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TREATMENT OF SEVERE 2,4-D AND MECOPROP INTOXICATION WITH ALKALINE DIURESIS

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1 Self-poisoning with a selective weedkiller containing 2,4-D and mecoprop in a 39 year old man resulted in prolonged deep coma, pyrexia, hyperventilation, hypoxaemia, myotonia, skeletal muscle damage and electrocardiographic changes consistent with cardiomyopathy.

2 The admission plasma concentrations of 2,4-D and mecoprop were 400 and 751 μg/ml respectively. The patient remained gravely ill with no signs of improvement for 2 days with supportive therapy and there was no fall in the 2,4-D level.

3 Alkaline diuresis greatly increased the renal clearance of 2,4-D, and there was a rapid fall in plasma concentration ($T_{\frac{1}{2}}$ 3.7 h) with corresponding clinical improvement. The effect on the elimination of mecoprop was similar, but less dramatic.

4 Forced alkaline diuresis may improve the otherwise very poor prognosis in severe intoxication with 2,4-D and related weedkillers.

Introduction

The chlorophenoxy acid 'hormone' herbicides have been used extensively over the last 30 years for the control of broadleaved weeds. They are sold without restriction in concentrated form and are widely used as selective weedkillers for lawns. 2,4-D (dichlorophenoxyacetic acid), mecoprop (4-chloro-2-methylphenoxypropionic acid) and related herbicides are considered to be of low toxicity (Way, 1969) but muscle weakness and peripheral neuropathy have been prominent features in the few cases of toxicity reported after occupational exposure (Goldstein, Jones & Brown, 1959; Berkeley & Magee, 1963; Paggiaro, Martino & Mariotti, 1974).

Acute intoxication from self-poisoning with these compounds is uncommon, but in most reported cases the outcome was fatal (Jones, Knight & Smith, 1967; Popham & Davies, 1964; Curry, 1962; Johnson & Koumides, 1965; Nielsen, Kaempe & Jensen-Holm, 1965; Larrard & Barbastie, 1969; Brandt, 1971; Dudley & Thapar, 1972). In the past, treatment has been essentially supportive. Little is known of the disposition of these herbicides in man but since they are moderately strong organic acids, and 2,4-D is excreted in the urine largely unchanged (Kohli, Khanna, Gupta, Dhar, Tandon & Sircar, 1974), forced alkaline diuresis would seem a logical form of treatment.

Methods

Case report

A 39 year old policeman was admitted 2 h after the deliberate ingestion of the contents of a lemonade bottle half-full of a weedkiller which was later shown to contain 10% 2,4-D and 20% mecoprop. Soon after ingestion the patient vomited, became aggressive and confused and then rapidly lost consciousness. On admission the pulse rate and blood pressure were normal but the respiratory rate was 35/min with a minute volume of 12 l. The pupils were small but reactive, muscle tone was increased and tendon reflexes were normal. Arterial blood analysis showed mild metabolic acidosis and hypoxia (H^+ 47 nmol/l, pCO_2 3.6 kPa, bicarbonate 14 mmol/l and pO_2 8.7 kPa). Gastric aspiration and lavage were performed.

Over the next few hours his condition deteriorated. He became unresponsive to painful stimuli, the tendon reflexes disappeared, the pulse rate increased to 140/min and the temperature rose to 39°C. He was vasodilated and sweating profusely. Cyanosis was evident despite a respiratory rate of 40–50/min and the chest was clear clinically and radiologically. A normal arterial oxygen tension could only be maintained with 6 l/min of oxygen through an M.C. mask and the temperature remained at 39°C despite the use of fans and

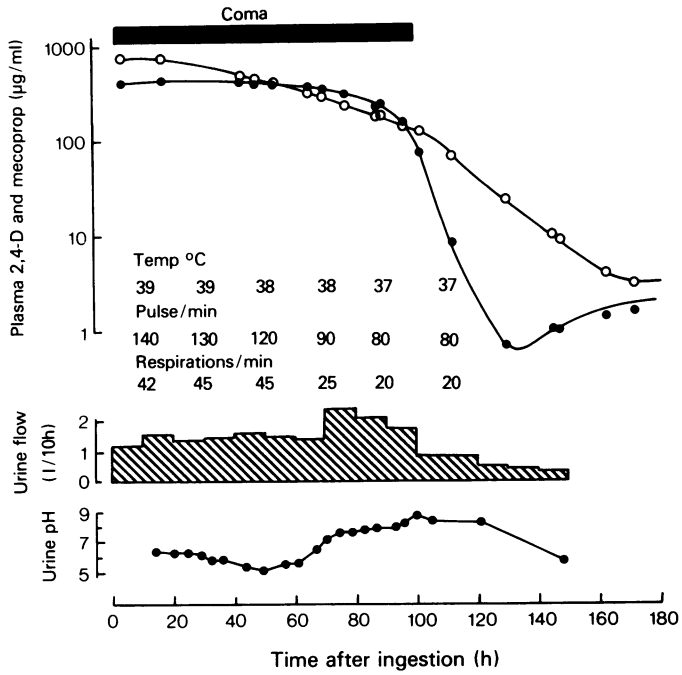

Figure 1 Plasma concentrations of 2,4-D (●) and mecoprop (○) in relation to clinical course and urine output and pH.

Table 1 Clinical and laboratory findings

	Time after ingestion (days)							
	1	*2*	*3*	*4*	*5*	*7*	*9*	*11*
Arterial blood								
H^+ (nmol/l)	44	37	35	30	—	—	35	—
pCO_2 (kPa)	4.9	5.1	5.2	5.4	—	—	4.1	—
HCO_3^- (mmol/l)	20	25	30	33	—	—	22	—
pO_2 (kPa)	10.5*	5.4	19.0*	7.9	—	—	11.8	—
Plasma								
Urea (mmol/l)	11.8	25	22	14.5	5.6	8.2	5.9	5.0
K^+ (mmol/l)	5.2	3.8	3.7	3.4	4.1	4.5	4.4	3.8
Creatinine (µmol/l)	—	—	—	150	101	87	76	—
Bilirubin (µmol/l)	—	—	11	—	9	17	12	8
AST (U/l)	—	—	123	—	145	147	127	92
CPK (U/l)	—	—	>3000	—	>3000	>3000	1404	712
Myotonia	–	+++	+++	++	0	0	0	0
Urine Hb test	+	++	+++	++	+	–	–	–
ECG	–	abnormal	abnormal	abnormal	normal	normal	normal	normal

* On oxygen. AST Aspartate aminotransferase. CPK Creatine phosphokinase.

tepid sponging. Hydrocortisone and antibiotics were given because of the possibility of aspiration pneumonia.

Forty hours after admission the patient was still deeply unconscious. Arterial blood analysis showed H^+ 37 nmol/l, pCO_2 5.1 kPa, pO_2 5.4 kPa and bicarbonate 25.5 mmol/l with a minute volume of 16 l and respiratory rate of 45/min. The chest was still clear and an electrocardiogram (ECG) showed sinus tachycardia with T wave flattening in the standard leads and marked T wave inversion in the chest leads. The plasma urea had risen to 28.4 mmol/l despite good peripheral perfusion, a systolic blood pressure of 90–100 mmHg and a urine output of 2–3 l/24 h.

Despite the potential hazards, it was decided to induce an alkaline diuresis and over the next 48 h 14 l of fluid containing 69.3 g sodium bicarbonate was given intravenously while the central venous pressure was monitored.

Within a few hours of starting the diuresis the pulse rate, respiration rate and temperature began to fall (Figure 1) and 18 h later he was responding readily to painful stimuli, deep tendon reflexes were brisk and marked myotonia was present. Consciousness was regained 4 days after admission but he remained confused and disorientated for a further 4 days. The myotonia persisted for several days and there was marked proximal muscle weakness which lasted for several weeks.

By the fifth day, the plasma urea had fallen to 5.6 mmol/l and the ECG reverted to normal. The creatinine clearance was 139 ml/min on the ninth day. There was biochemical evidence of severe muscle injury. The plasma creatine phosphokinase (CPK) rose to > 3000 u/l (normal < 180) and remained above this level for several days and the urine gave a strongly positive test for haemoglobin. The plasma aminotransferase and lactic dehydrogenase activities were also elevated but the alkaline phosphatase and bilirubin remained within normal limits. Electromyography performed 6 days after ingestion showed changes consistent with a mild myopathy. The clinical course and laboratory findings are shown in Figure 1 and Table 1.

The patient was discharged to a psychiatric ward 11 days after admission and at follow-up 2 months later was well, but still complaining of some weakness of the legs.

Analytical methods

Plasma and urine (1 ml) were acidified with 1N HCl and the herbicides were extracted into 5 ml ether containing 2, 4, 5-trichlorophenoxyacetic acid as internal standard. The aqueous phase was discarded and the chlorophenoxy acids extracted back into 100 µl 0.1M trimethylanilinium hydroxide in 50% aqueous methanol. Aliquots (2 µl) were injected into a Hewlett-Packard Model 402 gas chromatograph fitted with a 4 ft × 1/4 in glass column packed with 10% OV17 on Gaschrom Q. The injection port and oven temperatures were 310°C and 200°C respectively and the carrier gas (nitrogen) flow rate was 60 ml/min. The chlorophenoxy acids were chromatographed as methyl esters formed by thermal decomposition in the injection port. The mean standard deviation of replicate assays of plasma and urine containing 10–100 µg/ml of dichlorprop (dichlorophenoxypropionic acid), mecoprop and 2,4-D was 5.3%.

Total unchanged and conjugated chlorophenoxy acids in urine were estimated as above after hydrolysis with 3N HCl at 80°C for 1 h. The pKa values of 2,4-D and mecoprop were determined by titration.

Effects of alkaline diuresis

The plasma concentrations of 2,4-D and mecoprop on admission were 400 and 751 µg/ml respectively. Over the next 2 days there was no appreciable fall in the 2,4-D level, but the concentration of mecoprop declined slowly with a half-life of about 40 h. There was a delay before the urine became alkaline after the diuresis was started but as the pH rose there was an increasingly rapid fall in the plasma concentrations of 2,4-D. Above pH 7.0 the fall was precipitous, and over the period 96–112 h after ingestion the half-life fell to 3.7 h (Figure 1). As expected, there was a rebound rise in 2,4-D concentrations after the alkaline diuresis was discontinued. The effect on the plasma concentrations of mecoprop was much less dramatic and the half-life values just before, during and after the urine became alkaline were 24, 11 and 28 h respectively.

As the 2,4-D concentrations fell there was progressive clinical improvement as shown by the decline in pulse rate, respiratory rate and temperature and rise in conscious level (Figure 1). The patient regained consciousness 4 days after ingestion when the plasma concentrations of 2,4-D and mecoprop were each about 100 µg/ml.

The renal clearance of 2,4-D ranged from 0.14 ml/min at a urine pH of 5.1 to 63 ml/min at pH 8.3 and the log clearance corrected to a urine flow rate of 1 ml/min was directly related to the urine pH ($r=0.99$) (Figure 2). For each increase of 1 pH unit, the renal clearance of 2,4-D rose almost fivefold. There was a similar correlation between urine pH and mecoprop clearance ($r=0.94$) but the slope was less steep and an increase of one pH unit only doubled the clearance. The renal excretion of unchanged 2,4-D over the first 3 days amounted to only 0.73 g (10.1 mg/h), but 5.71 g was recovered from 72–134 h (83.5 mg/h). The corresponding amounts of mecoprop recovered were 1.42 and 2.15 g.

The measured pKa values for 2,4-D and mecoprop were 3.3 and 2.8 respectively.

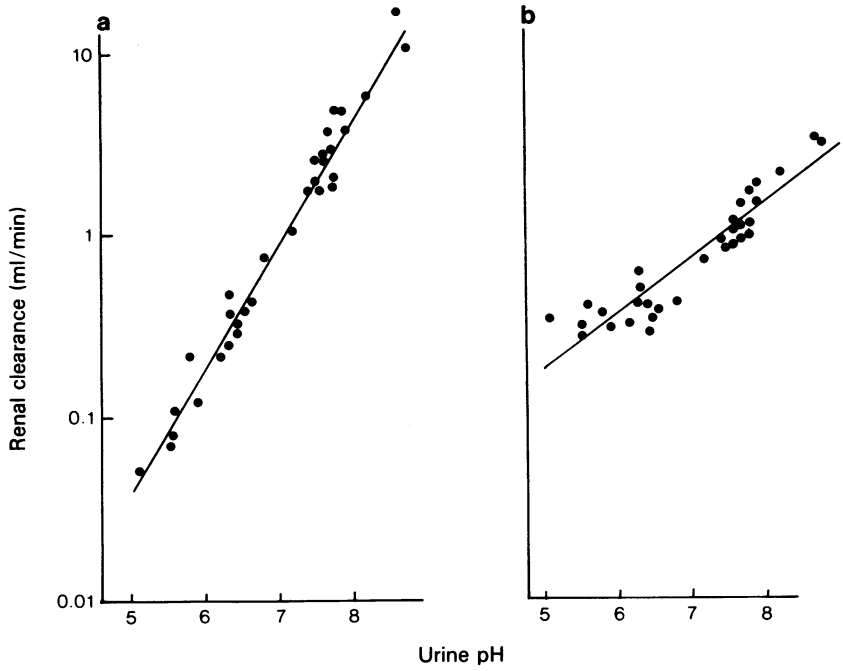

Figure 2 Relationship between urine pH and renal clearances of a) 2,4-D and b) mecoprop corrected to a urine flow rate of 1 ml/min.

Dose absorbed

The total amounts of 2,4-D and mecoprop recovered in the urine were 6.66 and 7.64 g. About 10% of the 2,4-D and 65% of the mecoprop were excreted as acid-labile conjugates. As judged by the urinary recovery of 2,4-D the patient must have absorbed about 70 ml of the weedkiller.

The apparent volume of distribution of 2,4-D derived from plasma half-life and clearance values calculated over the period 65–112 h after ingestion was about 17 l. The dose required to give the observed plasma concentration of 400 μg/ml on admission would therefore be about 6.8 g (400 μg/ml × 17 l). Although this figure does not take into account the minor metabolic elimination of 2,4-D or the possibility of pH-dependent distribution, it agrees well with the total amount recovered from the urine.

Discussion

Most selective weedkillers contain 2,4-D combined with one or more similar agents such as mecoprop and dichlorprop. These weedkillers are displayed in every gardening shop and in view of their widespread use it is surprising that serious poisoning with them does not occur more frequently. Of 4174 enquiries to the Scottish Poisons Information Bureau in 1976, 431 involved agricultural products and of these only 6 related to 2,4-D.

The features of intoxication with 2,4-D and mecoprop in this case included prolonged deep coma, pyrexia, hyperventilation, tachycardia, vasodilation, sweating, hypoxaemia, myotonia, muscle damage and ECG abnormalities. Most of these manifestations have been described previously in chlorophenoxy acid herbicide poisoning together with muscle twitching, convulsions and pulmonary oedema (Berwick, 1970; Brandt, 1971; Curry, 1962; Dudley & Thapar, 1972; Johnson & Koumides, 1965; Jones *et al.*, 1967; Larrard & Barbastie, 1969; Nielsen *et al.*, 1965; Paggiaro *et al.*, 1974; Popham & Davies, 1964). The severe hypoxaemia and normal pCO_2 despite hyperventilation without clinical or radiological evidence of a pulmonary abnormality in our patient was puzzling. Such changes have been described in deep coma caused by sedative drugs (Sutherland, Park & Proudfoot, 1977) but in this case uncoupling of oxidative phosphorylation with pyrexia induced by 2,4-D (Brodie, 1952) probably contributed. Inhibition of enzymes of intermediary metabolism might also explain the sharp rise in plasma urea despite apparently adequate renal perfusion and good urine output.

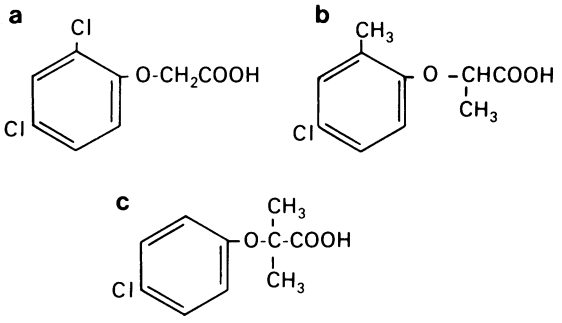

Figure 3 Chemical formulae of a) 2,4-D, b) mecoprop and c) clofibrinic acid.

Muscle damage with myotonia was a major complication, and the striking elevation of plasma CPK could not be attributed to prolonged coma alone (Wright, Clarkson, Brown & Fuster, 1971). The generalized T wave abnormalities on the ECG suggest myocardial as well as skeletal muscle damage. Similar muscle injury and cardiomyopathy has been reported in patients with and without renal failure given normal doses of clofibrate (Pierides, Alverez-Ude & Kerr, 1975; Smals, Beex & Kloppenborg, 1977). It is interesting to compare the structures of 2,4-D, mecoprop and clofibrinic acid, the active metabolite of clofibrate (Figure 3). (Clofibrate is the ethylester of clofibrinic acid, to which it is rapidly hydrolysed *in vivo*). The similarities are obvious, and mecoprop is actually an isomer of clofibrinic acid. Furthermore, both clofibrate and clofibrinic acid have some herbicidal activity (unpublished observations).

Diuresis with and without alkali has been used empirically in poisoning with selective weedkillers (Jones *et al.*, 1967; Brandt, 1971) but there has been no previous assessment of efficacy. Our patient remained gravely ill with no signs of improvement after 2 days of supportive therapy, and there had been no significant fall in the plasma concentrations of 2,4-D. The administration of alkali was followed by greatly increased renal clearance of 2,4-D, rapid fall in plasma concentrations and clinical improvement. Renal excretion is the major route of elimination of 2,4-D, and its renal clearance is highly dependent on urine pH. Forced alkaline diuresis appears to be very effective treatment for severe intoxication. Mecoprop, on the other hand is extensively metabolized, and although alkaline diuresis is probably worth-while it was much less effective in enhancing its elimination. It may also be relevant that the pKa of 2,4-D (3.3) is just above, and that of mecoprop (2.8) just below the critical value of 3.0 proposed by Milne (1965) for pH-dependent renal excretion of organic acids.

The very long plasma half-life of 2,4-D and related compounds was confirmed by observations on a 58 year old woman who tried to poison herself with a weedkiller containing 16.1% 2,4-D and 21.4% dichlorprop (2,4-dichlorophenoxypropionic acid). The plasma concentrations on admission were 335 and 400 μg/ml respectively but as the patient was fully conscious with no clinical evidence of toxicity, forced alkaline diuresis was not carried out. The plasma half-life values for 2,4-D and dichlorprop measured over 5 days were 143 and 95 h respectively with a mean urine pH of 5.74. Ninety-one per cent of the 2,4-D and 70% of the dichlorprop recovered in the urine over this period was excreted unchanged. Forced alkaline diuresis would probably be very effective treatment for severe dichlorprop poisoning.

According to published reports, chlorophenoxy acid weedkiller poisoning carries a very high mortality. Coma may be very prolonged and other serious complications include metabolic disturbances, skeletal muscle damage and cardiomyopathy. The early use of forced alkaline diuresis may greatly improve an otherwise poor prognosis.

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