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BUPIVACAINE *VERSUS* LIGNOCAINE FOR THIRD MOLAR SURGERY

A double blind randomised crossover study

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Abstract

The aim of this study was to compare bupivacaine to lignocaine for third molar removal under local anaesthesia. Pain experience, analgesic consumption, cardiovascular responses, blood concentrations and systemic toxicity were evaluated. Twenty-three patients underwent the surgical removal of asymptomatic, bilaterally symmetrical, third molar teeth. At the first appointment the third molar teeth on one side were removed using either bupivacaine or lignocaine while the contralateral teeth were removed one month later using the alternate local anaesthetic. Pain experience was recorded with visual analogue and global pain scales. Blood pressure and heart rate were recorded with an automated sphygmomanometer. The blood concentrations of the local anaesthetics were measured with enantio-sensitive high pressure liquid chromatography equipment. Results showed that bupivacaine significantly reduced the post-operative pain experience only at the eight hour period ($p < 0.05$). No difference in analgesic requirements and cardiovascular responses were observed between the two local anaesthetics. The mean peak blood concentrations of both agents were considerably lower than their respective toxic threshold concentrations. The mean blood concentration of R-(+) bupivacaine was significantly less than S-(-) bupivacaine ($p < 0.0005$). No signs or symptoms of systemic toxicity were observed in any subject.

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INTRODUCTION AND AIMS OF THE STUDY

The administration of local anaesthetic is the first step prior to any oral surgical procedure carried out on conscious patients. This also applies to the majority of oral surgical procedures performed under general anaesthesia. Lignocaine 2% with adrenaline 1:100,000 (NurocainTM) is regarded as the Australian standard to which all other local anaesthetics are compared. However, the last 30 years has seen bupivacaine 0.5% with adrenaline 1:200,000 (MarcainTM) become increasingly popular within the surgical fraternity due to its longer duration of action, and hence, its increased duration of post-operative anaesthesia and analgesia. It is therefore surprising that to date no study has been undertaken to evaluate the blood concentrations and systemic toxicity of bupivacaine when used in Oral and Maxillofacial Surgery. The objectives of this study are as follows:

1. To compare the efficacy of bupivacaine and lignocaine for the surgical removal of impacted third molar teeth.
2. To compare post-operative pain with both local anaesthetic agents.
3. To compare the post-operative analgesic requirements.
4. To monitor the cardiovascular responses following administration.
5. To measure the blood concentrations of lignocaine and the two bupivacaine enantiomers.
6. To observe any signs of systemic toxicity.

¹Astra Pharmaceuticals Pty. Ltd., Australia

CHAPTER 1

REVIEW OF THE LITERATURE

1.1. LIGNOCAINE

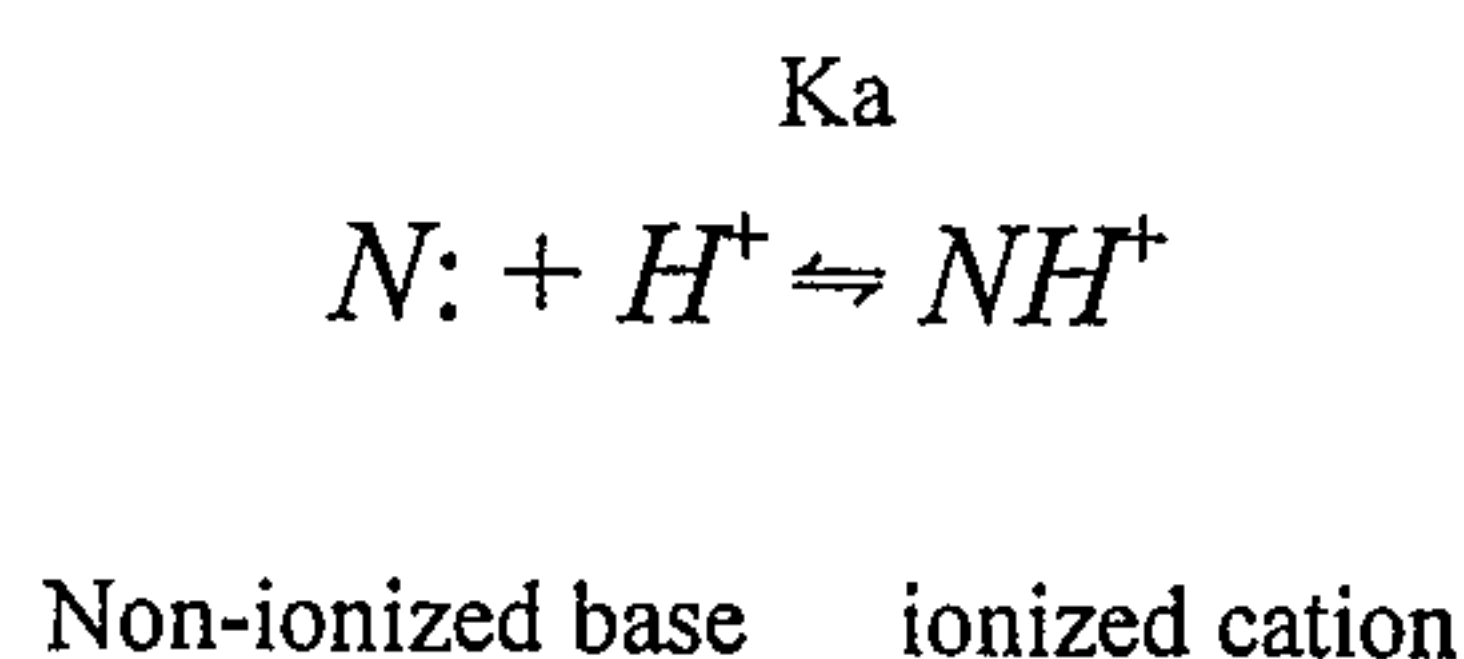
1.1.1. Chemistry

Lignocaine (N-diethylaminoacetyl-2,6-xylidide) (Fig.1a) was first synthesised by Lofgren, a Swedish chemist, in 1943 and was first introduced into clinical use in 1948. It has a molecular weight of 234.3 and its empirical formula is $C_{14}H_{22}N_2O$. As with all local anaesthetics, lignocaine has a common formula consisting of a lipophilic end, an intermediate chain and a hydrophilic end. Lignocaine base is a white crystalline powder and has a melting point of 66-69°C. The base is only slightly soluble in water but the acid salt of the base, lignocaine hydrochloride ($C_{14}H_{22}N_2O.HCl$), is highly soluble in water. It is this form of lignocaine that is used for administration by injection.

The composition of a 2.2 mL NurocainTM cartridge of 2% lignocaine solution with adrenaline is: lignocaine hydrochloride 44 mg, sodium chloride 13.2 mg, sodium metabisulphite 1.1 mg and adrenaline acid tartrate 0.04 mg (Astra, 1995). The development of a sterile packaging system has enabled the manufacturer to exclude preservatives such as methyl paraben, which have been implicated in allergic reactions to local anaesthetics in a number of patients (Aldrete and Johnson, 1970). Isotonicity of the solution is maintained by the sodium chloride, while the sodium metabisulphite is an antioxidant which prevents degradation of the adrenaline tartrate. The nature, role and effects of adrenaline will be discussed later in this chapter.

1.1.2. Physico-chemical properties

Lignocaine hydrochloride exists in solution as an equilibrium mixture of the non-ionized (free base) and the ionized (cationic) form.



The position of equilibrium depends on the dissociation constant (Ka) of the cationic form and on the local hydrogen ion concentration. This equation can be rearranged and logarithms taken to obtain the familiar Henderson-Hasselbach equation,

$$pKa = pH - \log \frac{[base]}{[acid]}$$

where pKa is defined as the pH at which the local anaesthetic is 50% ionized. With a pKa of 7.9, lignocaine exists at physiological pH (7.4) predominantly in the ionized form (65%)(Covino, 1986). However, it is the non-ionized form of the drug which penetrates the nerve and other biological membranes more easily and is therefore, a primary contributor to the onset of action (Feldman, 1994). Covino (1986) has described the onset of anaesthesia with lignocaine as rapid when compared to other local anaesthetics.

Lipid solubility is an expression of the relative ability of a chemical to penetrate lipids. Because nerve membranes are essentially a lipoprotein matrix, consisting of approximately 90%

lipids and 10% proteins, lipid solubility is the primary determinant of anaesthetic potency or depth. As a result, lipophilic agents penetrate the nerve membrane more easily, such that fewer molecules are required for conduction blockade (Covino, 1986). Lignocaine has a lipid solubility of 2.9 (Cousins and Mather, 1980) and it is the agent to which the potencies of all other local anaesthetics are compared.

Protein binding characteristics of local anaesthetics are the primary determinant of the duration of anaesthesia. Agents with high protein binding capabilities are thought to bind strongly with receptors in the sodium channels of nerves that are primarily protein in nature. Thus, they tend to remain longer than those that are less firmly bound, resulting in longer blockade of the nerves (Cousins and Mather, 1980). Lignocaine has a protein binding of 64.3% and is considered to produce anaesthesia of moderate duration.

1.1.3. Vasomotor activity

Much of the history of the haemodynamic study of local anaesthetic agents has been concerned with understanding the cardiovascular collapse occurring after toxic doses. The increased duration of action and decreased absorption of local anaesthetic agents, if given with vasoconstrictors, contributed to the assumption that local anaesthetics were vasodilators. Blair (1975) has shown that the effect of lignocaine on vascular smooth muscle can be either vasoconstriction or vasodilation, depending on the site of administration, the anaesthetic concentration and the existing tone of the vascular muscle. For some precapillary sphincters and venular sections, local anaesthetic agents in increasing concentrations can:

- 1) increase the height and rate of spontaneous contractions within the vascular smooth muscle
- 2) increase the basal tone with superimposed spontaneous contractions
- 3) increase and sustain the basal tone and
- 4) eventually inhibit all myogenic activity.

It has been suggested that the contractile effects of the local anaesthetic agents are caused by the increased cytoplasmic levels of calcium associated with decreased efflux from the cell, while relaxation is produced by a decreased calcium influx and cessation of electrogenic activity (Blair, 1975). Despite the potential for vasoconstriction, the variable response of vascular smooth muscle to lignocaine would mitigate for the use of a vasoconstrictor to reduce bleeding and decrease the rate at which the local anaesthetic is systemically absorbed.

1.1.4. Pharmacokinetics

The rate of absorption into the systemic circulation is dependent on: the choice of drug, the dose, the site of injection, the speed of injection, the presence of a vasoconstrictor and concomitant cardiovascular disease (Cousins and Mather, 1980). Absorption proceeds in a biphasic manner with an initial peak blood concentration occurring 10 to 20 minutes after injection and a continued decline in blood concentration as the net absorption of the local anaesthetic is exceeded by its distribution, metabolism and clearance. The pharmacokinetic parameters of lignocaine are related to blood/plasma ratio, volume of distribution, half-life and clearance rate.

The plasma and whole blood drug concentrations of any local anaesthetic are not identical.

The ratio of whole blood to plasma concentration varies amongst the amide type local anaesthetics, being lowest for the longer acting agents. This, in turn, reflects differences in their binding to plasma proteins which hinders access to the erythrocytes. The plasma/erythrocyte distribution correlates directly with the relative protein binding capacity of the drug. Lignocaine, with only modest protein binding capacity, has a low plasma/erythrocyte ratio. Most of the plasma binding is accounted for by association with high affinity low capacity sites on the α_1 -acid glycoprotein (Mather and Thomas, 1978). The ratio of the blood to plasma concentration of lignocaine is 0.84 (Tucker and Mather, 1975).

It is generally considered that pharmacological activity is related only to the free or unbound drug concentration (Tucker *et al.*, 1970; Tucker and Mather, 1975). Only unbound drug is subject to metabolism or excretion. The unbound fraction of lignocaine increases with total plasma drug concentration as binding sites approach saturation.

The volume of distribution (V_{DSS}) of lignocaine refers to the distribution of the local anaesthetic agent with respect to its concentration in blood and does not represent volumes of real physiological spaces (Holford and Benet, 1995). The relative V_{DSS} provides information concerning the differential uptake and accumulation of local anaesthetic agents by various bodily tissues. If a drug has a very small V_{DSS} , this implies very high binding to plasma proteins; if a drug has a very large V_{DSS} (e.g. larger than the body volume), this implies that the drug is highly concentrated in tissues or organs. The V_{DSS} of lignocaine is 91 litres and its concentration in bodily tissues is greater than that of bupivacaine.

The half-life characterizes the net rate of drug removal from the blood and from

compartments in which the drug has reached equilibrium with drug in reference blood. The half-life of lignocaine is 90 minutes which is less than that of bupivacaine. The mean total body clearance (Cl) expresses the efficiency with which eliminating organs can remove drug from the blood per unit time and is generally regarded as a more reliable parameter than half-life, which may be influenced by other factors such as V_{DSS} , clearance rate, disease states and multicompartmental drugs. Lignocaine has a clearance rate of 950 mL per minute which is similar to that of bupivacaine.

The clearance of all local anaesthetic agents can be equated almost entirely with metabolic clearance as renal excretion of unchanged forms accounts for less than 10% of the dose at normal urine pH values (Mather *et al.*, 1971b). Lignocaine is primarily eliminated by hepatic metabolism, which is dependant on liver blood flow and liver function. Patients with hepatic dysfunction or decreased cardiac output show a corresponding reduction in hepatic metabolism. In one study, Keenaghan and Boyes (1972) examined urine collected over 24 hours from healthy male subjects after oral ingestion of lignocaine hydrochloride. They identified a number of lignocaine metabolites in urine including: unchanged lignocaine (2.8%), monoethylglycinexylidide (3.7%), glycinexylidide (2.3%), 3-hydroxylignocaine (1.1%), 3-hydroxymonoethylglycinexylidide (0.3%), 2,6-xylidine (1.0%) and 4-hydroxy-2,6-dimethylaniline (72.6%). These metabolites represented 83.8% of the total drug.

Collingsworth *et al.* (1975) have demonstrated that in the presence of renal failure, lignocaine plasma concentrations, V_{DSS} , half-life and clearance rates were all within the normal range. However, two lignocaine metabolites, monoethylglycinexylidide and glycinexylidide, are pharmacologically active and the latter, with a half-life of 10 hours, has been shown to

accumulate in uraemic patients with the possibility of clinical toxicity.

Pharmacokinetic parameters in children and neonates have also been reported (Ecoffey *et al.*, 1983; Mihaly *et al.*, 1978). Despite an increased V_{DSS} and half-life, the total body clearance adjusted per body weight is the same as that of an adult. Placental transfer of lignocaine has also been documented. The rate of passive diffusion is mainly a function of the concentration gradient of the local anaesthetic between maternal and foetal blood, the pH gradient between mother and foetus, the lipophilicity of the agent and the maternal protein binding (Finster and Pedersen, 1975). A decrease in foetal blood pH produces a higher foetal blood lignocaine level through ion 'trapping'. This is because it is the non-ionized base that traverses biological membranes easily, including the placenta, and foetal acidosis increases the proportion of ionized base which then cannot diffuse back through the placenta. The presence of acidosis in the adult has the same net effect, that is to increase the plasma concentration of lignocaine, decrease plasma binding and increase the fraction of ionized base.

1.1.5. Toxicology

Toxicity due to lignocaine may arise from inadvertent intravascular administration or from an overdose. In general terms, the toxicity is proportional to the plasma concentration. While the following discussion of toxicity pertains to venous plasma concentrations which are more easily obtained, it should be remembered that differences in arterial and venous concentrations have been consistently observed, with significantly higher arterial values. The threshold toxic plasma concentration of lignocaine is 5 to 6 $\mu\text{g/mL}$ (Scott and Cousins, 1980). In patients receiving a combination of local and general anaesthesia, the toxic threshold is considered to be

approximately double (Gianelly *et al.*, 1967). Foetal blood levels above 3 µg/mL may cause toxicity due to reduced metabolic enzymes and decreased protein binding which result in a higher proportion of active non-bound drug. Contrary to this, Morishima *et al.* (1981) have shown that foetal sheep exhibit the same toxic plasma threshold as neonates and adult sheep.

Clinically, the therapeutic or toxic ratio of local anaesthetics can be expressed as the ratio between the blood level at which systemic toxic reactions occur (C_{tox}) and the peak blood level after a therapeutic epidural dose (C_{max}). The margin of clinical safety for a particular local anaesthetic is measured by this ratio; the higher the ratio, the safer the agent. Plain lignocaine has a ratio of 1.6 while lignocaine with adrenaline has a ratio of 2.3. The recommended dose for plain lignocaine is 4 mg/kg and 7 mg/kg for lignocaine with adrenaline (Scott and Cousins, 1980).

Systemic toxicity can be divided into two major categories, central nervous system (CNS) effects and cardiotoxicity. Furthermore, lignocaine may produce local neurogenic or muscular toxicity. The primary effects of lignocaine toxicity involve the CNS. Feldman (1994) provides an excellent review of toxicity. As the plasma concentration increases, a progression of signs and symptoms occurs, and these include: paraesthesia of the tongue and circumoral tissues, lightheadedness, tinnitus, visual disturbances, slurred speech, muscle twitching, irrational conversation, unconsciousness, electroencephalogram changes (Engleson and Matousek, 1975), grand mal convulsions, coma and respiratory arrest. The myriad of signs and symptoms reflects an initial suppression at low lignocaine levels, followed by excitation at higher levels and finally a state of complete depression. At low concentrations, lignocaine is an effective anticonvulsant as a result of depression of the hyperexcitable cortical neurons. The CNS stimulation is thought to be related to the suppression of inhibitory cortical synapses or neurons. As the plasma level

continues to rise, the facilitatory neurons are also blocked, leading to a state of overall CNS depression.

The cardiovascular system is considered more resistant to toxicity than the CNS (Feldman, 1994). In fact lignocaine, at concentrations below 6 $\mu\text{g/mL}$, has been used for over 30 years for its antiarrhythmic properties related to its ability to block sodium channels without causing haemodynamic effect. However, lignocaine has also been shown to cause depression of the maximal rate of rise (V_{max}) of the cardiac action potential, a decrease in intracardiac conduction, negative inotropy and chronotropy, arrhythmias, atrioventricular block, electromechanical dissociation, ventricular tachycardia and fibrillation, asystole and hypotension. Fujita (1994), in comparing direct effects of lignocaine and bupivacaine on regional myocardial function in dogs, has shown that both lignocaine and bupivacaine decrease regional myocardial function at concentrations of 10 $\mu\text{g/mL}$ and 2.5 $\mu\text{g/mL}$ respectively, as measured by the percentage systolic shortening. Liu *et al.* (1982) reported similar results in a study of the acute cardiovascular toxicity of intravenous amide local anaesthetics in anaesthetised ventilated dogs. Furthermore, Fujita (1994) has suggested that significant cardiac depression must be considered when the plasma concentration approaches the CNS toxic level. De Jong *et al.* (1982) concluded that subconvulsant doses of lignocaine do not precipitate cardiac arrhythmias and that adequate ventilation enables twice the convulsant dose of any amide local anaesthetic to be withstood, presumably as a result of controlling metabolic and respiratory acidosis. Despite the potential for cardiac arrhythmias with local anaesthetics, Plowman *et al.* (1974) have shown an increased incidence of arrhythmias under a general anaesthesia when local anaesthesia is not used conjointly.

In a study of myotoxicity, Foster and Carlson (1980) have shown that local anaesthetics, when injected directly into muscle, will produce muscle fibre degeneration and subsequent regeneration within one month. Lignocaine was shown to damage approximately 50% of the muscle cross-section where as bupivacaine damaged approximately 90% of the muscle cross-section. With either anaesthetic the only evidence of injury at 30 days was the persistence of central nuclei in the regenerating muscle fibres. The presence of adrenaline in the local anaesthetic worsens the damage to the muscle fibres and produces an ischaemic lesion.

With regard to local neurotoxicity, Barsa *et al.* (1982) have demonstrated that 12 days after exposure to 2% lignocaine or 0.5% bupivacaine with adrenaline, C-fibre impulse conduction was normal in nerves and there were no significant histological abnormalities. Epineurial cellular infiltration and fibrosis, perineurial fibrosis and axonal degeneration were not seen. Feldman (1994) has suggested that pH, preservatives and concentration may contribute to local neurotoxicity but clinically this only occurs with lignocaine and bupivacaine concentrations of 32% and 3.3% respectively.

A number of drug interactions have been reported with local anaesthetics. The concomitant use of β -adrenergic blockers, calcium channel blockers and cardiac glycosides with lignocaine and especially bupivacaine has produced cardiotoxicity and arrhythmias (Feldman, 1994). It has also been shown that both propranolol and cimetidine reduce hepatic blood flow and inhibit the metabolism and clearance of lignocaine and bupivacaine (Bowdle *et al.*, 1987; Knapp *et al.*, 1983).

The treatment of local anaesthetic induced toxicity is controversial. The protocol for

managing CNS toxicity is more widely accepted than the management of cardiovascular toxicity. The latter is exceedingly uncommon with lignocaine, and as such, will be discussed later with bupivacaine. The treatment of CNS complications is directed primarily at maintaining an open airway, providing proper ventilation to prevent hypoxia, and controlling seizure activity. Short acting barbiturates such as thiopental, and benzodiazepines such as diazepam have been used successfully (Moore *et al.*, 1979; Davis and De Jong, 1982).

1.2. BUPIVACAINE

1.2.1. Chemistry

Bupivacaine (1-butyl-2',6'-pipecoloxylidide) (Fig. 1b) was first synthesized in 1957 by Ekenstam, a Scandinavian chemist, and was first introduced into clinical use in 1963. It is the longer side chain with four methylene groups on the piperidine ring that is responsible for the different properties of bupivacaine when compared to lignocaine. It has a molecular weight of 288.4, an empirical formula of $C_{18}H_{28}N_2O$ and exists as white crystalline base with a melting point of 251-258°C. The base is not soluble in water but the acid salt, bupivacaine hydrochloride ($C_{18}H_{28}N_2O.HCl$), is slightly soluble. It is this form of bupivacaine that is used for administration by injection.

The composition of a 2.2 mL MarcainTM cartridge of 0.5% bupivacaine solution with 1:200,000 adrenaline is: bupivacaine hydrochloride 11 mg, sodium chloride 17.6 mg, sodium metabisulphite 1.1 mg and adrenaline acid tartrate 0.02 mg (Astra, 1995). As with lignocaine, preservatives have been excluded with the advent of a sterile packaging system. The remaining constituents serve a similar role to those included with lignocaine.

1.2.2. Physico-chemical properties

Bupivacaine hydrochloride exists in solution as an equilibrium mixture of the non-ionized (free base) and the ionized (cationic) form. As with lignocaine, the position of equilibrium depends upon the dissociation constant (K_a) of the cationic form and the local hydrogen ion concentration. With a pK_a of 8.1, bupivacaine will exist predominantly in the ionized form at

physiological pH. At this pH, the proportion of the non-ionized forms of lignocaine and bupivacaine are 35% and 20% respectively. This contributes in part to a slightly slower onset of anaesthesia with bupivacaine, particularly for nerve block anaesthesia (Moore, 1990), as it is the non-ionized form that diffuses more readily across biological membranes.

Bupivacaine is one of the most lipid soluble local anaesthetics and hence is one of the most potent. With a lipid solubility of 28 (Cousins and Mather, 1980), bupivacaine exhibits much greater lipophilicity than lignocaine and less bupivacaine molecules are required for conduction blockade. Consequently, bupivacaine is considered to be four times as potent as lignocaine. Equipotent doses of both local anaesthetics are achieved by variations in their concentrations, 0.5% and 2% respectively.

The long duration of anaesthesia produced by bupivacaine is a reflection of its high protein binding capacity. With a protein binding of 95.6% (Cousins and Mather, 1980), bupivacaine attaches to a greater proportion of the protein component of a nerve membrane and is less likely to diffuse from the site of action into the systemic circulation.

In addition to the anaesthetic properties described above, one other important clinical consideration is the ability of local anaesthetic agents to cause a differential blockade of sensory and motor fibres. It is only the longer acting local anaesthetics such as bupivacaine and etidocaine which have this quality. The factors responsible for the differential sensory/motor separation are not precisely known. The diameter of nerves and the presence of myelin are important. The C fibres are unmyelinated with a diameter of 0.5 to 1 μm , A_δ fibres are lightly myelinated with a diameter of 1 to 4 μm while A_α fibres are heavily myelinated with a diameter

of 12 to 20 μm . The first two types subserve pain and temperature while the latter is solely motor. At low concentrations it is believed that bupivacaine initially blocks unmyelinated C fibres followed, at a later time, by a block of myelinated A fibres. The slow block of A fibres by bupivacaine is believed to be attributable to the relatively high pKa of this agent, such that fewer uncharged molecules are available to penetrate the diffusion barriers surrounding large A fibres (Covino, 1986). High lipid solubility is also thought to play an important role in differential sensory/motor blockade. Recently it has been shown that axons are more sensitive to local anaesthetic blockade if the frequency of impulse traffic in the nerve is increased (Cousins and Mather, 1980).

1.2.3. Vasomotor activity

The effect of bupivacaine on vascular smooth muscle is not documented as well as that of lignocaine. In a study by Dhuner and Lewis (1966) in man, both bupivacaine and lignocaine caused vasodilation in the vascular bed of the arm muscle. In a comparative study by Blair (1975) in dogs, both local anaesthetics caused vasodilation in the hind limb when administered intra-arterially. Blood flow returned to normal within five minutes for lignocaine but not for bupivacaine. Blair also reported that bupivacaine has both vasoconstrictor and vasodilator activity. The effect on some precapillary sphincters and venular sections was identical to that of lignocaine, however, bupivacaine was a more potent vasodilator.

1.2.4. Pharmacokinetics

As with lignocaine, the absorption of bupivacaine proceeds in a biphasic manner with an

initial peak blood concentration occurring 10 to 20 minutes after injection and a continued decline in blood concentration as the net absorption is exceeded by its distribution, metabolism and clearance. The pharmacokinetic parameters for lignocaine apply to bupivacaine, namely blood/plasma ratio, volume of distribution, half-life and clearance rate.

The ratio of whole blood to plasma concentration is lower for long acting local anaesthetics such as bupivacaine. This reflects differences in protein binding characteristics and the decreased binding by erythrocytes (Tucker and Mather, 1975). The unbound fraction of bupivacaine increases with total plasma drug concentration and the percentage of bound drug on the individual plasma proteins decreases. Mather and Thomas (1978) have shown that the α_1 -acid glycoprotein is the one of the most important binding sites but a role also exists for albumin, α_2 -mucoprotein and γ -globulin. Differences in plasma binding between bupivacaine and lignocaine are reflected in a lower blood to plasma ratio of 0.73 for bupivacaine (Tucker and Mather, 1975).

The V_{DSS} and half-life of bupivacaine are 72 litres and 2.7 hours respectively (Tucker and Mather, 1979). The difference between bupivacaine and lignocaine is significant, and the concentration of bupivacaine in tissues and organs should be reduced when compared to lignocaine. This is a result of the higher protein binding capacity and lipid solubility. As a result of its high protein binding capacity and hence, reduced availability for erythrocyte binding, bupivacaine also has a high plasma/erythrocyte ratio.

Like other amide local anaesthetics, bupivacaine is metabolised in the liver and this is dependant on hepatic blood flow and liver function. Cardiovascular disease can decrease cardiac output and therefore hepatic blood flow which will reduce the rate of metabolism. Mather *et al.*

(1995) have shown that hepatic metabolism, and therefore clearance of bupivacaine, is reduced after liver transplantation. A number of bupivacaine metabolites have been identified in various species including man, monkey and rat (Boyes, 1975). Metabolites include: pipecolylxylidide (PPX), 3'hydroxy-bupivacaine, 4'hydroxy-bupivacaine, 4'hydroxy-desbutyl-bupivacaine, desbutyl-bupivacaine, pipecolic acid and 2,6-xylidine. Reynolds (1971) found that only 6% of bupivacaine was excreted unchanged in the urine while 5% was excreted as the N-delkylated metabolite, PPX. The latter had only one eighth the potency and toxicity of bupivacaine.

1.2.5. Bupivacaine Enantiomers

Bupivacaine, being a racemic local anaesthetic, exists as an equal mixture of its component enantiomers R(+)- and S(-)- bupivacaine. They behave pharmacokinetically as independent drugs after injection. The differences in vasomotor activity and pharmacokinetics are thought to be clinically significant. Aps and Reynolds (1978) reported that R(+)-bupivacaine has a greater vasodilator effect than S(-)-bupivacaine and would therefore tend to increase blood loss unnecessarily. Rutten *et al.* (1993) found that the plasma protein binding of R(+)-bupivacaine is significantly greater than that of S(-)-bupivacaine, however subsequent studies have shown that over time, the peak plasma concentration of R(+)-bupivacaine is less than that of S(-)-bupivacaine (Rutten *et al.*, 1993; Blake *et al.*, 1994; Mather *et al.*, 1995). This apparent paradox can be explained in terms of differences in V_{DSS} , metabolism and clearance. Studies on sheep have not only shown that R(+)-bupivacaine has a greater V_{DSS} than that of S(-)-bupivacaine (Burm *et al.*, 1994), but also a half-life approximately one-half that of the latter (Mather, 1991). The reduced half-life of R(+)-bupivacaine reflects the greater mean hepatic and total body clearances for this enantiomer (Mather, 1991; Rutten *et al.*, 1991; Mather *et al.*, 1995).

1.2.6. Toxicology

Increasing blood levels of bupivacaine due to inadvertent intravascular injection, overdosage or rapid absorption from the site of injection may cause toxic symptoms. The threshold toxic plasma concentration of bupivacaine at which central nervous system symptoms occur is 2.2 to 4.4 $\mu\text{g/mL}$ (Mather *et al.*, 1979). As with lignocaine, general anaesthesia is thought to increase the toxic threshold, but this has not been quantitated. However, Hasselstrom and Mogensen (1984) reported generalised seizures in a healthy 28 year old woman undergoing an intravenous bupivacaine infusion with a plasma concentration of 1.1 $\mu\text{g/mL}$. Plasma concentrations up to 2 $\mu\text{g/mL}$ have been consistently reported in neonates and children without evidence of toxicity. In a clinical trial by Abboud *et al.* (1982), no evidence of maternal or foetal CNS nor cardiovascular toxicity was observed for epidural anaesthesia with either bupivacaine or lignocaine. Despite the apparent safety of bupivacaine, foetal and neonatal plasma protein binding is known to be less than that of an adult and consequently the proportion of the unbound active drug may be higher. Foetal and neonatal metabolic enzyme systems are also known to be less well developed, and it would be prudent to be cautious with the use of bupivacaine in this age group.

With a therapeutic ratio of 2.0, plain bupivacaine has a greater safety margin than that of plain lignocaine, but a lesser safety margin than that of lignocaine with adrenaline. However, De Jong and Bonin (1980) have shown that the therapeutic ratio of bupivacaine, and in fact of all local anaesthetics, is affected considerably by the route of extravascular administration. The therapeutic ratio when bupivacaine is used for oral surgical procedures has not yet been established. The beneficial effects of adrenaline are minimal with bupivacaine, primarily a result

of the high protein binding capacity and lipid solubility which create a 'depot' effect at the site of administration and slow the systemic absorption. The recommended dose of plain bupivacaine or bupivacaine with adrenaline, for adults or children, is 2 mg/kg (Scott and Cousins, 1980).

Central nervous system toxicity develops in a similar manner to lignocaine with the same myriad of signs and symptoms but at a lower plasma concentration. It is the cardiovascular system however, which is most at risk of bupivacaine toxicity. While the latter invariably occurs at higher plasma concentrations than that required for CNS toxicity, the consequences of the cardiotoxicity are often fatal (Bacsik *et al.*, 1995). Bupivacaine has been shown to cause depression of the maximal rate of rise (V_{max}) of the cardiac action potential, atrioventricular block, negative inotropy and chronotropy, supraventricular and ventricular tachycardias, asystole and ventricular fibrillation. The greater cardiotoxicity of bupivacaine has been attributed to two possible mechanisms. At bupivacaine concentrations above 0.2 $\mu\text{g/mL}$, a substantial fraction of the myocardial sodium channels become blocked during the cardiac action potential (fast-in-slow-out) (Clarkson and Hondeghem, 1985). An identical sodium channel block with lignocaine occurs at 5 to 10 $\mu\text{g/mL}$, but recovery during diastole is almost 10 times faster with lignocaine (fast-in-fast-out). The cardiotoxicity is increased with an increase in heart rate. The alternate mechanism of bupivacaine induced cardiotoxicity is dependent on depression of the medulla within the CNS which has been shown to cause hypotension, bradycardia and arrhythmias in the rat (Thomas *et al.*, 1986).

The treatment of CNS complications is similar to that of lignocaine and is directed primarily at maintaining an open airway, providing proper ventilation to prevent hypoxia, and controlling seizure activity. Short acting barbiturates such as thiopental, and benzodiazepines

such as diazepam have been used successfully (Moore *et al.*, 1979; Davis and De Jong, 1982). With respect to cardiovascular toxicity, the evidence for the use of adrenaline in resuscitation is conflicting and requires further investigation (Heavner *et al.*, 1994). Some success has been observed with amrinone (Lindgren *et al.*, 1992), bretylium (Kasten and Martin, 1986), clonidine (De La Coussaye *et al.*, 1994a), hexamethonium (De La Coussaye *et al.*, 1994b), direct cardioversion (Feldman *et al.*, 1991) and intracardiac pacing (Pitkanen *et al.*, 1992). In extreme cases the rapid use of cardiopulmonary bypass has been successful (Long *et al.*, 1989).

1.3. ADRENALINE

1.3.1. History

Since 1901, when Braun first combined adrenaline with cocaine, the use of this and other vasoconstrictors has been a source of some controversy. While the rationale for the use of adrenaline relates to improved depth and duration of local anaesthesia, the safety of this compound when used in patients with significant cardiovascular disease has been questioned (Cheraskin and Prasertsuntarasai, 1958; Cheraskin and Prasertsuntarasai, 1959; Vernale, 1960; Holroyd *et al.*, 1960; Jastak and Yagiela, 1983). The mean basal value for adrenaline is usually between 20 and 60 pg/mL in a healthy individual. Mean plasma adrenaline concentrations rise approximately two fold during quiet standing, three fold during cigarette smoking and up to thirteen fold during heavy exercise (Clutter *et al.*, 1980).

1.3.2. Chemistry

Adrenaline is a hormone consisting of a benzene ring and an ethylamine side chain (Fig.1c). Substitutions on the aromatic ring, the α - and β -carbon atoms and the terminal amino group yield a great variety of compounds with sympathomimetic activity (Goodman and Gilman, 1985).

1.3.3. Effector Responses

Sympathomimetic amine vasoconstrictors such as adrenaline exert their effects by interacting functionally with several different adrenergic receptors. These include the α_1 , α_2 , β_1

and β_2 receptors which are found in a variety of tissues throughout the body. The responses of some effector organs to catecholamines are listed below (Goodman and Gilman, 1985).

Effector organ	Receptor type	Responses
<i>Heart</i>		
SA node	β_1	↑ heart rate
Atria	β_1	↑ contractility and conduction velocity
AV node	β_1	↑ automaticity and conduction velocity
His-Purkinje sys	β_1	↑ automaticity and conduction velocity
Ventricles	β_1	↑ contractility, automaticity and conduction velocity
<i>Arterioles</i>		
Coronary	$\alpha_1;\beta_2$	Constriction; dilatation (predominates)
Skin and mucosa	α_1	Constriction
Skeletal muscle	$\alpha_1;\beta_2$	Constriction; dilatation (predominates)
Cerebral	α_1	Constriction
Pulmonary	$\alpha_1;\beta_2$	Constriction; dilatation (predominates)
Salivary	α_1	Constriction
<i>Veins</i>	$\alpha_1;\beta_2$	Constriction (predominates); dilatation
<i>Skeletal muscle</i>	β_2	↑ contractility, glycogenolysis, K^+ uptake
<i>Liver</i>	$\alpha_1;\beta_2$	Glycogenolysis, gluconeogenesis

Effector organ	Receptor type	Responses
<i>Pancreas</i>		
Acini	α_1	↓ secretion
Islets	$\alpha_2; \beta_2$	↓ secretion (predominates); ↑ secretion

After sympathetic stimulation, the physiological responses are governed by the preferential release of adrenaline from the adrenal medulla and the relative specificity of adrenaline and noradrenaline for different receptor sites. Of the catecholamines released, 80% is adrenaline while the remaining 20% is predominantly noradrenaline. Adrenaline is a more potent stimulator of β -adrenergic receptors than is noradrenaline.

1.3.4. Cardiovascular Effects

When given rapidly, adrenaline evokes a characteristic effect on blood pressure and heart rate, which rises rapidly to a peak that is proportional to the dose. The increase in systolic pressure is greater than the rise in diastolic pressure, so that the pulse pressure increases. The mechanism for the rise in blood pressure is threefold: an increase in the strength of ventricular contraction (positive inotropic effect), an increased heart rate (positive chronotropic effect) and most importantly, vasoconstriction in many vascular beds. However, slow intravenous infusion or subcutaneous injection of adrenaline may cause the blood pressure to fall. There is a moderate increase in systolic pressure from positive inotropic and chronotropic effects but diastolic pressure usually falls due to a fall in total peripheral resistance secondary to the dominant action on the β_2 receptors in skeletal muscle.

The previous discussion elucidates the positive inotropic and chronotropic effects of adrenaline on the β_1 receptors of the myocardium. This stimulation is independent of alterations in cardiac function secondary to increased venous return and other peripheral vascular effects. The heart rate increases and the rhythm is often altered. Cardiac systole is shorter and more powerful, cardiac output is enhanced, oxygen consumption increases and cardiac efficiency is lessened. Electrocardiograph changes include decreased amplitude of T waves and ST segment deviation similar to that of ischaemic heart disease.

Tolas *et al.* (1982) have shown that a 1.8 mL cartridge of 2% lignocaine with 1:100,000 adrenaline causes a threefold increase in the plasma concentration of adrenaline after five minutes, when used for infiltration anaesthesia. Over the same time period, diastolic blood pressure fell, but neither systolic blood pressure nor heart rate were significantly altered. In a similar study on mandibular block anaesthesia, Salonen *et al.* (1988) showed that 3.6 mL of 2% lignocaine with 1:80,000 adrenaline produced a tenfold increase in plasma adrenaline levels, a significant increase in heart rate but no appreciable change in systolic or diastolic blood pressure.

The respective roles of endogenous and exogenous adrenaline on plasma concentration and cardiovascular responses has been a topic of much discussion. Lipp *et al.* (1993), using tritium labelled adrenaline as a vasoconstrictor for dental local anaesthesia in normal patients, found that 2 mL of articaine with 1:100,000 adrenaline (20 μ g) caused a five to tenfold increase in the plasma concentration of adrenaline. The increase in the total adrenaline plasma concentration was mainly a reflection of the exogenous catecholamine.

1.3.5. Metabolism

The metabolism of endogenous circulating and administered catecholamines is of considerable importance. The two enzyme systems responsible for the degradation of circulating adrenaline are monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). These enzymes are widely distributed throughout the body, including the brain, but the highest concentrations are in the liver and kidney. After systemic absorption, the greater part of a dose of adrenaline is excreted as metabolites in the urine.

1.3.6. Clinical Use

The advantages of using adrenaline in local anaesthetics include increased potency, increased duration, reduced systemic toxicity and reduced haemorrhage (Mumford and Geddes, 1959). An increased speed of onset of anaesthesia has also been shown with adrenaline (Caruana *et. al.*, 1982).

The optimal concentration of adrenaline in local anaesthetics has been exhaustively studied. In a prospective trial of lignocaine with various concentrations of adrenaline, Keesling and Hinds (1963) found that adrenaline 1:250,000 was the optimal concentration. Cardwell and Cawson (1969) showed however, that reducing the adrenaline concentration from 1:80,000 to 1:250,000 lowers the rate at which successful block or infiltration anaesthesia is achieved. Currently the most commonly used concentration of adrenaline in lignocaine local anaesthetic solutions is 1:100,000, which translates to 20 µg/mL. This concentration provides all the benefits of a vasoconstrictor yet reduces to a minimum the physiological side effects of such an agent.

The development of the newer longer acting local anaesthetics such as bupivacaine has brought about a similar concern with regard to the need for and, if so, the optimal concentration of adrenaline. Laskin *et al.* (1977) showed that 1:200,000 adrenaline improves the success of anaesthesia, increases the duration of anaesthesia and shortens the delay in onset when used with either 0.25% or 0.5% bupivacaine. Subsequent clinical trials with bupivacaine (Pricco, 1977; Chapnick *et al.*, 1980; Chapman and Macleod, 1985; Danielsson *et al.*, 1985; Chapman and Ganendran, 1987; Chapman, 1988) have all utilised 1:200,000 adrenaline and this is the concentration of vasoconstrictor that is currently used.

Figure 1a. Lignocaine

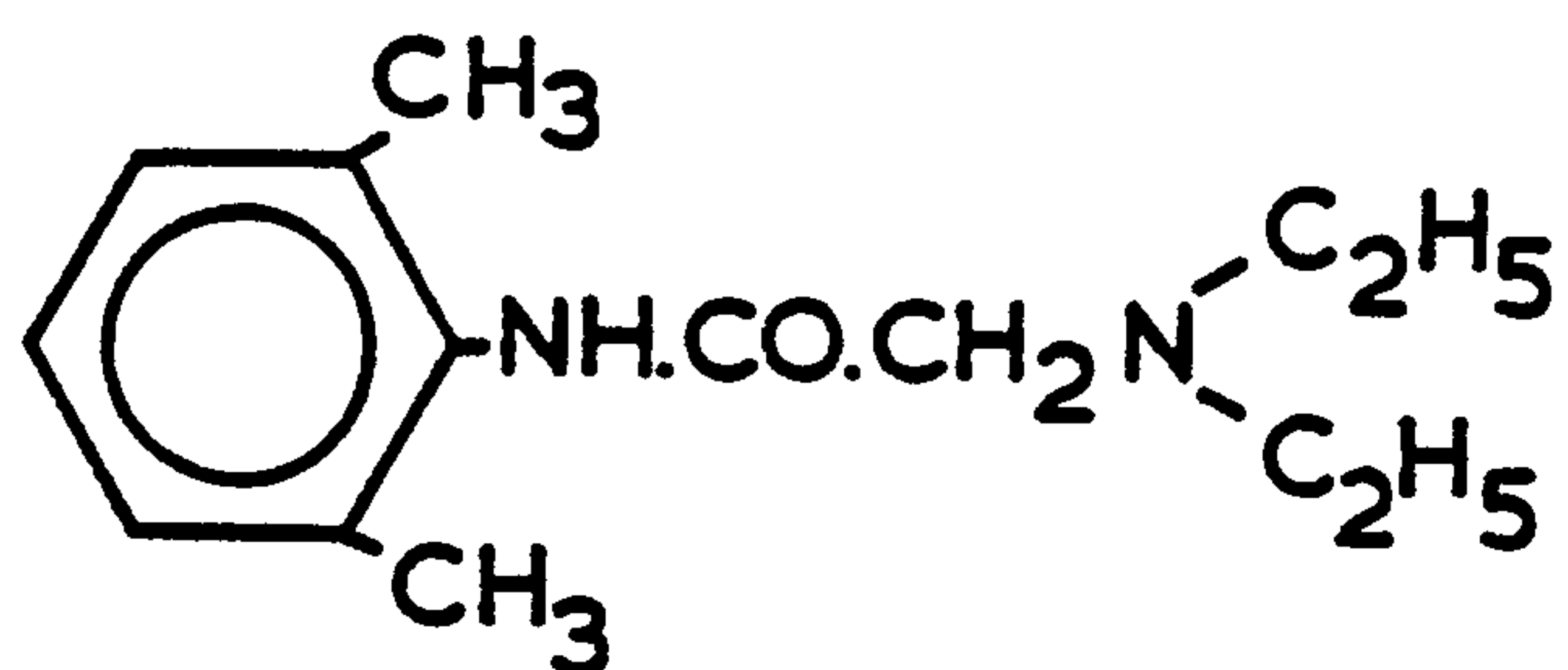


Figure 1b. Bupivacaine

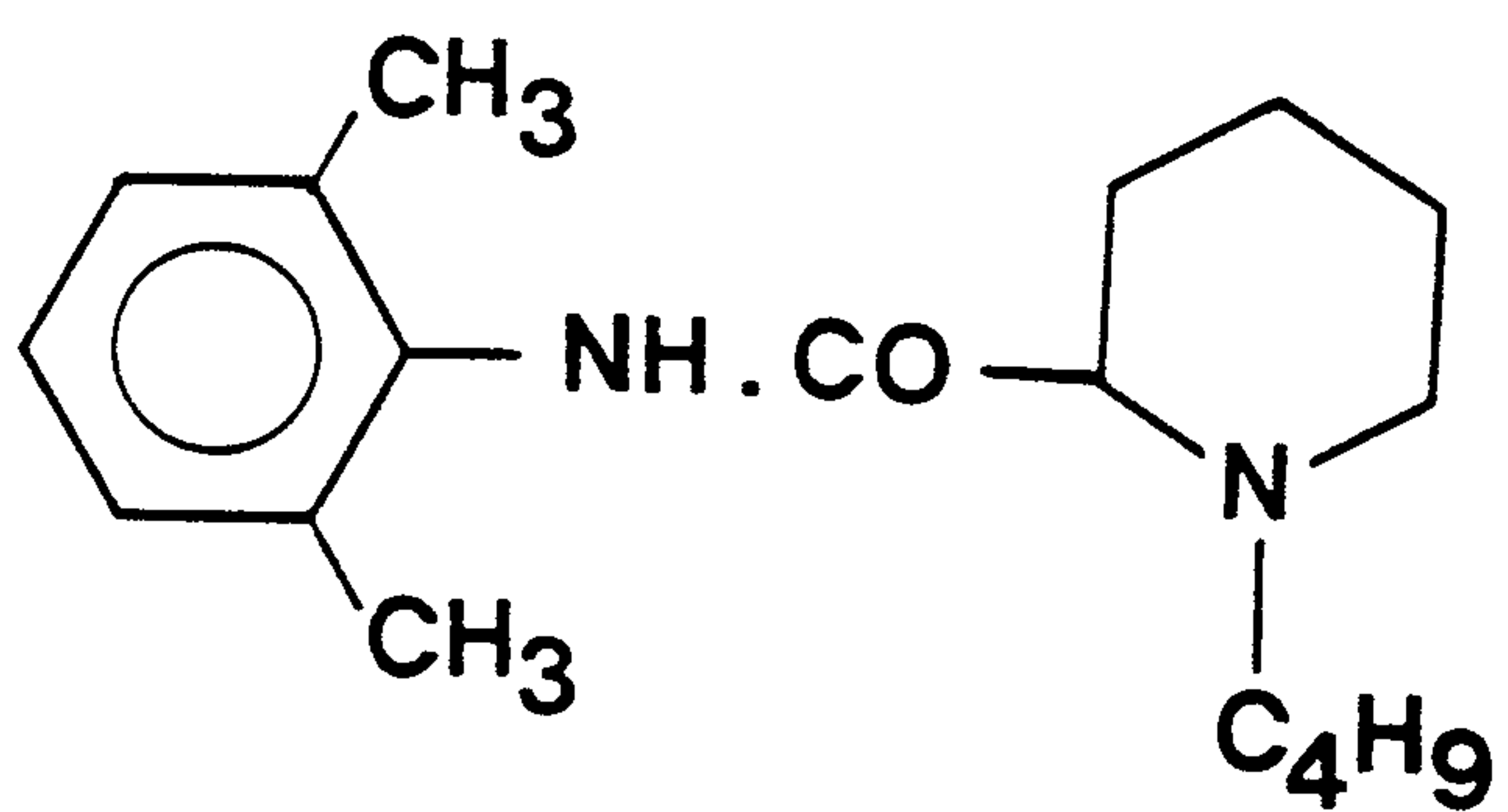
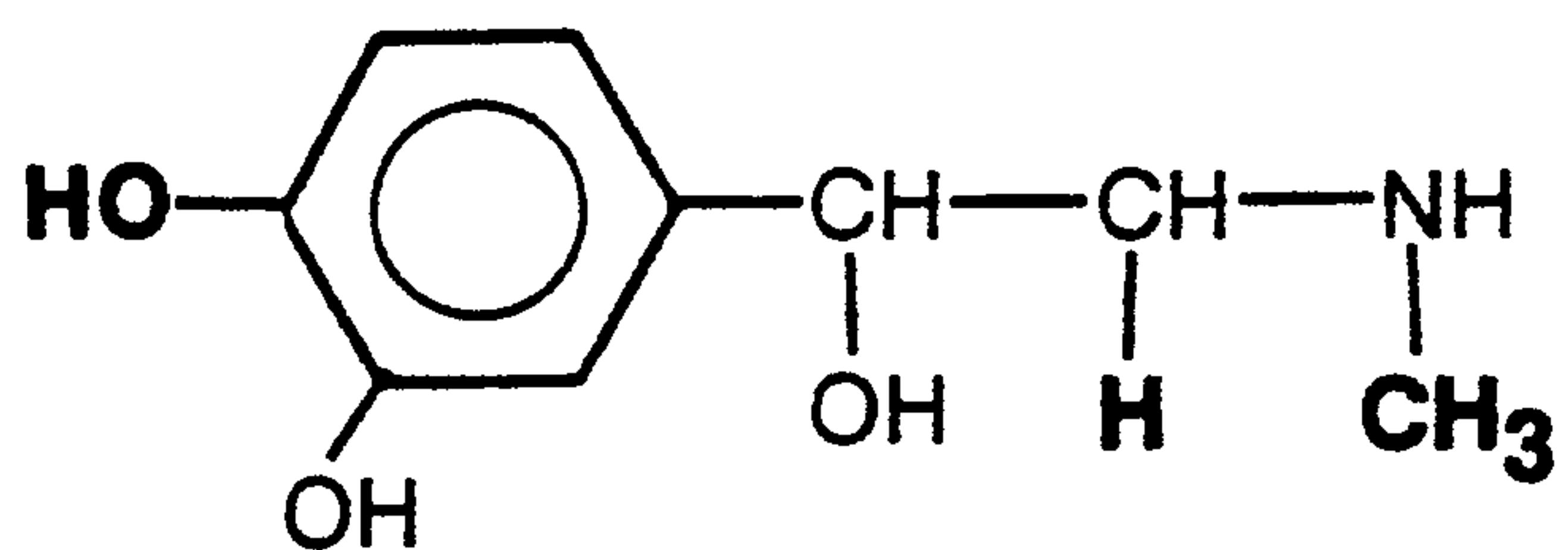


Figure 1c. Adrenaline



1.4. CLINICAL TRIALS

There have been numerous clinical trials evaluating the clinical applications of bupivacaine over the last 30 years. Some of these trials have involved patients treated under general anaesthesia, whilst others were confined to local anaesthesia. A search of the literature however, has failed to find a previous study that has determined the blood concentration of either lignocaine or bupivacaine when used for the removal of impacted, third molar teeth.

The terms 'anaesthesia' and 'analgesia' are used constantly throughout the following review of the literature. Anaesthesia means loss of all modalities of sensation whether it be the sense of pain, touch, temperature or position sense. Analgesia means absence of the sensation of pain alone although other modalities may be preserved. It is analgesia that has greater clinical significance in third molar surgery as it is known that after regional block with local anaesthetic, analgesia begins to regress before the other modalities of sensation.

Feldmann and Nordenram (1966) compared the clinical efficacy of bupivacaine 0.25% and 0.5% with mepivacaine 2%, all containing 1:100,000 adrenaline, for the surgical removal of mandibular, third molars. The study involved 212 patients in a double blind, clinical trial. All procedures were begun within three minutes of the administration of 3.6 mL of local anaesthetic. The parameters measured included: depth of analgesia as determined subjectively by the surgeon, duration of soft tissue anaesthesia and time to onset of post-operative pain. All anaesthetics were found to have a short onset time and an adequate depth of anaesthesia. The duration of soft tissue anaesthesia and post-operative analgesia was much longer for the two bupivacaine solutions than for mepivacaine. The mean duration of anaesthesia was 219, 296 and 188 minutes for

bupivacaine 0.5%, bupivacaine 0.25% and mepivacaine 2% respectively, while the mean duration of analgesia was 256, 298 and 170 minutes. Surprisingly, there was no statistically significant difference between the two bupivacaine solutions for any of the parameters measured. The study was not conducted as a crossover trial and despite the fact that each of the three groups was age and sex matched, there may have been differences in the degree of third molar impaction between groups which could have influenced the results.

In what appears to be the first clinical trial that compared bupivacaine to lignocaine, Hellden *et al.* (1974) divided 420 patients requiring the removal of mandibular, third molars into three groups matched for age, sex and degree of impaction. The first group received bupivacaine 0.25% with 1:200,000 adrenaline, the second group mepivacaine 3% and the last group lignocaine 2% with 1:80,000 adrenaline. A total of 3.6 mL of local anaesthetic was injected for each lower third molar (1.8 mL inferior alveolar block and 1.8 mL infiltration adjacent to the tooth) followed by surgery 10 minutes later. Patients recorded analgesic consumption for the first 24 hours (medication unspecified) as well as the time to regression of anaesthesia. The mean duration of analgesia after administration of the local anaesthetic was 285, 152 and 185 minutes for bupivacaine, mepivacaine and lignocaine respectively. The depth of anaesthesia within the lignocaine group was significantly greater than that within the bupivacaine and mepivacaine groups. In terms of the analgesic consumption, no differences were found between the three groups.

Nespeca (1976) included 262 patients in a clinical trial with bupivacaine 0.25%, bupivacaine 0.5% and lignocaine 2%. Each local anaesthetic was used with and without adrenaline. The concentration of adrenaline was 1:200,000 with bupivacaine and 1:100,000 with

lignocaine. The patients were treated for impacted third molars, facial fractures, tori removal, multiple extractions with alveolectomies and arch bar applications. The author makes no comment as to whether the groups were matched for age and sex and whether the distribution of surgical procedures within each group was uniform. Surgical anaesthesia was obtained with a total of 1.5 to 2.0 mL of local anaesthetic. Onset and duration of anaesthesia, time to regression of analgesia and the total number of analgesics consumed (paracetamol with codeine) were recorded. After the first 119 patients, the adrenaline free local anaesthetics were excluded from the trial due, in particular, to the variation in onset time and depth of anaesthesia with the bupivacaine solutions. The remaining 143 patients then participated in the remainder of the trial. The time to onset of anaesthesia with bupivacaine was significantly longer than that with lignocaine. The mean duration of anaesthesia showed a significant difference among the three agents. Bupivacaine 0.5% was shown to have a significantly longer duration of anaesthesia than bupivacaine 0.25% and lignocaine 2%. The time to regression of analgesia was significantly different between the three agents with bupivacaine 0.5% delaying onset of pain more so than the 0.25% solution or lignocaine 2%. Analgesic consumption within the first 24 hours was significantly less for both of the bupivacaine concentrations when compared to lignocaine.

Laskin *et al.* (1977) compared plain bupivacaine 0.25%, 0.5% and 0.75%, bupivacaine 0.25% and 0.5% with 1:200,000 adrenaline, lignocaine 2% with 1:100,000 adrenaline and mepivacaine 2% with necobefrine 1:20,000 for the removal of impacted, mandibular, third molars in 25 patients. The study was double blind, randomised and crossover in nature with each patient having two surgical procedures separated by one month. The volume of local anaesthetic that was used was not specified. The author makes no comment as to whether the impacted third molars were symmetrical. The onset, depth and duration of anaesthesia and the period of post-

operative analgesia were recorded. No difference in the time to onset of anaesthesia was noted for any of the local anaesthetic agents. Painless surgical removal occurred in 100% of the surgical procedures with bupivacaine 0.5% and 0.75%, both with and without adrenaline 1:200,000. Bupivacaine 0.25% with adrenaline 1:200,000 also provided painless surgery. The success of plain bupivacaine 0.25% and lignocaine 2% with adrenaline 1:100,000 adrenaline was 80% and 89% respectively. With the exception of bupivacaine 0.25% with adrenaline, the mean duration of anaesthesia was significantly longer for all bupivacaine solutions when compared to lignocaine. The mean duration of analgesia was significantly longer than lignocaine for all plain bupivacaine solutions. Interestingly there was no significant difference between bupivacaine 0.25% and 0.5% with adrenaline and the lignocaine 2% with adrenaline.

Pricco (1977) evaluated bupivacaine 0.5% with adrenaline 1:200,000 for the removal of impacted, third molars. Twenty-five maxillary and 25 mandibular procedures were performed in an attempt to describe differences between block and infiltration anaesthesia for bupivacaine. A total of 3 mL of anaesthetic was used for each procedure. The onset of profound anaesthesia occurred between 2 and 11 minutes. Onset time, time to profound anaesthesia and time to regression of anaesthesia were all shorter in the maxilla. There was no evidence of toxicity in any patient.

Chapnick *et al.* (1980) conducted two separate clinical trials. The first involved 400 patients undergoing general anaesthesia for the surgical removal of impacted, third molars. Patients received bupivacaine 0.75% with adrenaline 1:200,000, lignocaine 2% with adrenaline 1:100,000 or no local anaesthetic. Eighty-one per cent of the patients who received the bupivacaine solution required no analgesic prior to discharge three to four hours post-operatively,

as opposed to only 30% of those who received lignocaine. The second trial compared bupivacaine plain 0.5% and 0.75% with lignocaine 2% plain and with 1:100,000 adrenaline for the removal of impacted third molars in 200 patients. Some patients received nitrous oxide or intravenous diazepam in addition to the local anaesthetic, the volume of which was not specified. The mean time to maximal surgical anaesthesia was 8.5, 10, and 4.5 minutes for bupivacaine 0.5%, 0.75% and lignocaine 2% with adrenaline respectively. The duration of anaesthesia and post-operative analgesia was significantly longer for bupivacaine 0.5% and 0.75% compared to lignocaine both with and without adrenaline.

Chapman and Macleod (1985) compared bupivacaine with lignocaine in a double blind, randomised, crossover trial. The concentrations of local anaesthetic solutions used were bupivacaine 0.5% with 1:200,000 adrenaline and lignocaine 2% with 1:80,000 adrenaline. Each of 20 healthy patients had bilaterally symmetrical, impacted, mandibular, third molars removed on two separate appointments, four weeks apart. A total of 3.0 mL of local anaesthetic solution was used for each side, 2.5 mL as inferior alveolar block and 0.5 mL as infiltration. A visual analogue and global pain scale were used to record post-operative pain on up to four occasions over the first 24 hours. The mean duration of anaesthesia and analgesia was significantly longer for the procedures with bupivacaine. The mean initial pain score and at four hours was significantly less for bupivacaine. No significant difference in the 8 or 24 hour pain scores was seen. The mean number of analgesic tablets (paracetamol with codeine) required within the first 24 hours was significantly less for the procedures with bupivacaine.

Danielsson *et al.* (1985) examined the effect of bupivacaine 0.75% with 1:200,000 adrenaline, etidocaine 1.5% with 1:200,000 adrenaline and lignocaine 2% with 1:80,000

adrenaline when used as oral infiltration anaesthesia. On each of three separate occasions, one mL of a single local anaesthetic solution was deposited supraperiosteally in the apical area of the maxillary right lateral incisor. Time to onset of anaesthesia, duration of pulpal analgesia and time to complete regression of anaesthesia were recorded. Bupivacaine had a longer onset time and period of soft tissue anaesthesia but interestingly, a reduced duration of pulpal analgesia when compared to lignocaine.

Chapman (1988) compared bupivacaine 0.5% with 1:200,000 adrenaline with lignocaine 2% with 1:80,000 adrenaline for the removal of bilaterally symmetrical, impacted, third molars in 20 patients. The study was conducted as a double blind, randomised, crossover trial. A total of 3 mL of local anaesthetic was used for each procedure which were separated by one month. Mean duration of mental anaesthesia was 8.5 and 3.6 hours for bupivacaine and lignocaine respectively. Mean pain scores as measured by a visual analogue scale were significantly less for bupivacaine at both four and eight hours post-operatively. No difference at 12 hours was observed. Mean analgesic consumption (paracetamol with codeine) within the first 12 hours was significantly less for bupivacaine and there was a highly significant patient preference for this agent.

Review of the literature has failed to find any studies that have measured the blood concentrations of bupivacaine or lignocaine when used for oral and maxillofacial surgery. However, the blood concentration of bupivacaine has been measured after epidural anaesthesia (Mather *et al.*, 1971a; Hyman and Schnider, 1971; Abboud *et al.*, 1982), during interpleural infusion after abdominal surgery (Blake *et al.*, 1994) and after intercostal neural blockade in liver transplant patients (Mather *et al.*, 1995). Multiple case reports describing cardiovascular collapse

after epidural injections of bupivacaine have also been published after doses ranging from 20 to 40 mL of 0.5% bupivacaine (Albright, 1979). In what appears to be the first such case, cardiovascular toxicity has also been reported after intra-articular injection of 30 mL of 0.25% bupivacaine for knee arthroscopy (Sullivan and Abbott, 1994).

The blood concentration of lignocaine has also been measured after epidural injection (Axelsson and Widman, 1981). However, cardiovascular collapse after epidural injection does not appear to have been reported previously. Interestingly two deaths have been described after injection of the oral mucosa with less than 1.8 mL of lignocaine 2% (Tomlin, 1974). However it was the use of noradrenaline as the vasoconstrictor which was thought to be the cause of both mortalities.

Deficiencies in the methods of previous studies make the validity of their conclusions somewhat unreliable. Early previous studies conducted by Feldmann and Nordenram (1966), Hellden *et al.* (1974) and Nespeca (1976) were not randomised and crossover in nature. In the latter study, a multitude of different surgical procedures were also included in the trial without an attempt to match subjects for age, sex and type of surgical procedure. In the first double blind, randomised, crossover study, Laskin *et al.* (1977) failed to record the volume of local anaesthesia used and the post-operative analgesic consumption. In the study by Chapnick *et al.* (1980), the volume of local anaesthetic was also not specified and an unspecified proportion of patients received sedation as an adjunct to the local anaesthesia. Chapman and Macleod (1985) and Chapman (1988) have conducted double blind, randomised, crossover trials for the removal of bilaterally symmetrical, impacted, third molars. While both studies showed a reduction in post-operative analgesic consumption (paracetamol with codeine) with bupivacaine, the post-operative

visual analogue pain scores in each study were not in agreement.

CHAPTER 2

MATERIALS AND METHOD

2.1. Introduction

Long acting local anaesthetics have been used in oral and maxillofacial surgery for almost 30 years, with a view mainly to reduce the pain experience after surgical procedures. Bupivacaine is the most commonly used long acting local anaesthetic in oral and maxillofacial surgery. The toxicity of this agent relative to other local anaesthetics has been the focus of much research in recent times and questions regarding its clinical safety have been raised. As it appears that no information on the relative safety of bupivacaine when used for oral and maxillofacial surgery is available, it was felt that a study to assess the blood concentrations of both bupivacaine and lignocaine should be carried out for one of the most common oral surgical procedures, the removal of impacted, third molars.

2.2. Aims

The aims of this study were to compare the efficacy of bupivacaine 0.5% with 1:200,000 adrenaline and lignocaine 2% with 1:100,000 adrenaline for the surgical removal of impacted, mandibular third molars. This included pain experience and analgesic requirements following surgery as well as cardiovascular responses and blood concentrations following the administration of both local anaesthetics.

2.3 Patients and Methods

Materials used in this study were bupivacaine 0.5% with 1:200,000 adrenaline (MarcainTM) and lignocaine 2% with 1:100,000 adrenaline (NurocainTM). The investigation was conducted as a randomised, double blind, crossover study with the subject able to act as his or her own control. The local anaesthetic was selected with the toss of a coin by a research assistant who then removed the outer plastic label of four dental cartridges (2.2 mL) and marked the cartridges 'A' or 'B', depending on which of the two local anaesthetics was chosen. The identity of 'A' and 'B' was not made known to the surgeon until the trial was completed. For each subject, the choice of which side to operate at the first appointment was also made with the toss of a coin. All surgical procedures were undertaken by the same operator (GFB).

A total of 23 patients, ages ranging from 18 to 41 years, who required the elective surgical removal of bilaterally symmetrical, impacted third molars were selected. The symmetry of impaction was verified on a standard orthopantogram using Winter's lines. Subjects with a known allergy to local anaesthetic agents or with a history of asthma, cardiovascular disease, thyrotoxicosis, immunosuppression, diabetes mellitus, liver disease and tricyclic antidepressant medication were excluded. Approval for this study was granted by the Human Research Ethics Committee (Western Sydney Area Health service). All patients were counselled regarding the procedures and written consent for surgery and participation in the study was obtained.

Blood pressure and heart rate were recorded immediately prior to the administration of

local anaesthetic using an Omron^{®2} oscillometric blood pressure pulse monitor with inbuilt printer (illustration 1). The monitor has an accuracy of $\pm 3\%$ which was not verified manually. The blood pressure cuff was placed above the antecubital fossa on either the left or right arm. With a single depression of the 'start' button on the monitor, systolic and diastolic blood pressures and heart rate were measured. The measurements were written down by a registered nurse as well as stored in the memory of the monitor. Subsequent to local anaesthetic administration, blood pressure and heart rate were measured at 5, 15, 30, 45 and 60 minutes. All results were recorded by the same registered nurse and printed by the monitor after the last measurement at 60 minutes.

Venous blood was sampled prior to the administration of the local anaesthetic to ensure that neither local anaesthetic agent was present in any of the subjects (illustration 2). The antecubital fossa on the arm opposite to the blood pressure cuff was prepared for venous blood sampling by cleansing with a Webcol^{®3} sterile tissue containing 70 per cent isopropyl alcohol, prior to venous cannulation with a 21 gauge butterfly needle which was secured with adhesive tape. A 10 mL sterile plastic syringe was used to withdraw 5 mL of blood through the cannula (illustration 3). A single 1 mL injection of heparinised saline (10 units heparin per millilitre) was used immediately after each sample was withdrawn to maintain the patency of the cannula. The stagnant blood and heparinised saline were removed from the cannula immediately prior to subsequent blood samples by withdrawing 2 mL of blood which was then discarded. Subsequent blood samples were taken at 15, 30, 45 and 60 minutes after local anaesthetic administration with an expected peak blood concentration between 10 and 20 minutes (Cousins and Mather, 1980).

² Omron Corporation, Tokyo, Japan.

³ Kendall HealthCare Products Co., Mansfield, U.S.A.

All blood samples were stored in a separate 5 mL lithium heparin Vacutainer^{®4} at -70 °C.

For surgical removal of a mandibular third molar, a total of 3.4 mL of local anaesthetic was administered as a standard inferior alveolar nerve block, 0.5 mL as a lingual nerve block and further 0.5 mL as infiltration for the long buccal nerve. If the maxillary third molar was also to be removed, 2 mL of local anaesthetic was infiltrated buccal to the tooth and a further 0.2 mL as a greater palatine nerve block. All surgical procedures were begun 10 minutes after local anaesthetic administration. Anaesthesia was deemed to be unsuccessful if pain was experienced when a sharp probe was applied to the mucosal surfaces 10 minutes after local anaesthetic administration. A further 2.2 mL of local anaesthetic was then administered and five minutes allowed to pass before commencement of surgery. If after a further five minutes anaesthesia was still unsatisfactory, an additional cartridge of local anaesthetic was given but the subject was excluded from the trial.

A standardised surgical technique was used for all subjects. The procedure for mandibular third molars involved an envelope incision, buccal and lingual periosteal flaps, bone removal and tooth division with a bur (illustration 5). Where a maxillary third molar was also to be removed, either direct elevation or a standardised buccal flap with bone removal with a bur was used. All wounds were closed with 3/0 polyglactin 910 (Vicryl^{TM5}) interrupted sutures (illustration 6). The time to completion of surgery was recorded.

⁴ Becton Dickson, Rutherford, U.S.A.

⁵ Ethicon. Inc., Sommerville, U.S.A.

Patients received a pain assessment form at the completion of surgery. Each patient was asked to record their intra-operative pain experience, as well as their post-operative pain experience at 4, 8, 12, 16 and 24 hours. Pain experience was assessed by two methods:

1) Visual analogue scale

Each subject indicated the degree of pain experience on a plain, horizontal 100 mm visual analogue pain scale with 'no pain' at 0 mm and 'worst pain imaginable' at 100 mm.

2) Global scale

Subjects were asked to indicate the appropriate response from one of the following pain categories:- 'none', 'a little', 'some', 'a lot' or 'worst possible'.

All patients were provided with an analgesic medication (ibuprofen tablets, 400 mg) and were instructed to take one tablet every eight hours if they felt it necessary for pain control. All analgesic medications taken were recorded by time and date.

All patients received a five day course of antibiotics (phenoxymethyl penicillin tablets, 500mg), to be taken every six hours. Although the efficacy of prophylactic antibiotics in preventing postoperative infection has not been clearly established (Longman and Martin, 1991), the primary role of prophylactic antibiotics in this study was to prevent individual subjects from seeking antimicrobials from any other source including a general medical practitioner. Concern with regard to the development of resistant micro-organisms after the first regimen of antibiotics was considered highly unlikely (Nolte, 1982) and the same antibiotic was chosen for the second surgical procedure one month later. Patients were reviewed at seven days and pain assessment forms collected. Contralateral surgery was performed after one month with the same protocol but

using the other alphabetically labelled local anaesthetic agent.

2.4. Laboratory methods

1. All blood samples were thawed at room temperature for one hour. Using a 1 mL multidose micro-pipette with disposable plastic tips (illustration 7), 0.6 mL of each blood sample was pipetted into a 1.5 mL plastic centrifuge tube. A new tip was used for each sample. To this was added 50 μ L of internal standard (diphenhydramine 0.001 mg/mL for bupivacaine assays or prilocaine 0.005 mg/mL for lignocaine assays) using a 50 μ L tip on a micro-pipette, 0.8 mL hexane and 20 μ L 4 molar sodium hydroxide using a 10 μ L tip on a micro-pipette. The use of diphenhydramine as the internal standard for bupivacaine assays had been developed previously in the research laboratories of the Department of Anaesthesia and Pain Management, Royal North Shore Hospital, Sydney. The use of prilocaine as the internal standard for the lignocaine assays however, was developed specifically for this study to allow an adequate separation of the lignocaine and internal standard peaks in the chromatograms.

2. Each tube was then vortex mixed for two minutes prior to freezing in dry ice for 30 minutes. Each tube was then thawed in a 45°C waterbath for four minutes. After centrifuging for five minutes at 3000 rpm, each tube was then refrozen for 15 minutes in dry ice. The organic layer was then decanted by gently pouring into another 1.5 mL plastic centrifuge tube before being evaporated under vacuum.

3. The samples were finally prepared for analysis by reconstituting with 50 μ L of water of pH 3 using a 50 μ L tip on a micro-pipette. All samples were then sonicated for 10 minutes to remove

any air bubbles. A 200 μ L micro-pipette with a 50 μ L tip was used to transfer each 50 μ L sample to a plastic insert for placement in the High Pressure Liquid Chromatography apparatus (HPLC). A new tip was used for each sample.

HPLC Conditions

The measurement of the plasma concentrations of the local anaesthetic agents was carried out with Shimadzu⁶ chromatography equipment (illustration 8). The system hardware and software consisted of:

1. FCV-10AL switch valve mixer.
2. CBM-10A communication bus module.
3. LC-10AD pump.
4. SIL-10A autoinjector.
5. SPD-10A ultra-violet VIS detector (100 - 750 nm).
6. 486-DX IBM compatible computer running LC-10 software.

The mobile phase was freshly prepared and vacuum filtered through 0.22 μ m filter paper to remove extraneous gases. The mobile phase for bupivacaine consisted of 0.15 molar phosphate buffer of pH 6.8 and isopropanol. The solvent ratio was set at 95.5% phosphate buffer and 4.5% isopropanol. The flow rate of the mobile phase was 0.9 mL/min while the ultra-violet wavelength detector was set at 220nm with positive polarity and a detector sensitivity selected at 0.005 AUFS

⁶ Shimadzu corporation, Tokyo, Japan.

(Absorbance Units Full Scale). An injection of 40 μ L from each insert was selected to analyse through a ChromTech^{®7} 5 μ m CHIRAL-AGP (α 1-acid glycoprotein) column (illustration 9). Retention times were 8.0 minutes for the diphenhydramine internal standard, 13 minutes for R(+) bupivacaine and 17 minutes for S (-) bupivacaine.

The mobile phase for lignocaine consisted of 10mM phosphate buffer of pH 3.5 and acetonitrile. The solvent ratio was 90% phosphate buffer and 10% acetonitrile. The flow rate of the mobile phase was selected at 1 mL per minute. The ultra-violet wavelength detector was set as for bupivacaine. An injection of 40 μ L from each insert was analysed through a Waters^{®8} 7 μ m C8 column. The retention times were 11 minutes for lignocaine and 14 minutes for the prilocaine internal standard.

Peak integration of each chromatogram was then carried out. This measured the peak areas of the drugs. The ratio of the peak areas of bupivacaine and lignocaine were compared to the peak areas of the internal standards and the blood concentrations of both agents were determined.

2.5. Statistical analysis

Statistical analysis of the blood concentrations was performed using paired t-test with a normal distribution. Statistical analysis of the pain experiences, analgesic consumption and

⁷ ChromTech, Hagersten, Sweden.

⁸ Millipore Corp., Milford, U.S.A.

cardiovascular responses was performed with the non-parametric Wilcoxon signed rank test as a result of the abnormal distribution of responses. The results were considered significant at the five per cent level.

Illustration 1.

Omron[®] blood pressure pulse monitor.

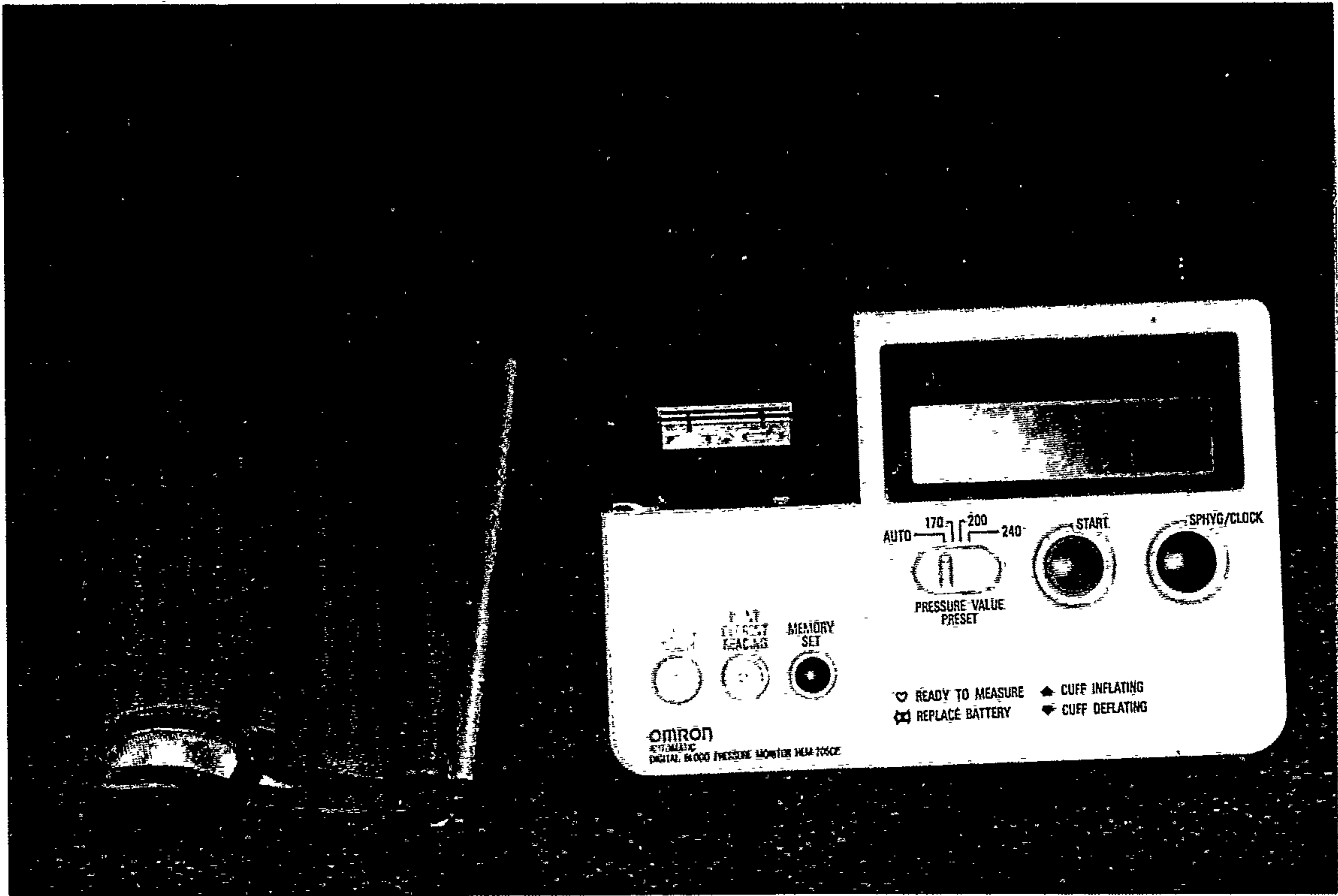
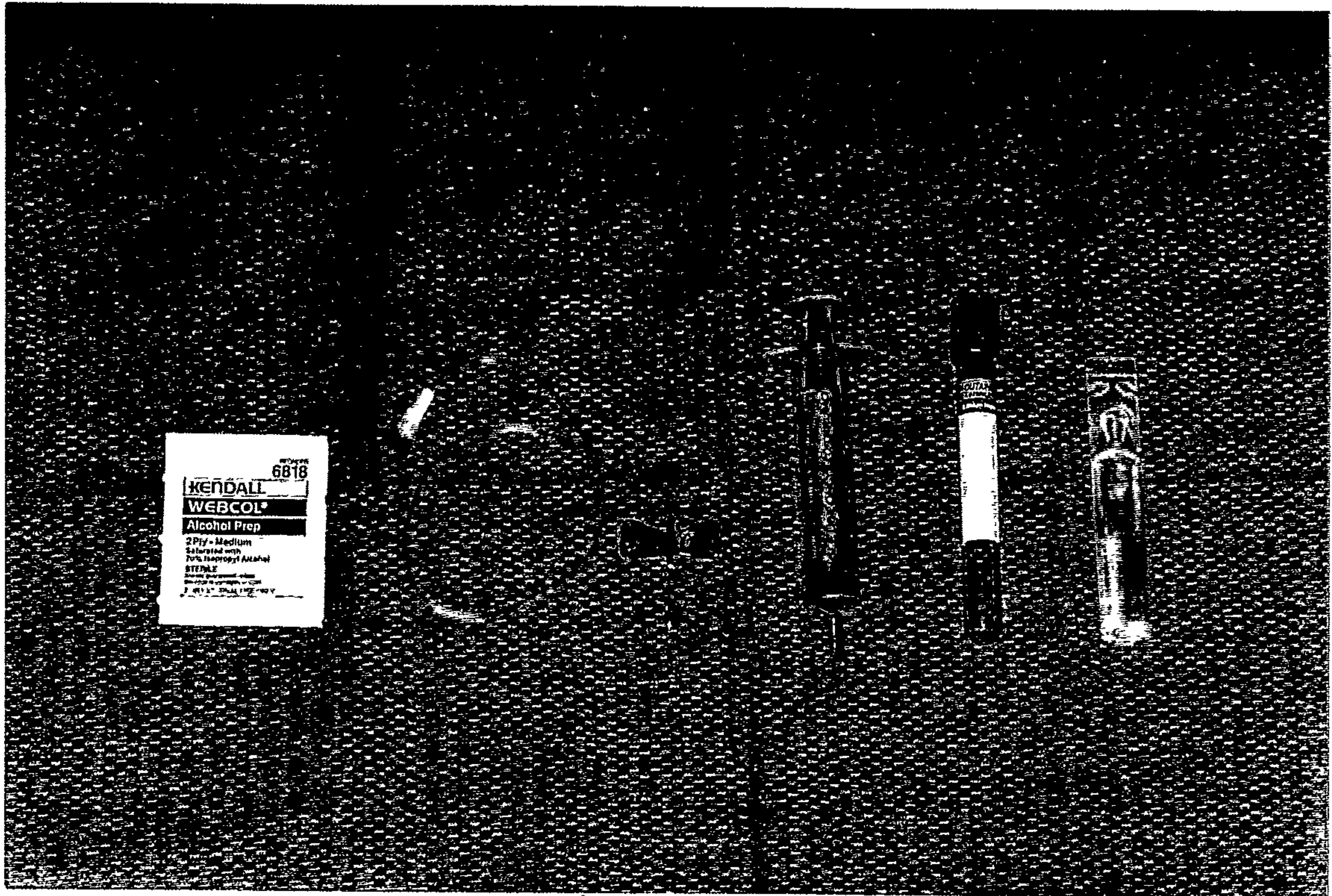


Illustration 2.

Blood sampling equipment.



From left to right:

1. Webcol[®] alcohol wipe.
2. 21 gauge butterfly needle with cap.
3. 10 mL syringe for collecting blood sample and heparinised saline flushes.
4. 5 mL Vacutainer[®] (with lithium heparin) for blood sample.
5. Heparinised saline.

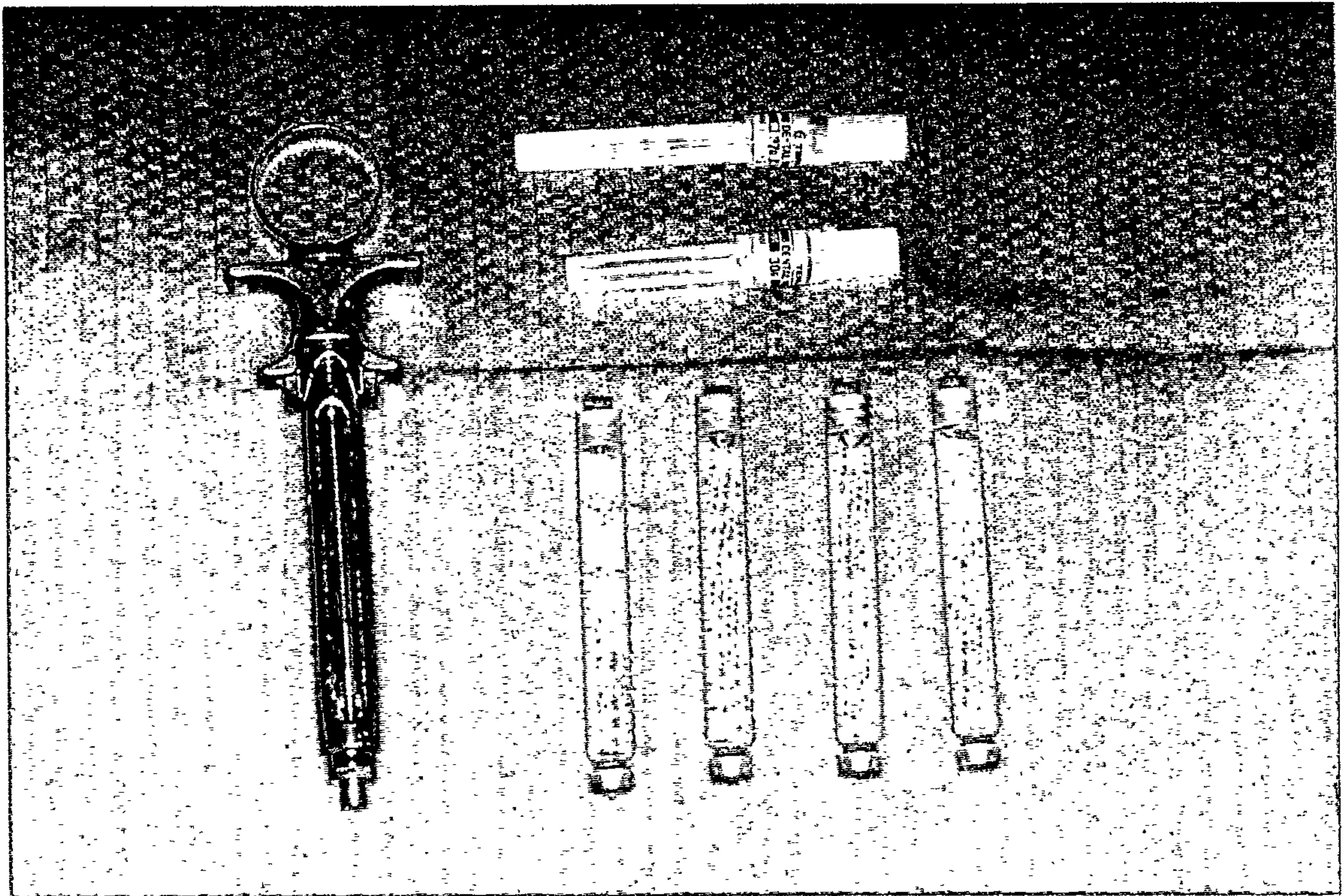
Illustration 3.

Blood sampling technique.



Illustration 4.

Local anaesthesia.



From left and clockwise:

1. Aspirating syringe.
2. 27 and 30 gauge needles.
3. Local anaesthetic cartridges (marked 'A' or 'B').

Illustration 5.

Surgical technique.



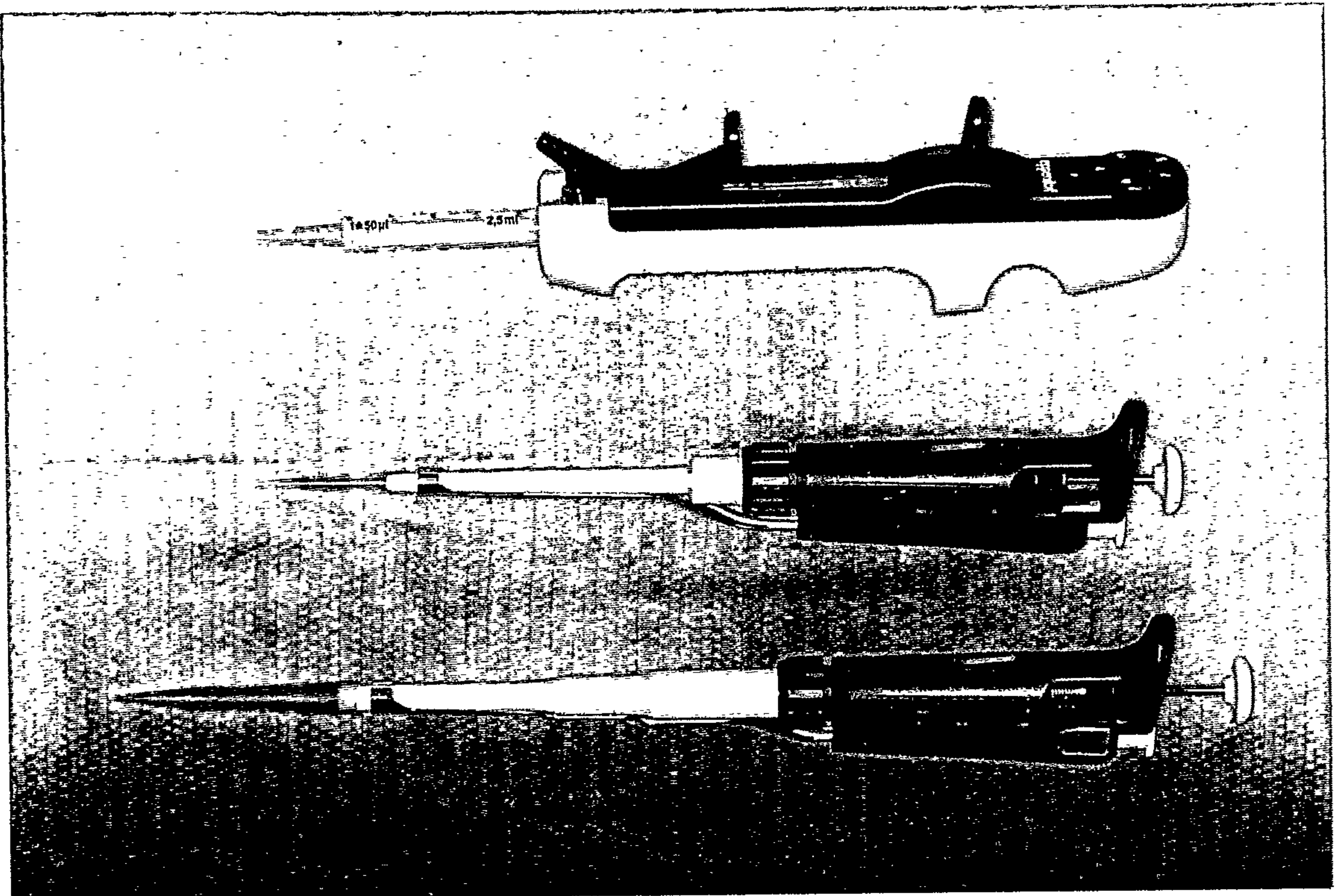
Illustration 6.

Surgical technique.



Illustration 7.

Laboratory equipment.

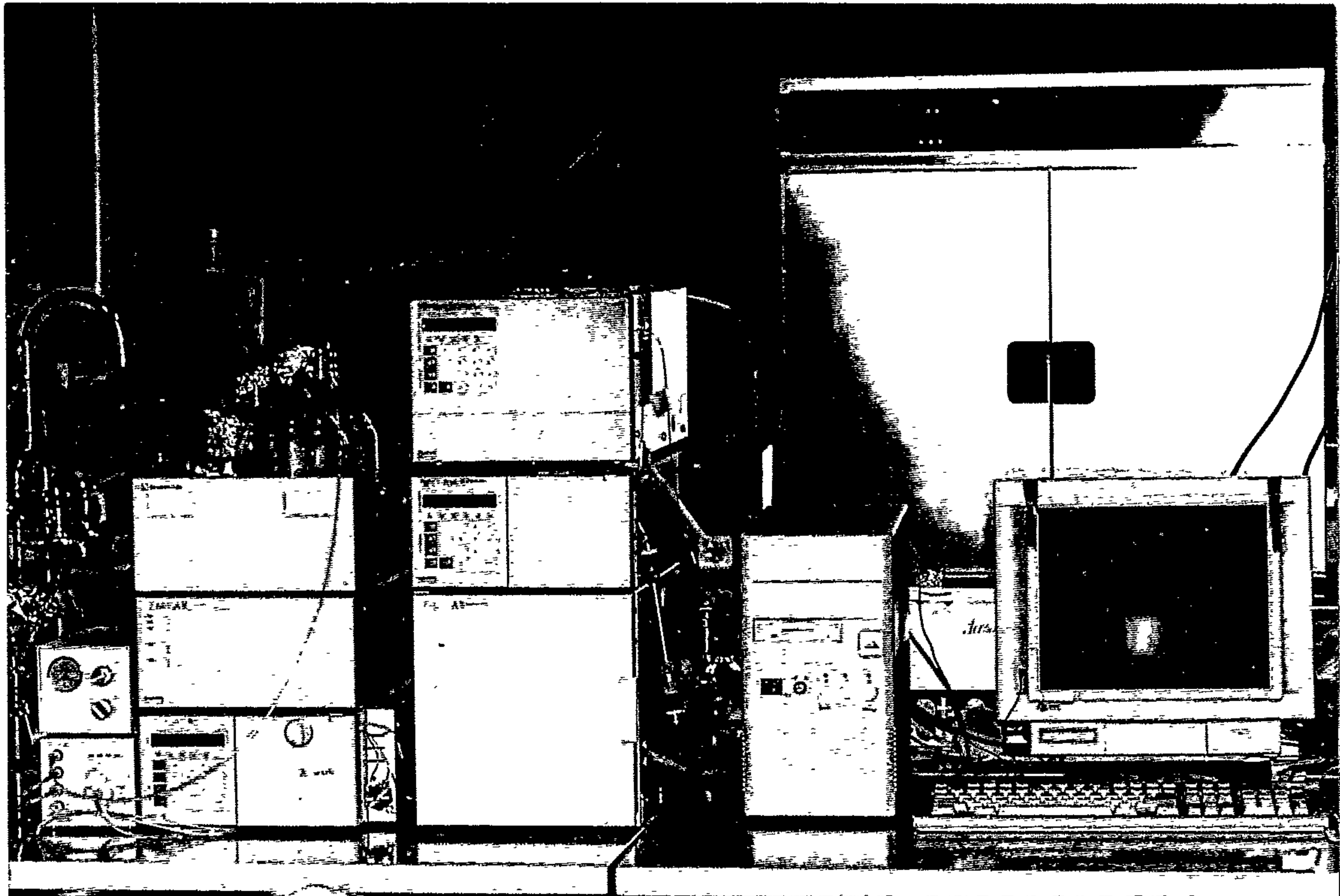


From top to bottom:

1. Micro-pipette with 50 μ L tip.
2. 200 μ L micro-pipette with disposable tip.
3. 1 mL micro-pipette with disposable tip.

Illustration 8.

Shimadzu® chromatography (HPLC) equipment.

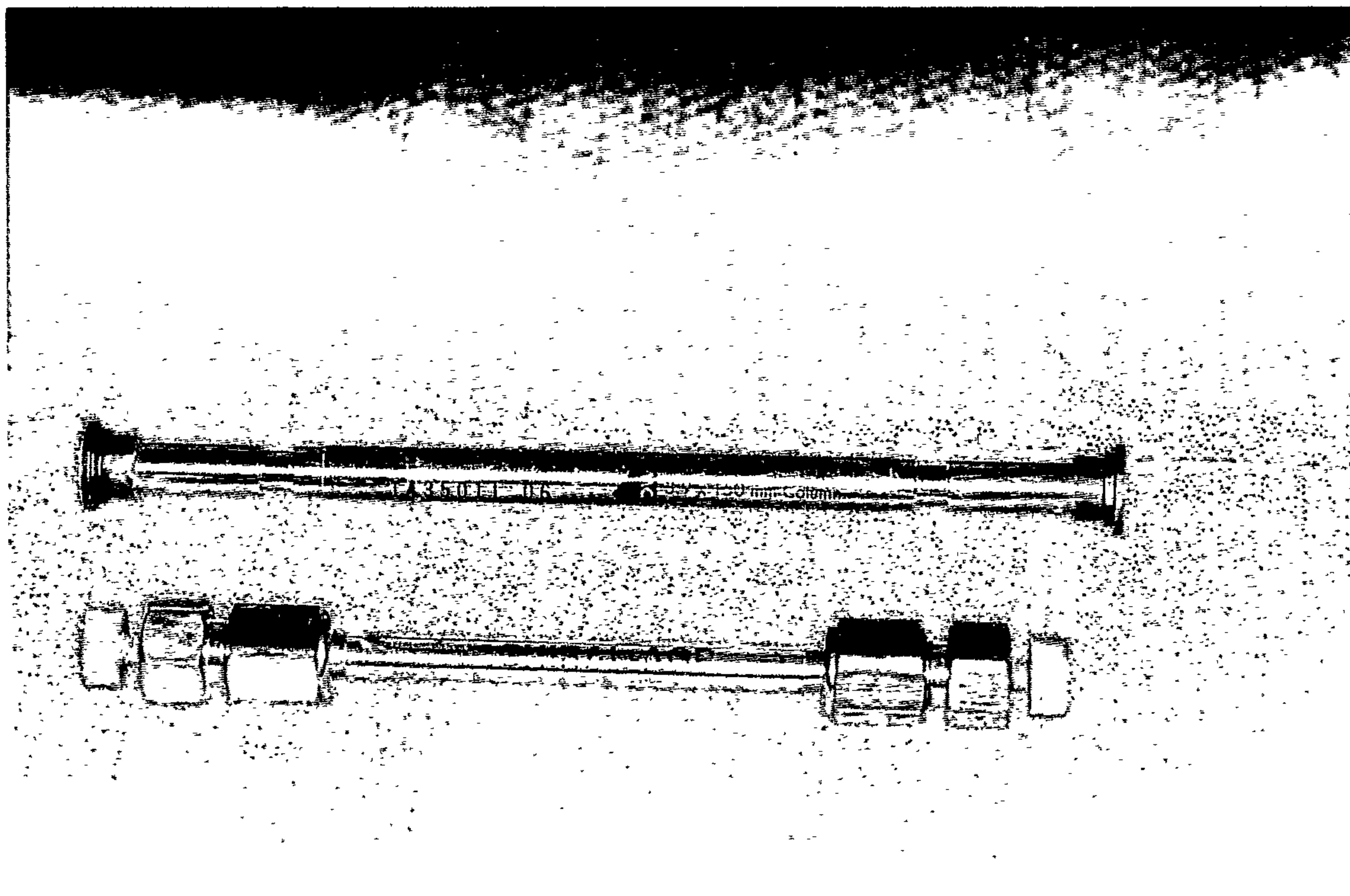


From left to right:

1. FCV-10AL switch valve mixer.
2. CBM-10A communication bus mobile.
3. LC-10AD pump.
4. SPD-10A ultraviolet detector.
5. SIL-10A autoinjector.
6. 486-DX IBM compatible computer.

Illustration 9.

HPLC columns.



From top to bottom:

1. Waters[®] C8 column for lignocaine assays.
2. ChromTech[®] Chiral-AGP column for bupivacaine assays.

CHAPTER 3

RESULTS

3.1. Distribution

The mean age of the patients was 24 years and the ratio of males to females was nine to fourteen.

3.2. Anaesthetic Volume

Fourteen subjects had the right side operated first and nine subjects the left. The mean volume of bupivacaine solution used for all subjects was 5.79 mL which translates to 28.93 mg bupivacaine. The mean volume of lignocaine solution used was 5.64 mL which is equivalent to 112.87 mg lignocaine. The difference in the mean volume of local anaesthetic used was not statistically significant.

3.3. Surgical time

The times taken for the surgical procedures with both bupivacaine and lignocaine are shown in table 1. The range of times taken for the surgical procedures with bupivacaine was 10 to 51 minutes while the range with lignocaine was 7 to 27 minutes. The longer operating times with bupivacaine was due to the retrieval of a fractured root apex when using bupivacaine in subject 17. The mean time for the surgical procedures was 16.7 minutes with bupivacaine and

15.8 minutes with lignocaine (Fig.2). The difference was not statistically significant.

3.4. Visual analogue and global pain scores

Tables 2, 3, 4 and 5 show the visual analogue and global pain scores for both groups. There was no significant difference between bupivacaine and lignocaine for intra-operative pain experience. Five subjects (1, 11, 20, 21 and 22) required an additional cartridge of bupivacaine for adequate anaesthesia while three subjects (13, 14 and 23) required an additional cartridge of lignocaine. In all patients the depth of anaesthesia was adequate for the completion of surgery.

The visual analogue (Fig. 3a) and global pain (Fig.3b) scores showed a similar trend for post-operative pain experience. The mean peak pain experience for both agents was at four hours. The mean visual analogue pain scores for bupivacaine and lignocaine were 33 and 45 respectively. The mean global pain scores were 2.05 and 2.39 respectively. While bupivacaine produced a measurable reduction in pain experience when compared to lignocaine, this was not statistically significant.

The difference in pain experience at eight hours was significant. The mean visual analogue pain scores for bupivacaine and lignocaine were 19 and 34 respectively ($p=0.013$). Similarly, the mean global pain scores were 1.35 and 2.0 ($p=0.012$).

The pain experience at 12 hours could not be determined as only one subject with bupivacaine made an entry and no subject with lignocaine. At 16 hours however, the mean visual analogue and global pain scores were almost identical for both agents. Somewhat unexpectedly,

the visual analogue and global pain scores at 24 hours showed a measurable reduction in pain experience with lignocaine compared to bupivacaine, but this was not significant.

3.5. Analgesic consumption

Tables 6 and 7 show the analgesic consumption at various post-operative time periods. The values obtained for the number of analgesics consumed were obtained from the patient's data sheets. No attempt was made to verify these values by counting the number of unused medications. The number of analgesics consumed was greater for lignocaine at all time frames measured, but this was not statistically significant (Fig.4). The mean total number of analgesic medications consumed was 5.95 for bupivacaine and 5.39 for lignocaine, but again the difference was not statistically significant.

3.6. Cardiovascular responses

The values for systolic blood pressure for both local anaesthetic agents are shown in tables 8 and 9. The mean baseline value prior to local anaesthetic administration for both bupivacaine and lignocaine was 124 mmHg. The mean systolic blood pressure remained relatively constant, however a small increase in mean peak blood pressure for both agents occurred at 15 minutes. There was however no significant difference between bupivacaine and lignocaine at any of the times measured.

The values for diastolic blood pressure are shown in tables 10 and 11. The mean baseline values were 72 and 70 mmHg for bupivacaine and lignocaine respectively. This difference was

not statistically significant. The mean diastolic blood pressure for bupivacaine decreased to 69 mmHg at 5 minutes and then remained relatively constant. The mean diastolic blood pressure for lignocaine showed a similar trend, but with a slightly greater reduction to 65 mmHg. However, an unexpectedly high diastolic blood pressure of 102 mmHg for subject 17 was recorded at 30 minutes. The differences in diastolic blood pressures for the two agents were not significant at any of the times measured. The mean systolic and diastolic blood pressures are shown (Fig.5a).

The heart rates for both local anaesthetics are shown in tables 12 and 13. The mean baseline heart rate for bupivacaine was 88 beats per minute while that for lignocaine was 83 beats per minute. For bupivacaine, the mean heart rate remained relatively constant to 15 minutes and then decreased to 78 beats per minute at 30 minutes before stabilising. With lignocaine however, the mean heart rate increased from a baseline of 83 beats per minute to 88 beats per minute at 5 minutes. The heart rate then remained stable until 15 minutes before decreasing to 81 beats per minute at 30 minutes. After 30 minutes the heart rate remained relatively constant. The differences in mean heart rates were not statistically significant at any of the times measured. With respect to the baseline heart rates, the decrease in heart rate at 30 minutes was significant for both bupivacaine ($p=0.002$) and lignocaine ($p=0.007$). The mean heart rates for both agents are shown (Fig. 5b).

3.7. Blood concentrations

Baseline blood samples taken prior to the administration of the local anaesthetic, showed that neither bupivacaine nor lignocaine was present in the blood of any subjects. The mean blood concentrations of both bupivacaine and lignocaine over the study period are shown in table 14.

The values for bupivacaine represent the sum of both the R(+) and S(-) enantiomers. The highest concentration of bupivacaine measured was 0.1680 µg/mL at 15 minutes in subject 20. The mean peak blood concentration was 0.0728 µg/mL and this also occurred at 15 minutes. Thereafter the concentration decreased minimally to a mean of 0.0519 µg/mL at 60 minutes. The highest concentration of lignocaine measured was 1.7876 µg/mL at 30 minutes in subject 7. The mean peak blood concentration was 0.6166 µg/mL and did not occur at 15 minutes as with bupivacaine, but rather at 30 minutes. After this peak, there was a more rapid reduction in the mean blood concentration than occurred with bupivacaine, with a mean of 0.5064 µg/mL at 60 minutes (Fig.6a).

Table 15 shows the difference in blood concentrations of R(+) and S(-) bupivacaine. The blood concentration of the S(-) enantiomer was consistently higher than R(+) enantiomer at 15, 30, 45 and 60 minutes (Fig.6b). The highest concentration of the R(+) enantiomer measured was 0.0775 µg/mL at 15 minutes in subject 20. The highest concentration of the S(-) enantiomer was 0.0917 µg/mL, also in subject 20 but at 30 minutes. The mean peak concentration of both enantiomers occurred at 15 minutes, with values of 0.0336 µg/mL and 0.0392 µg/mL for the R(+) and S(-) enantiomers respectively. The difference in mean blood concentration was highly statistically significant at 15 minutes ($p=0.00003$), 30 minutes ($p=0.000019$), 45 minutes ($p=0.000049$) and 60 minutes ($p=0$, to 6 decimal places).

An example of the chromatograms used to determine blood concentration of both local anaesthetic agents is shown (Figs. 7 and 8).

Table 1

Surgical time (mins)

Subject	Bupivacaine	Lignocaine
1	15	14
2	18	27
3	19	19
4	10	8
5	13	23
6	11	12
7	17	14
8	21	18
9	15	12
10	12	15
11	11	7
12	23	16
13	17	20
14	10	17
15	26	18
16	14	11
17	51	25
18	13	17
19	15	12
20	12	15
21	12	12
22	14	17
23	15	15
Mean	16.70	15.82
S.D.	8.54	4.91

Figure 2. Time taken for surgical procedures

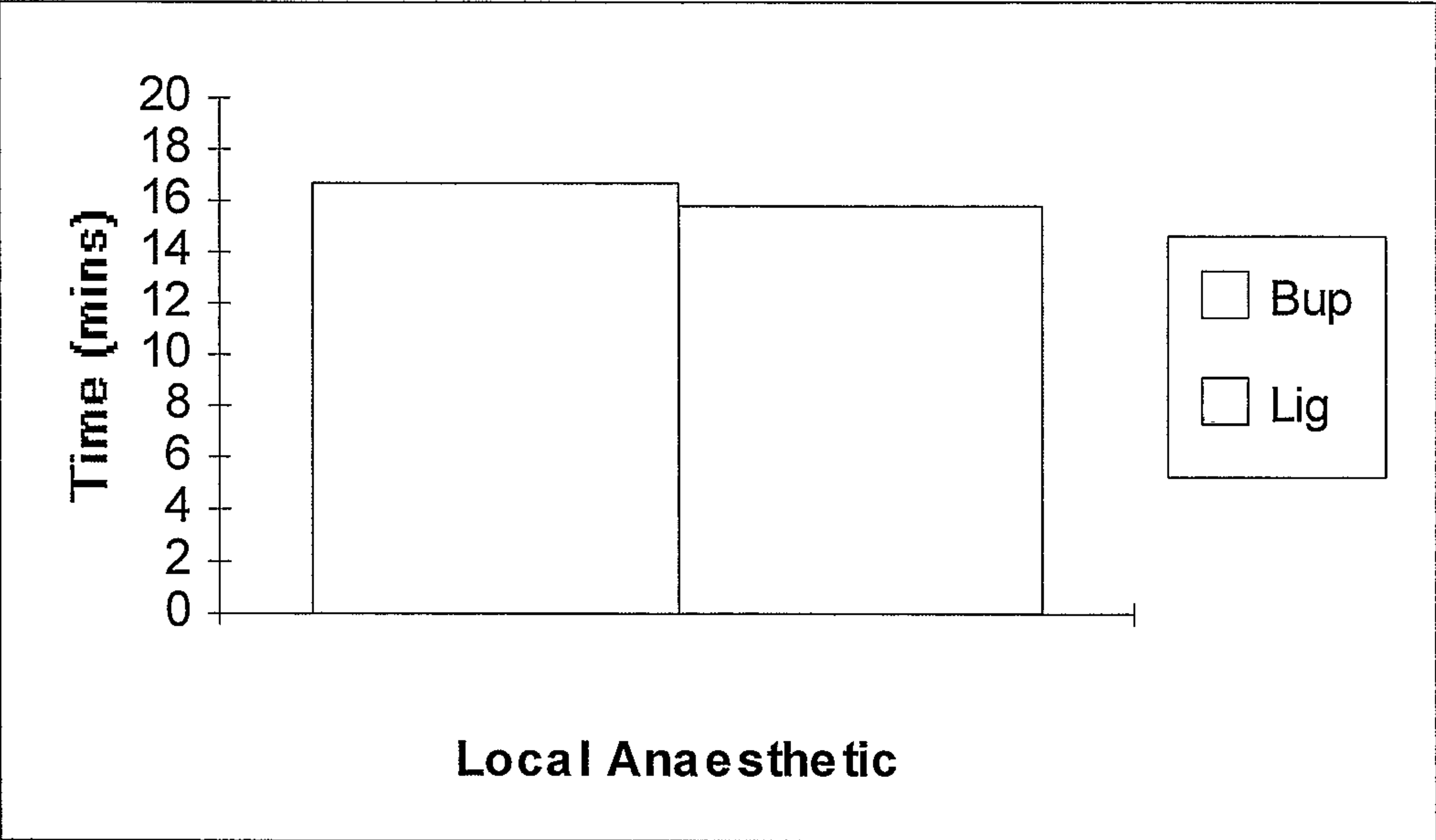


Table 2

Visual analogue pain scores

Subject	Intra-operative		4 hours post-op		8 hours post-op	
	Bup	Lig	Bup	Lig	Bup	Lig
1	13	10	11	35	18	nr
2	16	6	18	20	6	8
3	46	0	56	55	12	57
4	0	0	29	0	6	33
5	13	26	9	36	11	25
6	13	26	16	100	14	78
7	12	1	19	28	36	29
8	2	1	26	3	0	3
9	67	18	64	42	0	4
10	9	3	81	72	42	72
11	13	12	23	21	26	26
12	6	0	nr	19	nr	2
13	9	4	13	59	15	26
14	16	42	42	36	48	15
15	41	1	nr	17	nr	nr
16	11	62	nr	77	nr	nr
17	15	54	70	61	18	45
18	20	61	33	100	5	60
19	43	61	46	76	56	nr
20	7	0	26	22	22	13
21	15	8	2	77	1	69
22	35	17	19	37	15	41
23	22	19	60	38	32	37
Mean	19	19	33	45	19	34
S.D.	16.27	21.90	22.57	28.60	16.23	24.25

nr = no response recorded

Table 3

Visual analogue pain scores

Subject	12 hours post-op		16 hours post-op		24 hours post-op	
	Bup	Lig	Bup	Lig	Bup	Lig
1	nr	nr	18	24	9	26
2	nr	nr	6	nr	1	2
3	nr	nr	36	nr	40	33
4	nr	nr	7	nr	5	0
5	nr	nr	13	25	9	14
6	nr	nr	15	20	17	14
7	nr	nr	67	nr	54	29
8	nr	nr	nr	nr	0	0
9	nr	nr	nr	1	7	0
10	nr	nr	18	nr	18	14
11	nr	nr	27	18	34	9
12	nr	nr	nr	nr	nr	0
13	nr	nr	nr	22	3	23
14	nr	nr	31	8	18	27
15	nr	nr	nr	1	nr	2
16	nr	nr	nr	nr	nr	3
17	nr	nr	27	nr	32	23
18	53	nr	16	29	21	29
19	nr	nr	nr	52	30	0
20	nr	nr	nr	54	9	3
21	nr	nr	nr	nr	4	17
22	nr	nr	19	nr	7	9
23	nr	nr	28	28	12	17
Mean	N/A	N/A	23	24	17	13
S.D.	N/A	N/A	15.31	16.77	14.63	11.34

nr = no response recorded

N/A = not applicable

Table 4

Global pain scores

Subject	Intra-operative		4 hours post-op		8 hours post-op	
	Bup	Lig	Bup	Lig	Bup	Lig
1	1	1	1	2	2	nr
2	1	1	2	2	1	1
3	2	0	3	3	2	3
4	0	0	2	0	1	2
5	1	2	1	3	1	2
6	1	2	1	4	1	3
7	1	0	1	2	2	2
8	0	0	2	1	0	1
9	3	3	3	3	0	1
10	1	0	3	3	2	3
11	1	1	2	1	1	2
12	1	0	nr	2	nr	1
13	1	1	1	3	1	2
14	2	2	3	2	3	1
15	3	0	nr	3	nr	nr
16	1	3	nr	3	nr	nr
17	1	2	3	3	2	2
18	1	2	2	4	0	3
19	2	3	3	3	2	nr
20	1	0	2	1	1	1
21	1	1	1	3	1	3
22	2	1	2	2	2	3
23	1	2	3	2	2	2
Mean	1.26	1.17	2.05	2.39	1.35	2.00
S.D.	0.75	1.07	0.83	0.99	0.81	0.82

nr = no response recorded

Table 5

Global pain scores

Subject	12 hours post-op		16 hours post-op		24 hours post-op	
	Bup	Lig	Bup	Lig	Bup	Lig
1	nr	nr	1	2	1	2
2	nr	nr	1	nr	0	1
3	nr	nr	2	nr	2	2
4	nr	nr	1	nr	1	0
5	nr	nr	1	2	1	1
6	nr	nr	1	2	1	1
7	nr	nr	3	nr	3	2
8	nr	nr	nr	nr	0	0
9	nr	nr	nr	0	1	0
10	nr	nr	1	nr	1	1
11	nr	nr	2	1	3	1
12	nr	nr	nr	nr	nr	0
13	nr	nr	nr	2	0	2
14	nr	nr	2	1	1	2
15	nr	nr	nr	0	nr	0
16	nr	nr	nr	nr	nr	1
17	nr	nr	1	nr	2	1
18	3	nr	1	2	2	1
19	nr	nr	nr	1	1	0
20	nr	nr	nr	3	1	0
21	nr	nr	nr	nr	1	2
22	nr	nr	2	nr	1	1
23	nr	nr	2	2	1	1
Mean	N/A	N/A	1.5	1.5	1.2	0.96
S.D.	N/A	N/A	0.65	0.90	0.83	0.76

nr = no response recorded

N/A = not applicable

Figure 3a. Visual analogue pain scores

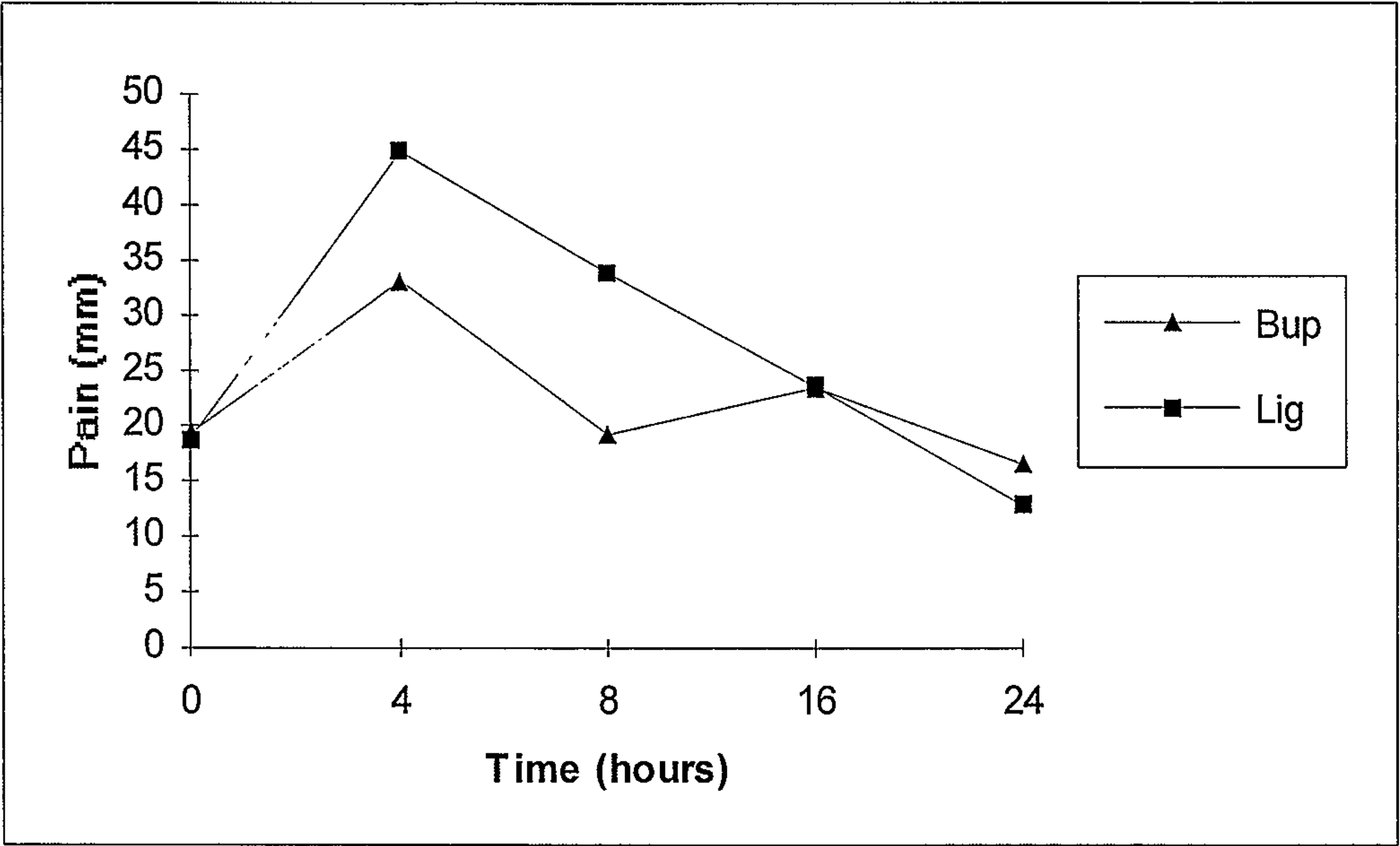
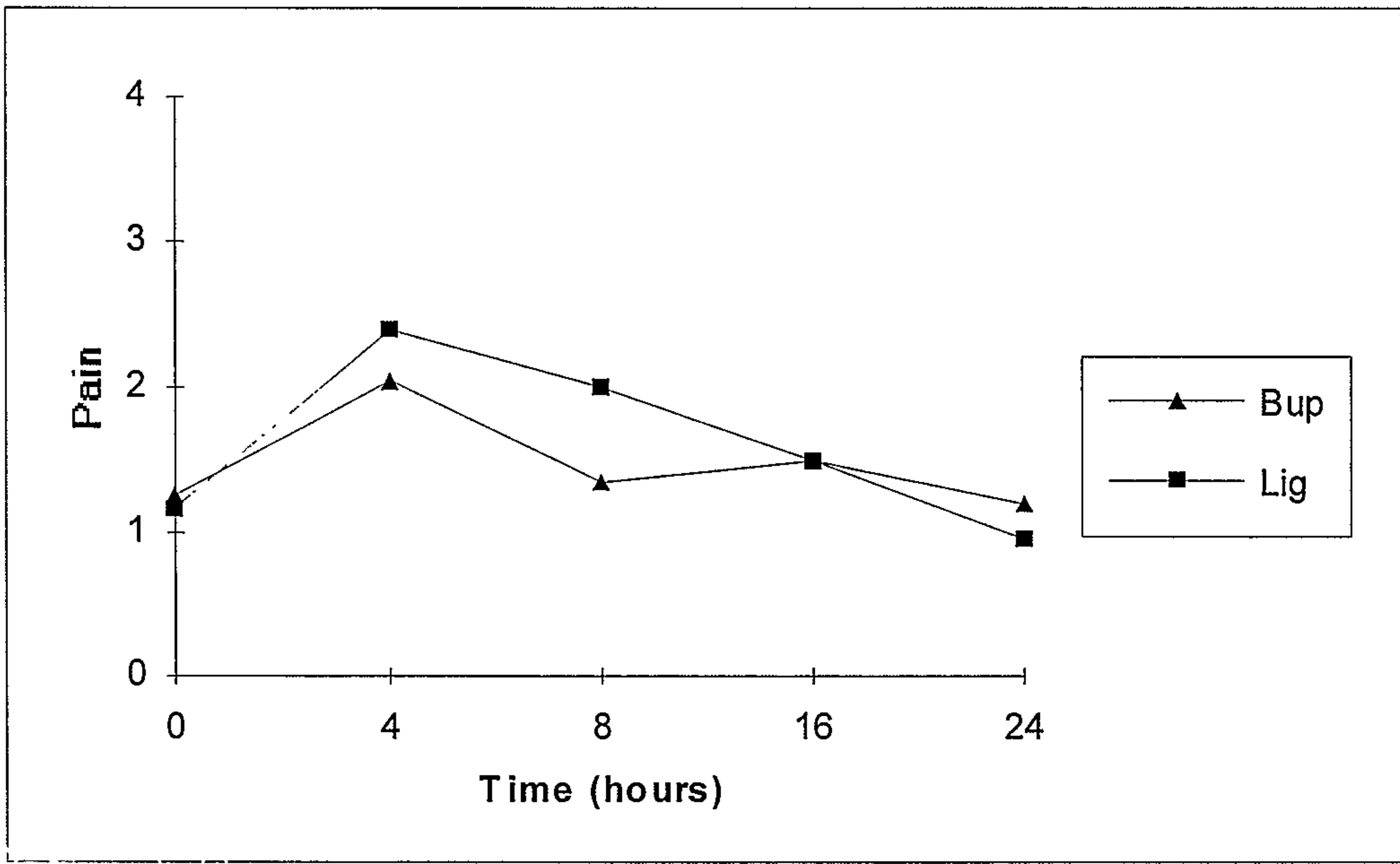


Figure 3b. Global pain scores



(pain: 0 - none, 1 - a little, 2 - some, 3 - a lot, 4 - worst possible)

Table 6

Analgesic consumption

Subject	0 - 4 hours		4 - 8 hours		8 - 12 hours	
	Bup	Lig	Bup	Lig	Bup	Lig
1	1	2	0	0	0	0
2	0	1	1	1	0	0
3	1	1	0	1	0	0
4	0	1	2	0	0	1
5	1	1	0	1	0	0
6	1	1	0	0	0	0
7	0	1	0	0	0	1
8	1	1	0	0	0	0
9	1	0	1	2	0	2
10	2	0	0	1	0	0
11	0	0	1	1	0	0
12	0	1	0	0	0	1
13	1	1	0	0	0	0
14	1	0	0	1	0	0
15	nr	1	nr	0	nr	0
16	nr	0	nr	0	nr	0
17	1	1	0	0	0	0
18	0	2	1	1	1	0
19	0	1	1	0	1	0
20	1	2	1	1	1	0
21	0	1	0	1	0	0
22	1	1	1	1	0	0
23	1	2	1	0	0	2
Mean	0.67	0.96	0.50	0.52	0.15	0.30
S.D.	0.58	0.64	0.61	0.59	0.37	0.63

nr = no response recorded

Table 7

Analgesic consumption

Subject	12 - 24 hours		After 24 hours		Total	
	Bup	Lig	Bup	Lig	Bup	Lig
1	2	2	12	5	15	9
2	1	0	2	0	4	2
3	3	2	9	9	13	13
4	0	0	0	0	2	2
5	0	1	1	0	2	3
6	2	2	10	12	13	15
7	1	1	2	5	3	8
8	0	0	1	0	2	1
9	2	2	1	0	5	6
10	0	0	0	0	2	1
11	1	3	1	2	3	5
12	0	1	0	1	0	4
13	0	0	0	3	1	4
14	1	0	0	1	2	2
15	nr	0	nr	0	nr	1
16	nr	0	nr	0	nr	0
17	2	2	17	12	20	16
18	1	1	18	5	21	9
19	1	1	0	0	3	2
20	1	2	4	4	8	9
21	0	0	0	1	0	3
22	1	2	1	1	4	5
23	0	0	0	0	2	4
Mean	0.90	0.96	3.95	2.65	5.95	5.39
S.D.	0.89	0.98	5.87	3.78	6.45	4.57

nr = no response recorded

Figure 4. Analgesic consumption

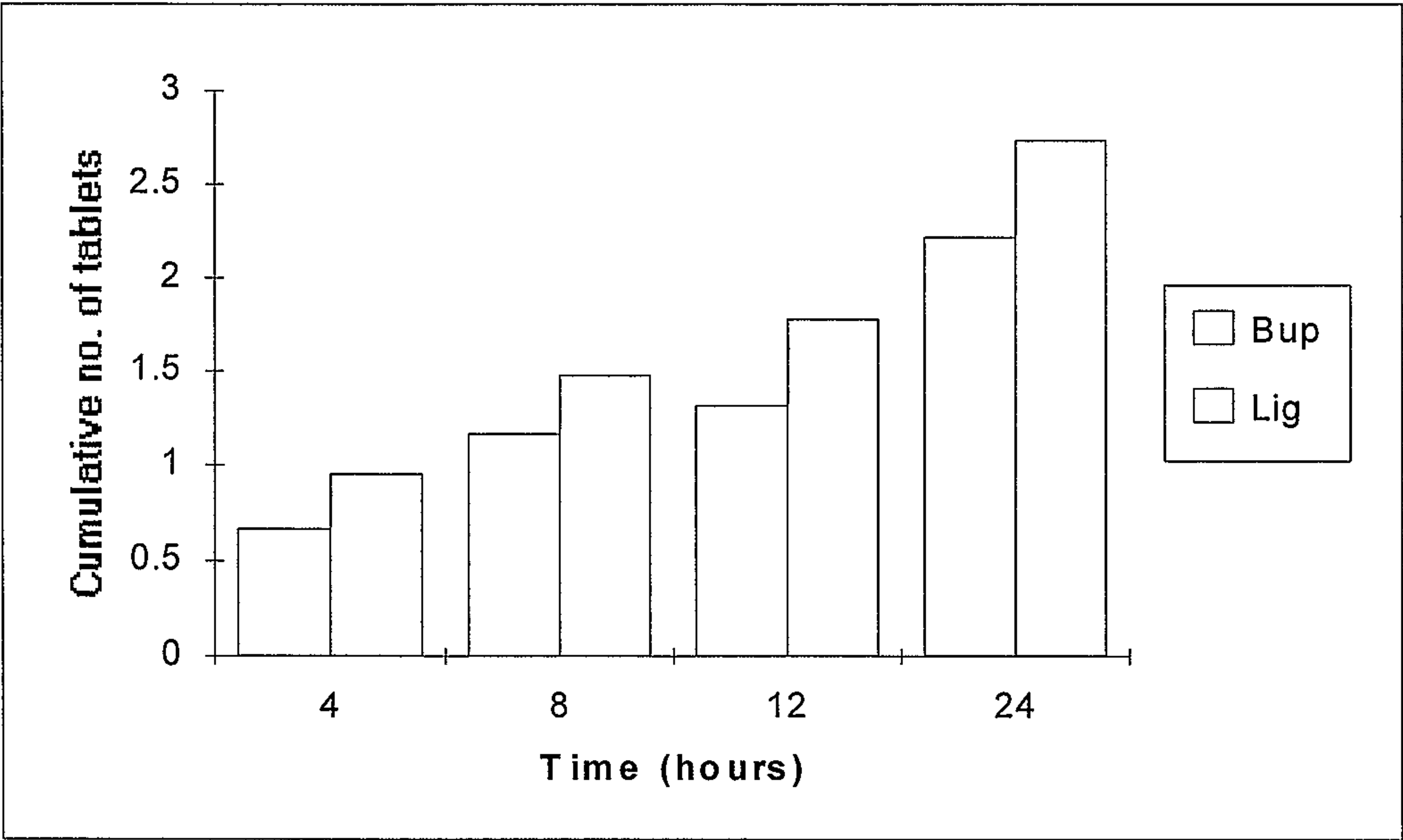


Table 8

Systolic blood pressure (mm Hg)

Subject	Baseline		5 mins		15 mins	
	Bup	Lig	Bup	Lig	Bup	Lig
1	117	107	104	112	105	112
2	154	150	140	139	162	152
3	120	120	122	130	128	102
4	115	118	116	108	120	107
5	126	149	131	140	137	156
6	149	123	146	116	132	115
7	137	117	130	111	117	115
8	136	111	137	114	124	114
9	107	100	114	99	124	116
10	149	132	135	123	131	120
11	125	134	145	136	155	156
12	131	141	122	140	150	142
13	141	107	124	118	132	114
14	133	110	118	113	113	131
15	114	116	114	124	128	122
16	95	93	95	85	102	95
17	94	151	121	143	123	146
18	99	151	99	103	111	106
19	136	150	135	139	141	141
20	129	122	120	123	117	121
21	96	106	112	107	111	124
22	145	141	169	135	154	125
23	104	114	108	103	127	104
Mean	124	124	124	120	128	123
S.D.	18.56	18.15	16.92	15.77	16.11	17.72

Table 9

Systolic blood pressure (mm Hg)

Subject	30 mins		45 mins		60 mins	
	Bup	Lig	Bup	Lig	Bup	Lig
1	103	106	124	99	102	103
2	128	141	131	126	129	128
3	135	120	130	119	128	126
4	111	103	111	105	131	104
5	129	149	143	127	127	136
6	122	132	120	122	123	116
7	121	110	110	120	113	112
8	121	112	121	113	124	116
9	115	101	114	103	108	107
10	130	115	129	119	135	123
11	126	121	125	123	142	110
12	133	124	141	140	148	138
13	130	115	121	106	121	110
14	107	124	114	124	108	118
15	135	115	113	117	139	111
16	96	99	90	100	97	89
17	135	157	125	127	128	132
18	97	97	98	92	92	96
19	144	128	137	138	142	143
20	117	135	116	130	105	131
21	119	108	101	104	113	101
22	156	140	152	138	143	139
23	101	99	93	105	104	106
Mean	122	120	120	117	122	117
S.D.	15.12	16.72	15.73	13.51	16.07	14.85

Table 10

Diastolic blood pressure (mm Hg)

Subject	Baseline		5 mins		15 mins	
	Bup	Lig	Bup	Lig	Bup	Lig
1	69	62	54	61	54	67
2	92	94	75	74	88	85
3	74	72	72	73	77	61
4	72	70	63	60	70	60
5	70	81	68	83	69	76
6	83	69	66	64	41	60
7	91	74	74	60	78	62
8	82	71	81	68	76	57
9	71	71	69	62	76	76
10	71	69	69	59	68	61
11	75	60	78	89	78	68
12	74	83	70	68	63	79
13	73	67	72	59	71	63
14	74	64	65	62	55	48
15	64	62	68	59	71	63
16	60	62	57	48	63	58
17	55	81	74	77	65	85
18	54	55	62	52	59	50
19	79	71	70	68	74	74
20	73	65	74	64	72	79
21	59	61	71	64	68	72
22	76	76	62	59	67	57
23	66	71	65	63	81	62
Mean	72	70	69	65	69	66
S.D.	9.80	8.83	7.33	9.32	10.16	10.32

Table 11

Diastolic blood pressure (mm Hg)

Subject	30 mins		45 mins		60 mins	
	Bup	Lig	Bup	Lig	Bup	Lig
1	56	63	52	59	55	61
2	74	85	80	78	77	72
3	85	72	81	76	77	70
4	60	57	63	61	81	60
5	65	83	67	90	68	74
6	65	67	66	64	70	74
7	71	61	65	71	87	71
8	68	68	77	53	85	75
9	67	61	69	73	68	67
10	63	63	69	66	71	66
11	74	82	74	68	82	84
12	71	67	78	76	77	69
13	72	64	66	60	71	60
14	63	64	66	64	61	55
15	74	60	62	61	65	57
16	58	53	57	57	60	57
17	80	102	78	87	76	88
18	60	50	58	50	57	58
19	68	70	72	71	71	68
20	71	65	64	70	76	65
21	71	60	65	60	64	60
22	75	67	76	64	73	68
23	58	59	53	64	66	64
Mean	68	67	68	67	71	67
S.D.	7.33	11.56	8.31	9.88	8.62	8.45

Table 12

Heart rate (beats/min)

Subject	Baseline		5 mins		15 mins	
	Bup	Lig	Bup	Lig	Bup	Lig
1	79	72	94	71	99	92
2	81	70	82	76	80	76
3	86	86	94	87	88	74
4	86	79	86	88	82	59
5	82	80	81	75	78	79
6	110	77	112	102	105	102
7	76	74	75	74	68	66
8	106	86	95	88	121	88
9	75	92	78	83	94	94
10	94	77	86	77	83	76
11	98	81	91	108	99	90
12	98	116	84	120	63	114
13	105	87	100	108	98	104
14	89	76	87	78	80	73
15	88	87	83	90	83	92
16	72	80	76	79	80	88
17	69	90	86	105	94	105
18	71	68	87	64	95	87
19	107	92	81	126	88	103
20	86	96	82	86	73	102
21	95	88	97	95	82	120
22	76	65	60	68	68	68
23	91	87	90	82	108	83
Mean	88	83	86	88	87	88
S.D.	12.24	10.95	10.22	16.44	13.97	15.77

Table 13

Heart rate (beats/min)

Subject	30 mins		45 mins		60 mins	
	Bup	Lig	Bup	Lig	Bup	Lig
1	84	76	77	83	74	73
2	76	77	71	72	73	68
3	86	82	76	77	67	81
4	83	78	77	83	78	81
5	75	81	76	79	75	75
6	80	91	84	81	77	87
7	63	64	60	63	63	66
8	70	81	87	61	85	82
9	72	80	69	82	71	79
10	72	73	73	67	80	73
11	80	72	89	94	89	79
12	103	111	102	114	102	111
13	89	103	78	93	80	84
14	76	80	83	79	73	83
15	77	83	70	84	81	80
16	75	76	67	69	73	77
17	90	82	84	75	77	86
18	77	75	80	63	68	76
19	82	86	81	91	81	91
20	63	93	74	85	79	85
21	90	71	78	76	83	86
22	58	70	62	66	53	62
23	74	72	78	74	87	76
Mean	78	81	77	79	77	80
S.D.	10.03	10.67	9.06	12.15	9.71	9.74

Figure 5a. Blood pressure

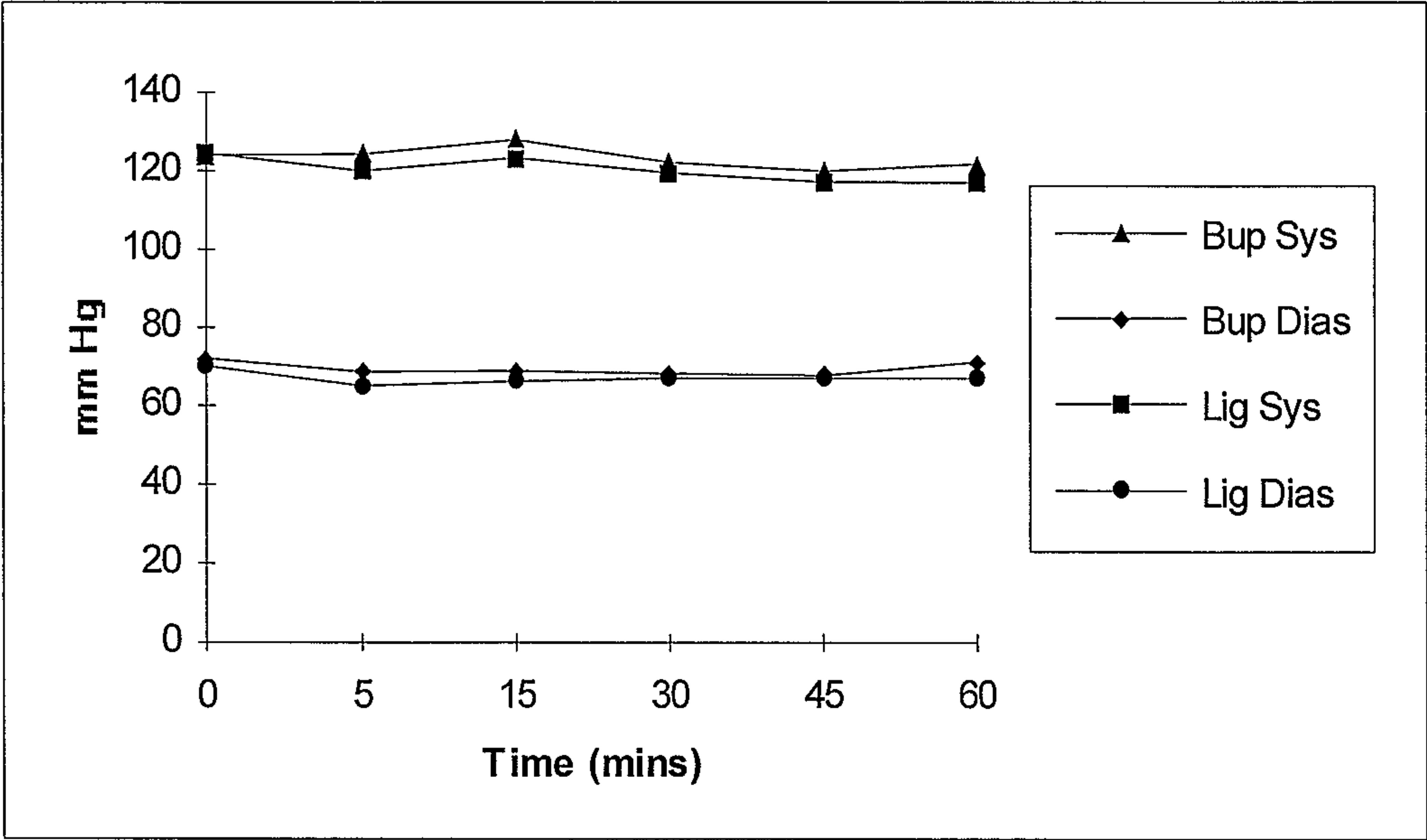


Figure 5b. Heart rate

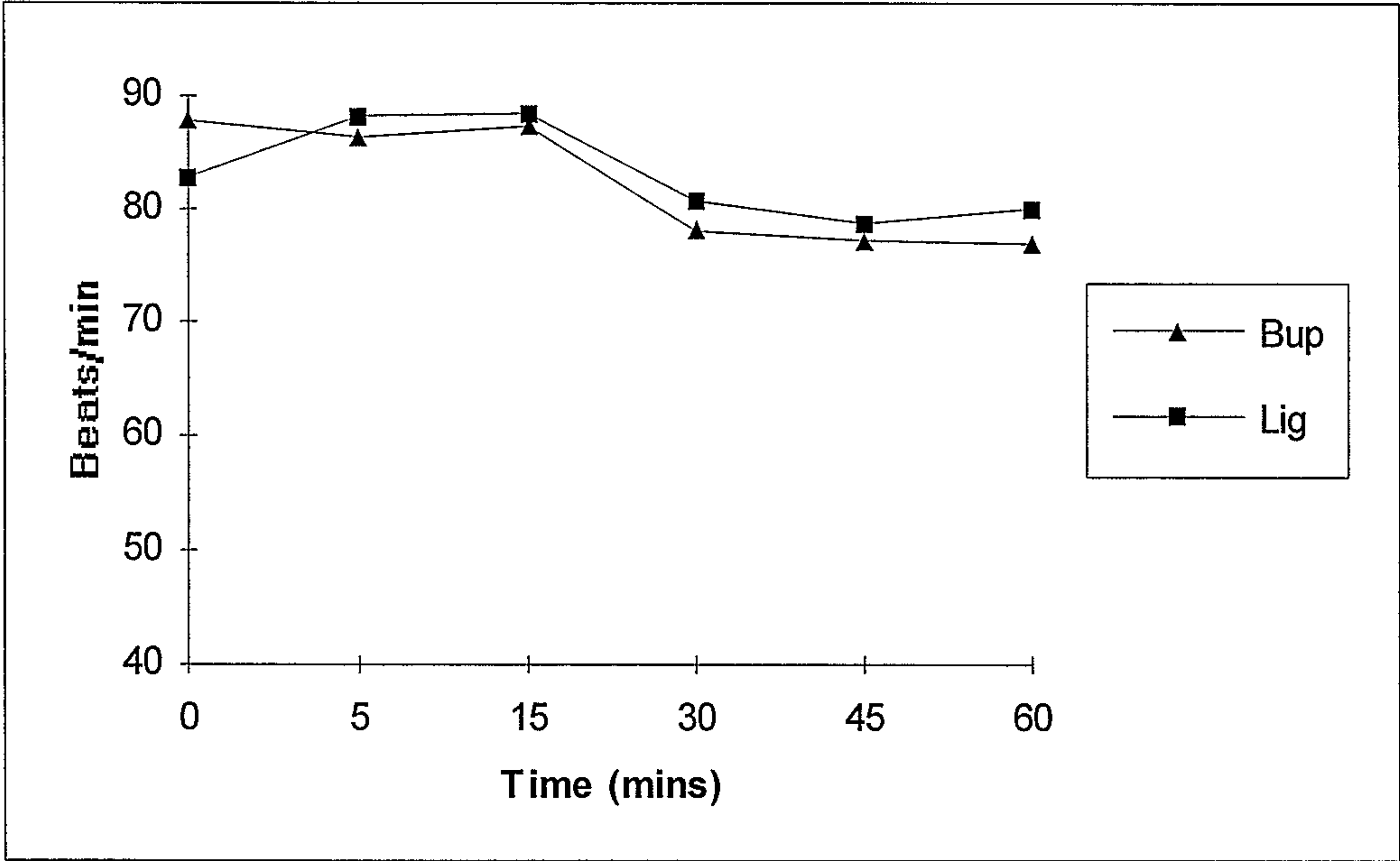


Table 14

Blood concentration ($\mu\text{g/mL}$)

Subject	15 mins		30 mins		45 mins		60 mins	
	Bup RS	Lig	Bup RS	Lig	Bup RS	Lig	Bup RS	Lig
1	0.0435	0.5652	0.0561	0.9165	0.0787	0.8954	0.644	0.8542
2	0.0366	0.9747	0.0718	0.8197	0.0368	0.5498	0.0396	0.4865
3	0.0610	0.4286	0.0664	0.4768	0.0628	0.4874	0.0474	0.4274
4	0.0603	0.2376	0.0469	0.3559	0.0336	0.4934	0.0413	0.4332
5	0.0332	0.2625	0.0316	0.2828	0.0340	0.2362	0.0345	0.2005
6	0.0457	0.6035	0.0557	0.6983	0.0406	0.5891	0.0383	0.6407
7	0.0639	1.3326	0.0911	1.7876	0.0690	1.2952	0.0639	1.3274
8	0.1048	0.5300	0.1199	0.6759	0.0876	0.5951	0.0811	0.5689
9	0.1197	0.4366	0.0934	0.5670	0.0756	0.5148	0.0611	0.4466
10	0.0616	0.3960	0.0364	0.3676	0.0326	0.3194	0.0284	0.2563
11	0.0564	0.8337	0.0832	0.9437	0.0661	1.1039	0.0646	0.8828
12	0.0462	0.3003	0.0442	0.2595	0.0309	0.2295	0.0187	0.2558
13	0.0337	0.4545	0.0348	0.8684	0.0276	0.8675	0.0242	0.4878
14	0.0204	0.4925	0.0138	0.5868	0.0243	0.5807	0.0239	0.5648
15	0.0706	0.3744	0.0495	0.3183	0.0419	0.3026	0.0471	0.2792
16	0.0735	0.5538	0.0651	0.4837	0.0394	0.4475	0.0426	0.3666
17	0.1242	0.8703	0.1189	0.7215	0.0855	0.5999	0.0538	0.6375
18	0.0694	0.6985	0.0744	0.5180	0.0645	0.5109	0.0637	0.4430
19	0.0669	0.4363	0.0558	0.2881	0.0438	0.3067	0.0423	0.2376
20	0.1680	0.6576	0.1654	0.6574	0.1148	0.6124	0.0906	0.3617
21	0.1139	0.6419	0.1006	0.6285	0.0747	0.5544	0.0742	0.4878
22	0.1166	0.3820	0.1067	0.4924	0.1000	0.4611	0.0826	0.4073
23	0.0843	0.3490	0.0677	0.4671	0.0748	0.6077	0.0652	0.5936
Mean	0.0728	0.5586	0.0717	0.6166	0.0582	0.5722	0.0519	0.5064
S.D.	0.0363	0.2538	0.0348	0.3268	0.0255	0.2601	0.0200	0.2523

Table 15

Blood concentration ($\mu\text{g/mL}$)

Subject	15 mins		30 mins		45 mins		60 mins	
	Bup R	Bup S	Bup R	Bup S	Bup R	Bup S	Bup R	Bup S
1	0.0198	0.0237	0.0259	0.0302	0.0354	0.0433	0.0271	0.0373
2	0.0185	0.0181	0.0291	0.0427	0.0175	0.0193	0.0175	0.0221
3	0.0288	0.0322	0.0339	0.0325	0.0273	0.0355	0.0204	0.0270
4	0.0281	0.0322	0.0212	0.0257	0.0175	0.0161	0.0175	0.0238
5	0.0162	0.0170	0.0180	0.0136	0.0168	0.0172	0.0172	0.0173
6	0.0201	0.0256	0.0246	0.0311	0.0191	0.0215	0.0161	0.0222
7	0.0242	0.0397	0.0393	0.0518	0.0282	0.0408	0.0282	0.0357
8	0.0497	0.0551	0.0547	0.0652	0.0375	0.0501	0.0339	0.0472
9	0.0594	0.0603	0.0422	0.0512	0.0357	0.0399	0.0270	0.0341
10	0.0251	0.0365	0.0162	0.0202	0.0172	0.0154	0.0115	0.0169
11	0.0272	0.0292	0.0373	0.0459	0.0314	0.0347	0.0277	0.0369
12	0.0233	0.0229	0.0209	0.0233	0.0125	0.0184	0.0096	0.0091
13	0.0149	0.0188	0.0168	0.0180	0.0161	0.0115	0.0090	0.0152
14	0.0073	0.0131	0.0068	0.0070	0.0134	0.0109	0.0103	0.0136
15	0.0366	0.0340	0.0225	0.0270	0.0194	0.0225	0.0194	0.0277
16	0.0338	0.0397	0.0316	0.0335	0.0171	0.0223	0.0204	0.0222
17	0.0569	0.0673	0.0511	0.0678	0.0391	0.0464	0.0282	0.0256
18	0.0321	0.0373	0.0338	0.0406	0.0283	0.0362	0.0288	0.0349
19	0.0337	0.0332	0.0270	0.0288	0.0207	0.0231	0.0185	0.0238
20	0.0775	0.0905	0.0737	0.0917	0.0524	0.0624	0.0440	0.0466
21	0.0492	0.0647	0.0440	0.0566	0.0341	0.0406	0.0337	0.0405
22	0.0561	0.0605	0.0522	0.0545	0.0472	0.0528	0.0377	0.0449
23	0.0348	0.0495	0.0309	0.0368	0.0323	0.0425	0.0269	0.0383
Mean	0.0336	0.0392	0.0328	0.0389	0.0268	0.0315	0.0231	0.0288
S.D.	0.0171	0.0195	0.0153	0.0197	0.0111	0.0146	0.0093	0.0110

Figure 6a. Blood concentrations of bupivacaine and lignocaine

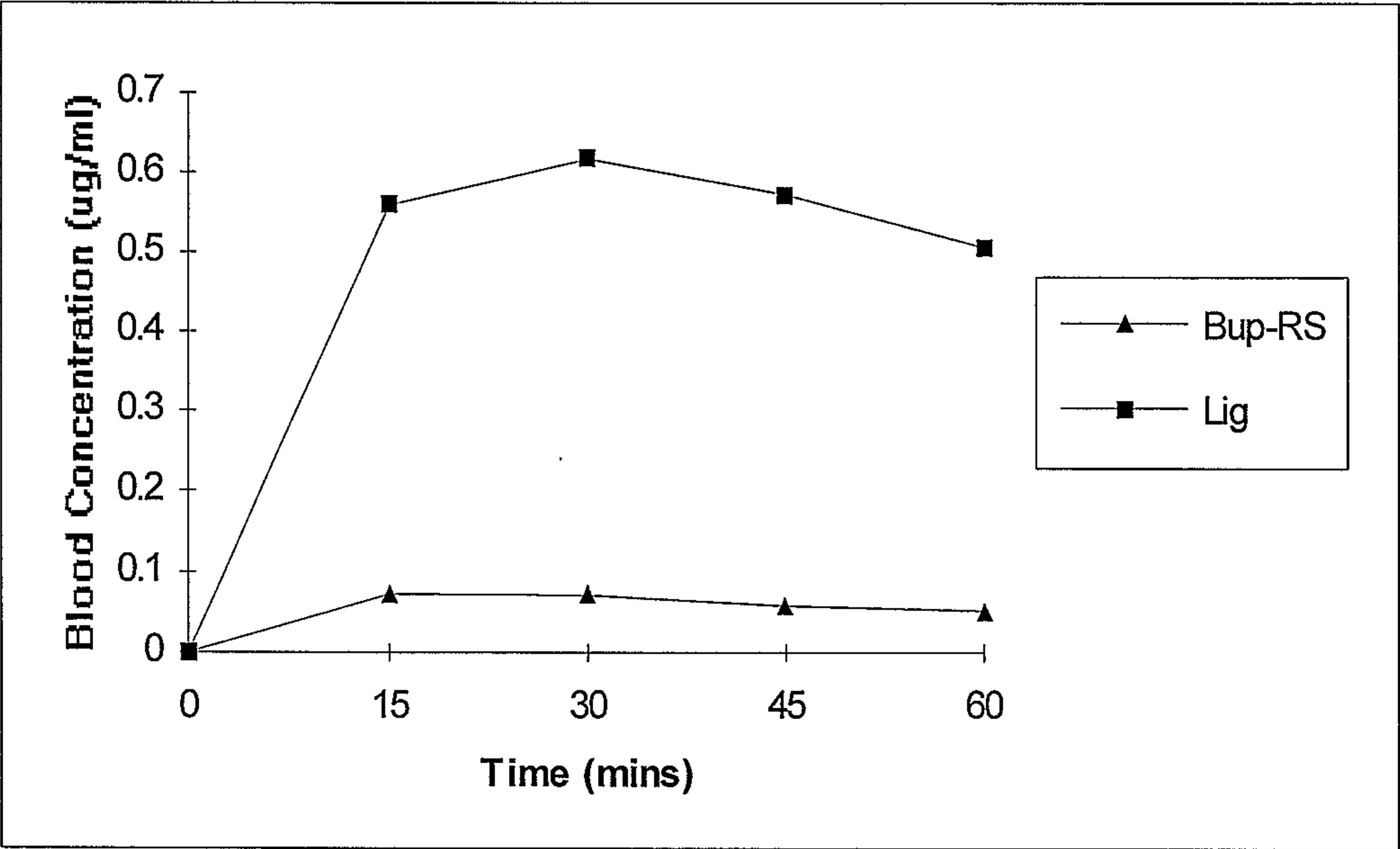


Figure 6b. Blood concentrations of the bupivacaine enantiomers

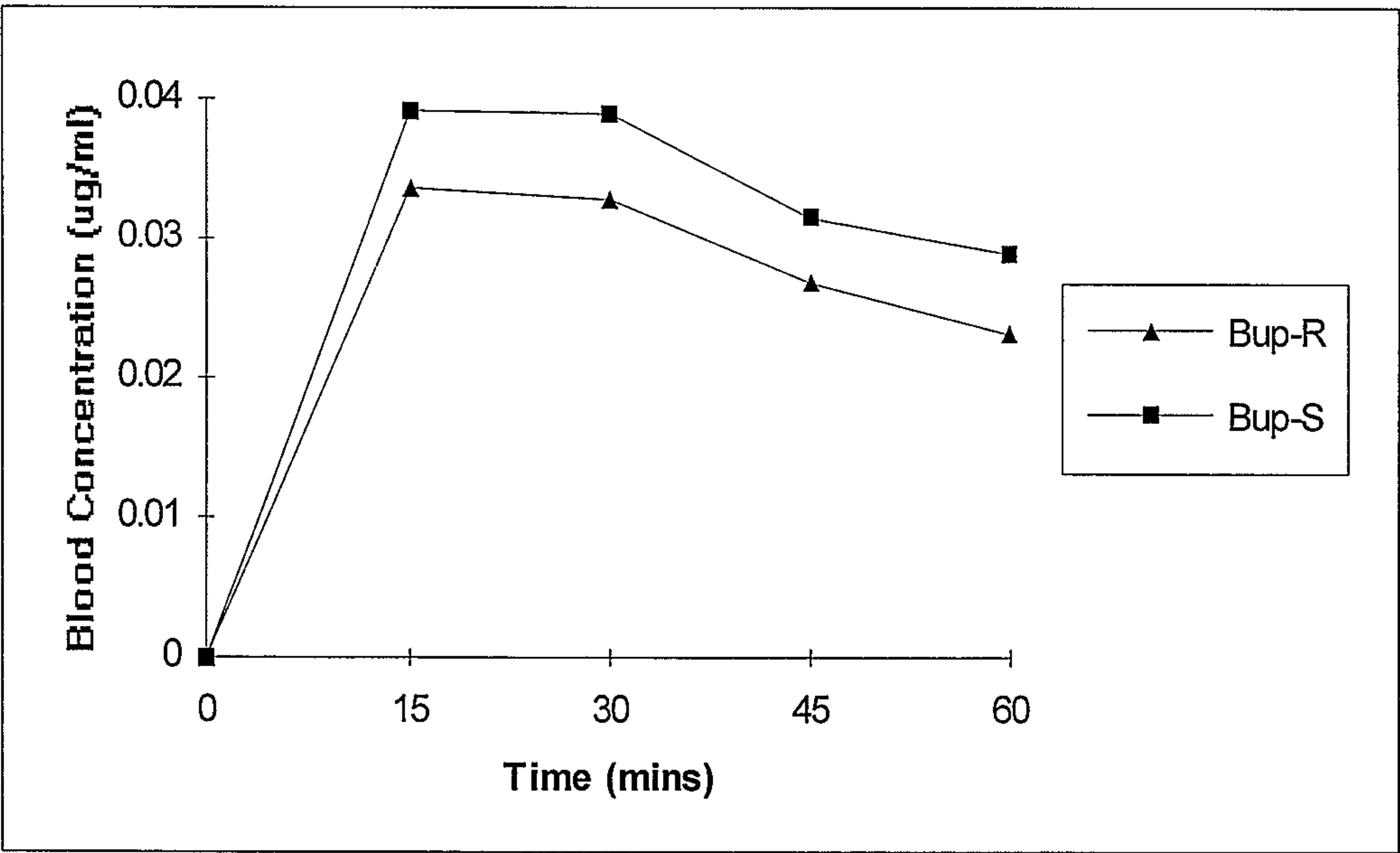


Figure 7a.

Chromatogram, lignocaine,
15 minute blood sample

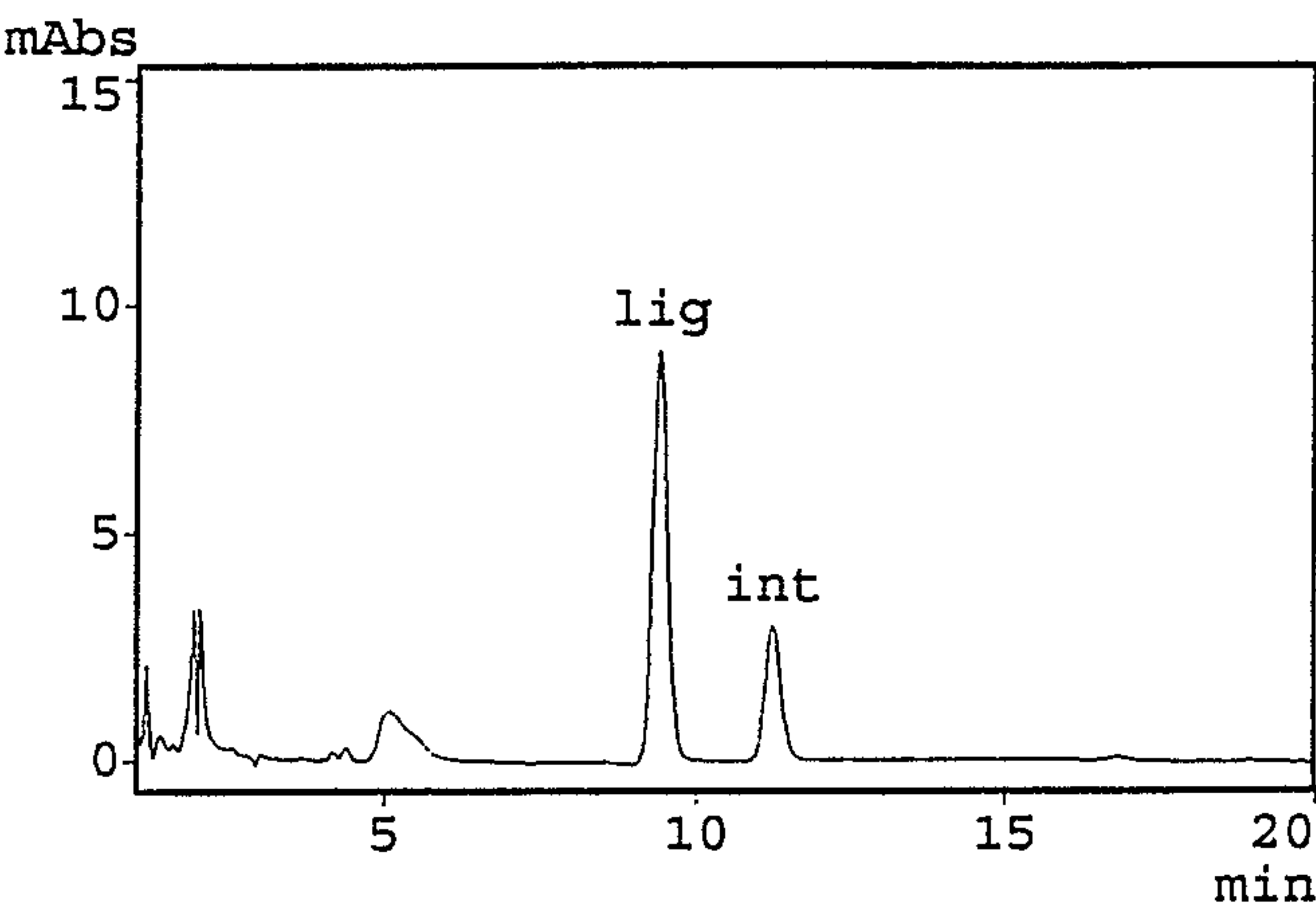


Figure 7b.

Chromatogram, lignocaine,
30 minute blood sample

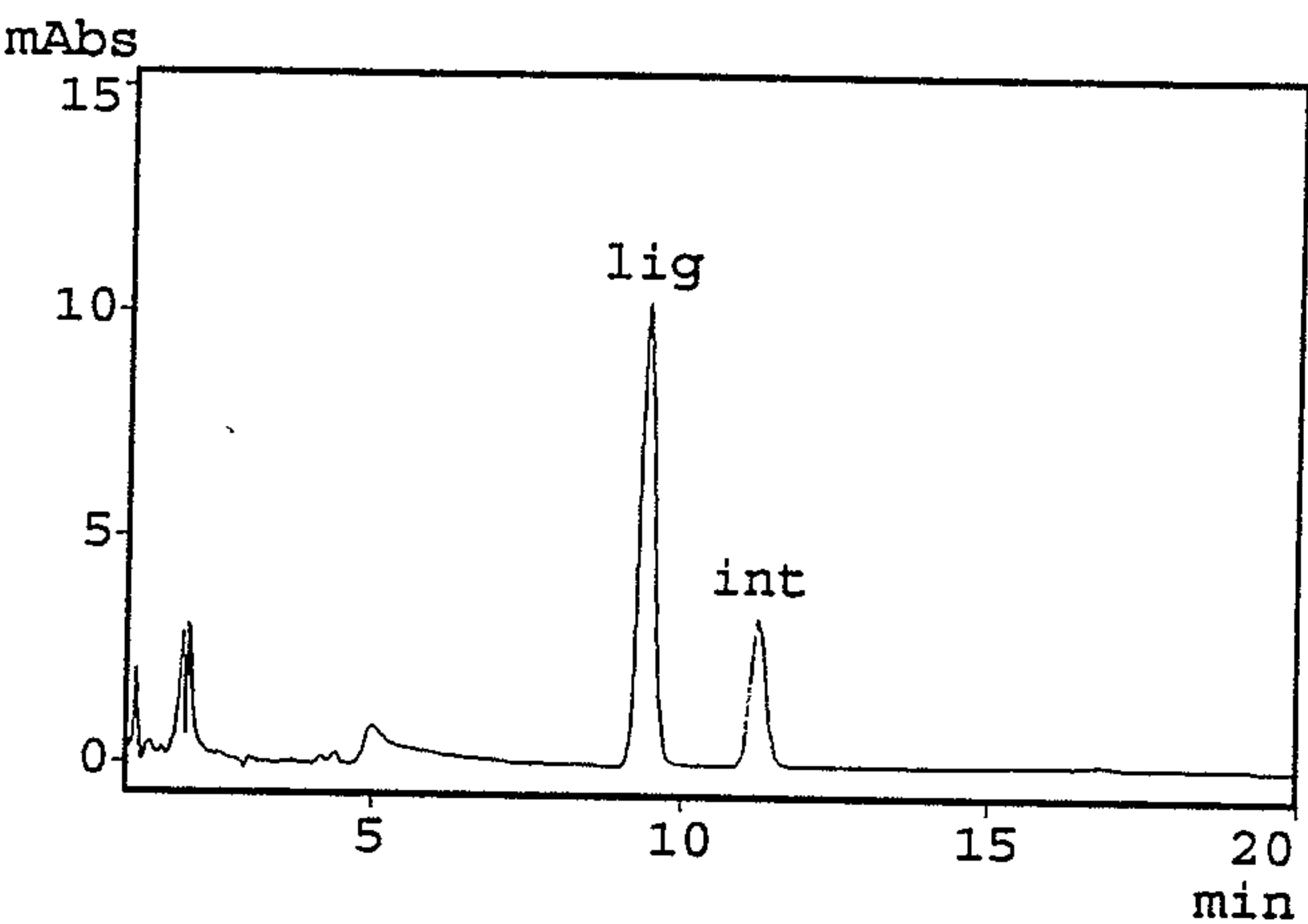


Figure 7c.

Chromatogram, lignocaine,
45 minute blood sample

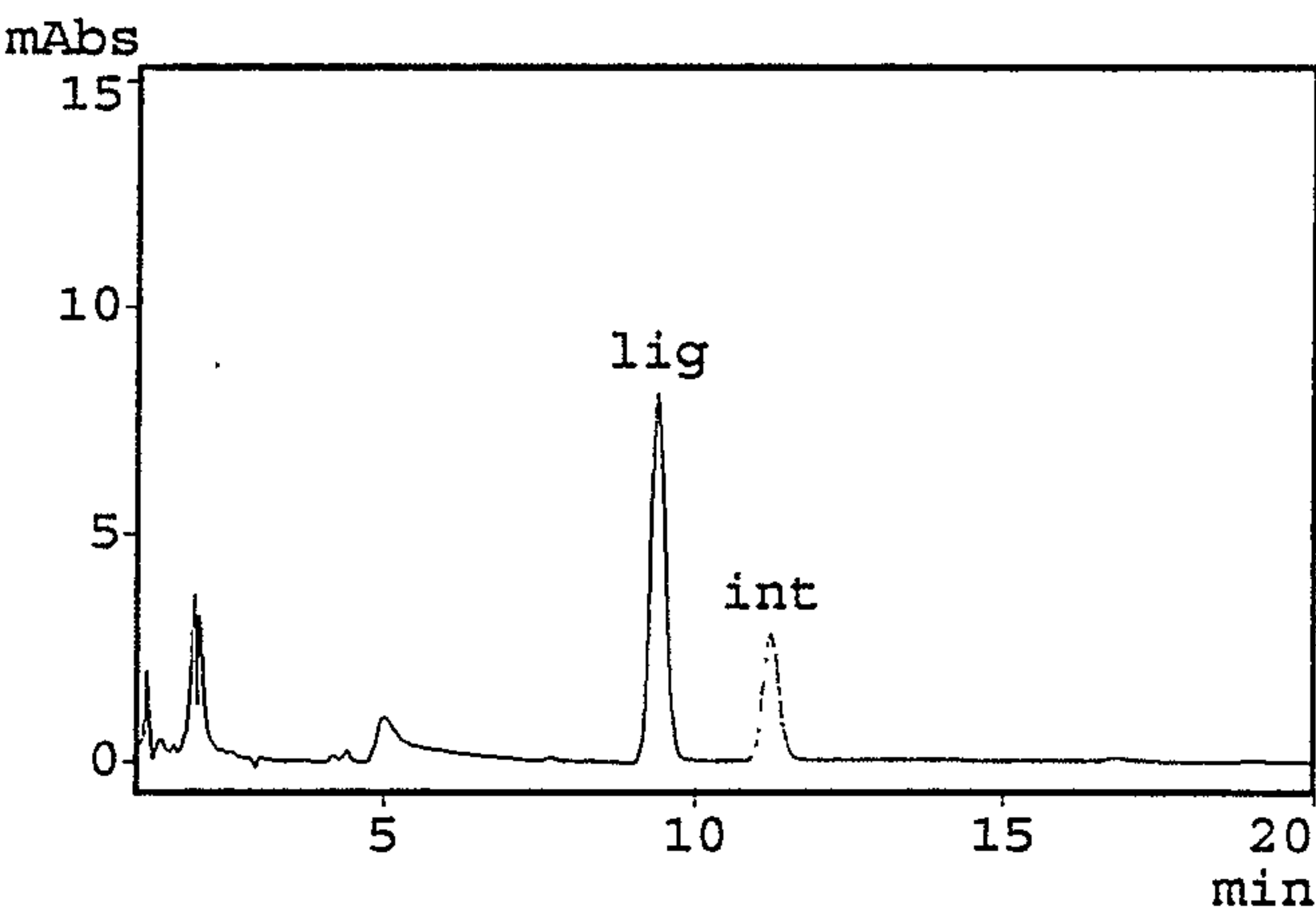


Figure 7d.

Chromatogram, lignocaine,
60 minute blood sample

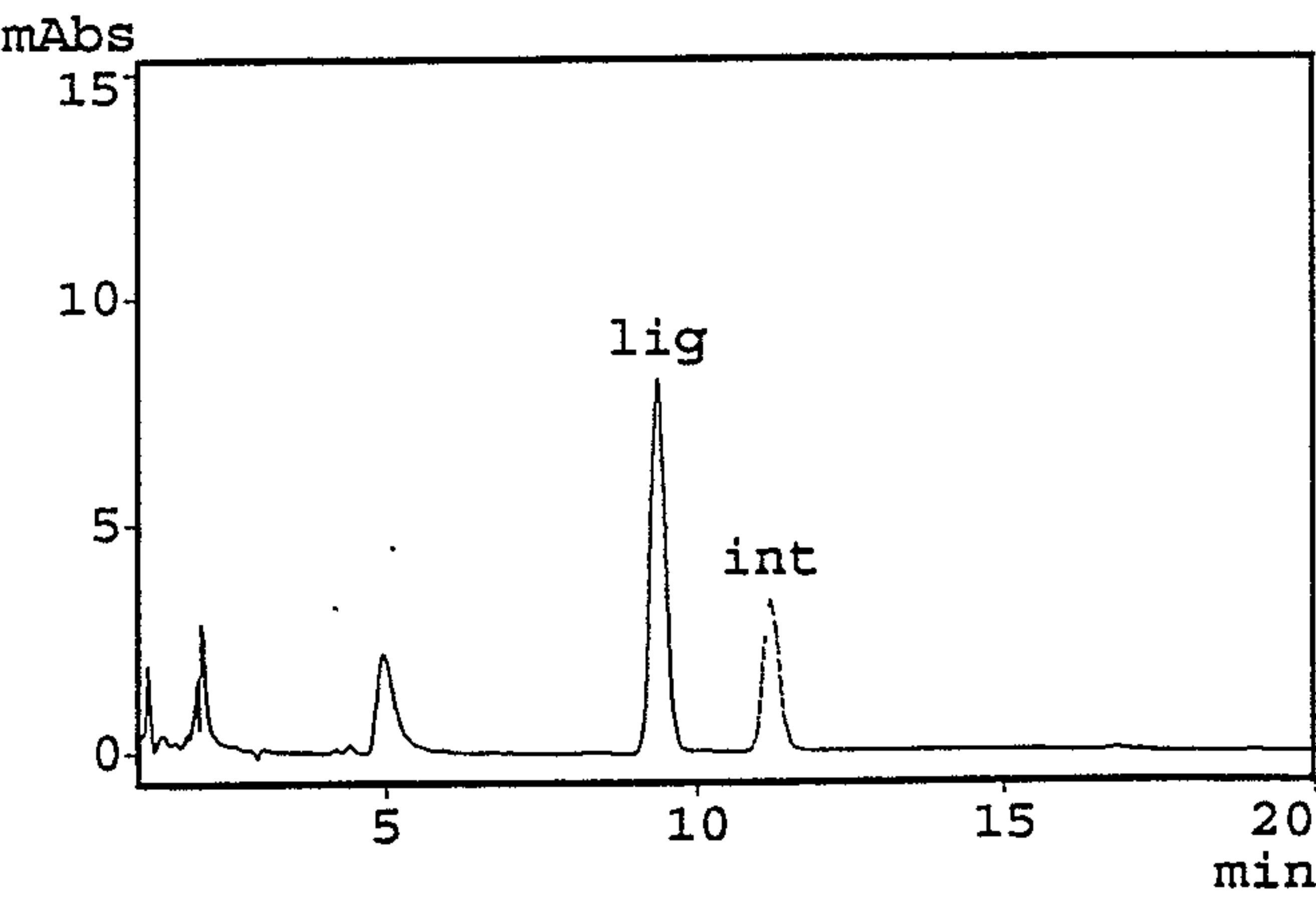


Figure 8a.

Chromatogram, bupivacaine,
15 minute blood sample

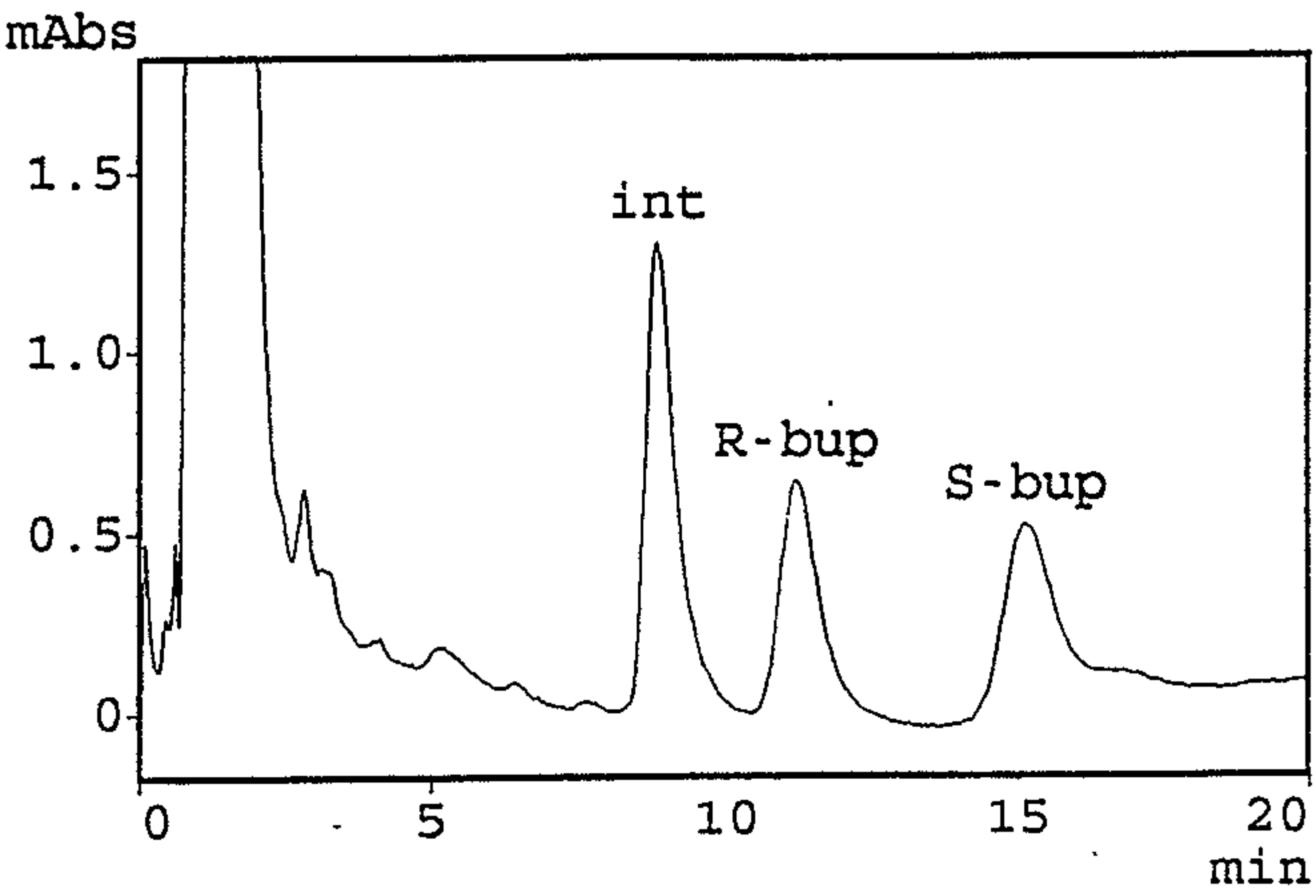


Figure 8b.

Chromatogram, bupivacaine,
30 minute blood sample

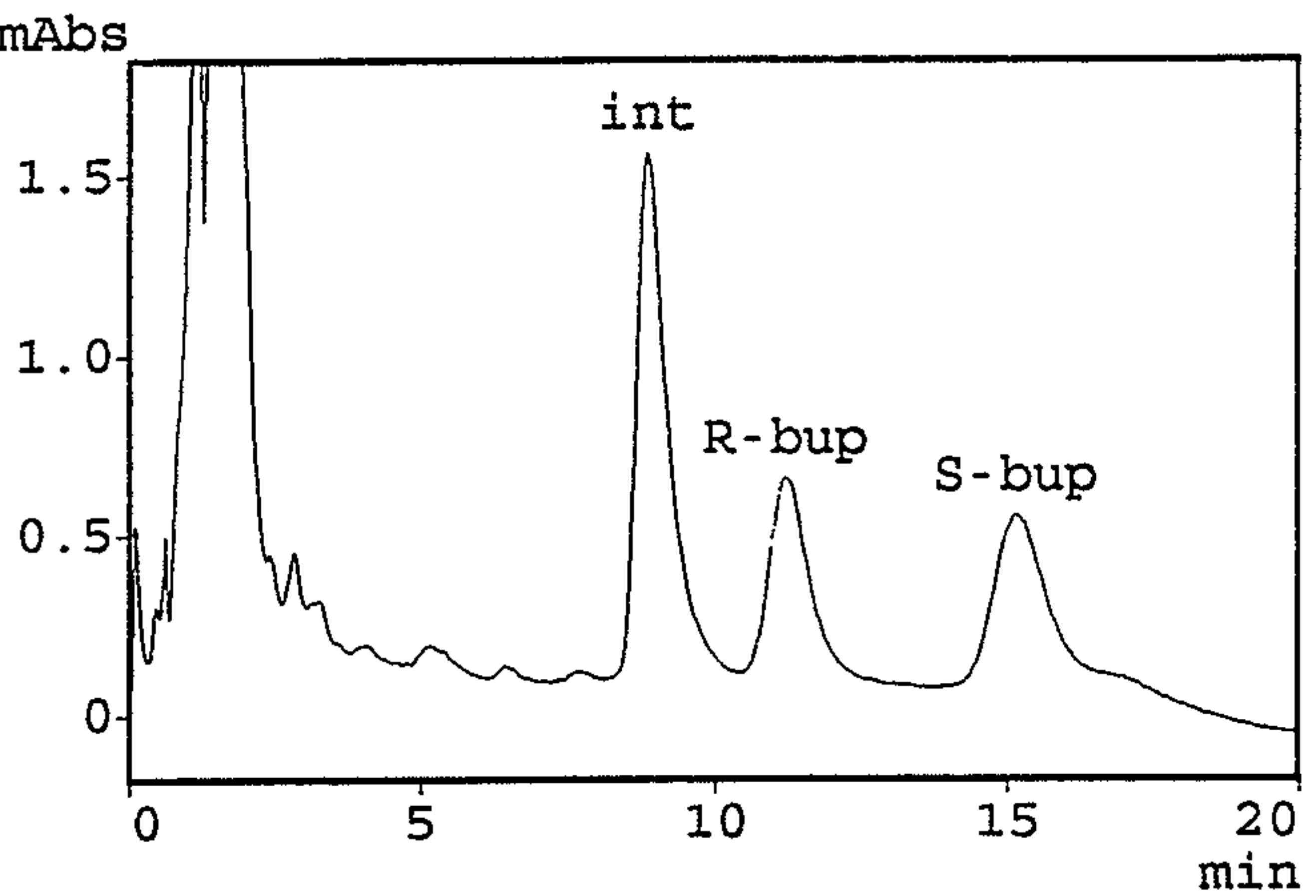


Figure 8c.

Chromatogram, bupivacaine,
45 minute blood sample

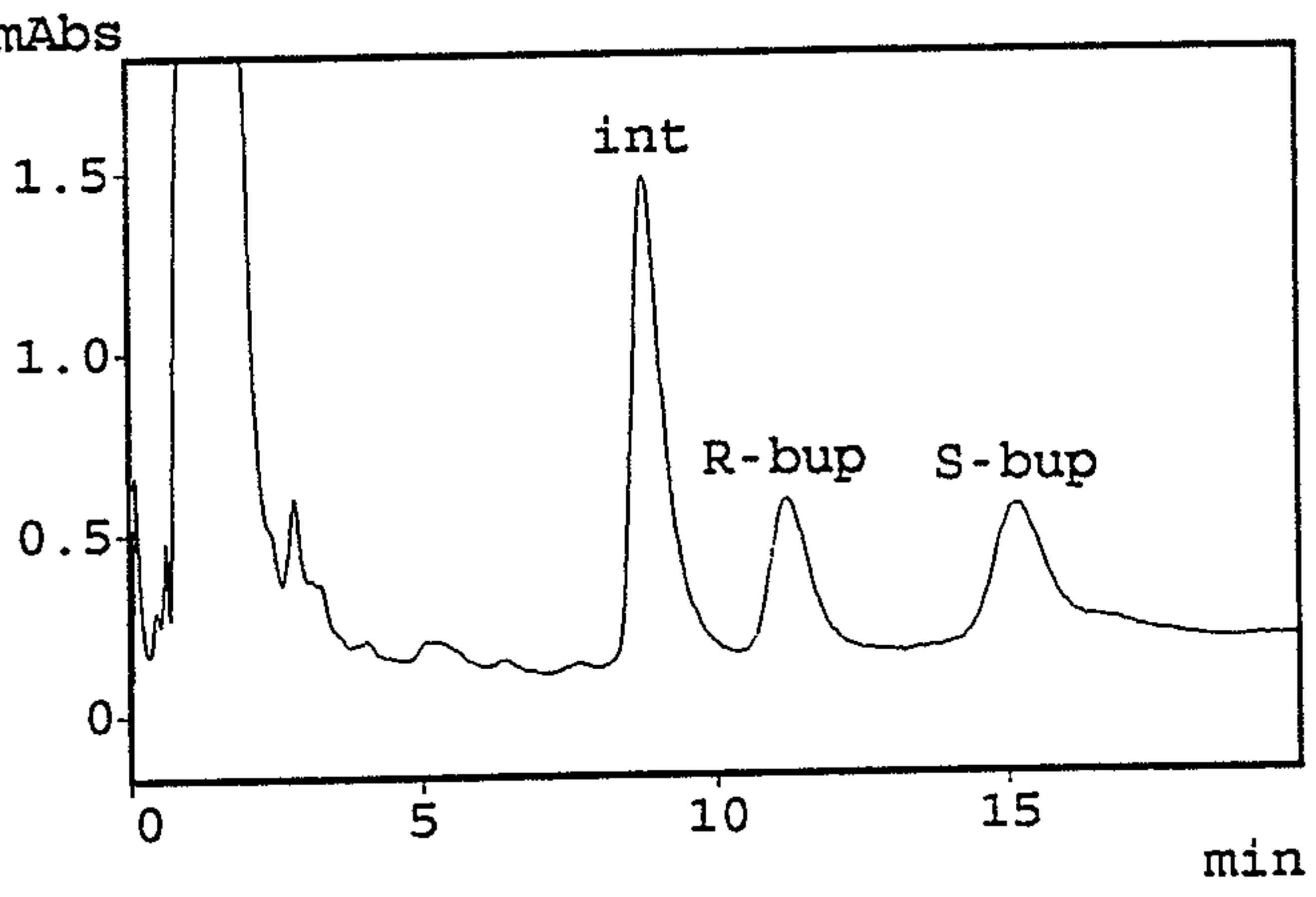
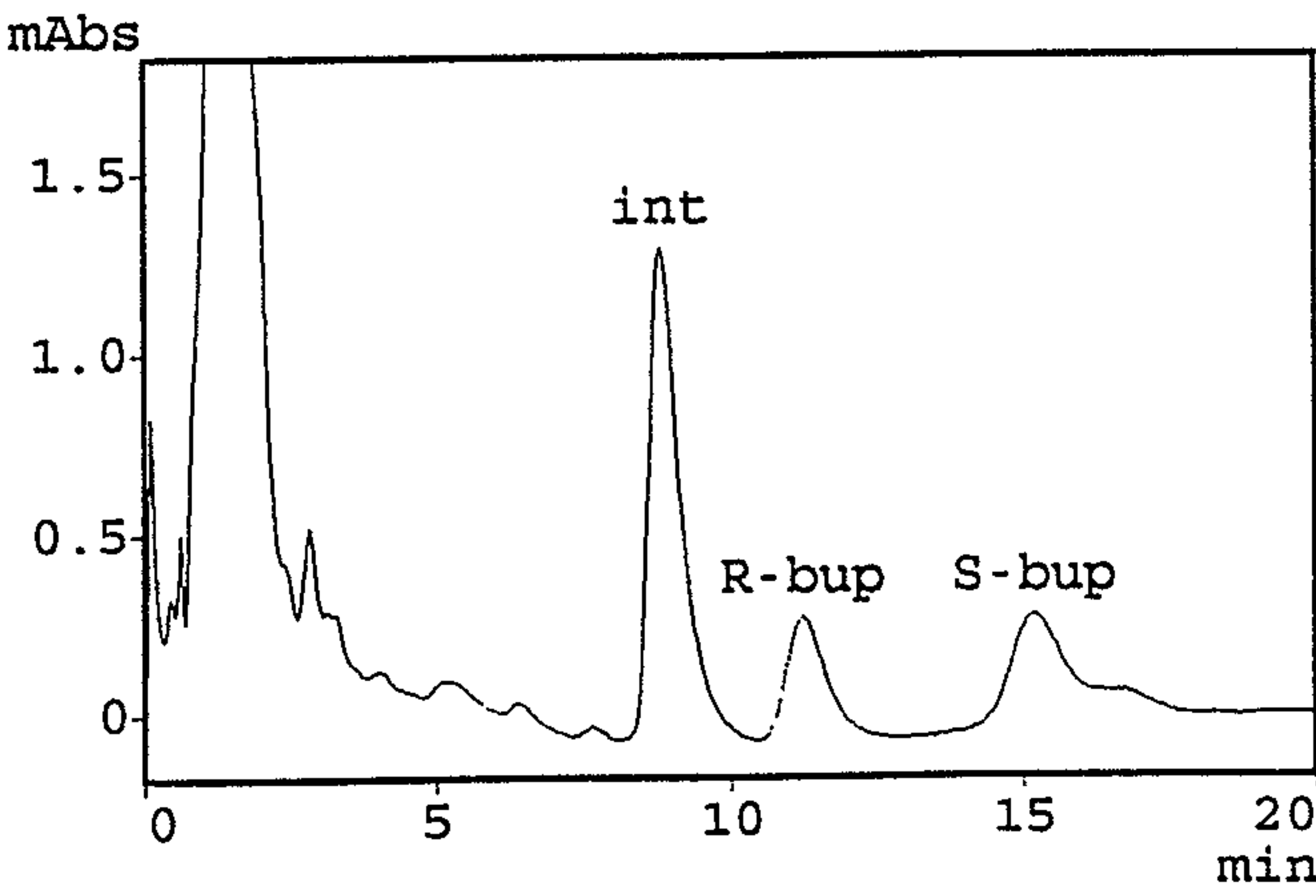


Figure 8d.

Chromatogram, bupivacaine,
60 minute blood sample



CHAPTER 4

DISCUSSION OF RESULTS

4.1. Distribution

Due to an insufficient number of patients with bilaterally symmetrical, impacted, third molars, it was not possible to provide an equal sex distribution. The ratio of males to females was nine to fourteen. The age range of the subjects was 18 to 41 years with a mean of 24 years. Fourteen subjects had the right side operated first and nine subjects the left. All subjects were healthy and free from any systemic disease that would be likely to affect the results. The use of a double blind, randomised, crossover protocol ensured that each subject acted as his or her own control, and therefore results are likely to be a true reflection of differences between bupivacaine and lignocaine.

4.2. Anaesthetic Volume

The mean volume of bupivacaine solution used for each subject was 5.79 mL and the mean volume of lignocaine solution used was 5.64 mL. The difference in the mean volume of local anaesthetic used was not statistically significant which would suggest that 0.5% bupivacaine and 2% lignocaine are equipotent when used in similar volumes. The largest volume of anaesthetic solution used was 8.8 mL for both bupivacaine and lignocaine. This volume corresponds to a dose of 44 mg bupivacaine and 176 mg lignocaine. For an average 70 kg adult this represents 0.63 mg/kg bupivacaine and 2.51 mg/kg lignocaine.

4.3. Surgical Time

All subjects had either two or four impacted third molars surgically removed. Only those patients that had bilaterally symmetrical, impacted, third molars were selected for the trial. The symmetry of impactions was established using Winter's lines on a standard orthopantograph taken with the same x-ray machine. The difference in the mean time taken for the surgical procedures with bupivacaine and lignocaine was not statistically significant. The mean time for the bupivacaine procedures was 16.7 minutes while that for the lignocaine procedures was 15.8 minutes. Retrieval of a fractured root apex when using bupivacaine for subject 17 dramatically increased the operating time to 51 minutes, more than twice the time taken to remove the contralateral tooth. It is possible that such an outlier is responsible for the slight increase in surgical time with bupivacaine. In the absence of any statistically significant difference in surgical time between the two local anaesthetics, it is likely that differences in any other parameters measured will reflect differences between the two agents.

4.4. Visual Analogue and Global Pain Scores

A visual analogue and five point global pain score was recorded by each subject at the completion of surgery. This was supervised by the author to ensure that each subject was completely familiar with both scales and therefore would be able to record pain scores at home in the post-operative period. Subsequent pain scores were recorded by the subject at four hourly intervals for 24 hours. Subjects 12,15 and 16 did not return their pain scores for bupivacaine and therefore no score other than that immediately post-operatively was recorded. All subjects returned their pain scores for lignocaine. Within both the bupivacaine and lignocaine pain scores,

there are a number of missing entries which represent the times when subjects were asleep. It is for this reason that the majority of missing pain scores occurred at 12 hours post-operatively.

With a mean visual analogue pain score of 19 for both bupivacaine and lignocaine, there does not appear to be a difference in the perception of pain intra-operatively. The mean global pain scores for bupivacaine and lignocaine, 1.26 and 1.17 respectively, also indicate that there is no significant difference in pain perception intra-operatively. The visual analogue pain scale, with 100 possible scores, is likely to be a more sensitive measure of subjective pain than any five point descriptive global pain scale, and as such the difference in the global pain scores for both agents is likely to reflect the lesser sensitivity inherent in the global pain scale. Five subjects required an additional cartridge of bupivacaine prior to the commencement of surgery when probing ten minutes after local anaesthetic administration elicited some pain. With lignocaine however, only three subjects required an additional cartridge of local anaesthetic. The depth of anaesthesia with both agents was considered adequate in all subjects for the completion of surgery. These results differ from those reported by Laskin *et al.* (1977) and Chapman and Macleod (1985) who found bupivacaine to be superior to lignocaine for intra-operative anaesthesia. It is possible that the use of small volumes of local anaesthetic in these studies may favour bupivacaine with its greater potency due to increased lipid solubility and protein binding capacity. However, despite the differences in physical properties, both agents have been shown to produce adequate anaesthesia for the removal of impacted third molars in this trial.

The mean visual analogue scores four hours post-operatively were 33 and 45 for bupivacaine and lignocaine respectively. The corresponding mean global pain scores were 2.05 and 2.39 respectively. While the difference between the agents was not statistically significant,

it would be expected that the bupivacaine would continue to provide analgesia in the majority of subjects, while lignocaine analgesia would have begun to regress. The time to regression of analgesia with bupivacaine has been consistently shown to exceed four hours and the time to regression of analgesia with lignocaine to precede four hours (Feldmann and Nordenram, 1966; Hellden *et al.*, 1977; Nespeca, 1976; Laskin, 1977; Chapnick *et al.*, 1980; Chapman and Macleod, 1985; Chapman, 1988). The lack of a statistically significant difference in pain scores in this trial is possibly a result of the increased volumes (4.4 mL) of both local anaesthetics administered. It has also been reported that preemptive analgesia reduces post-operative pain by preventing the establishment of central sensitization (Woolf and Chong, 1993). The optimal form of pain treatment may be one that is applied pre, intra and post-operatively to preempt the establishment of peripheral and central pain hypersensitivity during and after surgery. Therefore, it is possible that both local anaesthetic agents reduce central sensitization equally in the immediate post-operative time period and thus uniformly reduce pain in the post-operative period.

A statistically significant difference in both the visual analogue and global pain scores was seen at eight hours post-operatively, with bupivacaine being superior to lignocaine. The mean visual analogue pain scores for bupivacaine and lignocaine were 19 and 34 respectively ($p=0.013$). The respective mean global pain scores were 1.35 and 2.0 ($p=0.012$). The mean duration of analgesia with bupivacaine has been shown to approach or exceed eight hours (Nespeca, 1976; Laskin *et al.*, 1977; Chapman and Macleod, 1985). Lignocaine however, has not been shown to produce analgesia of this duration. The results obtained in this trial are therefore in agreement with those reported previously.

The sparsity of pain scores at 12 hours makes any conclusions about pain experience impossible as all but one subject was asleep during this time. It was decided to include pain experience at 12 hours in the original trial protocol to ensure that if pain experience was severe enough to prevent sleep, it could potentially motivate patients to resort to the use of analgesics.

It is apparent that a proportion of subjects were also asleep at 16 hours post-operatively. Of the subjects who recorded pain scores at 16 hours, the mean visual analogue pain scores for bupivacaine and lignocaine were 23 and 24 respectively while the mean global pain score for both agents was 1.5. The difference in the mean visual analogue scores was not statistically significant. The regression of analgesia for both agents would be expected to be complete in all subjects at 16 hours and it would not be anticipated that any significant difference in pain scores would be present. However, the effect of local anaesthetic agents with different durations of action on preemptive analgesia has not been investigated adequately. With respect to local anaesthetic agents of different duration, it is possible that the degree of central sensitization is not equal. Pain experience may therefore be modified well after the complete regression of anaesthesia.

There was no significant difference in the mean visual analogue and global pain scores at 24 hours. The mean visual analogue pain scores for bupivacaine and lignocaine were 17 and 13 respectively. The respective mean global pain scores for both agents were 1.2 and 0.96. The difference in mean pain scores is only slight and not significant. The reasons for the higher mean pain scores with bupivacaine at 24 hours are not clear and are likely to be a reflection of the small sample size.

4.5. Analgesic Consumption

Each subject recorded the number of analgesics and the time consumed, from completion of surgery until no further medication was required. The analgesics were provided by the principal investigator at the completion of surgery at the same time as the antibiotics. The analgesic chosen for this trial was ibuprofen 400 mg, a non steroidal anti-inflammatory drug (NSAID), which has been shown to be superior to paracetamol and codeine combinations for the control of post-operative pain following third molar surgery (Hart and Huskisson, 1984; Seymour and Walton, 1984; Seymour, 1984). For the purpose of statistical analysis, the analgesics consumed were grouped into six post-operative time frames: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, after 24 hours and total. It was felt that the total number of analgesics consumed should be used for analysis in order to determine whether the choice of local anaesthetic agent influenced the total number of analgesics consumed.

The mean number of analgesics consumed for the procedures with bupivacaine were 0.67, 0.5, 0.15, 0.90, 3.95 and 5.95 for each of the six time frames measured. The corresponding mean number of analgesics consumed for the procedures with lignocaine were 0.96, 0.52, 0.30, 0.96, 2.65 and 5.39. There was no statistically significant difference in analgesic consumption for any time frame measured including the total number of analgesics consumed. The nature and sparsity of the data makes this analysis somewhat unreliable. Hellden *et al.* (1974) found that there was no difference in analgesic consumption in the first 24 hours when comparing bupivacaine 0.25% with 1:200,000 adrenaline with lignocaine 2% with 1:80,000 adrenaline, however, the analgesic used was not specified. Contrary to this, subsequent studies have shown that analgesic consumption is significantly less with bupivacaine in the first 12 to 24 hours

(Nespeca, 1976; Chapman and Macleod, 1985; Chapman, 1988). However, the previous studies did not use a potent non steroidal anti-inflammatory drug such as ibuprofen.

It is possible that the newer and better NSAIDs such as ibuprofen are able to reduce the need for analgesics to a minimum and therefore are less likely to highlight any differences in analgesic consumption between bupivacaine and lignocaine. It is also possible that because all surgical procedures were undertaken in the late afternoon, the time at which anaesthesia and analgesia regress is likely to be when patients are asleep and hence they are unlikely to consume analgesics unless they are in extreme pain.

4.6. Cardiovascular Responses

The mean systolic blood pressure for both bupivacaine and lignocaine prior to the administration of either local anaesthetic was 124 mm Hg. The mean systolic blood pressure remained relatively constant over time and no significant difference was seen between the agents at any of the times measured. The mean diastolic blood pressures prior to the administration of bupivacaine and lignocaine were 72 mm Hg and 70 mm Hg respectively. No significant difference in mean diastolic blood pressure was seen between the agents for any of the times measured. The preoperative systolic and diastolic blood pressures of several subjects were considerably higher than the mean. This is most likely to be a reflection of the apprehension associated with surgical procedures and should not be interpreted as evidence of essential hypertension. The unexpectedly elevated diastolic blood pressure of 102 mmHg in subject 17 at 30 minutes is not in keeping with the diastolic pressures measured in the same subject at other times and is most likely to be a recording error. The results of this trial are in agreement with

previous investigators who have reported no change in systolic or diastolic blood pressure after the administration of adrenaline containing local anaesthetics (Vernale, 1960; Salonen *et al.*, 1988; Meecham *et al.*, 1991). However other studies have reported a decrease in both systolic and diastolic blood pressure (Lipp *et al.*, 1993) and others only a decrease in diastolic blood pressure (Tolas *et al.*, 1982).

The mean baseline heart rates prior to local anaesthetic administration were 88 beats per minute and 83 beats per minute for bupivacaine and lignocaine respectively. This difference was not statistically significant. The mean heart rates five minutes after injection were 86 beats per minute and 88 beats per minute respectively. The mean heart rates remained relatively constant at 15 minutes but decreased significantly at 30 minutes to 78 beats per minute for bupivacaine and 81 beats per minute for lignocaine. Thereafter the heart rates remained relatively stable. There was no significant difference in heart rate between the local anaesthetics for any of the times measured. However, when compared to the mean baseline values, there was a statistically significant decrease in heart rate at 30 minutes for bupivacaine ($p=0.002$) and lignocaine ($p=0.007$). Heart rate has been shown to increase immediately after injection of adrenaline containing local anaesthetics (Salonen *et al.*, 1988; Lipp *et al.*, 1993) but this was not the finding in this study. It would appear that the exogenous adrenaline in both the bupivacaine and lignocaine solutions did not affect the cardiovascular responses as might have been expected. A careful technique for injection of the local anaesthetic with multiple aspirations may have reduced the number of inadvertent intravascular injections. The significant fall in heart rate at 30 minutes for both agents would appear to be a result of the decrease in endogenous catecholamines associated with the termination of the surgical procedure. Vernale (1960) has shown that there is a significant reduction in heart rate immediately after the extraction of a tooth

is completed.

The role of both endogenous and exogenous catecholamines in regulating cardiovascular responses in patients having local anaesthetic injections containing adrenaline has been the focus of much controversy. This study has failed to document changes in heart rate and blood pressure that arise from exogenous adrenaline in local anaesthetic solutions, but the possible role of endogenous catecholamines on heart rate has been demonstrated.

4.7. Blood Concentrations

The mean blood concentrations of bupivacaine (R and S enantiomers) were 0.0728, 0.0717, 0.0582 and 0.0519 $\mu\text{g/mL}$ at 15, 30, 45 and 60 minutes respectively. The mean peak blood concentration was 0.0728 $\mu\text{g/mL}$ at 15 minutes and thereafter the blood concentration decreased slowly. The lowest bupivacaine plasma concentration at which systemic toxicity has been observed is 1.1 $\mu\text{g/mL}$ (Hasselstrom and Mogensen, 1984) and the mean peak blood concentration of bupivacaine in this trial was only seven per cent of this value. Of greater importance might be the highest blood concentration of 0.168 $\mu\text{g/mL}$ measured in subject 20 at 15 minutes. This concentration is more than twice the mean peak blood concentration of 0.0728 $\mu\text{g/mL}$ and is 15% of the lowest concentration at which toxicity has been reported. The high blood concentration for this subject is probably due to the larger volume of local anaesthetic used (8.8mL). However, no subject in this study developed any signs or symptoms of either central nervous system or cardiovascular system toxicity.

The mean R-(+) bupivacaine concentrations at 15, 30, 45 and 60 minutes were 0.0336,

0.0327, 0.0268 and 0.0231 $\mu\text{g/mL}$ respectively. The corresponding concentrations of S-(-) bupivacaine were 0.0392, 0.0389, 0.0315, and 0.0288 $\mu\text{g/mL}$. The higher blood concentrations of the S-(-) enantiomer were highly significant at 15 minutes ($p=0.00003$); 30 minutes ($p=0.000019$), 45 minutes ($p=0.000049$) and 60 minutes ($p=0$ to six decimal places). The R-(+) bupivacaine enantiomer has been shown to have a shorter duration of neural block, a higher propensity towards CNS and CVS toxicity, a greater volume of distribution and a shorter half-life and increased clearance rate (Rutten *et al.*, 1993; Mather *et al.*, 1995). The lower blood concentrations of the R-(+) enantiomer in this study are in agreement with the known pharmacokinetic parameters described in these two previous studies.

Lignocaine does not exist as enantiomers and as such, the blood concentrations represent a single isomer. The mean blood concentrations of lignocaine were 0.5586, 0.6166, 0.5722 and 0.5064 $\mu\text{g/mL}$ at 15, 30, 45 and 60 minutes respectively. The mean peak blood concentration was 0.6166 $\mu\text{g/mL}$ at 30 minutes. Differences in the absorption from the site of administration are most likely to have caused the mean peak concentration to occur later than that of bupivacaine. The higher lipid solubility and greater protein binding of bupivacaine are likely to reduce the systemic absorption from the site of deposition where as lignocaine can more readily diffuse into the systemic circulation. The highest blood concentration of lignocaine was 1.7876 $\mu\text{g/mL}$ at 30 minutes in subject 7 and followed the use of 6.6 mL of local anaesthetic. The toxic threshold for lignocaine is generally considered to be 5 to 6 $\mu\text{g/mL}$ (Scott and Cousins, 1980). If one was to take the lower value of 5 $\mu\text{g/mL}$ as being the toxic threshold plasma concentration, the highest blood concentration of lignocaine measured, 1.7876 $\mu\text{g/mL}$, represents 35% of this value. However, no subject in this study developed any signs or symptoms of toxicity.

Bupivacaine is considered to have a therapeutic ratio of 2.0 while lignocaine in combination with adrenaline has a therapeutic ratio of 2.3. These values are expressed as the ratio between the blood concentration at which systemic toxic reactions occur, C_{tox} , and the peak blood level after a therapeutic epidural dose, C_{max} . Based on these figures, lignocaine is considered less toxic than bupivacaine. However, it has been shown that the injection route alters the relative toxicity of local anaesthetics (De Jong and Bonin, 1980), and the blood concentrations measured in this study suggest that the therapeutic ratios quoted might not be applicable when either local anaesthetic is used for oral surgery. The highest blood concentrations of bupivacaine and lignocaine measured in this study, represent 15% and 35% of the toxic plasma thresholds respectively. It would therefore seem that bupivacaine has a greater therapeutic ratio than lignocaine when used for the surgical removal of impacted third molars.

CHAPTER 5

CONCLUSION

The purpose of this study was to compare the efficacy of bupivacaine and lignocaine for the surgical removal of impacted third molars. The study focussed on pain experience, analgesic consumption, cardiovascular responses and blood concentrations.

Visual analogue and global pain scores were recorded in the post-operative period at 4, 8, 12, 16 and 24 hours. Bupivacaine and lignocaine were both found to produce adequate analgesia for the completion of all surgical procedures. The only statistically significant difference found between the two agents was at eight hours post-operatively where bupivacaine was found to be superior to lignocaine in reducing pain. As was found in this study, the reduction in pain experience with bupivacaine does not necessarily correlate with a reduction in analgesic consumption. It was anticipated that the number of analgesics consumed would be less with bupivacaine, however there was no significant difference in the number of analgesics consumed between the two agents. Bupivacaine is clearly of benefit to the patient in delaying the onset of pain but, based on the outcome of this study, some caution must be exercised in recommending its use to reduce analgesic requirements. The timing of the surgery may play an important role in reducing the analgesic consumption if as in this study, the regression of analgesia corresponds with a period of sleep. It may also be significant that the newer non steroidal anti-inflammatory drugs such as ibuprofen have greater analgesic potencies and longer half-lives than the paracetamol and codeine combinations which have traditionally been used in the post-operative period.

While lignocaine is not considered to possess inherent cardiodepressant properties, the cardiodepressant properties of bupivacaine have received much attention. Concerns in regard to the effect of bupivacaine on blood pressure and heart rate have not been supported in this study. The effects of both endogenous and exogenous adrenaline on blood pressure and heart rate are well known. However, in this study, the blood pressure and heart rate were shown to remain unchanged with both bupivacaine 0.5% with 1:200,000 adrenaline and lignocaine 2% with 1:100,000 adrenaline. The reduction in heart rate that was seen with both agents at 30 minutes is most certainly due to the decrease in circulating endogenous catecholamines associated with the completion of surgery. The results of this study showed that when up to four cartridges of either local anaesthetic is used for the surgical removal of third molars, there was no significant changes in blood pressure or heart rate as a result of the local anaesthetic or adrenaline content. The importance of endogenous catecholamines would appear to be of a greater significance in determining cardiovascular responses.

The blood concentrations of both bupivacaine and lignocaine have not previously been determined after injection in the oral cavity for the removal of impacted third molar teeth. It was the key aim of this study to determine the blood concentrations of both agents and to correlate them with any observed signs of systemic toxicity. The absorption of bupivacaine and lignocaine appear to be biphasic. There is an initial absorption after the administration of the agent which peaks at 15 minutes with bupivacaine and at 30 minutes with lignocaine. Thereafter the net absorption of both agents is exceeded by the distribution, metabolism and clearance and the plasma concentrations begin to fall. The mean peak blood concentration of bupivacaine was 0.0728 µg/mL and the highest measured concentration was 0.1680 µg/mL. These values represent 3% and 8% respectively, of the toxic threshold plasma concentration as suggested by

Mather *et al.* (1979). The maximum volume of bupivacaine solution used in this study was 8.8 mL. Knowing that 8.8 mL of bupivacaine solution equals 44 mg bupivacaine or 0.63 mg/kg for a 70 kg adult and that this only represents 8% of the toxic threshold, the maximum suggested dose of bupivacaine would appear not to be 2 mg/kg, as previously suggested, but significantly higher. As a result of this study it would seem more likely that a dose in the order of 7 mg/kg is required to obtain a toxic blood concentration. The mean peak plasma concentration of lignocaine was 0.6166 µg/mL and the highest measured concentration 1.7876 µg/mL. These values represent 15% and 35% respectively, of the threshold toxic plasma concentration as suggested by Scott and Cousins (1980). The maximum volume of lignocaine solution used in this study was also 8.8 mL or 176 mg lignocaine which translates to 2.51 mg/kg for a 70 kg body weight. Such a dose has been shown in this study to produce a blood concentration that is 35% of the toxic threshold. The results of this study would therefore appear to support the previously recommended maximum dose of 7 mg/kg for 2% lignocaine with 1:100,000 adrenaline.

The therapeutic ratios of both agents are 2.0 and 2.3 for bupivacaine and lignocaine respectively. The ratios have been determined from the plasma concentrations of both agents after epidural administration and would suggest that lignocaine has the lesser potential toxicity. However, the blood concentrations determined in this study would suggest that the oral tissues modify the pharmacokinetics of both agents to the extent that the absorption of bupivacaine may be slowed more than when used in other sites. Further research is undoubtedly required, but the current therapeutic ratio and maximum recommended dose of bupivacaine may not be applicable when this agent is used in the oral cavity.

There were no signs or symptoms of central nervous system or cardiovascular system

toxicity in this study and the routine use of bupivacaine in oral surgery would appear to be a safe and effective method of producing adequate surgical analgesia and an increased post-operative pain free period.

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Appendix A1.

Consent for research.

Westmead Hospital and
Community Health Services



CONSENT FOR RESEARCH

Name		Date	
Current address		Phone	
Address	Street	City	State
Suburb		Postcode	Home phone

Title of Project: The purpose of the study is to compare two common local anaesthetics for wisdom tooth surgery to see if a particular local anaesthetic provides less pain after surgery and reduces the need for medications for pain relief.

Name(s) of Chief Investigator(s):

Principal Investigator: Gary Bouloux BDS (Hons), FRACDS
Supervisor: A. Punnia-Moorthy PhD, FDSRCS, FFDRCS.

Methods and Demands:

You will have two separate appointments for the removal of wisdom teeth under local anaesthesia. Two commonly-used anaesthetics will be used, one on each appointment. Blood pressure and heart rate will be measured. A small needle will be placed in a vein on your forearm and a small quantity of blood, 10 mls, will be taken at 0, 15, 30, 45 and 60 minutes. After the surgery you will be asked to complete a form detailing your pain experience and analgesic intake.

Risks, Inconveniences and Discomforts which may occur:

- 1) Minimal discomfort associated with the placement of the needle in a vein in the back of your hand. Apart from the discomfort associated with the placement of a needle in a vein in your forearm, there is a small risk you may have swelling or bruising at the site of the needle puncture.
- 2) A blood pressure cuff will need to be inflated on your arm on several occasions for blood pressure measurement.
- 3) You will be asked to complete a simple form in the week after each of the two surgeries.

I have been asked to participate in the above research study and give my consent by signing this form, on the understanding that:

- 1 The research study will be carried out in a manner conforming with the principles set out by the National Health & Medical Research Council.
- 2 The general purposes, methods and demands and the possible risks, inconveniences and discomforts which may occur during the study, have been made known.
- 3 Refusal to take part in this study will not affect the treatment of my condition.
- 4 I am volunteering to take part in this study and I may withdraw at any time.
- 5 This research has been approved by the Western Sydney Area Health Service Research and Ethics Review Committee.
- 6 The sponsoring pharmaceutical company and Drug Regulatory Authorities may have access to my medical records for the purpose of monitoring the research, however my identity will be protected.

Signature: _____ Relationship: _____ Date: ____/____/____

(By subject, if over 16 years : Otherwise please state relationship)

If adult, subject unable to consent, by Guardian/spouse/de facto/care giver/Guardianship Board.

If between 14-16 years, subject plus parent to sign : If under 14 years, parent or guardian to sign)

Witnessed by: _____ Project Approval No: _____

of: _____

Appendix A2.

Surgeon's information sheets.

Patient name and DRN :

Date :

Type of surgery and teeth :

Type of impaction :

Canula size and location :

Initial blood pressure, heart rate and time measured :

	BP	HR	Time
1) - 0mins			

Initial blood sample and time :

1) -

Local anaesthetic and quantity :

Time local anaesthetic given :

Time that surgery begins :

Time surgery completed :

Blood pressure and heart rate and time measured :

	BP	HR	Time
2) - 5mins (after LA)			
3) - 15mins			
4) - 30mins			
5) - 45mins			
6) - 60mins			

Blood samples and time taken :

2) - 15mins (after LA)

3) - 30mins

4) - 45mins

5) - 60mins

Surgical procedure :

Check :

Appendix A3.

Patient's immediate post-operative questionnaire.

Name and DRN :

Date :

Time surgery completed :

Pain immediately after surgery :

Place a mark on the line to show how much pain you are having.

NO PAIN

WORST POSSIBLE PAIN



Which of the Following describes the pain ?

0 = NONE

1 = A LITTLE

2 = SOME

3 = A LOT

4 = WORST POSSIBLE

ANSWER =

Appendix A4.

Patient's post-operative questionnaire.

Date :

Time :

Name and DRN :

Pain :

Place a mark on the line to show how much pain you are having.

NO PAIN

WORST POSSIBLE PAIN



How would you describe the pain?

0 = NONE

1 = A LITTLE

2 = SOME

3 = A LOT

4 = WORST POSSIBLE

ANSWER =

Appendix A5.

Patient's analgesic record.

PAIN KILLERS :

[illegible]

Appendix B1.

A.N.Z.A.O.M.S., Proceedings, 16th Biennial Conference (1995),

Sydney, Australia.

A DOUBLE BLIND STUDY OF BUPIVACINE AND LIGNOCAINE FOR THIRD MOLAR SURGERY

Author(s): **Bouloux G F, Punnia-Moorthy A**

Presenting Author: **G F Bouloux**
Dept of Oral and Maxillofacial Surgery
Dental Clinical School
Westmead Hospital
Sydney

The aim of this double blind study was to evaluate the efficacy of 0.5% Bupivacaine with 1:200,000 Adrenaline and 2% Lignocaine with 1:100,000 Adrenaline for thirty conscious patients who underwent the removal of third molar teeth. Their pain experiences, analgesic requirements, cardiovascular responses and plasma concentrations were all examined.

Each patient had two separate appointments for the removal of wisdom teeth under local anaesthesia. Blood pressure and heart rate were measured and venous blood sampled before the procedure, five minutes after the administration of the local anaesthetic agent and at fifteen minute intervals for one hour. Bloods were analysed using High Pressure Liquid Chromatography to assay plasma concentrations of the local anaesthesia. Patients were asked to record their post-operative pain on visual analogue global pain scales immediately post operatively and over the following 24 hours. Analgesic intake was also recorded. The dosage and frequency of analgesic medication used were recorded. The results were analysed using the paired t-test with a normal distribution and are presented for discussion.

Appendix B2.

Luhr Travelling Fellowship.



Howmedica

This is to certify that

Dr Gary Bouloux

has been awarded the

Luhr Travelling Fellowship

4 March 1995

L. Buchanan

President
Dr Michael Buchanan

Robert Mitchell

Secretary
Dr Robert Mitchell