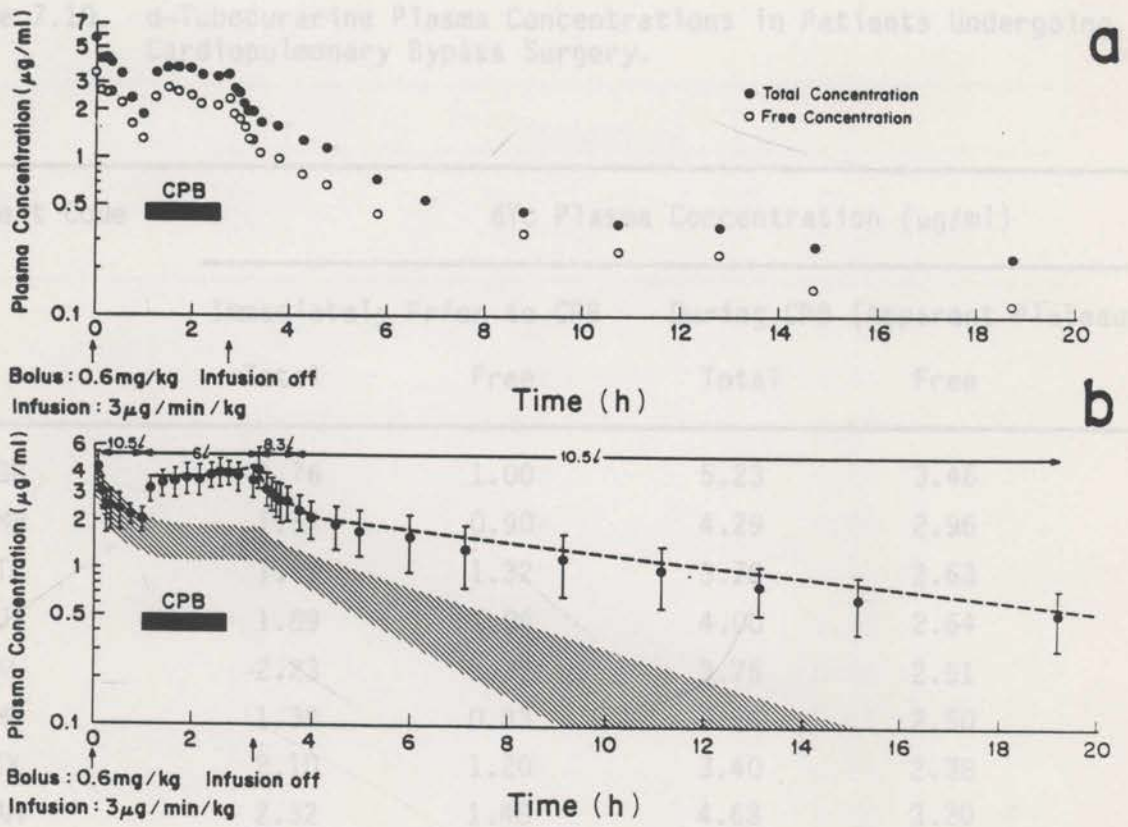


Figure 7.11 (a) d-Tubocurarine (dTc) plasma concentration-time profile in patient KL undergoing surgery involving cardiopulmonary bypass (CPB). The closed circles represent total plasma concentrations, while the open circles represent free concentrations of dTc. (b) dTc total plasma concentration-time profiles in 13 patients undergoing surgery involving cardiopulmonary bypass. All data are mean ± S.D. The shaded area represents the range of plasma concentrations observed in a group of normal subjects (65). Also shown are the predicted plasma concentrations if a time-dependent change in the volume of the central compartment (V_1) is incorporated at the start of CPB (---).

Table 7.10. d-Tubocurarine Plasma Concentrations in Patients Undergoing Cardiopulmonary Bypass Surgery.

Patient Code	dTc Plasma Concentration (μg/ml)			
	Immediately Prior to CPB		During CPB (Apparent Plateau)	
	Total	Free	Total	Free
GB	1.76	1.00	5.23	3.46
MW	1.57	0.90	4.29	2.96
TQ	1.89	1.32	3.70	2.63
JT	1.89	1.04	4.00	2.64
KL	2.23	1.32	3.75	2.51
ME	1.38	0.83	3.54	2.50
TK	2.10	1.20	3.40	2.38
AM	2.32	1.48	4.63	3.20
RW	2.17	1.39	3.80	2.62
FD	1.99	1.13	2.48	1.84
TT	2.66	1.76	4.60	3.40
BC	2.43	1.43	3.55	2.41
ER	2.14	1.28	3.30	2.31
Mean ± S.D.	2.04 ± 0.35	1.24 ± 0.26	3.87 ± 0.70	2.68 ± 0.46

Table 7.11. Model-Independent Pharmacokinetic Parameters of d-Tubocurarine in Patients Undergoing Surgery Involving Cardiopulmonary Bypass.

Patient Code	Parameters		
	$t_{1/2\beta}$ (min)	V_{ss} (ml/kg)	Cl (ml/min/kg)
GB	782	357	0.33
MW	745	392	0.46
TQ	568	521	0.88
JT	413	363	0.79
KL	648	519	0.69
ME	559	375	0.43
TK	592	405	0.52
AM	533	311	0.59
RW	1155	583	0.47
FD	660	609	0.94
TT	548	264	0.48
BC	508	337	0.60
ER	523	410	0.56
Mean ± S.D.	590 ± 104[a] 633 ± 185[b]	405 ± 98 419 ± 106	0.61 ± 0.19 0.60 ± 0.18

a Excluding patient RW
b For all patients

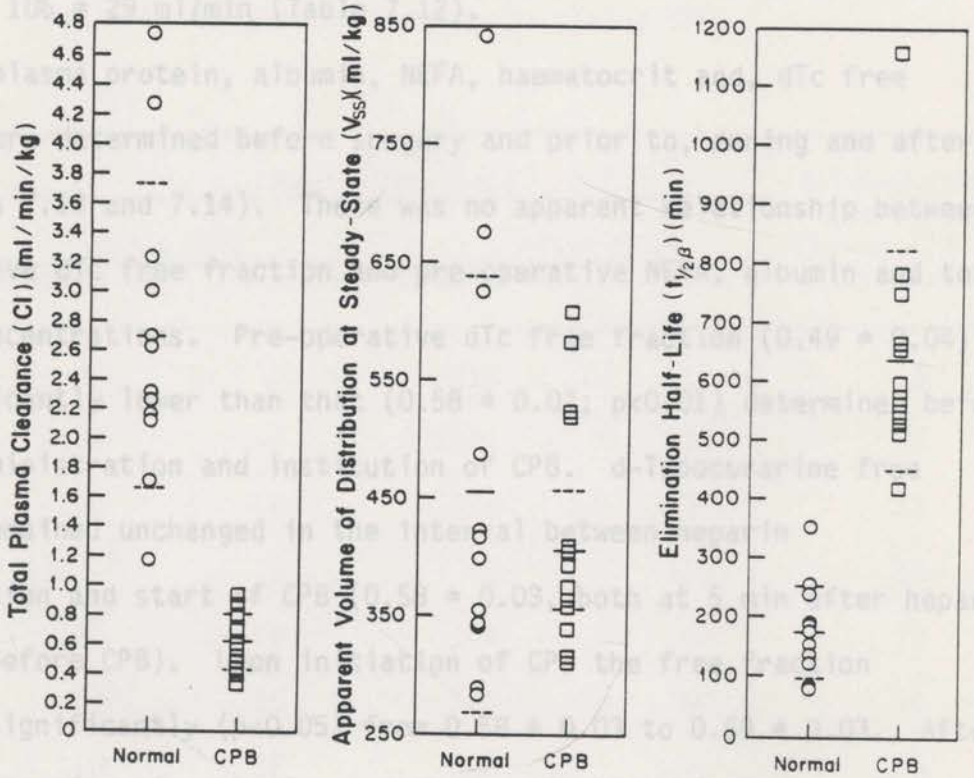


Figure 7.12. Comparison of the d-tubocurarine pharmacokinetic parameters obtained from the cardiopulmonary bypass (CPB) patients with those from a normal patient group (65). The horizontal bars represent the mean ± S.D.

clearance of dTc during CPB was 11 ± 6 ml/min compared to 52 ± 35 ml/min determined immediately after CPB. Creatinine clearance did not vary prior to, during and immediately after CPB. The mean value over a 4 hr period was 106 ± 29 ml/min (Table 7.12).

Total plasma protein, albumin, NEFA, haematocrit and, dTc free fraction were determined before surgery and prior to, during and after CPB (Tables 7.13 and 7.14). There was no apparent relationship between pre-operative dTc free fraction and pre-operative NEFA, albumin and total protein concentrations. Pre-operative dTc free fraction (0.49 ± 0.04) was significantly lower than that (0.58 ± 0.03; $p<0.01$) determined before heparin administration and institution of CPB. d-Tubocurarine free fraction remained unchanged in the interval between heparin administration and start of CPB (0.58 ± 0.03, both at 5 min after heparin and 1 min before CPB). Upon initiation of CPB the free fraction increased significantly ($p<0.05$) from 0.58 ± 0.03 to 0.69 ± 0.03. After the administration of protamine and the termination of CPB, the free fraction of dTc decreased to 0.64 ± 0.03 ($p<0.05$) during the first hour with a gradual recovery to 0.58 ± 0.03 and 0.50 ± 0.03 at 8 and 16 hrs respectively after completion of CPB (Table 7.14).

Pre- and post-dialysis NEFA concentrations did not differ in plasma samples obtained before surgery but post-dialysis concentrations were approximately 20 percent higher in plasma samples taken after heparin administration during and after CPB (Table 7.15). Post-dialysis NEFA concentrations tripled from 687 ± 182 μmol/ℓ at 5 min prior to surgery and before heparin administration to 2248 ± 1024 μmol/ℓ at 5 min after heparin administration. Thirty min after initiation of CPB, NEFA concentrations were 1411 ± 653 μmol/ℓ and at 1-12 hr, 24 hr and 48 hr

Table 7.12. Creatinine and d-Tubocurarine Renal Clearance Parameters in Patients Undergoing Surgery Involving CPB.

Patient Code	Renal Clearance				d-Tubocurarine Excretion
	During CPB		After CPB[a]		During CPB
	Creatinine	dTc	Creatinine	dTc	(% of dose)
GB	52	7	118	12	9
MW	108	--	122	18	6
TQ	100	6	148	35	13
JT	--[b]	5	75	109	19
KL	127	8	144	43	13
ME	93	15	140	60	14
TK	120	15	86	--	3
AM	114	--	57	--	3
RW	89	11	116	19	9
FD	68	5	150	92	7
TT	110	23	84	78	--
BC	119	11	61	--	5
ER	112	--	147	--	17
Mean ± S.D.	101 ± 22	11 ± 6	111 ± 35	52 ± 35	10 ± 5

[a] Determined immediately after CPB, during the infusion of dTc.

[b] Data not available

Table 7.13 Biochemical Parameters in Patients Undergoing Surgery Involving Cardiopulmonary Bypass

Patient Code	Biochemical Parameters														
	Before CPB					During CPB[a]				After CPB					
	Total Protein (g/ℓ)	Plasma Albumin (g/ℓ)	Plasma NEFA Pre-heparin (μmol/ℓ)	Plasma NEFA Post-heparin (μmol/ℓ)	Haematocrit (percent)	Total Protein (g/ℓ)	Serum Albumin (g/ℓ)	NEFA (μmol/ℓ)	Haematocrit (percent)	Total[b] Protein (g/ℓ)	Serum[b] Albumin (g/ℓ)	Plasma NEFA 1-12 hr (μmol/ℓ)	Plasma NEFA 24 hr (μmol/ℓ)	Plasma NEFA 48 hr (μmol/ℓ)	Haematocrit[b] (percent)
GB	79	44	598	---[d]	48	--	--	716	32	69	32	677	---	524	42
MW	78	42	---	1242	43	--	--	828	24	--	--	558	676	369	37
TQ	--	--	763	1447	37	--	--	1232	25	--	--	763	---	529	29
JT	--	--	851	2530	38	--	--	1580	--	66	40	1968[c]	---	---	38
KL	79	43	---	3700	32	36	19	2248	--	--	34	754	653	--	--
ME	65	38	796	1634	42	36	19	1037	24	62	39	365	608	225	32
TK	90	49	631	2919	--	32	15	1268	--	84	38	943[c]	---	---	--
AM	66	38	---	1545	32	32	15	822	23	--	--	1200[c]	1089	913	27
RW	63	39	---	1812	51	36	21	1212	29	--	--	1481[c]	---	---	50
FD	80	42	699	---	49	33	17	1226	40	--	--	1095[c]	546	---	40
TT	70	45	780	916	34	30	19	994	25	64	42	---	---	779	31
BC	--	--	808	3127	42	40	23	2627	30	69	35	---	---	257	--
ER	76	43	256	3855	49	37	21	2554	--	55	29	365	495	256	34
Mean	75	43	687	2248	41	35	19	1411	28	73	36	924	677	482	36
± S.D.	8	4	182	1024	7	3	3	653	5	17	4	488	212	256	7

a 90 min during CPB
b Determined 2-3 days post CPB
c 120 min after CPB
d Not determined due to insufficient sample volume

Table 7.14 d-Tubocurarine Free Fraction in Patients Undergoing Surgery Involving Cardiopulmonary Bypass

Patient Code	d-Tubocurarine Free Fraction						
	Before CPB			During CPB[a]	After CPB		
	Pre-Surgery[b]	Pre-Heparin[c]	Post Heparin[d]		1 hr[e]	8 hr[f]	16 hr[g]
GB	0.44	0.58 ± 0.02	0.58 ± 0.01	0.65 ± 0.02	0.65 ± 0.01	0.56 ± 0.02	0.51 ± 0.01
MW	0.48	0.58 ± 0.01	0.58 ± 0.01	0.69 ± 0.02	0.62 ± 0.01	0.59 ± 0.04	0.50 ± 0.02
TQ	0.55	0.63 ± 0.03	0.65 ± 0.04	0.70 ± 0.04	0.67 ± 0.03	0.58 ± 0.03	0.53 ± 0.02
JT	0.50	0.55 ± 0.01	0.55 ± 0.01	0.66 ± 0.01	0.62 ± 0.04	0.60 ± 0.01	0.51 ± 0.01
KL	0.53	0.54 ± 0.02	0.55 ± 0.03	0.67 ± 0.03	0.66 ± 0.02	0.60 ± 0.01	0.51 ± 0.01
ME	0.50	0.59 ± 0.02	0.59 ± 0.02	0.70 ± 0.03	0.68 ± 0.04	0.62 ± 0.02	0.51 ± 0.02
TK	0.46	0.57 ± 0.02	0.57 ± 0.01	0.69 ± 0.04	0.62 ± 0.03	0.58 ± 0.02	0.45 ± 0.03
AM	0.53	0.56 ± 0.01	0.58 ± 0.03	0.69 ± 0.01	0.65 ± 0.03	0.58 ± 0.04	0.49 ± 0.02
RW	0.52	0.60 ± 0.03	0.61 ± 0.03	0.69 ± 0.04	0.60 ± 0.02	0.57 ± 0.03	0.53 ± 0.01
FD	0.40	0.52 ± 0.03	0.53 ± 0.03	0.74 ± 0.02	0.59 ± 0.05	0.50 ± 0.02	0.45 ± 0.02
TT	0.53	0.58 ± 0.01	0.60 ± 0.03	0.74 ± 0.01	0.69 ± 0.03	0.62 ± 0.03	0.48 ± 0.01
BC	0.50	0.61 ± 0.01	0.60 ± 0.01	0.69 ± 0.03	0.67 ± 0.03	0.60 ± 0.01	0.57 ± 0.01
ER	0.45	0.56 ± 0.02	0.57 ± 0.02	0.70 ± 0.03	0.63 ± 0.04	0.60 ± 0.02	0.56 ± 0.01
Mean	0.49	0.58	0.58	0.69	0.64	0.58	0.51
± S.D.	0.04	0.03	0.03	0.03	0.03	0.03	0.03

a n = 7
b 5 min before start of surgery (n = 2 to 6)
c During first 40 min of surgery (n = 5)
d Before start of CPB (n = 2)
e n = 9
f n = 5
g n = 3

Table 7.15 Effect of Equilibrium Dialysis on NEFA Concentrations

NEFA Concentrations (μmol/ℓ)					
Pre-Surgery (pre-heparin)		During CPB (post-heparin)		After CPB	
Pre-Dialysis	Post-Dialysis	Pre-Dialysis	Post-Dialysis	Pre-Dialysis	Post-Dialysis
851[a]	865	3091[c]	3855	663[d]	781
699[b]	725	2041[c]	2549	996[b]	1095

Patient Code:

a JT
b FD
c ER
d TT

after completion of CPB the concentrations declined to 924 ± 488, 677 ± 212 and 482 ± 256 μmol/ℓ respectively (Table 7.13). In spite of these parallel changes in dTc free fraction and plasma NEFA concentrations no apparent relationship could be demonstrated between the free fraction of dTc and NEFA concentrations at any time during the study (either prior to or after heparin administration).

The haematocrit decreased significantly ($p < 0.01$) due to haemodilution by the pump priming solution from 42 ± 7 percent before CPB to 28 ± 5 percent during CPB. During the first 16 hrs after CPB, the haematocrit increased to 36 ± 7 percent but was still below that measured pre-operatively (Table 7.12). There was a significant ($R^2 = 0.72$, $p < 0.05$) inverse linear relationship between dTc free fraction and haematocrit when data gathered prior to, during and following CPB were used (Fig. 7.13a). There was also an inverse relationship between both dTc free fraction and plasma albumin ($R^2 = 0.88$, $p < 0.01$) and plasma total protein ($R^2 = 0.94$, $p < 0.01$) concentrations (Fig. 7.13b and c).

The free fraction of dTc determined one (mean ± S.D.; 0.45 ± 0.04) and two (0.41 ± 0.03) days after CPB were significantly different from each other and significantly lower as compared to the free fraction determined pre-operatively (mean ± S.D.; 0.49 ± 0.04; Fig. 7.14). The concentrations of AGP measured on these three days did not differ significantly from each other (100 ± 32; 106 ± 23; 95 ± 26 mg percent respectively; Fig. 7.14).

The free fraction in Hartmann's solution was approximately equal to unity (0.97) and in Haemaccel alone it was equal to 0.69. Simulation of haemodilution by the pump priming solution <u>in vitro</u> using different proportions of Haemaccel produced a decrease in haematocrit from 40 to 30 percent while the free fraction in plasma increased from 0.59 to 0.67

(Table 7.16). By varying the proportions of Hartmann's solution a decrease in haematocrit from 51 percent to 24 percent was produced with a subsequent <u>in vitro</u> increase in dTc free fraction from 0.41 to 0.66 (Table 7.16).

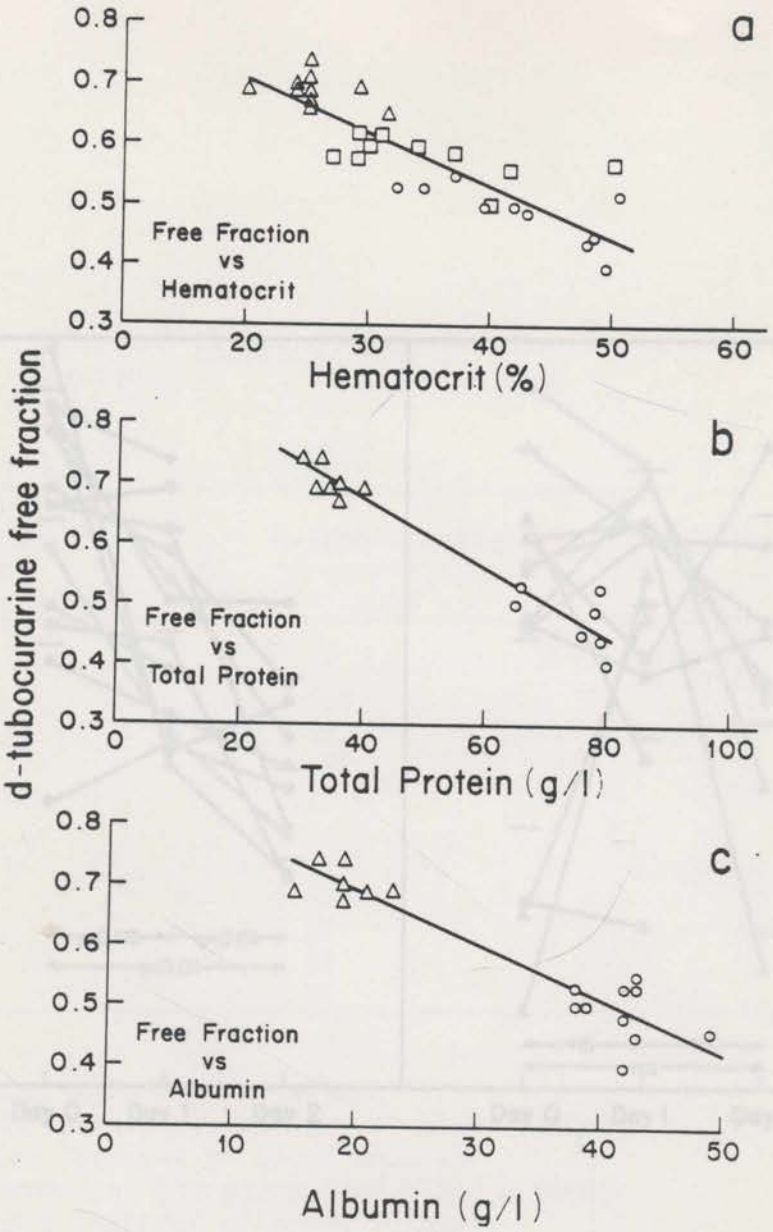


Figure 7.13 Relationship between d-tubocurarine free fraction and (a) haematocrit, (b) total protein concentrations and (c) plasma albumin concentrations. The open circles represent data gathered prior to CPB, while the open triangles are data gathered during CPB, and the open squares represent data obtained after CPB.

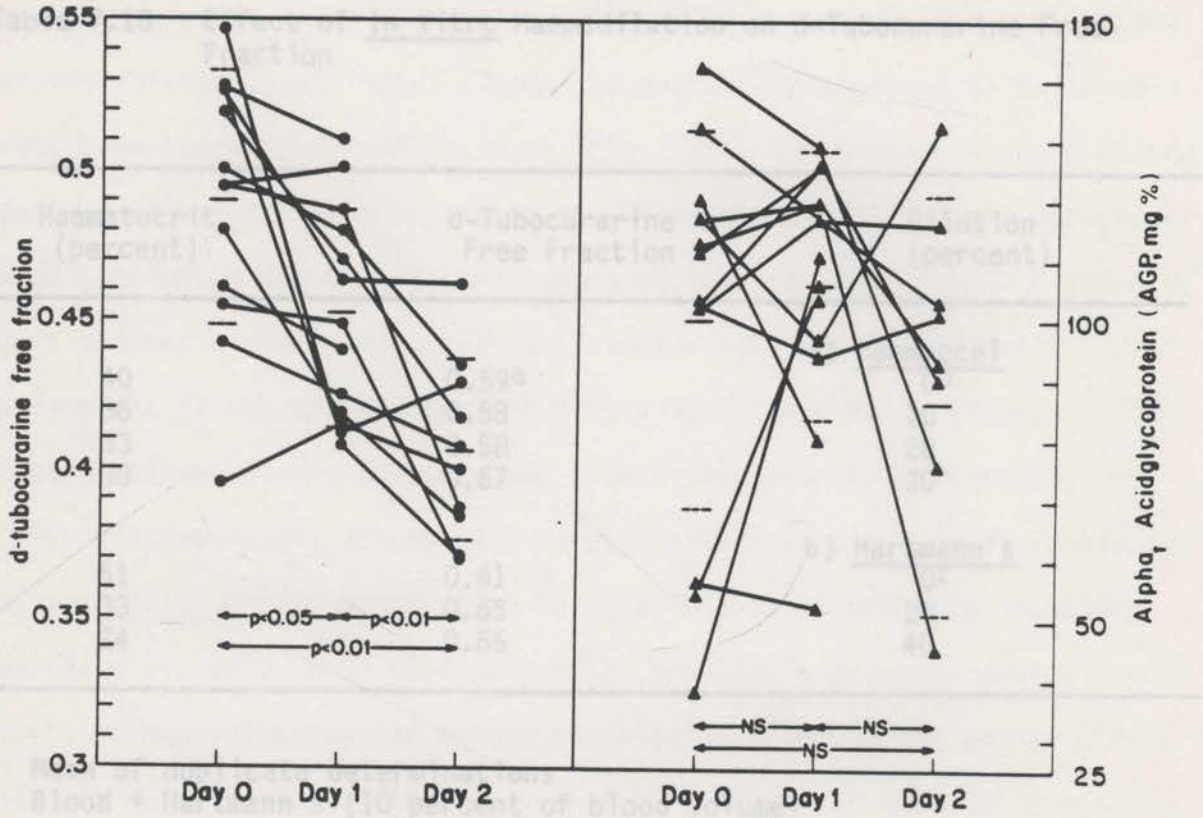


Figure 7.14 A comparison of the free fraction values of d-tubocurarine (●) and alpha$_1$-acid glycoprotein concentrations (▲) determined on day 0, day 1, and day 2 after CPB. The horizontal bars represent the mean ± S.D.

Table 7.16 Effect of *In Vitro* Haemodilution on d-Tubocurarine Free Fraction

Haematocrit (percent)	d-Tubocurarine Free Fraction	Dilution (percent)
		a) Haemaccel
40	0.59[a]	0[b]
36	0.58	10
33	0.58	20
30	0.67	30
		b) Hartmann's
51	0.41	0[c]
33	0.65	20
24	0.66	40

a Mean of duplicate determinations
b Blood + Hartmann's (10 percent of blood volume) + Haemaccel (percent of blood volume)
c Blood + Haemaccel (20 percent of blood volume) + Hartmann's (percent of blood volume)

DISCUSSION

The pre-CPB total plasma concentration-time profiles in all patients were consistent with data gathered from a normal patient group (Fig. 7.11). With the institution of CPB there was either an immediate or gradual increase in the dTc total plasma concentraions followed by an apparent plateau. Upon completion of the CPB procedure (and termination of the infusion), dTc total plasma concentrations declined at a slower rate than those in normal patients (Fig. 7.11). A similar rise in plasma concentrations followed by a plateau with the onset of CPB was observed with alcuronium and to a lesser extent with gallamine (Section A and B to this chapter respectively). In the studies with alcuronium and gallamine, it was considered most likely that the rise in plasma concentrations during CPB resulted from a decrease in the central (plasma) compartment volume (V_1) related either to a reduction in blood volume per se and/or a reduction in distribution of the drug to highly perfused tissues. Both these processes are likely to contribute since in spite of haemodilution, effective circulating blood volume during CPB is reduced owing to haemorrhage and the fact that one of the most highly perfused tissues, the lungs are excluded from the general circulation during CPB. In the period prior to CPB, a large proportion of the administered dose of dTc is presumably sequestered by the lung (in rats the lung/blood dTc concentration ratio is approximately 4 to 7; ref 252) which would be distributed to other tissues in proportion to the fraction of cardiac output accorded to each tissue. However, with the intervention of extracorporeal circulation and the exclusion of the lungs from the circulation a major site of drug uptake or distribution is lost while the dTc infusion continues. Hence the plasma concentration rises. This rise is further augmented by the low cardiac output and hypotension

during CPB which is associated with diminished perfusion of peripheral and other tissues and organs of clearance. That a change in V_1 during CPB is also occurring with dTc is evident from the simulated concentration-time profile of dTc presented in Fig. 7.11b. There is good agreement between measured and predicted dTc concentrations during the period of CPB and immediately following if V_1 is decreased at CPB from 10.5 ℓ (mean value in the normal group, ref. 65) to 6.0 ℓ. Postinfusion dTc concentration data could also be characterized if V_1 was restored to 8.3 ℓ during the first hour and 10.5 ℓ during the elimination phase (Fig. 7.11b). Although the proposed time-dependent changes in V_1 satisfactorily account for the dTc plasma concentration-time data, the fact that dTc time averaged plasma clearance was reduced 4 fold and the elimination half-life increased 3 fold in the CPB patients suggests that the clearance processes <u>per se</u> are also diminished as a result of the CPB procedure. Further supporting evidence is apparent from the fact that the renal clearance of dTc during CPB was one-fifth the value which was obtained immediately after CPB. Hypothermia (a profound physiological stress during CPB), has been shown to reduce total dTc plasma clearance in cats owing to reduction in both urinary and biliary excretion (148).

It is important to consider dTc plasma protein binding and the factors which may affect it during cardiac surgery. Pre-surgical dTc free fraction (0.49 ± 0.04) determined before heparin administration was significantly lower than that (0.58 ± 0.03) determined at the beginning of surgery but also before heparin administration and the start of CPB. The exact reason for this decreased binding is not known, but is likely to be due to haemodilution since most patients received 1 ℓ of crystalloid solution during this interval. All subsequent dTc free fraction determinations were made after heparin administration and are

therefore potentially subject to artifactual changes due to in vitro increases in plasma NEFA concentrations (254,255) and its subsequent effect on drug binding processes. NEFA concentrations increased approximately 25 percent during in vitro equilibrium dialysis as compared to a three fold increase in concentrations (post-dialysis) in plasma collected following heparin administration. However, the concentrations after heparin administration may still be artifactual if in vitro changes occurred within the first several minutes after blood collection. In the present study, heparin administration and the associated increased NEFA concentration, however, did not appear to alter dTc plasma protein binding since the apparent free fraction determined before initiation of CPB (and 7 to 25 min after heparin adminstration) was also 0.58 ± 0.03. This suggests that the well reported heparin/NEFA binding artifact may not influence dTc binding. However, marked changes in dTc free fraction were noted concomitant with haemodilution and the start of CPB. The apparent free fraction during CPB was 0.69 ± 0.03 which decreased to 0.64 ± 0.03 upon completion of CPB with a further decrease to pre-CPB (0.58 ± 0.03) and pre-surgical (0.51 ± 0.03) values at 8 and 16 hrs after CPB respectively. Thus, although the 'heparin effect' cannot be completely ruled out, the observed apparent changes in dTc binding appear to be associated with the progress of CPB procedure itself. The latter view is supported by the absence of a relationship between dTc free fraction and post-dialysis NEFA concentrations in these patients. A positive correlation would be expected if the free fraction were artifactually increased as a result of in vitro increases in plasma NEFA concentrations. Further support that the CPB procedure itself is directly affecting dTc plasma protein binding comes from the fact that a highly significant relationship was found between the apparent free

fraction of dTc and plasma albumin concentrations, total plasma protein and haematocrit, respectively, over the entire study period. This, together with the fact that similar changes in dTc free fraction could be produced by simulating haemodilution in vitro prompts the hypothesis that the observed 27 percent increase in dTc free fraction with the commencement of CPB is attributable to haemodilution, and the associated reduction in concentrations of total proteins and plasma albumin which has been shown to be the major plasma binding protein component for dTc (Ch. 6, p. 148; ref. 103). The free fraction of dTc continued to decline to 0.43 ± 0.03 and 0.41 ± 0.03 at 24 and 48 hrs after completion of CPB surgery. The reasons for these continued changes in the dTc free fraction is not known but they cannot be attributed to plasma AGP concentrations since the latter surprisingly did not change over a period of 3 days (Fig. 7.14).

From a pharmacokinetic viewpoint, the observed decrease in dTc binding alone might be expected to increase total plasma clearance of dTc and thus lower the apparent steady-state concentration of total but not the free (unbound) drug. However, in these patients (as depicted in Fig. 7.11a) there is an increase in both total and free concentrations. This implies that other factors (such as reduced perfusion to peripheral tissues and clearance organs and perhaps altered tissue binding of dTc) are operating in concert effectively to diminish the total plasma clearance of dTc during CPB.

The elevation in dTc concentrations during CPB observed in this work has major implications for its use in cardiac surgery. Lower doses of dTc will need to be used in patients undergoing CPB surgery unless the concentration-effect relationship for dTc is also altered such that higher concentrations are needed to elicit the same response as in normal

patients.

In summary, there appear to be quantitative differences between the effect of CPB on the disposition kinetics of alcuronium, gallamine and d-tubocurarine. There were marked pertubations in the plasma concentrations of d-tubocurarine and alcuronium with little disruption in gallamine concentrations. The basis of these quantitative differences between the three relaxants is unknown but may be related to the binding and distributional characteristics of the three drugs. Gallamine, which was least affected by the CPB procedure, has the smallest (of the three agents) volume of distribution (V_1 and V_{ss}) and is reputedly not bound to plasma proteins (109). On the other hand, d-tubocurarine plasma concentrations were disrupted most severely. This agent has the highest volume of distribution and lowest free fraction in plasma. In comparison, alcuronium, whose volume of distribution and free fraction values are between those for d-tubocurarine and gallamine, was moderately affected by the CPB procedure. However, it must be appreciated that the observed differences in the effect of the CPB procedure on the disposition kinetics of these three drugs may also be related to the dosage regimen employed in these studies. Alcuronium and d-tubocurarine were administered as a bolus plus infusion regimen and the cardiopulmonary bypass procedure was instituted when the drug was being continuously infused such that pertubations in the concentration-time profile may have been more apparent. On the other hand, gallamine was administered as bolus doses and CPB was commenced while concentrations were generally in the post-distribution (elimination) phase. Thus, changes may therefore not have been apparent.

ABSTRACT

Numerous *in vitro* and *in vivo* studies have suggested that the muscles of the diaphragm are less sensitive to neuromuscular blocking agents than the limb muscles. However this difference has not been characterized directly in terms of relaxant plasma concentrations. The pharmacodynamics of alcuronium were therefore investigated in nine dogs using a constant-rate infusion regimen and with simultaneous measurement of muscle paralysis in the limb and diaphragm. In the majority of the dogs maximum paralysis between 95 to 100 percent was achieved in both muscle groups, within approximately the same time interval. However, during onset and offset of effect the pharmacodynamic parameters EC_{p50} and EC_{p95} given by the sigmoid equation were different with respect to the limb muscle. Using pharmacodynamic theory it was predicted that $C_{ss(50)}$ and $C_{ss(95)}$ for the diaphragm. Thus it was observed that the diaphragm is less sensitive to the action of alcuronium than are limb muscles. The half-time for equilibration between plasma concentration and effect was lower by two-fold for the diaphragm and the rate of recovery from paralysis in diaphragmatic muscles was twice that observed in limb muscles. Collectively, these data suggest that there is a greater margin of safety in the diaphragmatic muscles and that the response of the peripheral limb muscles to nerve stimulation provides only a conservative index of recovery from competitive neuromuscular block in the diaphragmatic muscles.

Chapter 8

ALCURONIUM PHARMACODYNAMICS IN DOGS: EFFECT-CONCENTRATION RELATIONSHIP IN THE DIAPHRAGMATIC AND LIMB MUSCLES

ABSTRACT

Numerous *in vitro* and *in vivo* studies have suggested that the muscles of the diaphragm are less sensitive to neuromuscular blocking agents than the limb muscles. However this difference has not been characterized directly in terms of relaxant plasma concentrations. The pharmacodynamics of alcuronium were therefore investigated in nine dogs using a constant-rate infusion regimen and with simultaneous measurement of muscle paralysis in the limb and diaphragm. In the majority of the dogs maximum paralysis between 95 to 100 percent was achieved in both muscle groups, within approximately the same time interval. However, during onset and offset of effect the pharmacodynamic parameters EC_{p50} and EC_{p95} given by the Hill equation were lower with respect to the limb muscle. Using a pharmacodynamic effect model it was predicted that $C_{ss(50)}$ and $C_{ss(95)}$ for the limb muscle are half those values for the diaphragm. Thus it was observed that the diaphragm is less sensitive to the action of alcuronium than are limb muscles. The half-time for equilibration between plasma concentration and effect was lower by two-fold for the diaphragm and the rate of recovery from paralysis in diaphragmatic muscles was twice that observed in limb muscles. Collectively, these data suggest that there is a greater margin of safety in the diaphragmatic muscles and that the response of the peripheral limb muscles to nerve stimulation provides only a conservative index of recovery from competitive neuromuscular block in the diaphragmatic muscles.

INTRODUCTION

One major function of neuromuscular blockade during anaesthesia is the relaxation of respiratory musculature, including the diaphragm and the muscles of the abdomen. Clinically, motor nerve stimulation can conveniently be applied to peripheral muscles only. Postoperatively, however, restoration of muscle power in the respiratory muscles, particularly the diaphragm, is of immediate concern since it is necessary to assess conditions for tracheal extubation.

Differential sensitivity of the various muscle groups to nondepolarizing relaxant agents has been reported since the late 1940s. Numerous studies, both in humans (256-258) and in animals *in vivo* (225,259-262) and *in vitro* (263,264) using isolated muscle preparations have shown that the respiratory muscles are more resistant to blockade by nondepolarizing neuromuscular blocking drugs. In a very elegant study Waud and Waud (225) have shown that this "sparing" of the respiratory muscles is related to the large "margin of safety" of neuromuscular transmission. Specifically, in a limb muscle 75-80 percent of the receptors have to be blocked by curare-like drugs before the most sensitive muscle fibres fail to respond to a single nerve stimuli and 90-95 percent must be blocked before transmission fails completely. In contrast, the diaphragm needs only 5-10 percent of receptors to be free to respond normally. These workers also showed *in vitro* that the concentration of nondepolarizing neuromuscular blocking drugs needed to block the diaphragm is double that needed to block peripheral muscles (266). Further, it has been shown that this difference in sensitivity is not related to the affinities of the respiratory and limb muscles to the nondepolarizing agents (263).

Unfortunately, in most *in vivo* studies where the differential

sensitivity of the various muscle groups has been studied, only indirect measures of muscle function have been employed and the difference in response has been interpreted on the basis of relaxant drug dosage rather than concentrations.

This study was thus undertaken to characterize the reported differences in response of the diaphragmatic and peripheral muscles using quantitative assessment of both muscle function and relaxant drug concentration. For ethical and practical reasons it was not possible to conduct such a study in humans. Therefore, the study was carried out in dogs. By producing progressive paralysis with alcuronium, the relationship between alcuronium concentration and diaphragm and limb muscle paralysis was examined using pharmacodynamic modelling techniques.

METHODS

Greyhound dogs were chosen for these studies because of their ready availability. They are lean, carrying little excess fat. Thus surgical manipulations are easier.

Nine adult animals of either sex were used (Table 8.1). The anaesthetic technique was as described previously (Ch. 3, p. 55).

A constant-rate infusion of alcuronium was used. After the control twitch height had become stabilized, alcuronium was infused at a rate of 66.7 µg/min, until 95-99 percent depression of twitch tension occurred in the diaphragm. This infusion rate was chosen after a preliminary study in one dog so that complete paralysis was attained within 30 minutes.

Degree of neuromuscular blockade was assessed simultaneously in the diaphragmatic and limb muscles as described earlier (Ch. 3, p. 56). After surgical exposure in the neck and thigh respectively, the phrenic and sciatic nerves were simultaneously stimulated directly at ten second intervals (0.1 Hz) with a supramaximal stimulus of 0.1 msec duration. The diaphragmatic e.m.g. was recorded from insulated wires placed intramuscularly via a small anterolateral thoracotomy while the limb e.m.g. was recorded via needle electrodes placed percutaneously into the small muscles of the hind foot.

Blood samples were obtained from iliac artery contralateral to that of the stimulated limb. Samples were withdrawn at one minute intervals until 10 min post infusion thence at five to ten minute intervals for a further 90 min or until full recovery of the twitch response occurred in the diaphragm.

Plasma concentration-time and paralysis data were available in all dogs during onset and offset of paralysis in the limb and diaphragmatic muscles respectively. As for the human studies (Ch. 4, p. 80) two

Table 8.1 Pertinent Details in Dogs who Received a Constant-Rate (66.7 µg/min) Infusion of Alcuronium

Subject Code	Sex	Weight (kg)	Duration of Infusion (min)	Alcuronium (mg)	Total Dose (mg/kg)
D1	M	29	22	1.47	0.05
D2	M	28	30	2.01	0.07
D3	F	20	30	2.01	0.10
D4	M	33	40	2.67	0.08
D5	F	25	25	1.67	0.07
D6	M	28	30	2.01	0.07
D7	M	26	30	2.01	0.08
D8	M	30	30	2.01	0.07
D9	F	22	20	1.33	0.07

approaches were again used to model the pharmacodynamic data. Firstly both the onset and the offset paralysis-concentration data from each set of muscles were fitted to the nonlinear form of the Hill equation (Eq. 3.1, p. 68). Secondly, plasma concentration-time-paralysis data for each muscle group gathered during onset and offset were fitted simultaneously to a pharmacodynamic effect model (Ch. 4, p. 82). For effect modelling, the parameters α, β, k_{21} and V_1 were generated using the pharmacokinetic Equation 8.1 for a constant-rate infusion and the amount of alcuronium in the effect compartment was calculated according to Equation 8.2.

$$Cp = \frac{ko.(k_{21} - \alpha)(1 - e^{\alpha T})}{V_1.\alpha(\alpha - \beta)} .e^{-\alpha t} + \frac{ko\ (\beta - k_{21})(1 - e^{\beta T})}{V_1.\beta(\alpha - \beta)} .e^{-\beta t} \qquad \text{Eq. 8.1}$$

Where each term is defined as in Chapter 4 (p. 105).

$$Ae = k_{1e}.ko \left[\frac{(k_{21} - \alpha)(1 - e^{\alpha T})}{\alpha\ (\alpha - \beta)\ (k_{eo} - \alpha)} .e^{-\alpha t} + \frac{(\beta - k_{21})(1 - e^{\beta T})}{\beta\ (\alpha - \beta)\ (k_{eo} - \beta)} .e^{-\beta t} + \frac{(k_{eo} - k_{21})(1 - e^{keoT})}{k_{eo}\ (\alpha - k_{eo})\ (\beta - k_{eo})} .e^{-keot} \right] \qquad \text{Eq. 8.2}$$

Where again all terms are as defined previously (Ch. 4, p. 106).

Recovery from paralysis in the 20–80 percent effect range in each muscle group was assessed using linear regression analysis of the paralysis-time data.

Although the pharmacokinetics of alcuronium in the dog was not the central concern of this study, the model-independent pharmacokinetic

parameters Cl, $t_{1/2\beta}$, and V_{ss} were also calculated (Ch. 3, p. 66) for comparison with human data.

RESULTS

Times to peak effect, maximum paralysis achieved in each muscle group and the corresponding plasma concentrations of alcuronium at these times in each animal are shown in Table 8.2. Maximum paralysis in the limb muscles was greater than in the diaphragm and was achieved in a shorter time interval ($p < 0.05$). Alcuronium plasma concentrations did not differ significantly between the two muscle groups. Figure 8.1a shows the limb muscle paralysis-concentration data in one dog (D9) both during onset and offset of effect, while Fig. 8.1b shows similar data from the diaphragmatic muscles in another dog (D7). The response-concentration relationship was sigmoid in nature for both muscle groups but the plasma concentration corresponding to a particular degree of paralysis was higher during onset than during offset of effect. Figure 8.2a displays the onset data for both the limb and diaphragmatic muscles in a single dog (D9). The curves appeared superimposable and this was true for all but two dogs. However, during offset of effect, the effect-concentration curves from the limb and diaphragmatic muscles were not superimposable in any dog. An example of a typical plot during offset in one dog (D8) is shown in Figure 8.2b.

Mean effect-concentration data in the limb and diaphragmatic muscles are shown in Fig. 8.3a (onset) and Fig. 8.3b (offset). The diaphragm effect-concentration curve is shifted to the right of that for the limb muscle.

The Hill equation parameters, s and EC_{p50} and the calculated EC_{p95} value obtained during onset and offset of effect in both muscle groups are presented in Table 8.3. When onset and offset data were compared s, EC_{p50} and EC_{p95} were each significantly higher ($p < 0.01$, respectively) during onset of effect in the limb, but only EC_{p50} and

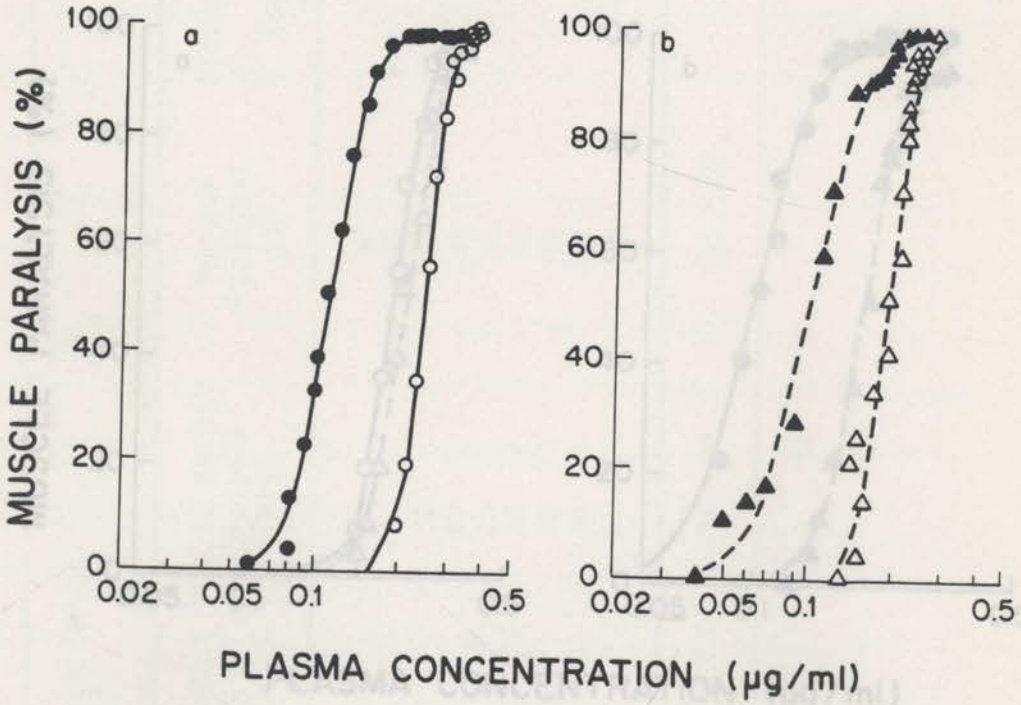


Figure 8.1 Relationship between muscle paralysis and alcuronium plasma concentration in (a) the limb (o,●) and (b) diaphragmatic (△,▲) muscles during onset (open symbols) and offset (closed symbols) of effect. The curves were generated from the Hill equation.

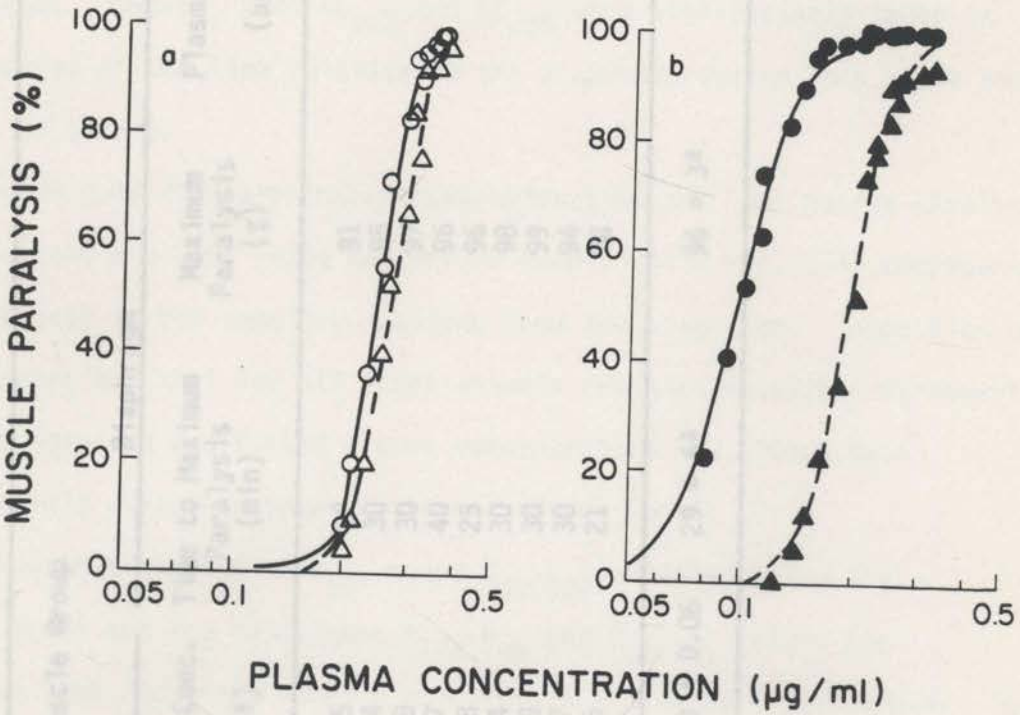


Figure 8.2 Relationship between muscle paralysis and alcuronium plasma concentrations during (a) onset and (b) offset of effect in the limb (o,●) and diaphragmatic (△,▲) muscles. The curves were generated from the Hill equation.

Table 8.2 Time to Onset of Maximum Neuromuscular Blockade in the Hind Limb and Diaphragmatic Muscles Respectively of the Dog and the Corresponding Plasma Concentrations of Alcuronium

	Muscle Group					
	Peripheral			Diaphragm		
Subject Code	Time to Maximum Paralysis (min)	Maximum Paralysis (%)	Plasma Conc. (µg/ml)	Time to Maximum Paralysis (min)	Maximum Paralysis (%)	Plasma Conc. (µg/ml)
D1	22	96	0.25	22	91	0.25
D2	27	97	0.24	30	95	0.28
D3	20	100	0.38	30	97	0.43
D4	37	97	0.27	40	96	0.28
D5	25	100	0.38	25	96	0.38
D6	27	99	0.24	30	98	0.23
D7	23	98	0.23	30	99	0.28
D8	25	100	0.27	30	94	0.35
D9	20	98	0.36	21	98	0.36
Mean ± SD	25 ± 5[a]	98 ± 2[a]	0.29 ± 0.06	29 ± 6[a]	96 ± 3[a]	0.32 ± 0.07

[a] $p < 0.05$ (t-test for paired data)

EC_{p95} were significantly ($p < 0.01$) higher during onset of effect in the diaphragm. The values of the exponent, s, did not differ significantly between the limb and diaphragmatic muscles either during onset or offset of effect. However, both EC_{p50} and EC_{p95} were significantly lower in the muscles of the limb relative to the diaphragm during both onset and offset of effect.

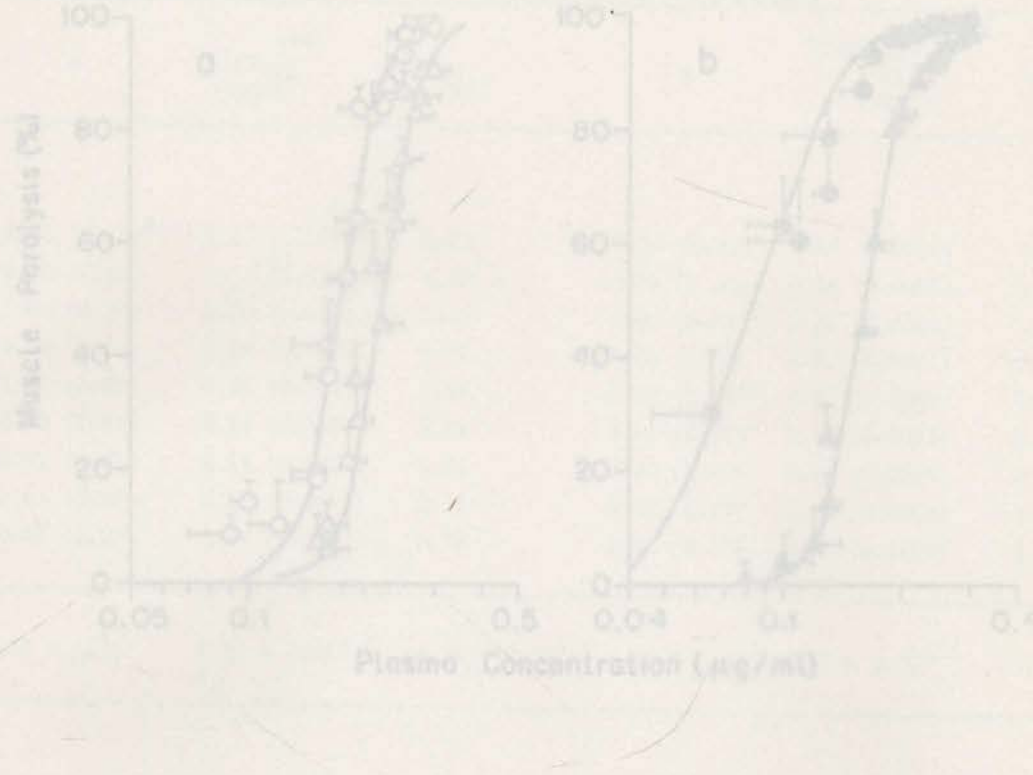
Figure 8.4a displays the concentration-time and limb muscle paralysis data for one dog (D2) using the effect model, while Fig. 8.4b represents similar data in the same dog obtained from the diaphragm. Inspection of this figure and that for all other animals revealed excellent agreement between observed and fitted plasma concentration and effect data respectively using the pharmacodynamic effect model.

Computer estimates of k_{eo}, s and $C_{ss(50)}$ obtained using the effect model and the calculated $t_{1/2}\ k_{eo}$ and $C_{ss(95)}$ values for both the limb and diaphragmatic muscles are presented in Table 8.4. The estimate of k_{eo} was significantly lower using data obtained from the limb muscles, and thus the $t_{1/2}\ k_{eo}$ was longer than that obtained with the diaphragm data. Estimates of the exponent (s) did not differ significantly for the two muscle groups but both the $C_{ss(50)}$ and the $C_{ss(95)}$ values were significantly higher in the diaphragm.

The rates of recovery from paralysis in the linear 20–80 percent effect range in the limb and diaphragmatic muscles are presented in Table 8.5. Recovery in the diaphragm was approximately twice as fast as the limb muscle.

The pharmacokinetic parameters for alcuronium in dogs are presented in Table 8.6. Alcuronium half-life in dogs was approximately five times shorter than in humans and the plasma clearance was markedly increased. Although the volume of distribution was two-fold lower in the dogs

in absolute terms, this difference could be accounted for by differences in body weight.



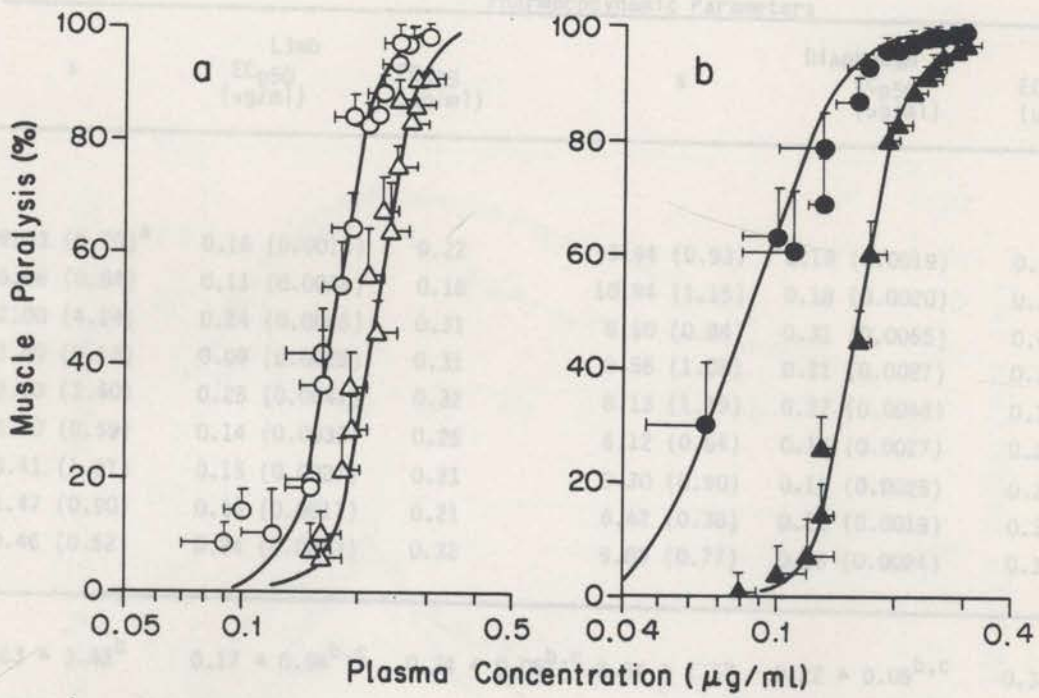


Figure 8.3 Effect-concentration relationship for alcuronium during (a) onset and (b) offset of action in the limb (o,●) and diaphragmatic (△,▲) muscles. Each data point represents the mean from nine dogs. The horizontal and vertical bars represent the standard error of the mean plasma concentration and muscle paralysis data points respectively. The curves were generated using the mean estimate of s and EC_{p50}.

Table 8.3 Hill Equation Pharmacodynamic Parameter Estimates for Alcuronium During Onset and Offset of Effect from the Canine Limb and Diaphragmatic Muscles

	Pharmacodynamic Parameters					
	Limb			Diaphragm		
Subject Code	s	EC_{p50} (µg/ml)	EC_{p95} (µg/ml)	s	EC_{p50} (µg/ml)	EC_{p95} (µg/ml)
Onset						
D1	9.93 (0.70)[a]	0.16 (0.0013)	0.22	9.44 (0.93)	0.19 (0.0019)	0.26
D2	5.96 (0.84)	0.11 (0.0034)	0.18	10.94 (1.15)	0.18 (0.0020)	0.24
D3	12.00 (4.24)	0.24 (0.0045)	0.31	8.10 (0.84)	0.31 (0.0055)	0.45
D4	2.40 (0.13)	0.09 (0.0025)	0.31	8.56 (1.08)	0.21 (0.0027)	0.30
D5	12.00 (3.40)	0.25 (0.0041)	0.32	8.13 (1.19)	0.27 (0.0048)	0.39
D6	5.00 (0.59)	0.14 (0.0033)	0.25	6.12 (0.64)	0.16 (0.0027)	0.26
D7	8.41 (1.21)	0.15 (0.0027)	0.21	9.30 (0.90)	0.19 (0.0025)	0.26
D8	11.47 (0.90)	0.16 (0.0011)	0.21	6.42 (0.30)	0.21 (0.0018)	0.33
D9	10.46 (0.52)	0.24 (0.0013)	0.32	9.89 (0.77)	0.26 (0.0024)	0.35
Mean ± SD	8.63 ± 3.45[b]	0.17 ± 0.06[b,c]	0.24 ± 0.05[b,c]	8.54 ± 1.57	0.22 ± 0.05[b,c]	0.32 ± 0.07[b,d]
Offset						
D1	3.18 (0.20)	0.07 (0.0014)	0.18	6.94 (0.63)	0.16 (0.0019)	0.25
D2	2.55 (0.13)	0.05 (0.0011)	0.16	4.65 (0.42)	0.12 (0.0027)	0.23
D3	6.52 (0.90)	0.12 (0.0051)	0.19	6.67 (0.65)	0.25 (0.0054)	0.39
D4	1.74 (0.12)	0.04 (0.0026)	0.22	6.49 (0.71)	0.15 (0.0030)	0.24
D5	11.96 (0.74)	0.16 (0.0010)	0.20	7.18 (0.62)	0.18 (0.0026)	0.27
D6	3.44 (0.49)	0.09 (0.0048)	0.21	12.0 (2.74)	0.13 (0.0030)	0.17
D7	3.30 (0.37)	0.08 (0.0035)	0.20	4.71 (0.29)	0.10 (0.0017)	0.19
D8	5.54 (0.31)	0.10 (0.0010)	0.17	8.38 (0.47)	0.19 (0.0016)	0.27
D9	6.34 (0.26)	0.11 (0.0007)	0.18	12.11 (0.67)	0.17 (0.0010)	0.22
Mean ± SD	4.95 ± 3.12[b]	0.09 ± 0.04[b,c]	0.19 ± 0.02[b,d]	7.68 ± 2.74	0.16 ± 0.04[b,c]	0.25 ± 0.06[b,d]

[a] Estimate ± S.D.

[b] $p < 0.01$ onset vs offset

[c] $p < 0.01$ limb vs diaphragm

[d] $p < 0.05$ limb vs diaphragm

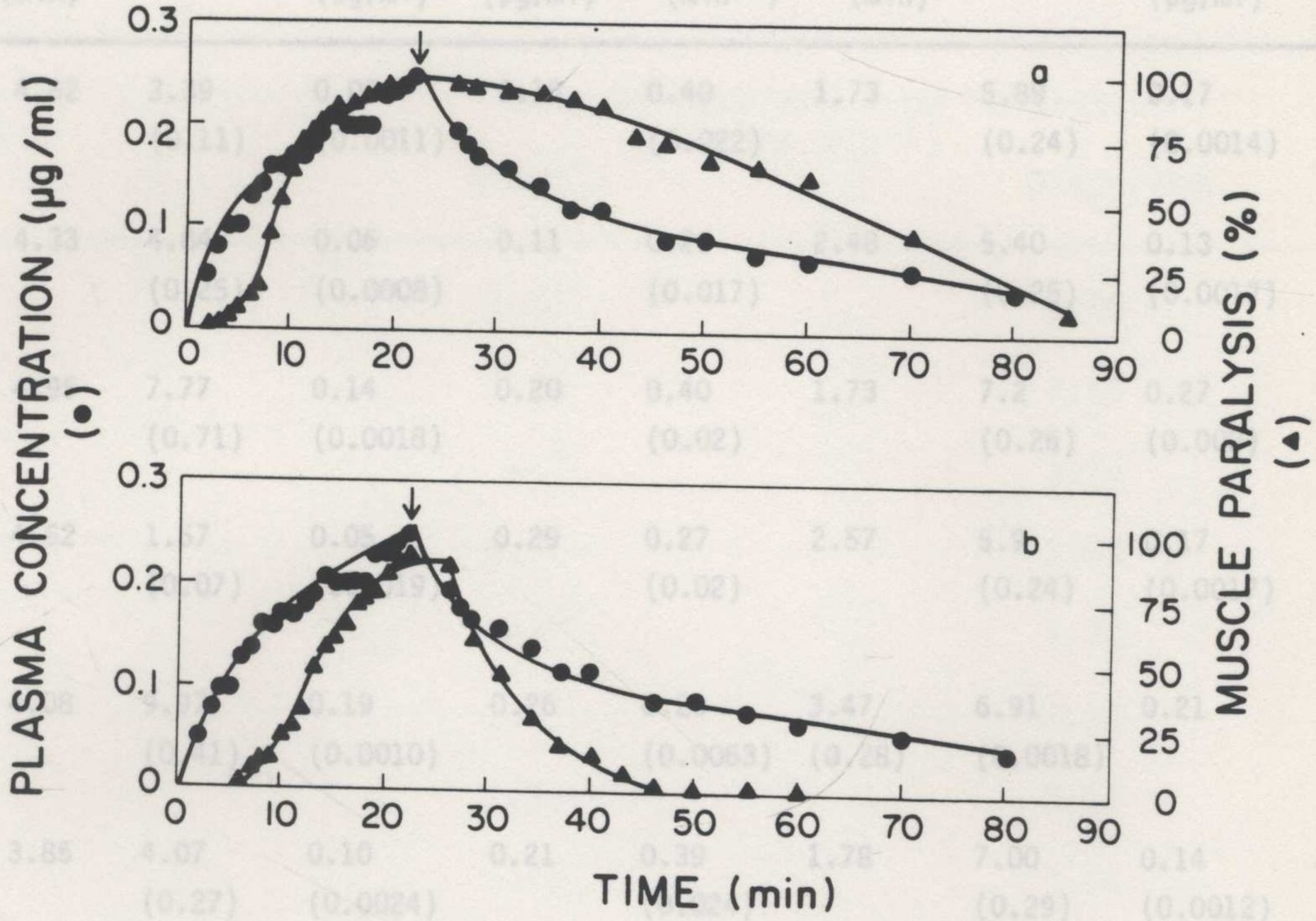


Figure 8.4 Relationship between effect-time and alcuronium plasma concentration in a single dog (D2) for (a) the limb and (b) diaphragmatic muscle. The curves joining the concentration-time data points (•) were generated by the use of a biexponential (two-compartment) model equation, while the curves joining the paralysis time data points (▲) were generated by use of the pharmacodynamic effect model. The arrows indicate the time at which the alcuronium infusion was terminated.

Table 8.4. Pharmacodynamic Parameter Estimates for Alcuronium from the Canine Peripheral Limb and Diaphragmatic Muscles

	Pharmacodynamic Parameters									
	Limb					Diaphragm				
Subject Code	k_{eo} (min^{-1})	$t_{1/2}\,k_{eo}$ (min)	s	$C_{ss(50)}$ (µg/ml)	$C_{ss(95)}$ (µg/ml)	k_{eo} (min^{-1})	$t_{1/2}\,k_{eo}$ (min)	s	$C_{ss(50)}$ (µg/ml)	$C_{ss(95)}$ (µg/ml)
D1	0.15[a] (0.0043)	4.62	3.39 (0.11)	0.08 (0.0011)	0.19	0.40 (0.022)	1.73	5.89 (0.24)	0.17 (0.0014)	0.28
D2	0.16 (0.0051)	4.33	4.84 (0.25)	0.06 (0.0008)	0.11	0.28 (0.017)	2.48	5.40 (0.25)	0.13 (0.0017)	0.22
D3	0.14 (0.0052)	4.95	7.77 (0.71)	0.14 (0.0018)	0.20	0.40 (0.02)	1.73	7.2 (0.26)	0.27 (0.002)	0.41
D4	0.15 (0.01)	4.62	1.67 (0.07)	0.05 (0.0019)	0.29	0.27 (0.02)	2.57	5.9 (0.24)	0.17 (0.0017)	0.28
D5	0.17 (0.0027)	4.08	9.97 (0.41)	0.19 (0.0010)	0.26	0.20 (0.0063)	3.47 (0.28)	6.91 (0.0018)	0.21	0.32
D6	0.18 (0.012)	3.85	4.07 (0.27)	0.10 (0.0024)	0.21	0.39 (0.024)	1.78	7.00 (0.29)	0.14 (0.0012)	0.21
D7	0.18 (0.0076)	3.85	4.32 (0.23)	0.09 (0.0015)	0.18	0.14 (0.0033)	4.95 (0.18)	5.29 (0.0012)	0.12	0.21
D8	0.19 (0.003)	3.64	6.69 (0.19)	0.10 (0.0006)	0.16	1.69[b] (0.24)	0.41	7.21 (13)	0.20 (0.0007)	0.30
D9	0.13 (0.0024)	5.33	5.90 (0.21)	0.12 (0.0009)	0.20	0.30 (0.0072)	2.31 (0.24)	8.22 (0.0011)	0.20	0.29
Mean ± S.D.	0.16[b] (0.02)	4.36[b] (0.56)	5.40 (2.49)	0.10[b] (0.04)	0.20[b] (0.05)	0.45 (0.47)	2.38[b] (1.27)	6.56 (0.98)	0.18[b] (0.05)	0.28[b] (0.06)

[a] Estimate (± S.D.)

[b] $p < 0.01$ limb vs diaphragm

Table 8.5. Rate of Recovery from Neuromuscular Paralysis in the Linear (20–80 percent) Effect Range in the Limb and Diaphragmatic Muscles

Subject Code	Rate of Recovery from Paralysis (percent.min^{-1})	
	Limb	Diaphragm
D1	1.57	5.08
D2	1.73	2.54
D3	--[a]	3.24
D4	0.77	2.69
D5	--[a]	3.34
D6	1.35	4.88
D7	1.86	3.12
D8	1.75	3.54
D9	2.05	5.80
Mean ± S.D.	1.58 ± 0.42[b]	3.80 ± 1.16

[a] Insufficient data in the 20–80 percent recovery range

[b] $p < 0.01$ limb vs diaphragm

Table 8.6 Model-Independent Pharmacokinetic Parameters of Alcuronium in Dogs

	Pharmacokinetic Parameters				
Subject	$t_{1/2\beta}$	V_{ss}		Cl	
Code	(min)	(ℓ)	(ml/kg)	(ml/min)	(ml/min/kg)
D1	28	5.85	202	156	5.38
D2	27	7.96	284	195	6.96
D3	86	5.72	286	89	4.45
D4	32	9.69	294	176	5.33
D5	38	4.99	200	114	4.56
D6	25	8.46	302	194	6.93
D7	21	7.20	277	185	7.12
D8	43	7.01	234	126	6.17
D9	40	4.57	208	97	4.41
Mean	38[a]	6.83[a]	254	148[b]	5.70
± SD	21	1.69	43	42	1.12
Humans[c]					
Mean	200[a]	20.9[a]	316	90[d]	1.32[a]
± SD	76	7.0	94	26	0.34

a $p < 0.001$ dog vs humans
b $p < 0.01$ dog vs humans
c Pooled data from single and multiple i.v. doses of alcuronium (n=19), Chapter 4, p 89)

DISCUSSION

In order to achieve maximal paralysis in the limb and diaphragm muscles over a short time period a relatively fast constant-rate infusion of alcuronium was administered to dogs. This dosage regimen was successful in providing effect-concentration-time data both during onset and offset of effect, in all animals studied.

For both muscle groups it was possible to accurately characterize the relationship between plasma concentration and effect during onset and offset of action respectively using the nonlinear form of the Hill equation. However EC_{p50} and hence EC_{p95} estimates obtained during onset were substantially higher than that obtained during offset of effect, for both muscle groups. This discrepancy arises because the Hill equation does not account for the fact that onset data are gathered during a relatively rapid infusion when plasma concentration and effect are maximally out of phase (61), whereas, offset data are gathered when disequilibrium between concentration and effect is minimal. However, using a pharmacodynamic effect model the discrepancy between the onset and offset effect-concentration data may be reconciled and an estimate obtained of the steady-state effect-concentration relationship for both muscle groups.

The time to peak effect was significantly shorter and the maximum effect higher in the peripheral muscle than in the diaphragm during onset and offset. However, these differences were small and corresponding plasma alcuronium concentrations did not differ significantly. The similar plasma concentrations probably reflect the relatively rapid infusion of alcuronium used in this study which would have obscured any possible differences in response between the limb and diaphragmatic muscles. However, the EC_{p50} (and EC_{p95}) estimate for alcuronium

during onset of effect in the diaphragm was approximately 30 percent higher than in the limb muscle.

The offset data in each dog clearly showed that the effect-concentration curves for the diaphragm muscles was shifted to the right of the limb muscles. Thus EC_{p50} and EC_{p95} during offset of effect were higher in the diaphragm than with the peripheral limb. Similarly the $C_{ss(50)}$ and $C_{ss(95)}$ were approximately two-fold higher in the diaphragm than in the limb muscles. These results imply that canine diaphragmatic muscle is less sensitive to the action of alcuronium than are limb muscles.

The results of the present study confirm previous findings of others which indicate that there are differences in sensitivity between the limb and diaphragmatic muscles. For example, Wymore and Eisele (258) found that the sensitivity to d-tubocurarine, of human peripheral musculature was about twice that in diaphragmatic muscles while Taylor et al. (263) showed in vitro that guinea pig peripheral muscles are more sensitive to dTc than the diaphragm.

The data obtained here with alcuronium are also consistent with the classical findings of Waud and Waud (225) which showed that the concentration of dTc required to block nerve transmission in the diaphragm was double that needed to block the peripheral musculature (33).

In addition to being less sensitive to alcuronium, the diaphragmatic muscles also recovered from neuromuscular paralysis at a rate double that noted in peripheral muscles. Previous work in humans (256-258) and animals (225,261) have also shown that recovery in the diaphragm precedes that in the peripheral muscles.

The observed differences in sensitivity of the limb and diaphragmatic muscles to curare-like drugs may result from a number of possible factors

including differences in receptor affinity, muscle temperature, blood flow and diffusional characteristics. The first possibility seems unlikely since the affinity of dTc and other nondepolarizing blocking agents to the neuromuscular junction receptors of the limb and diaphragm is similar (263). That temperature affects the action of nondepolarizing relaxant drugs is well recognized. Alderson and Maglagan (259) observed that the temperature of the limb muscles of cats was always about 2-3°C lower than the respiratory muscles. They attributed their finding of a difference in sensitivity to dTc to a difference in muscle temperature. When the temperature of the two muscles was brought to the same level, the magnitude of the block produced by dTc was similar. However, they did note that the difference in sensitivity between the soleus muscle on one hand and the tibialis and respiratory muscles on the other hand was a true difference and not the result of a temperature gradient. Despite attempts to control temperature in the present study, the limb muscle temperature was 2-3°C lower than the oesophageal temperature (Chapter 3, p. 55). Notwithstanding, the observation of a difference in temperature between the limb and respiratory muscles in the cat, Waud and Waud (225) concluded that temperature differences were not responsible for differences in sensitivity to dTc. Their conclusions are supported by in vitro experiments showing differences in muscle sensitivity at controlled temperatures.

Muscle blood flow may also play a role in the difference in sensitivity of the limb and diaphragmatic muscles since the time for alcuronium plasma concentration to equilibrate with effect was shorter in the diaphragm than in the limb muscles ($t_{1/2\ k_{eo}}$; 2 vs. 4 min respectively). One of the major determinants of k_{eo} (and thus $t_{1/2\ k_{eo}}$) is muscle perfusion (61) and the diaphragm muscles are better

perfused than the limb muscles (256). However $t_{1/2}\ k_{eo}$ may also be temperature dependent (149).

Little information is available on the contribution of the processes distribution and elimination to the differences in sensitivity between the limb and diaphragm musculature. However, these cannot be very important since distributional barriers are minimal in in vitro preparations.

Although the exact reason for the differences in sensitivity to alcuronium between the limb and diaphragmatic muscles, cannot be established from the present work the experimental results clearly demonstrate that a higher plasma concentration of alcuronium is needed to elicit the same response in the diaphragm than in the limb. Furthermore, recovery of the diaphragmatic musculature precedes that in the limb and occurs at a rate double that in the latter.

Although the pharmacokinetics of alcuronium was not a central concern in this study, the pharmacokinetic parameter estimates indicate that the disposition of alcuronium in dogs is markedly different from that in humans. Furthermore, effective concentrations in the dogs were approximately five times less than in humans ($C_{ss(95)}$, humans vs dogs = 0.91 vs 0.20 µg/ml). These facts suggest that the dog is not a suitable animal model for alcuronium pharmacokinetics and pharmacodynamics.

In summary, the findings with alcuronium demonstrate that in the dog the muscles of the diaphragm are more resistant to blockade than the limb muscles and that they recover faster from the neuromuscular paralysis. Thus, the response of the peripheral muscles to nerve stimulation provides only a conservative index of recovery from competitive neuromuscular block in the diaphragmatic muscles of the dog.

Chapter 9

SUMMARY AND CONCLUSIONS

Reported in this thesis are the results of pharmacokinetic and pharmacodynamic research carried out with nondepolarizing neuromuscular blocking drugs, alcuronium, d-tubocurarine and gallamine. The studies with alcuronium included an examination of its disposition and pharmacologic response in healthy patients undergoing elective surgery, in patients with various diseases and in particular cardiac patients undergoing cardiopulmonary bypass surgery. Alcuronium effect-concentration relationships have also been examined in greyhound dogs. The investigations of the latter two relaxant drugs, d-tubocurarine and gallamine included studies of their disposition in patients undergoing surgery involving cardiopulmonary bypass and a re-examination of d-tubocurarine protein binding in normal patients and in patients with various diseases.

The studies with alcuronium in normal patients demonstrated that this relaxant drug possesses pharmacokinetic properties which are similar to those for the commonly used nondepolarizing relaxant drugs, d-tubocurarine and gallamine. Its disposition in humans, following single and multiple intravenous bolus doses and a bolus and concomitant infusion regimen was well characterized by a bi-exponential equation which was interpreted as a two-compartment open mammillary model. Alcuronium is eliminated from the body with an elimination half-life of approximately three hours and the data suggest that it undergoes limited distribution in the body, mainly to extracellular fluid.

Alcuronium's neuromuscular response (muscle paralysis) in patients is related to its plasma concentration as has also been noted with the nondepolarizing relaxant prototype, d-tubocurarine. However, the effect-concentration relationships obtained during onset of effect during the distributive phase following a bolus dose or during a constant-rate

infusion regimen respectively are different from those obtained during the phase of recovery from neuromuscular paralysis. This difference arises from the disequilibrium existing between the plasma concentration and effect during non-equilibrium conditions and can be reconciled with the use of a pharmacodynamic effect model. A model utilizing a separate hypothetical effect compartment connected to the central plasma compartment was found to be appropriate in characterizing the effect-plasma concentration relationship for alcuronium during onset and offset of effect. However, effect-concentration data obtained only during offset of effect provides good estimates of the steady-state effect-concentration relationship.

The pharmacokinetic and pharmacodynamic properties of alcuronium could be examined in various diseases only in a limited number of patients. Nevertheless, the results demonstrate that renal dysfunction has a marked influence on alcuronium pharmacokinetics such that its elimination and clearance from the body is greatly diminished relative to patients with normal renal function. In contrast, in a single patient with obstructive biliary disease, alcuronium distribution and clearance were both increased compared to normal patient groups. There was no detectable alteration in the disposition of alcuronium in a patient with severe tetanus who required a prolonged infusion of the drug over a period of nineteen days. Unfortunately, quantitative-effect data were not available in the tetanus patient. However, there appeared to be increased sensitivity to alcuronium in the patient with biliary dysfunction and unaltered senstivity in renal disease. Thus, it appears that clinical reports that paralysis is prolonged in patients with renal dysfunction can be explained entirely on a pharmacokinetic basis, namely that diminished clearance of alcuronium inhibits the rate of decline of

plasma concentration.

The pharmacodynamics of alcuronium have also been investigated in greyhound dogs who received a constant-rate infusion regimen. Simultaneous measurement of muscle paralysis in the diaphragm and limb were made. The diaphragmatic muscles were shown to be less sensitive to the action of alcuronium than the peripheral limb muscles. In addition, the diaphragmatic muscles recovered from neuromuscular paralysis at double the rate observed with the peripheral muscles. The half-time for equilibration between plasma concentration and effect in the diaphragm was half that in the peripheral muscle. These results collectively suggest that a higher plasma concentration of alcuronium is needed to elicit a response in the diaphragm than in the limb. Thus, the response of peripheral muscles to nerve stimulation provides only a conservative index of the intensity of neuromuscular blockade and recovery from such blockade in the diaphragmatic muscles.

There is wide inter-individual variation in the clinical response to d-tubocurarine and other nondepolarizing relaxant drugs which has been attributed to differences in the extent of their plasma protein binding. However, the results obtained in the present investigation show that d-tubocurarine is approximately 50 percent bound to plasma proteins and that variation in its binding is highly insensitive to plasma concentrations of total protein, albumin, total globulin, total lipids, α_1-acid glycoprotein or the presence of renal, hepatic or cardiac disease. Thus, plasma protein binding variations do not explain the reported variation in clinical response to d-tubocurarine and possibly other nondepolarizing muscle relaxants.

The disposition of alcuronium, gallamine and d-tubocurarine respectively, were found to be altered in cardiac patients during surgery

involving cardiopulmonary bypass. However, there were quantitative differences in the effect of the cardiopulmonary bypass procedure on the pharmacokinetics of these three agents. There were marked pertubations in the plasma concentrations of d-tubocurarine and alcuronium with little disruption to the plasma concentration-time profile of gallamine. These observed differences may be related to altered binding and distributional characteristics of the three relaxant drugs. Gallamine, whose disposition was least affected by the cardiopulmonary bypass procedure, has the smallest distribution volume and is only very weakly plasma protein bound. On the other hand, d-tubocurarine whose plasma concentrations were most severely disrupted has the highest volume of distribution and the highest percentage bound to plasma proteins. In comparison, alcuronium whose distribution volume and plasma protein binding properties lie between d-tubocurarine and gallamine exhibited moderate disruptions to its plasma concentrations as a result of cardiopulmonary bypass. However, the observed differences in the effect of the cardiopulmonary bypass procedure on these three drugs may also be related to the dosage regimen employed in these studies. Alcuronium and d-tubocurarine were administered as bolus and infusion regimens and the cardiopulmonary bypass procedure was instituted while drug was being continuously infused. Thus, perturbations in the concentration-time profile may have been more obvious and pronounced. Gallamine, however, was administered as bolus doses and the cardiopulmonary bypass procedure was started when concentrations were generally in the post-distribution and/or elimination phase so that changes may not have been so readily apparent. From a pharmacokinetic viewpoint, gallamine use is not contraindicated in patients undergoing cardiopulmonary bypass surgery provided that renal function is not impaired. However, lower doses of

d-tubocurarine and alcuronium are required in these patients unless it is established that the concentration-effect relationship for d-tubocurarine and alcuronium is also altered such that higher concentrations are needed to elicit the same response as in normal patients.

The results of the research described here provide information on the pharmacokinetics and pharmacodynamics of selected neuromuscular blocking drugs in healthy patients and in patients with various diseases. Such knowledge should prove valuable clinically in assessing when further doses of muscle relaxant drugs are needed and when antagonism of neuromuscular blockade can be expected to produce rapid recovery. This information is especially important in the critically ill patient. In this respect, the present work provides the first comprehensive report on the disposition of alcuronium, gallamine and d-tubocurarine during cardiac surgery involving cardiopulmonary bypass. It is hoped that this information will add to the success of cardiopulmonary bypass surgery.

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Table 18: Plasma Concentration-Time and Paralysis Data in Dogs

Dog 1				Dog 2				Dog 3				Dog 4			
Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm	Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm	Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm	Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm
2	0.05	2	0	4	0.04	—	—	3	0.08	—	—	4	0.04	13	—
3	0.08	2	0	4	0.06	—	—	5	0.17	—	—	5	0.05	19	—
4	0.10	4	0	5	0.06	—	—	7	0.19	—	—	6	0.06	25	—
5	0.10	7	0	6	0.07	—	—	8	0.21	—	—	7	0.07	35	—
6	0.13	13	3	7	0.09	2	0	9	0.23	9	−2	8	0.07	40	—
7	0.14	17	8	8	—	6	2	10	0.23	24	4	9	0.09	47	—
8	0.16	39	12	9	0.10	23	2	11	0.24	48	10	10	0.09	56	0
9	0.16	50	12	10	0.10	57	7	12	0.24	67	16	11	0.11	58	2
10	0.17	63	21	13	0.16	87	23	13	0.26	74	30	13	0.13	63	6
11	0.17	72	24	14	0.17	92	30	15	0.31	89	38	14	0.14	65	14
12	0.18	77	33	15	0.18	94	47	19	0.35	98	78	16	0.16	71	17
13	0.19	83	48	17	0.20	94	67	20	0.38	100	84	18	0.20	76	19
14	0.21	87	56	19	0.20	95	73	21	0.41	100	88	22	0.19	86	39
15	0.20	87	58	20	0.19	95	80	22	0.38	100	90	24	0.21	89	42
16	0.20	90	64	21	0.21	95	83	24	0.41	100	92	25	0.20	90	50
17	0.20	92	73	22	0.21	96	89	29	0.43	100	96	26	0.21	92	54
18	0.20	93	74	23	0.21	96	90	30	—	100	97	27	0.21	92	58
19	0.23	93	76	24	0.22	96	90	31	0.44	100	97	28	0.22	92	64
20	0.23	95	85	25	0.21	96	90	32	0.42	100	96	29	0.23	92	67
21	0.24	95	88	26	0.25	96	91	34	0.34	100	94	32	0.26	94	81
22	0.25	96	91	27	0.24	97	92	35	0.34	100	93	33	0.24	95	83
26	0.19	95	87	30	0.28	97	95	36	0.35	100	90	34	0.25	96	89
27	0.18	95	71	31	0.22	97	95	37	0.34	100	88	37	0.27	97	93
28	0.17	93	59	32	0.20	97	93	38	0.34	100	86	38	0.27	97	94
31	0.16	93	46	33	0.22	97	92	40	0.34	100	80	39	0.28	97	94
34	0.14	93	28	34	0.21	97	90	45	0.28	100	62	40	0.28	97	96
37	0.12	90	18	36	0.19	97	88	50	0.23	100	48	42	0.29	96	94
40	0.12	87	15	40	0.14	93	78	55	0.21	98	28	43	0.24	96	94
43	0.09	76	7	45	0.13	93	63	60	0.19	98	16	44	0.24	96	91
46	0.09	73	3	55	0.10	91	27	65	0.19	97	2	46	0.20	94	90
50	0.09	68	3	65	0.08	81	17	70	0.18	94	0	47	0.20	94	88
55	0.08	67	3	80	0.05	55	7	80	0.18	89	—	48	0.20	94	80
60	0.07	62	1					85	0.16	85	—	49	0.18	94	78
70	0.06	39	—					90	0.15	83	—	50	0.17	94	77
90	0.04	16	—									55	0.17	92	62
												60	0.16	90	48
												70	0.12	90	22
												80	0.11	84	7
												95	0.07	78	4
												105	0.06	64	4

Dog 5				Dog 6				Dog 7				Dog 8				Dog 9			
Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm	Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm	Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm	Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm	Time (min)	Cp (µg/ml)	% Paralysis leg	diaphragm
3	0.10	—	—	7	0.04	1	2	3	0.04	—	—	5	0.04	2	—	3	0.08	—	—
5	0.15	—	—	9	0.06	4	9	4	0.06	—	—	6	0.07	3	—	4	0.09	—	—
6	0.16	—	—	11	0.06	13	13	5	0.07	—	—	7	0.09	3	—	5	0.11	—	—
7	0.18	—	—	12	0.11	25	16	6	0.09	—	—	8	0.11	3	—	6	0.12	—	—
8	0.20	—	—	13	0.14	35	22	7	0.11	1	—	9	0.12	5	—	7	0.15	—	—
9	0.22	—	—	14	0.13	48	24	8	0.12	2	—	10	0.13	10	0	8	0.19	—	—
10	0.24	—	—	15	0.15	65	40	9	0.13	6	—	11	0.14	19	2	9	0.20	9	4
11	0.23	15	9	16	0.16	71	51	10	0.13	22	0	12	0.16	35	8	10	0.21	20	10
13	0.25	40	39	17	0.16	73	58	11	0.15	42	4	13	0.16	54	16	11	0.23	37	20
14	0.26	57	46	18	0.16	75	64	12	0.16	52	14	14	0.17	71	24	12	0.25	56	40
16	0.26	81	61	19	0.19	77	69	13	0.14	62	21	15	0.18	84	28	13	0.26	72	53
17	0.32	85	76	20	0.19	81	73	14	0.15	74	26	16	0.20	90	40	14	0.29	83	66
18	0.33	94	80	21	0.23	85	84	15	0.17	78	34	17	0.21	94	48	15	0.31	90	76
20	0.37	96	93	22	0.25	90	90	16	0.19	84	41	18	0.23	96	56	16	0.30	94	84
21	0.37	97	94	23	0.24	92	91	17	0.19	86	51	19	0.24	97	60	17	0.32	95	94
22	0.37	98	94	24	0.24	94	92	18	0.21	88	59	20	0.25	98	70	18	0.34	96	94
23	0.39	99	96	27	0.24	99	97	19	0.21	90	71	21	0.25	99	76	19	0.35	98	96
25	0.38	100	96	28	0.24	99	97	20	0.22	92	80	22	0.27	99	80	20	0.36	98	96
26	0.37	100	96	29	0.23	99	97	21	0.22	94	83	23	0.27	99	86	21	0.32	98	98
27	0.38	100	96	30	0.23	99	98	22	0.22	96	86	24	0.28	99	88	22	0.30	98	98
28	0.34	100	96	31	0.20	99	98	23	0.23	98	90	25	0.27	100	87	23	0.29	98	98
29	0.30	100	94	32	0.20	99	98	24	0.23	98	91	26	0.30	100	92	24	0.26	98	98
30	0.29	100	91	35	0.18	99	98	25	0.24	98	93	27	0.30	100	92	25	0.26	98	97
31	0.28	100	90	36	0.15	98	97	26	0.23	98	94	28	0.32	100	93	26	0.24	98	97
32	0.27	100	89	37	0.17	96	96	27	0.24	98	96	29	0.34	100	94	27	0.23	98	97
33	0.26	100	86	38	0.15	94	95	28	0.25	98	96	30	0.35	100	94	28	0.24	98	95
34	0.23	100	84	39	0.14	92	92	29	0.25	98	97	31	0.31	100	94	29	0.22	98	94
35	0.21	100	83	40	0.16	88	88	30	0.28	98	99	32	0.29	100	93	30	0.20	98	92
40	0.20	95	69	45	0.14	79	69	31	0.25	98	99	33	0.26	100	92	35	0.18	96	58
45	0.19	85	55	50	0.13	71	29	32	0.23	98	99	34	0.25	100	91	40	0.16	91	28
50	0.16	55	29	55	0.11	67	20	33	0.22	98	99	35	0.24	100	90	45	0.15	85	16
55	0.14	23	11	60	0.10	56	11	34	0.20	98	97	36	0.25	100	88	50	0.13	76	4
60	0.13	4	3	70	0.07	35	2	35	0.20	98	96	37	0.24	100	84	55	0.12	62	4
70	0.12	0	0	90	0.04	21	0	36	0.19	98	94	38	0.22	100	80	60	0.11	51	3
								37	0.18	98	93	39	0.22	100	78	65	0.10	39	2
								38	0.18	98	92	40	0.21	100	74	70	0.10	33	1
								39	0.17	98	91	45	0.20	99	52	75	0.09	24	0
								40	0.16	98	90	50	0.18	99	36	80	0.08	13	—
								45	0.14	93	89	55	0.16	99	22	85	0.08	4	—
								50	0.12	76	71	60	0.15	96	12	90	0.06	1	—
								55	0.11	60	59	65	0.14	90	6				
								60	0.09	44	29	70	0.13	83	0				
								65	0.07	36	17	75	0.11	74					
								70	0.06	34	14	80	0.11	63					
								75	0.05	28	11	85	0.10	54					
								85	0.04	—	0	90	0.09	41					
												100	0.08	33					

Table 1 : Plasma Concentration-Time Data in Patients Undergoing Elective Surgery who Received Single (0.25 mg/kg) i.v. Bolus Doses of Alcuronium

HK			CA			DA			TE			KB		
t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P
3	—	98	5	1.49	95	5	1.98	87	5	1.63	86	5	1.67	92
5	2.51	99	10	1.26	95	10	1.51	94	10	1.53	100	10	1.02	97
10	1.98	100	15	1.16	95	15	1.25	99	15	1.31	100	15	0.89	97
15	1.72	100	20	0.97	95	20	1.06	99	20	1.11	100	20	0.81	96
20	1.59	100	30	0.80	95	30	0.92	99	30	1.04	100	30	0.69	96
30	1.37	100	45	0.80	91	45	0.69	94	45	0.82	99	45	0.64	75
45	1.03	99	60	0.68	89	60	0.51	90	60	0.68	95	57	0.65	63
60	0.86	98	80	0.58	81	75	0.52	81	75	0.65	91	90	0.46	—
90	0.72	—	120	0.46	—	90	0.51	70	90	0.62	84	120	0.40	—
117	0.70	—	233	0.27	—	105	0.47	51	105	0.59	79	183	0.30	—
188	0.51	—	487	0.13	—	120	0.45	48	120	0.57	—	251	0.17	—
400	0.24	—				180	0.33	—	180	0.41	—	357	0.11	—
						300	0.20	—	240	0.34	—	483	0.06	—
						420	0.11	—	302	0.30	—			
						510	0.07	—	410	0.23	—			

SH			AS			AD			AK			EJ		
t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P
5	2.18	—	5	1.21	—	5	2.05	62	5	1.90	100	5	1.83	89
10	1.89	—	10	0.93	—	10	1.57	86	11	1.66	100	10	1.34	98
15	1.77	—	15	0.79	—	15	1.38	95	15	1.60	100	15	1.31	98
20	1.45	—	20	0.65	—	20	1.09	93	20	1.38	100	20	1.05	98
30	1.18	—	30	0.56	—	30	0.87	93	30	1.12	100	30	0.76	96
45	0.96	—	47	0.44	—	45	0.73	86	40	—	98	45	0.59	92
60	0.87	—	62	0.36	—	60	0.57	66	45	0.86	95	60	0.49	—
92	0.68	—	90	0.24	—	75	—	52	60	0.71	91	90	0.43	—
120	0.51	—	123	0.28	—	85	0.52	—	75	0.60	78	120	0.41	—
180	0.32	—	181	0.26	—	90	—	38	102	0.55	—	180	0.28	—
240	0.22	—	245	0.19	—	110	0.47	—	120	0.45	—	248	0.22	—
464	0.14	—	365	0.16	—	120	0.41	—	180	0.30	—	350	0.20	—
			475	0.12	—	186	0.33	—	270	0.18	—	467	0.12	—
						265	0.32	—	360	0.14	—			
						364	0.28	—	485	0.08	—			
						468	0.22	—						

Table 2 : Plasma Concentration-Time Data in Patients Undergoing Elective Surgery who Received Multiple (0.25 + 0.125 mg/kg) Bolus Doses of Alcuronium

PS		PL			GC			RM			DJ		
t	Cp	t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P
5	1.59	5	2.56	94	5	2.17	100	6	1.45	35	2.5	2.08	87
10	1.23	10	1.68	99	10	1.54	100	10	1.16	63	5	1.38	91
15	1.02	15	1.41	100	15	1.28	100	16	1.03	99	10	1.01	92
20	0.94	20	1.30	100	20	1.13	100	21	1.50	100	15	0.89	95
30	0.78	30	1.14	100	30	0.94	97	26	1.27	100	20	0.85	95
45	0.69	40	—	99	43	0.75	82	31	1.07	100	30	0.68	94
52	0.58	45	0.87	97	44	—	71	41	0.78	99	45	0.59	85
50	1.32	60	0.64	96	49	1.61	97	56	0.72	94	57	0.32	80
63	1.01	75	—	84	54	1.40	98	71	0.63	83	62	0.32	75
68	0.91	77	0.54	78	59	1.20	98	86	0.69	75	65	0.15	92
73	0.79	85	1.84	100	64	1.09	97	101	0.67	47	70	0.89	96
83	0.81	90	1.52	100	74	0.94	96	113	0.66	33	75	0.79	98
93	0.79	95	1.26	100	89	0.73	85	131	0.69	—	80	0.75	98
105	0.75	100	1.12	100	102	0.65	48	191	0.54	—	85	0.70	98
113	0.72	110	0.86	100	132	0.53	—	251	0.49	—	95	0.68	97
131	0.59	122	0.75	99	164	0.49	—	359	0.43	—	103	—	95
143	0.36	140	0.75	—	226	0.35	—	456	0.27	—	110	0.71	93
158	0.32	170	0.58	—	284	0.24	—				120	—	90
173	0.35	200	0.38	—	389	0.15	—				125	0.66	89
233	0.21	326	0.21	—	473	0.11	—				140	0.63	80
302	0.21	440	0.13	—							167	0.52	—
406	0.15	541	0.06	—							190	0.43	—
514	0.07										327	0.19	—
											453	0.12	—

TP			AB			LC		
t	Cp	%P	t	Cp	%P	t	Cp	%P
5	2.25	100	5	2.00	93	5	1.03	83
10	1.68	100	10	1.43	100	10	0.86	90
15	1.40	100	15	1.24	100	15	0.66	91
20	1.24	100	20	1.02	100	20	0.59	89
33	1.03	99	30	0.80	99	30	0.49	83
45	0.86	97	45	0.64	93	37	1.06	97
60	0.75	94	60	0.50	86	42	0.89	97
76	0.75	84	70	0.43	79	47	0.73	97
95	0.62	76	—	1.19	99	52	0.60	91
92	2.29	100	81	1.01	99	62	0.52	89
90	1.83	100	86	0.87	99	77	0.48	87
102	1.53	100	91	0.88	99	92	0.46	83
106	1.43	100	101	0.76	98	98	0.46	89
116	1.26	100	116	0.70	96	103	0.96	100
129	1.03	99	131	0.63	88	108	0.90	100
146	0.86	97	140	0.58	76	114	0.82	100
150	0.78	96	146	1.79	99	123	0.63	97
176	0.69	88	151	1.33	99	138	0.73	95
192	0.59	85	156	1.12	99	153	0.54	83
206	0.54	71	161	1.01	99	168	0.53	76
221	0.50	57	171	0.85	98	183	0.58	73
266	0.36	—	186	0.81	96	216	0.54	—
335	0.27	—	201	0.69	88	273	0.42	—
446	0.16	—	216	0.59	79	337	0.33	—
			233	0.57	77	473	0.18	—
			261	0.49	—			
			318	0.42	—			
			394	0.29	—			
			515	0.18	—			

Table 3 : Plasma Concentration-Paralysis-Time Data in Patients who Received a Combined Intravenous Bolus and Infusion Regimen of Alcuronium

JR			KJ			OG			EE			GJ			LM		
t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P
5	2.08	96	5	2.20	93	5	1.93	100	5	1.69	99	5	1.81	100	6	1.35	99
10	1.73	97	10	1.67	97	10	1.78	100	10	1.28	100	10	1.37	100	10	1.21	100
15	1.31	93	15	1.53	98	15	1.57	100	15	1.20	100	15	1.17	100	15	1.09	100
20	1.18	93	30	1.32	98	20	1.53	100	20	0.97	100	20	1.07	100	20	1.02	100
30	1.06	93	45	1.09	98	30	1.41	100	30	0.93	99	30	0.90	97	30	0.89	100
45	0.92	82	60	0.90	98	45	1.15	100	45	0.81	98	45	0.72	96	40	0.78	100
60	0.83	68	75	0.92	97	60	1.11	100	60	0.76	98	60	0.77	91	60	0.70	100
80	0.77	55	90	0.84	96	75	0.98	100	75	0.66	96	75	0.78	90	80	0.70	100
100	0.70	50	105	0.66	95	90	0.92	100	90	0.63	93	90	0.76	88	100	0.63	99
109	0.57	41	120	0.69	94	105	0.91	99	105	0.60	92	105	0.72	93	120	0.64	99
114	0.55	32	135	0.75	94	120	0.90	98	120	0.61	89	120	0.75	91	140	0.65	99
119	0.50	23	140	0.68	92	135	0.94	97	140	0.40	89	135	0.76	93	160	0.60	99
124	0.50	18	145	0.68	90	150	0.92	96	146	0.58	—	150	0.74	91	180	0.63	99
132	0.45	11	150	0.61	88	165	0.89	96	151	0.55	—	155	0.67	89	185	0.61	99
149	0.43	—	155	0.60	77	170	0.90	95	156	0.54	—	160	0.62	88	190	0.61	99
173	0.38	—	165	0.58	68	175	0.78	92	161	0.48	—	165	0.58	85	195	0.56	99
199	0.34	—	180	0.54	—	180	0.71	90	171	0.44	—	170	0.58	82	200	0.55	99
224	0.29	—	195	0.51	—	185	0.69	86	186	0.41	—	180	0.53	74	210	0.56	98
314	0.21	—	225	0.44	—	195	0.63	81	201	0.37	—	195	0.52	68	225	0.54	98
404	0.14	—	249	0.42	—	210	0.54	63	229	0.35	—	210	0.46	60	240	0.50	97
489	0.13	—	317	0.27	—	225	0.50	—	261	0.27	—	240	0.37	—	260	0.45	96
589	0.09	—	379	0.19	—	255	0.41	—	328	0.22	—	270	0.32	—	300	0.38	—
			498	0.13	—	285	0.37	—	411	0.16	—	330	0.28	—	421	0.20	—
			622	0.07	—	405	0.22	—	521	0.11	—	390	0.21	—	548	0.14	—
						525	0.14	—	629	0.07	—	510	0.19	—	650	0.09	—
						640	0.11	—				630	0.14	—			
						805	0.06	—				870	0.06	—			

DC			SH			CM			JB			SS			AM		
t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P
5	2.06	100	5	1.88	98	5	4.17	100	5	1.65	91	5	2.91	99	5	3.16	91
10	1.78	100	10	1.29	100	10	2.96	100	10	1.59	99	10	2.46	100	10	2.22	98
15	1.44	100	15	1.02	100	15	2.51	100	15	1.42	99	15	2.09	100	15	2.10	98
20	1.56	100	20	0.99	100	20	2.51	100	20	1.32	99	20	1.88	100	20	1.96	98
30	1.35	99	30	1.03	100	30	2.06	100	30	1.04	99	25	1.52	100	30	1.78	97
45	1.30	99	45	0.92	100	45	1.64	100	45	0.77	99	45	1.32	100	45	1.46	97
60	1.26	99	60	1.18	100	60	1.58	99	60	0.74	99	60	1.27	99	58	1.40	97
80	1.20	99	75	1.15	100	74	1.58	99	65	0.77	99	70	1.20	99	63	1.17	96
100	1.16	99	83	0.71	100	93	1.05	—	70	0.77	99	75	1.08	99	68	1.05	91
120	1.27	98	88	0.67	100	98	0.83	—	75	0.78	99	80	1.03	98	78	1.03	—
140	1.21	98	93	0.66	100	103	0.75	—	80	0.74	99	85	0.96	97	88	1.02	—
157	1.14	98	98	0.63	100	108	0.69	—	90	0.73	98	90	0.84	96	104	0.92	—
162	1.10	98	108	0.57	100	113	0.66	—	104	0.75	—	100	0.82	—	120	0.79	—
167	1.08	98	123	0.49	100	123	0.61	90	121	0.55	—	115	0.77	—	148	0.68	—
172	1.03	95	138	0.49	99	138	0.56	—	150	0.49	—	130	0.66	—	183	0.60	—
182	1.02	—	153	0.47	97	153	0.55	—	180	0.42	—	160	0.54	—	238	0.49	—
206	0.93	—	168	0.43	90	183	0.44	—	285	0.34	—	190	0.42	—	298	0.38	—
261	0.86	—	189	—	87	213	0.34	—	545	0.22	—	256	0.29	—	421	0.29	—
326	0.68	—	198	0.36	—	283	0.20	—				340	0.17	—	548	0.22	—
414	0.59	—	258	0.30	—	391	0.12	—				433	0.11	—			
502	0.41	—	318	0.24	—	453	0.06	—				550	0.07	—			
622	0.35	—	498	0.14	—												
			636	0.10	—												

Table 4 : Plasma Concentration-Time Paralysis Data in Patients with Various Diseases who Received Alcuronium

Biliary Disease			Renal Disease									Tetanus Patient		
	MC			SP			VL			LA		During Infusion		Post Infusion
t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	% P	t	Cp	t Cp
5	0.87	98	5	1.47	97	5	1.67	92	5	1.83	98	6	2.52	192.6 1.70
10	0.72	98	10	1.10	96	10	1.25	100	10	1.47	98	14	3.43	192.7 1.46
15	0.62	98	15	0.94	92	15	1.05	100	15	1.33	100	22	2.93	192.8 1.37
20	0.56	98	20	0.85	90	20	1.01	99	20	1.25	100	46	1.68	192.9 1.36
30	0.48	97	25	0.78	86	30	0.84	95	30	1.11	99	54	1.30	193.1 1.25
45	0.37	93	31	1.38	98	45	0.75	90	45	0.99	98	62	1.03	193.4 1.16
60	0.31	89	36	1.03	97	60	0.64	88	60	0.85	97	71	1.22	193.6 1.02
75	0.28	71	41	0.93	97	75	0.59	85	75	0.88	93	86	1.37	193.9 0.94
90	0.27	64	46	0.93	95	90	0.55	82	90	0.84	90	94	1.42	194.8 0.72
105	0.26	60	56	0.91	93	105	0.53	78	105	0.78	88	102	1.30	196.6 0.62
120	0.27	52	71	0.92	90	120	0.52	—	120	0.76	87	110	1.29	198.6 0.41
194	0.18	—	86	0.90	86	188	0.56	—	135	0.81	85	114	1.55	201.6 0.24
240	0.17	—	101	0.92	84	270	0.46	—	150	0.81	83	122	2.26	202.6 0.20
360	0.14	—	116	0.86	78	425	0.41	—	180	0.77	82	130	1.17	206.6 0.12
480	0.07	—	131	0.81	71	540	0.38	—	240	0.77	—	134	1.03	
600	0.05	—	146	0.75	66				360	0.67	—	138	1.54	
			161	0.67	58				480	0.59	—	146	1.32	
			208	0.55	54				720	0.53	—	154	1.40	
			273	0.44	—				960	0.47	—	162	1.55	
			406	0.39	—				1440	0.26	—	166	1.46	
			506	0.32	—							181	1.18	
												186	1.58	
												193	1.70	

a min
b Hours

Table 5 : Pre-operative Medications and Anaesthetic Agents Received by the Normal Surgical Patients Receiving Alcuronium

Patient Code	Pre-Operative Medications (mg)	Anaesthetic Agents (mg)	I.V. Fluids	Reversal Agents (mg)
HK	Pe 75mg Ph 0.5mg Dp 5mg	Th 200	a	A 2.5mg N 5mg
JH	Ph 0.5mg Dp 7.5mg	Th 750	NS	A 2.5mg N 5mg
CA	Pe 100mg Ac 300mg Ery 250mg Dp 8mg Na 0.5mg A 0.6mg	Th 350	—	A 2.5mg N 5mg
AS	Pa 20mg Ne 1g Fl 200mg Ph 0.5mg Dp 10mg	Th 450	NS	—
DA	Pa 15mg Sc 0.3mg Ph 0.5mg Dp 5mg	Th 500	NS	—
AD	Pa 15mg Ph 1.5mg Dp 7.5mg	Th 375	NS	A 2.5mg N 5mg
TE	A 0.6mg Pe 75mg Dp 8mg Ph 0.5mg H 5000IU	Th 500	—	A 2.6mg N 5mg
MA	Pe 100mg Ph 0.5mg Dp 8mg	Th 500	NS	A 2.5mg N 5mg
KB	Pa 20mg Sc 0.4mg H 5000IU Ph 0.5mg Dp 8mg	Th 450	NS	—
MK	Pa 15mg Sc 0.3mg Dp 10mg Ph 0.5mg	Th 300	—	—
FO	Ph 0.5 Cep 1g	Th 375	Ns+Tr	A 2.5mg N 5mg
PL	Dp 5mg Ph 0.5mg	Th 600	NS	—
GC	Pe 100mg Dp 10mg Ph 0.5mg	Th 400	—	—
RW	Pe 100mg Ne 1g Fl 200mg Ph 0.5mg Dp 8mg	Th 250	—	—
DJ	Dp 8mg Ph 0.5mg	Th 400	CO	A 2.5mg N 5mg
TP	Pe 100mg Ph 0.5mg Dp 10mg	Th 250	—	—
AB	Pe 75mg Dp 0.5mg Ph 7mg Am 1g	Th 300	—	—
LC	Pe 75mg Ph 0.5 Dp 5mg H 5000I.U.	Th 200	—	—
SS	Pa 10mg Sc 0.2mg Dp 8mg Ph 0.5mg	Th 300	—	—
OG	Dp 10mg Ph 0.5mg Sc 7 Cm, Oz, Thx	Th 250	Fe 100µg	A 2.5 mg N 5mg
DC	Pe 50mg A 0.6mg Tox Dp 7mg Ph 0.5mg Am 1g	Th 200	NS	A 2.5 N 5mg
KE	Pe 100mg Dp 10mg Ph 1mg Ce 2g Thx SO	Th 400	NS	—
EE	Pa 20mg Ce 1g Dp 10mg Ph 0.5mg	Th 300	—	—
AM	Ph 0.5mg Dp 8mg	Th 500	—	—
LM	Pa 20mg Dp 10mg Ph 2.0mg A 0.6mg	Th 500	—	—
JR	Pa 20mg Sc 0.4mg Ph 0.5mg Dp 10mg	Th 550	—	—
CM	Ph 0.5mg Dp 5mg	Th 250	—	A 2.5mg N 5mg
EM	Dp 5mg Ph 1mg Hy 100mg	Th 250	NS	—
JB	Pa 15mg Dp 7mg Ph 0.5mg H 2500IU Ce 2g	Th 275	—	—
GW	Pe 50mg Dp 7mg Ph 0.5mg Sc 0.4mg	Th 300	NS	—
EJ	Pe 10mg Dp 10mg Ph 1mg	Th 400	NS	A 2.5mg N 5mg
DK	Tr, Ph	—	NS	A 2.5mg N 5mg
SP	Ce 2g Pl 10mg Ph 1.5mg	—	NS	A 1.2mg N 2.5mg
LA	Dp 8mg Ce 1g Pg 25mg	Th 400	Fe 100µg	—
VL	Am, Dp 8mg Ph 0.5mg Ce 2g	Th 400	—	—
SP	Pe 250mg Mt 100mg Mp 5mg Pa 15mg Dp 8mg Ph 0.5mg Pg 25mg Hy 500mg	Th 500	—	—
MC	Pa 15mg Dp 5mg Ph 2mg Ce 2g	Th 100	—	—

Ce	Cephalothin	Ha	Haloperidol
Pe	Pethidine	Pa	Papavertum
Ph	Phenoperidine	Ne	Neomycin
Dp	Droperidol	Ery	Erythromycin
Th	Thiopentone	Fl	Flagyl
A	Atropine	Am	Ampicillin
Sc	Scopolamine	Co	Collold
H	Heparin (Uniparin)	Fe	Fentanyl
Tr	Trasylol	Thx	Thyroxine
NS	Saline	Tox	Tomoxiphen
Ac	Acetylsalicylic acid	Hy	Hydrocortisone

Cm	Cimetidine		
Oz	Oxazepam		
Mp	Minipress		
Pl	Propranolol		
Pg	Phenergan		
Am	Amphogel		
Me	Methyldopa		
Mt	Metoprolol		

a Data not available

Table 6 : Individual Clinical Characteristics and d-Tubocurarine Free Fraction in Normal Surgical Patients

Patient Code	Age (yr)	Sex	Total Protein (g/ℓ)	Serum Albumin (g/ℓ)	Total Globulins (g/ℓ)	Lipids Cholesterol (mmol/ℓ)	Lipids Triglyceride (mmol/ℓ)	Free Fraction[a]
N1	38	M	60	36	34	3.7	1.0	0.55 ± 0.01
N2	50	M	57	36	21	5.1	1.1	0.47 ± 0.01
N3	26	F	75	44	31	4.9	0.6	0.54 ± 0.01
N4	54	F	76	44	32	7.1	1.4	0.48 ± 0.01
N5	54	M	77	39	38	5.7	1.1	0.47 ± 0.01
N6	21	M	70	46	24	4.5	1.1	0.54 ± 0.01
N7	27	M	74	47	27	6.8	1.3	0.54 ± 0.01
N8	46	F	59	32	27	5.5	0.9	0.44 ± 0.01
N9	19	F	68	40	28	4.0	0.6	0.44 ± 0.01
N10	31	M	69	44	25	4.0	0.8	0.51 ± 0.01
N11	17	F	79	47	32	—b	—	0.53 ± 0.01
N12	29	F	73	43	30	—	—	0.48 ± 0.01
N13	57	M	68	42	26	5.6	1.0	0.49 ± 0.01
N14	23	F	66	38	28	4.4	0.8	0.51 ± 0.01
N15	59	F	69	38	31	7.0	—	0.51 ± 0.01
N16	66	F	51	32	19	5.1	0.9	0.44 ± 0.02
N17	62	F	67	36	31	5.7	0.7	0.41 ± 0.01
N18	70	M	60	35	25	6.3	2.3	0.50 ± 0.01
N19	73	F	58	36	22	6.1	0.5	0.57 ± 0.01
N20	63	F	—	38	—			0.49 ± 0.01
N21	83	F	64	27	27	4.7	1.1	0.51 ± 0.01
N22	75	M	70	28	42	4.1	1.2	0.48 ± 0.01
Mean	47		67	39	29	5.3	1.0	0.50
± SD	20		8	6	5	1.1	0.4	0.04

a Mean of duplicate determinations
b Not determined because of insufficient plasma volume

Table 7 : Individual Clinical Characteristics and d-Tubocurarine Free Fraction in Renal Disease Patients

Patient Code	Age (yr)	Sex	Total Protein (g/ℓ)	Serum Albumin (g/ℓ)	Total Globulins (g/ℓ)	Creatinine (µmol/ℓ)	Lipids Cholesterol (mmol/ℓ)	Lipids Triglyceride (mmol/ℓ)	AAG[a] (g/ℓ)	Free Fraction[b]
Acute Renal Failure										
RF1	40	M	57	26	31	346	2.7	1.3	3.7	0.42 ± 0.01
RF2	53	F	56	20	16	416	2.5	2.1	1.4	0.54 ± 0.01
RF3	36	M	62	27	35	837	4.5	4.8	2.5	0.47 ± 0.01
Chronic Renal Failure										
RF4	59	F	48	25	23	952	5.1	2.2	2.3	0.45 ± 0.01
RF5	29	F	65	39	26	1136	6.2	2.3	0.87	0.42 ± 0.01
RF6	52	F	64	36	28	875	4.9	1.8	0.40	0.48 ± 0.01
RF7	57	M	68	35	33	1088	4.9	1.6	2.3	0.37 ± 0.01
RF8	53	M	63	37	26	513	8.7	2.6	0.4	0.42 ± 0.01
RF9	46	F	48	29	19	644	5.4	2.4	0.8	0.57 ± 0.01
RF10	47	M	83	51	32	625	6.2	3.3	0.8	0.42 ± 0.01
RF11	37	M	75	37	38	133	—c	—	0.8	0.43 ± 0.01
RF12	50	F	67	38	29	820	6.2	1.7	1.6	0.44 ± 0.01
RF13	63	M	66	28	38	245	4.6	1.0	0.4	0.40 ± 0.01
RF14	62	F	53	25	28	1250	5.8	1.8	0.8	0.46 ± 0.01
RF15	62	M	40	21	27	348	3.5	0.6	2.5	0.37 ± 0.01
Mean	50		60	32	29	682	5.1	2.1	1.4	0.44
± SD	10		12	6	6	345	1.6	1.0	1.0	0.05

a α1-acid glycoprotein
b Mean of duplicate determinations
c Not determined because of insufficient plasma volume

Table 8 : Individual Clinical Characteristics and d-Tubocurarine Free Fraction in Liver Disease Patients

Patient Code	Age (yr)	Sex	Total Protein (g/ℓ)	Serum Albumin (g/ℓ)	Total Globulins (g/ℓ)	Bilirubin (µmol/ℓ)	Lipids Cholesterol (mmol/ℓ)	Lipids Triglyceride (mmol/ℓ)	ALT[a] (IU/ℓ)	AST[b] (IU/ℓ)	AAG[c] (g/ℓ)	Free Fraction[d]
LD1	52	M	59	37	22

Table 10: Details of the Cardiopulmonary Bypass Procedure in Patients who Received Alcuronium

Patient Code	Pump Prime Volume (ℓ)	Lowest Body Temp. during CPB (°C)	Blood Flow During CPB (ℓ/min)	Heparin Dose (IU) X 10^3	Time Rewarming Commenced[a] (min)
DF	3.4	26	4.2	42	56
AG	2.5	—[b]	3.7	32	—
LF	2.6	—	4.3	36	—
UB	3.6	27	3.6	39	—
FB	2.5	28	3.3	30	34
MW	2.5	—	4.2	35	35
AD	2.0	—	3.8	35	38
TM	2.0	25	4.3	—	35
MM	4.5	—	4.3	35	36
HR	2.5	—	—	35	40
Mean ± SD	2.8 ± 0.8	27 ± 1	3.9 ± 0.4	35 ± 4	39 ± 8

a Prior to end of CPB
b Data not available

Table 11: Plasma Concentration-Time Data in Patients Undergoing Surgery Involving Cardiopulmonary Bypass who Received Alcuronium

DF		AG		LF		UB		FB	
t	Cp	t	Cp	t	Cp	t	Cp	t	Cp
5	1.34	5	1.59	5	1.38	5	1.39	5	1.02
10	1.01	10	1.16	10	0.98	10	0.81	10	0.70
15	0.71	15	0.88	15	0.73	15	0.68	15	0.66
20	0.60	20	0.76	20	0.67	20	0.56	20	0.54
30	0.66	30	0.68	30	0.89	30	0.48	30	0.51
45	0.89	45	0.64	45	0.68	45	0.42	37	0.56
57	0.83	53	0.73	54	0.46	46	0.36	45	0.59
67	0.83	62	0.85	63	0.98	64	0.75	52	0.53
75	0.83	72	0.93	73	1.03	74	0.87	62	0.76
90	0.70	82	0.99	90	1.10	90	0.91	75	0.92
105	0.46	92	1.00	105	1.08	105	0.89	90	0.95
120	0.57	105	1.00	120	1.09	120	0.99	105	1.00
135	0.61	120	1.03	135	1.01	135	1.00	120	0.98
150	0.85	135	1.13	150	0.98	150	1.04	135	1.15
165	0.92	150	1.21	165	1.10	165	1.18	150	1.48
180	0.96	165	1.09	180	1.16	180	1.00	162	0.79
195	1.00	180	1.08	195	1.19	200	1.10	167	0.69
210	0.78	195	1.04	208	1.45	210	1.12	172	0.68
219	0.73	210	0.98	216	1.36	215	1.07	177	0.59
225	0.85	225	1.06	223	1.28	220	0.95	187	0.47
229	0.85	240	1.06	228	1.20	225	0.87	202	0.47
234	0.77	248	0.96	233	1.21	230	0.82	217	0.43
244	0.66	253	0.91	238	0.93	260	0.68	237	0.38
259	0.63	263	0.75	248	0.99	270	0.63	256	0.36
274	0.57	273	0.70	263	0.93	300	0.60	341	0.35
294	0.48	288	0.60	278	0.88	330	0.52	396	0.29
349	0.43	303	0.52	318	0.81	450	0.36	516	0.18
444	0.44	333	0.65	343	0.76	570	0.36	696	0.15
564	0.39	483	0.41	358	0.60	690	0.34	756	0.13
684	0.29	753	0.22	578	0.41	810	0.26	876	0.10
804	0.22	843	0.17	698	0.37			1116	0.06
924	0.18	963	0.13	938	0.26				
1179	0.12	1203	0.08	1274	0.17				

MW		AD		TM		MM		HR	
t	Cp	t	Cp	t	Cp	t	Cp	t	Cp
5	0.86	5	0.68	5	0.51	5	1.70	5	1.21
10	0.77	10	0.51	10	0.27	10	0.99	10	0.81
15	0.64	15	0.48	15	0.21	15	0.74	15	0.85
20	0.55	20	0.38	20	0.15	20	0.69	20	0.82
30	0.75	30	0.38	30	0.19	30	0.77	30	0.81
45	0.69	45	0.36	45	0.23	45	0.71	45	0.56
60	0.60	58	0.60	60	0.29	56	0.63	59	0.60
75	0.60	75	0.63	75	0.28	66	1.07	70	0.78
90	0.63	90	0.53	94	0.29	75	1.18	80	0.77
94	0.74	105	0.61	94	0.72	90	1.30	90	0.90
105	0.95	120	0.66	105	0.71	105	1.34	105	0.94
120	1.09	135	0.69	120	0.82	120	1.19	120	1.00
135	0.98	150	0.68	135	1.03	135	1.18	135	0.98
150	0.98	165	0.74	150	1.08	150	1.15	150	1.03
165	0.96	180	0.74	165	1.18	165	1.23	165	0.98
180	1.07	195	1.52	180	1.19	180	1.19	180	1.21
195	1.08	204	1.30	195	1.09	186	1.16	195	1.09
210	1.06	210	1.24	210	1.05	191	1.04	200	1.04
217	0.91	216	1.15	225	1.09	196	1.05	205	0.87
222	0.86	220	1.10	240	1.37	206	0.95	210	0.87
227	0.81	225	1.09	256	1.56	216	0.86	215	0.94
232	0.77	235	0.98	262	1.44	236	0.78	225	0.88
242	0.79	250	0.95	267	1.31	246	0.76	240	0.77
257	0.72	265	0.83	272	1.20	274	0.68	254	0.81
273	0.64	295	0.67	277	1.16	306	0.68	290	0.78
303	0.53	325	0.50	287	1.14	376	0.49	320	0.71
334	0.48	390	0.41	302	0.95	426	0.37	385	0.58
394	0.40	445	0.40	317	0.87	546	0.33	440	0.50
459	0.33	565	0.31	352	0.86	616	0.35	560	0.38
574	0.26	685	0.22	377	0.76	786	0.32	680	0.34
695	0.21	805	0.19	437	0.58	906	0.27	800	0.33
815	0.16	925	0.16	497	0.43	1146	0.23	920	0.29
935	0.13	1165	0.10	617	0.31	1386	0.20	1160	0.20
1175	0.11	1405	0.09	737	0.30	1624	0.18	1400	0.18
1415	0.06	1645	0.08	857	0.20			1640	0.14
				977	0.18				
				1097	0.14				
				1337	0.07				

Table 12: Details of the Cardiopulmonary Bypass Procedure in Patients who Received Gallamine

Patient Code	Pump Prime Volume (ℓ)	Lowest Body Temp. during CPB (°C)	Blood Flow During CPB (ℓ/min)	Heparin Dose (IU) X 10^3
Group 1[a]				
PS	2.8	28	4.3	25
TD	2.8	31	4.0	28
RD	2.8	28	4.2	27
MM	2.8	27	4.0	24
BA	2.8	27	4.0	17
ID	2.8	28	3.8	22
EC	2.8	29	---c	20
LB	2.8	31	4.3	20
UF	2.8	27	3.8	22
BL	2.8	26	---	28
BK	3.3	30	4.0	28
Mean ± SD	2.8 ± 0.2	28 ± 2	4.0 ± 0.2	24 ± 4
Group 11[b]				
FI	2.8	25	3.8	39
PK	3.4	24	3.7	41
NB	2.8	28	4.5	32
DM	2.8	28	5.2	39
NC	2.8	27	3.8	19
JC	2.8	23	3.3	25
AK	3.7	28	3.7	34
ML	3.3	31	3.3	23
HC	2.8	27	4.0	32
RR	2.5	30	3.6	19
KD	3.0	25	3.7	31
Mean ± SD	3.0 ± 0.3	27 ± 3	3.9 ± 0.5	25 ± 11
Pooled Data				
Mean ± SD	2.9 ± 0.3	28 ± 2	4.0 ± 0.4	27 ± 7

a Dose = 480 mg
b Dose = 240 + 240 mg
c Not determined

Table 13: Plasma Concentration-Time Data in Patients Undergoing Surgery Involving Cardiopulmonary Bypass who Received 480 mg of IV of Gallamine

LB		MM		TD		RD		ID	
t	Cp	t	Cp	t	Cp	t	Cp	t	Cp
5	47.92	5	73.65	5	50.33	5	43.01	5	59:21
10	41.15	10	57.07	10	44.57	10	36.67	10	45.39
15	36.46	15	52.72	15	38.04	15	33.89	15	39.37
20	31.51	20	48.37	20	33.70	20	29.17	20	35.53
30	29.17	30	38.86	30	23.91	28	23.34	30	30.92
45	23.96	45	33.43	45	27.17	45	20.44	45	28.16
54	18.96	59	25.54	60	24.46	60	18.17	60	24.61
64	13.44	69	23.91	73	23.70	76	17.22	65	25.26
74	18.75	79	25.00	84	17.80	86	13.44	76	19.47
84	17.14	95	23.26	94	17.28	96	13.56	86	20.53
120	13.44	122	18.15	104	15.87	106	12.44	96	17.50
150	12.24	180	15.00	120	14.35	120	9.56	130	16.58
242	6.67	239	10.07	180	9.57	180	9.33	177	12.24
360	4.06	362	6.84	240	8.48	240	6.88	241	8.03
507	2.24	480	3.85	360	3.70	365	3.22	361	5.00
607	1.30	600	2.30	480	2.23	480	2.44	606	1.71
720	0.94			600	1.20	600	1.33	721	1.25
				720	0.65	720	0.67		

BK		BL		DF		RS		BA		EC	
t	Cp	t	Cp	t	Cp	t	Cp	t	Cp	t	Cp
5	63.02	5	52.22	5	65.34	5	47.40	5	60.94	5	46.25
10	47.40	10	42.22	10	57.95	10	41.15	10	51.04	10	36.25
15	40.63	15	35.56	15	47.73	15	35.94	15	44.01	15	31.25
20	35.94	20	32.22	20	43.18	20	33.85	20	40.63	20	28.44
30	33.85	30	25.56	30	35.80	30	29.17	30	35.42	30	23.50
45	30.21	45	21.78	45	31.82	45	27.08	45	29.17	45	23.06
51	30.21	52	11.78	55	25.00	60	21.88	60	19.79	58	17.00
60	18.54	70	16.89	65	19.55	71	21.67	70	19.69	68	13.38
70	13.54	80	19.00	75	21.14	81	16.46	80	19.06	78	12.69
80	20.21	90	18.11	90	20.91	91	16.46	90	16.36	88	12.38
90	17.29	135	17.00	120	18.75	101	16.93	120	12.65	120	16.25
120	15.21	180	13.78	244	10.34	120	16.04	190	8.13	180	11.67
180	9.90	240	12.67	361	7.33	190	12.60	240	5.73	251	9.72
240	6.88	360	7.00	480	4.66	245	9.37	366	3.13	360	5.20
360	4.27	480	4.44	600	3.01	300	6.04	490	1.46	420	3.45
480	2.29	605	3.22	720	2.05	480	4.38	605	0.83	600	1.95
610	1.35	740	1.61			585	3.39	720	0.42	720	1.38
730	0.73					720	2.40			795	0.30

Table 14: Plasma Concentration-Time Data in Patients Undergoing Surgery Involving Cardiopulmonary Bypass who Received 240 + 240 mg of Gallamine

JC		KD		PK		AK		NB	
t	Cp	t	Cp	t	Cp	t	Cp	t	Cp
5	33.09	5	41.67	5	28.89	5	27.72	5	26.67
10	28.09	10	30.21	10	21.94	10	21.30	10	19.20
15	24.85	15	24.48	15	18.05	15	18.59	15	16.27
20	21.32	20	22.00	20	17.22	20	16.09	20	16.53
30	18.97	26	19.17	30	15.14	30	14.02	30	12.67
45	15.88	31	17.50	45	13.33	57	12.71	45	10.40
60	14.26	46	30.94	60	12.22	63	34.24	60	9.87
65	40.44	56	27.60	62	30.55	68	31.62	66	30.33
70	35.66	71	20.21	67	25.97	73	30.43	71	24.27
75	35.29	86	26.04	72	26.52	78	28.26	76	21.87
80	33.09	116	22.00	77	25.42	88	27.71	81	25.20
90	30.74	151	18.44	82	23.06	103	26.09	91	24.67
105	29.12	202	14.25	92	21.25	118	21.74	106	23.47
120	25.88	362	9.48	107	21.11	148	18.48	121	19.87
150	22.94	1112	1.20	122	20.83	178	16.85	151	18.40
180	20.00			152	19.86	238	10.11	181	14.93
300	8.97			182	14.38	298	7.83	241	10.80
420	5.44			242	11.67	426	5.92	301	6.73
540	3.24			302	8.47	541	5.54	421	3.93
660	1.84			435	6.81	666	5.11	542	2.47
735	1.18			555	6.11	781	4.02	661	1.47
					5.00			781	1.30
					1.67				

NC		ML		FI		HC		RR		DM	
t	Cp	t	Cp	t	Cp	t	Cp	t	Cp	t	Cp
5	33.10	5	32.98	5	32.43	5	28.61	5	32.43	5	20.13
10	29.32	10	23.40	10	25.20	10	23.47	10	23.38	10	16.32
15	25.68	15	22.02	15	20.95	15	19.72	15	20.14	15	14.34
20	22.70	20	18.72	20	18.38	20	16.94	20	19.97	20	12.43
30	17.84	30	17.02	30	16.49	30	15.70	30	14.80	30	10.20
45	15.14	45	31.91	45	14.05	45	13.06	45	12.61	45	8.16
51	18.38	50	33.24	60	13.72	60	12.78	53	11.89	51	30.26
56	39.86	55	31.38	66	13.24	65	33.20	59	30.41	56	26.31
61	34.46	60	30.85	71	38.51	70	31.94	64	29.46	61	24.47
66	33.78	70	25.74	76	29.73	75	30.56	69	27.16	66	23.16
71	31.42	85	24.47	81	29.73	80	28.19	74	28.38	76	22.24
81	26.22	100	21.28	86	28.51	90	26.67	84	21.62	91	20.52
111	21.62	130	14.73	96	24.86	105	24.44	99	21.89	106	19.74
141	18.51	160	13.72	111	25.81	120	21.67	114	16.76	136	16.45
215	12.16	220	10.48	126	23.11	150	17.50	144	14.73	166	12.24
291	8.92	280	7.61	156	19.46	180	14.78	174	10.94	229	7.37
413	5.42	425	5.80	306	8.11	240	10.97	294	5.54	346	5.13
538	2.43	520	4.15	429	5.00	303	8.06	414	3.92	466	2.50
658	1.82	640	2.76	546	3.04	440	4.31	534	2.36	586	1.38
		1115	1.06	664	1.89	518	3.13	654	1.62	706	0.92
				786	1.22	668	2.08	777	0.88	826	0.59
						788	1.32				

Table 15: Details of the Cardiopulmonary Bypass Procedure in Patients who Received d-Tubocurarine

Patient Code	Pump Prime Volume (ℓ)	Blood Flow During CPB (ℓ/min)	Heparin Dose (IU) X 10^3	Time of Heparin Admin.[a] (min)
GB	2.0	4.2	35	48
MW	2.0	4.7	44	50
TQ	2.5	4.5	35	38
JT	2.5	4.6	40	46
KL	2.5	4.1	23	33
ME	4.0	4.4	34	30
TK	2.5	4.2	33	34
AM	2.0	3.6	30	43
RW	2.0	3.7	28	34
FD	2.5	4.4	40	46
TT	3.0	4.1	30	33
BC	2.0	4.4	37	40
ER	4.5	3.8	30	42
Mean	2.6	4.2	34	40
± SD	0.8	0.3	6	6

a Assigning time of dTc dose as zero

Table 16: Plasma Concentration-Time Data in Patients Undergoing Surgery Involving Cardiopulmonary Bypass who Received d-Tubocurarine

GB		BC		ME		KL		MW		TQ	
t	Cp	t	Cp	t	Cp	t	Cp	t	Cp	t	Cp
5	4.65	5	5.08	5	3.00	5	3.56	5	3.24	5	5.85
10	3.82	10	3.58	10	1.76	10	3.66	10	2.93	10	4.24
15	2.29	15	2.22	15	1.62	15	3.27	15	2.46	15	4.23
20	2.00	20	2.32	20	1.43	20	2.85	20	2.80	20	4.00
30	1.88	30	3.03	30	1.50	30	2.59	30	2.51	30	3.41
45	2.12	45	2.60	45	1.72	38	2.23	45	2.10	45	2.42
60	1.76	60	2.43	61	1.38	48	3.51	60	1.57	60	1.89
74	3.26	70	3.25	71	1.77	60	3.55	73	3.43	73	3.41
90	3.93	80	3.55	80	1.94	75	3.37	80	3.50	90	3.74
105	4.53	90	3.56	90	2.31	90	3.68	90	4.14	105	3.74
120	5.07	105	3.28	105	2.33	105	3.70	105	4.05	120	3.64
135	5.10	120	3.52	120	2.53	120	3.88	120	4.22	135	3.27
150	5.29	135	3.65	135	2.75	135	4.20	135	4.28	150	3.22
165	6.02	150	3.70	150	3.24	150	4.30	150	4.59	166	3.34
180	5.25	165	3.75	165	3.33	163	4.13	165	4.50	171	2.71
195	4.93	180	3.28	180	3.62	168	3.42	180	4.22	176	2.56
210	5.11	199	3.63	195	3.38	173	3.12	195	3.60	181	2.17
227	5.10	204	3.55	210	3.69	178	2.91	210	3.62	186	1.96
232	4.45	209	3.35	225	3.60	183	2.95	225	4.41	191	1.96
237	4.17	214	3.38	255	3.60	193	2.57	240	4.06	206	1.67
242	3.77	219	3.58	260	2.90	208	2.27	255	4.50	226	1.56
247	3.75	229	2.73	265	2.94	223	1.78	267	4.06	256	1.26
257	3.12	244	2.40	270	2.74	253	1.63	272	3.81	286	1.13
272	2.66	259	2.00	275	2.74	283	1.48	277	3.44	346	0.72
287	2.71	289	1.87	285	3.04	343	1.19	282	3.36	409	0.62
322	2.84	319	1.50	300	2.83	405	0.59	287	3.26	526	0.54
365	2.51	379	1.58	315	2.54	523	1.03	297	2.88	646	0.47
407	2.41	439	1.28	345	2.34	643	0.86	317	2.87	776	0.45
467	2.13	579	1.00	375	2.43	763	0.79	327	2.58	886	0.26
587	1.91	679	0.80	440	2.37	883	0.60	357	2.39	1126	0.22
707	1.72	799	0.82	495	2.40	1243	0.50	390	2.25	1456	0.19
827	1.23	919	0.60	625	2.13			452	2.26		
947	0.98	1159	0.47	735	1.70			510	1.84		
1187	0.90			915	1.26			627	1.47		
1427	0.76			1035	1.13			750	1.06		
1667	0.73			1215	0.96			867	0.98		
				1455	0.73			985	0.84		
				1695	0.52			1227	0.70		
								1483	0.56		
								1707	0.43		

JT		TK		AM		RW		FD		TT		ER	
t	Cp	t	Cp	t	Cp	t	Cp	t	Cp	t	Cp	t	Cp
5	5.16	5	2.79	5	4.68	5	5.94	5	3.93	5	4.18	5	4.18
10	3.13	10	2.28	10	3.05	10	2.89	10	2.92	10	3.52	10	2.45
15	2.34	15	1.96	15	1.71	15	2.41	15	1.92	15	3.14	15	1.95
20	1.64	20	2.24	20	1.95	20	2.44	20	2.66	20	2.51	20	1.83
30	1.75	30	1.96	30	1.71	30	2.53	30	2.13	30	3.29	30	2.29
45	1.56	45	2.06	45	1.91	45	2.14	45	2.21	45	2.90	45	2.21
60	1.89	52	2.10	57	2.32	46	2.17	60	1.99	47	2.66	60	2.14
70	2.49	62	3.21	68	3.09	59	3.82	70	2.47	57	4.23	70	3.21
80	2.94	75	3.33	78	3.80	75	3.78	80	2.61	67	4.21	80	3.48
90	2.81	90	3.40	90	4.15	90	3.96	90	2.99	75	4.57	90	3.25
105	3.23	105	3.30	105	4.63	105	3.69	105	3.11	90	4.79	105	3.27
120	3.31	120	3.25	120	4.84	120	3.85	120	3.26	105	4.47	120	3.24
135	2.73	135	3.13	135	4.63	135	3.69	135	1.93	120	4.48	135	3.40
150	1.71	150	2.81	150	4.43	150	3.72	150	1.95	135	4.94	150	3.00
165	4.06	165	3.36	165	3.98	165	3.65	165	1.61	150	4.91	165	3.00
180	3.44	180	3.06	180	4.39	180	2.94	160	1.61	165	5.07	180	2.81
195	4.02	185	2.76	194	4.27	185	2.83	165	1.32	163	4.35	187	2.60
210	3.89	190	2.60	199	3.82	190	2.72	170	1.22	188	4.02	192	2.12
222	3.67	197	2.47	204	3.37	195	2.51	180	1.17	193	3.69	197	1.86
227	3.27	200	2.26	209	3.15	200	2.31	195	1.00	198	3.63	202	1.86
232	2.40	210	2.68	214	3.11	210	2.25	210	1.00	203	3.49	212	2.27
237	2.31	225	2.32	224	2.81	225	1.72	240	0.99	213	3.35	227	1.82
242	2.14	240	2.15	239	2.64	245	1.46	270	0.83	228	3.10	242	1.82
252	1.95	270	2.01	254	2.69	270	1.13	332	0.74	243	2.61	272	1.73
267	2.04	300	1.80	284	2.14	300	1.15	390	0.63	273	2.52	302	1.79
282	1.67	360	1.47	314	1.85	360	0.91	472	0.54	313	2.17	372	1.57
312	1.33	429	1.51	374	1.52	420	1.72	530	0.50	393	1.93	427	1.45
342	1.25	559	1.32	434	1.05	540	0.87	620	0.43	423	1.54	542	1.43
402	0.90	660	1.11	554	0.85	660	0.83	752	0.36	543	1.23	657	1.07
462	0.87	780	0.81	674	0.59	780	0.66	870	0.32	663	1.05	782	0.81
582	0.64	900	0.81	794	0.60	1020	0.68	1002	0.30	783	0.83	902	0.62
822	0.49	1140	0.51	914	0.55	1370	0.58	1190	0.24	903	0.65	1202	0.41
942	0.38	1362	0.49	1164	0.41	1380	0.51	1262	0.21	1143	0.50	1382	0.40
				1394	0.31	1630	0.43			1383	0.40	1622	0.35
				1634	0.20					1633	0.29		

Table 17: d-Tubocurarine Free Fraction and α1-Acid Glycoprotein Concentrations in Patients on Day 0, day 1, and day 2 after Cardiopulmonary Bypass Surgery

Patient Code	Day 0		Day 1		Day 2	
	AAG[a] (g/ℓ)	FF[b]	AAG (g/ℓ)	FF	AAG (g/ℓ)	FF
GB	1.17	0.44	0.97	0.43	1.32	0.41
MW	1.32	0.48	---	0.42	1.03	0.38
TQ	1.42	0.55	1.29	0.41	0.76	0.37
JT	0.38	0.50	1.10	0.50	---	---
KL	0.56	0.53	0.52	0.51	---	---
ME	1.03	0.50	1.26	0.48	0.90	0.44
TK	1.20	0.46	0.80	0.44	---	---
AM	1.01	0.53	1.17	0.