2-methyl-4-chlorophenoxyacetic acid and bromoxynil herbicide death

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Introduction

Acute overdose with herbicides is a significant problem in resource poor countries and an uncommon but potential life-threatening poisoning in other parts of the world. The clinical course of some herbicide poisonings appears to be unpredictable. Patients with 2-methyl-4-chlorophenoxyacetic acid (MCPA) poisoning often appear well on admission and many develop only minor effects (1). A small proportion of patients develop life-threatening poisoning which is fatal within 48 hours. Currently the mechanism of this death is unclear and predicting which patients will develop delayed severe toxicity is difficult. Even less is known about bromoxynil (2). We report a fatal case of MCPA/bromoxynil poisoning which provides insight into the metabolic changes prior to death.

Case report

A 37 year old male was brought to the emergency department two hours after intentionally ingesting 200mls of ‘Bin-Die’ weed control(200g/L 4-chloro-2-methylphenoxyacetic acid

[MCPA] and 200g/L 3,5-dibromo-4-hydroxybenzonitrile [Bromoxynil] mixed with a hydrocarbon solvent). Prior to presentation he had nausea, vomiting and diarrhoea and was given intravenous fluids pre-hospital. He had a history of depression but no medical past history. His regular medications included sodium valproate, escitalopram and olanzapine. He smoked and regularly used synthetic cannabis and alcohol.

In the emergency department he was alert and diaphoretic, with a heart rate (HR) 95 beats per minute and blood pressure (BP) 140/102 mmHg and (RR) respiratory rate of 22 breaths per minute. Based on the large ingestion, and not his clinical presentation, he was admitted to the intensive care unit (ICU) for observation and urinary alkalisation. He was initially mildly agitated and given 10mg oral diazepam. Initial bloods showed a white cell count (WCC) of 18 $/L^{-9}$(reference range: 4-11$/L^{-99}$) and neutrophils of 15.4$/L^{-9}$(reference range 1.8-7.7 $/L^{-9/}$). His creatinine was 103 µmol/L (reference range 64-104 µmol/L) and all other pathology was within normal limits.

About 8 hours post-ingestion he became diaphoretic and tachypnoeic with a respiratory rate (RR) of 30 breaths per minute (bpm), but was not hypoxic according to peripheral oxygen saturations. He became more agitated and restless despite a further 15mg oral diazepam. His RR gradually increased and was 36 bpm 12 hours post-ingestion. He maintained his oxygen saturations at 100% on room air despite the low pO_2 on blood gases. He was given another 15mg diazepam. His arterial blood gas showed his pH was 7.48, pCO_2 33mmHg, pO_2 51mmHg, base excess (BE) 1.6 mmol/L (Table 1). He continued to deteriorate, with increasing agitation, tachypnoea, hypoxia (on ABG) and lactic acidosis (Figure 1). His RR increased to over 50 bpm, but his HR and BP remained normal. Repeat clinical examination and CXR were normal and there was no evidence of aspiration. Urinary alkalisation was increasingly less effective with urine pH dropping from 8.0 to 7.0. The WCC increased to 28.5$/L^{-9}$ (neutrophils 25.7$/L^{-9}$) and creatinine to 112 µmol/L. Over the next four hours the

patient had increasing tachypnoea and hypoxia despite supplemental oxygen. He became confused and was too agitated to manage despite 1:1 nursing care. At 16 hours post ingestion a rapid sequence intubation was performed using ketamine 200mg and suxamethonium 150mg. He was subsequently commenced on a midazolam and fentanyl infusion. His RR was 56 before intubation but only 36 with ventilation. He remained tachycardic, diaphoretic and developed hyperthermia (40°C) with hypotension. Continuous veno-venous haemodialysis (CVVHD; lactate free, blood flow of 150mls/hr) was commenced based on two previous reports of chlorophenoxy herbicide poisoning being removed by haemodialysis (3). A noradrenaline infusion was started for hypotension. He was actively cooled with ice packs, wet towels and cooled fluids. Examination showed no rigidity, normal reflexes and tone, with no clonus. His temperature continued to rise to 42.5°C at 20 hours post-ingestion followed 5 minutes later by an asystolic cardiac arrest from which he could not be resuscitated.

Plasma samples were collected for later analysis. MCPA and bromoxynil were quantified using LC-MS/MS (see appendix for full method).

Two hours after ingestion the serum MCPA concentration was 83.9 µg/mL and bromoxynil concentration was 137 µg/mL. Just prior to death, 19 hours after ingestion the MCPA concentration was 100 µg/mL and bromoxynil concentration was 78.8 µg/mL.

Discussion

MCPA is a chlorphenoxy herbicide that is used in a number of commercially and domestically available products which can easily be purchased. It is often available as a co-formulated product with another herbicide, such as bromoxynil in our patient's case. Chlorophenoxy herbicides generally have a small volume of distribution and pH and dose-dependent distribution and elimination. Bromoxynil is a nitrile herbicide with restricted use in the United States but widely available in Australia. MCPA and bromoxynil are both weak acids with pKa of 4.1 and 3.1 respectively (2).

The mechanism of toxicity of chlorophenoxy herbicides (such as MCPA) and bromoxynil leads to generalised cellular dysfunction. It is believed they disrupt the lipid membranes, interfere with metabolic pathways involving acetyl-coenzyme A and uncouple oxidative phosphorylation (3). In humans this results in gastrointestinal effects, including nausea, vomiting and diarrhoea, tachycardia, metabolic acidosis and hyperthermia. Hyperthermia is most likely due to the uncoupling of oxidative phosphorylation in the mitochondria, which causes increased production of heat and CO_2, but decreased production of ATP.

In the English literature there are two published case reports of ingestions of ioxynil (very similar structure to bromoxynil) and one small case series of 11 patients with show a high mortality from such ingestions (Supplementary Table 1). A case series by Roberts et al (1) of intentional ingestions of MCPA noted a mortality of about 5%, with all deaths occurring within 48 hours post ingestion. It is unclear if the toxicity is directly related to the MCPA compound, or to surfactants and other co-formulations. The lower MCPA concentration compared to previous cases (1) provides some support to the idea that bromoxynil may be the more toxic agent in this case.

Our patient appeared to develop severe tachypnoea with an unusual arterial blood gas which initially showed primary respiratory alkalosis with only a mild partial metabolic acidosis, perhaps due to stimulation of the respiratory centre or contributed to by the bicarbonate infusion used for urinary alkalinisation. Then later the excess CO_2 production caused a respiratory acidosis (when the capacity of the increased RR to eliminate the excess pCO_2 was exceeded). While the patient continued to be able to breath off the CO_2 he did not develop an acidosis. However, as the patient tired and was unable to breath off all the CO_2, he gradually developed a respiratory acidosis despite a very high RR and normal lungs. In the last hour or so he became clinically hypoxic (both on ABG and saturations with a sensation of dyspnoea), which may have related to increased oxygen demand from the hyper-catabolic process. Finally, the patient needed to be intubated, but the RR and tidal volume could not be maintained, resulting in a large rise in pCO_2, heat production leading to hyperthermia, metabolic acidosis and ultimately an asystolic cardiac arrest and death (Figure 1). In addition, the administration of a bicarbonate infusion in this patient may have increased CO_2 production due to buffering.

The mechanism of death in our patient is likely to have been diffuse cellular anoxia (due to inadequate ATP use) resulting in rapidly rising CO_2 and hyperthermia. Interventions should aim to maximise CO_2 removal and control hyperthermia, acknowledging this as only a potentiating measure due to an inability to treat the underlying process. In this case intubation resulted in a rapid deterioration with increasing CO_2 (figure 1). In future cases the aim should be to hyperventilate to remove CO_2 with high RR and large tidal volumes. In addition, caution should be used with bicarbonate infusions as they potentially cause harm by increasing CO_2 production, and there is little evidence to support increased urinary toxin elimination.

References

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2. Flanagan RJ, Meredith TJ, Ruprah M, Onyon LJ, Liddle A. Alkaline diuresis for acute poisoning with chlorophenoxy herbicides and ioxynil. Lancet. 1990 Feb 24;335(8687):454-8.

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4. Smysl B, Smyslova O, Kosatik A. [Acute fatal ioxynil intoxication (author's transl)]. Arch Toxicol. 1977 Jul 19;37(3):241-5.

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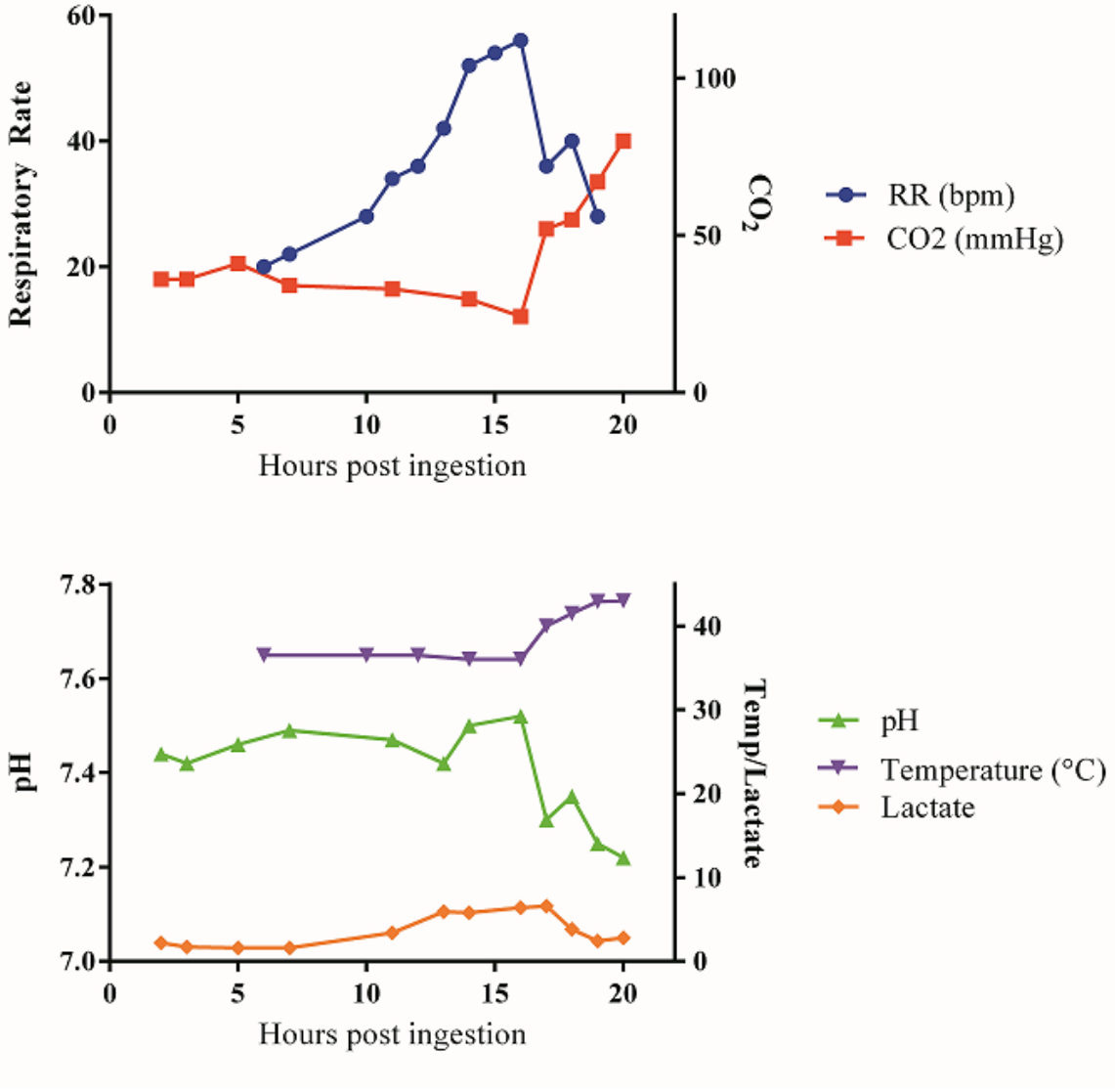
Appendix

Drug Analysis Methods

A LC-MS/MS method for quantitation of MCPA and Bromoxynil in plasma was developed. 4-amino phenol was used as internal standard. 50 µL aliquots of plasma (clinical sample, standard or quality control) were spiked with internal standard and the plasma proteins were precipitated with 100 µL of acetonitrile. 5 µL of the supernatant were injected into the HPLC..The analysis was performed using an API 2000 (Applied Biosystems/MDS Analytical Technologies Inc., Foster City, CA, USA) triple quadrupole mass spectrometer equipped with electrospray ionization.

The mass spectrometer was coupled to a Shimadzu HPLC system of two pumps and a SIL-20AC-HT autosampler maintained at 15°C. Chromatographic separation was achieved on Luna 5 µm C18(2) (Phenomenex) 50×2.0 mm using isocratic flow using 65 % of solvent A(10 mM NH4OAc) and 35 % of solvent B (10 mM NH4OAc in 95:5 Acetonitrile: Water). The negative -ion mass spectrometric detection method utilised electrospray ionization and multiple reaction monitoring at 198.7 → 140.8 for MPCA ,275.8 → 80.8 for Bromoxynil and 137.9 → 107.9 for 4-amino phenol . The retention times of MPCA, Bromoxynil and 4-amino phenol were 1.50, 1.85 and 2.5 min respectively. Linearity was achieved from 3.9 to 160 µg/mL. The precision and accuracy of quality controls (at 120, 60 and 8µg/mL) for both intra- and inter-day measurements were within 15%.

Figure 1



Clinical observations at hours post ingestion
217x233mm (300 x 300 DPI)

Supplementary Table 1: Blood gas results at hour post ingestion

Intubated

Hours post ingestion	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Normal (arterial) values
Gas type	VBG	VBG		VBG		ABG					ABG	VBG	ABG		ABG	ABG	CV	ABG	ABG	
pH	7.44	7.42		7.46		7.49					7.48	7.42	7.5		7.52	7.3	7.35	7.25	7.22	7.35-7.45
pCO2	36	38		41		34					33	42	30		24	52	55	67	80	35-48 mmHg
pO2						78					51		69		74	152	40*	107	35	83-108 mmHg
FiO2	Room air															.5	.4	.6	.5	
RR	22				20	22	30	25	28	34	36	42	52	54	56	36	40	20		
Temp (°C)					36.5				36.5		36.5		36.0		36.0	40.0	41.5	42.9	43	36.5-37.5
Bicarbonate	24	24		29		26					24	27	23		19	25	30	29	32	22-26 mmol/L
Lactate	2.2	1.7		1.6		1.6					3.4	5.9	5.8		6.4	6.6	3.8	2.4	2.8	0.5-1.6 mmol/L
Base excess	0.6	0.5		5.1		3.1					1.6	2.4	1.3		-1.6	-2.0	3.2	1.2	1.2	
Bicarbonate infusion		80	25	25	25	25	18.75	18.75	18.75	18.75	30	30	30	30	30	30				mmols/hr
Potassium						3.8				4.4		3.9		3.9		4.3				3.5-5 mmol/L
Urine output					80	180	110	120	90	70	110	100	60	80	80	80	140	80		mls/hr
Urine pH						8.5			8.5		8.0		7.5	7.0		7.5				

*pO2 85 on concurrent ABG

Reference		Clinical features	Outcome
1990, Flanagan [1]	11 **ioxynil** coingestions	Drowsiness, vomiting, high temperatures, tachycardia, agitation, sweating and asystolic cardiac arrest (Plasma diuresis did not influence ioxynil clearance)	7/11 died 5-8hrs after admission
1977, Smysl [2]	54 yr old man with gastrectomy accidentally swallowed **ioxynil**		Death 45 mins (? Faster with gastrectomy)
1988, Dickey [3]	37 yr old housewife 190ml 'clovercide extra' MCPP 105g/L and **ioxynil** 35g/L	Alert and orientated, HR 100, BP 130/80, CK 3901 10hrs: flushed and agitated, HR 130, pH 7.34 Settled with oral diazepam 17hrs: temperature suddenly rose – 39^0C Rapid deterioration, seizures, cardiac asystole	death 17hrs MCPP 515mg/L at 8 hours Ioxynil 317 mg/L

Supplementary Table 2: Ioxynil cases in the literature

References

1. Flanagan, R.J., et al., *Alkaline diuresis for acute poisoning with chlorophenoxy herbicides and ioxynil.* Lancet, 1990. **335**(8687): p. 454-8.
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