

Severe dothiepin intoxication—a report of two cases

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Summary

Two patients with severe dothiepin intoxication are described. The management of these cases is discussed and we draw attention to the prolonged elimination half-life of dothiepin and its metabolites, and the implication for treatment.

KEY WORDS: supraventricular tachycardia, epilepsy, haemoperfusion.

Introduction

Dothiepin hydrochloride (Prothiaden®, Boots Co. Ltd) is a tricyclic antidepressant and severe intoxication with this group of drugs is becoming an increasingly common method of self-poisoning (Crome *et al.*, 1977) although, to our knowledge, the behaviour of dothiepin in severe overdosage has not been previously reported. Recommended treatment of tricyclic overdosage includes gastric lavage with activated charcoal, but the role of haemoperfusion in severe intoxication, either over activated charcoal or resin columns, remains controversial and has been authoritatively described as unhelpful (Editorial, 1979; Crome *et al.*, 1978). The controversy, based mainly on pharmacokinetic grounds, is that, being extremely lipid soluble compounds, the proportion of the dose available for clearance from the vascular compartment is minute compared with that sequestered by the tissues and therefore the total amount of drug removed by this means is small.

Case 1

A 36-year-old female was admitted having ingested 2-3 g of dothiepin and approximately one half-bottle of spirits 3 hr earlier as a deliberate act of self-poisoning. She responded without purpose to painful stimuli, the gag reflex was present and there were no lateralizing neurological signs. She had a supraventricular tachycardia of 150 beats/min with

generalized S-T segment depression on electrocardiogram (ECG). Gastric lavage was performed (without activated charcoal) but the conscious level deteriorated with impairment of respiratory function necessitating intermittent positive pressure ventilation (IPPV). A grand mal convulsion was terminated after 2 min with intravenous diazepam. Severe acidosis (pH 7.12, base deficit 18.5) was corrected with serial infusions of 2.74% sodium bicarbonate solution over 2 hr. Charcoal column haemoperfusion (Haemocol®, Smith and Nephew) was instituted and, during the 6 hr of this procedure, there was a dramatic return to a normal neurological and cardio-respiratory state. Dothiepin clearance for the duration of the haemoperfusion is shown in Table 1.

The patient remained in the intensive care unit for a further 24-hr observation period during which time she appeared to be making a full recovery. As serial arterial blood acid-base and blood gas analyses and venous blood electrolyte determinations revealed no further metabolic disturbance, she was transferred to the medical ward. Some hours later, and approximately 48 hr post-overdose, she was noted to be hallucinating mildly. This was attributed to a withdrawal state following suspected chronic alcohol abuse and no medical action was considered necessary at that time. That same evening, she was noted to have a dry cough, low grade pyrexia and sinus tachycardia (90-105/min). There were no auscultatory findings and it was considered probable that she had a mild upper respiratory tract infection for which a simple linctus expectorant was prescribed. During the early hours of the following morning, and some 56 hr post-overdose, she became suddenly apnoeic with ventricular fibrillation. Blood samples taken post-mortem established death to be the result of an unrecognized rebound of dothiepin toxicity (Table 2).

Case 2

An 18-month-old child weighing 10 kg was admit-

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TABLE 1. Case 1. Dothiepin clearance during charcoal column haemoperfusion

Time (hr)	Precoil ($\mu\text{g/ml}$)	Postcoil ($\mu\text{g/ml}$)	Difference	Flow rate (ml/min)	Total drug clearance up to given time (mg)	Plasma clearance (ml/min)
1	1.13	1.05	0.08	250	1.20	18
2	1.05	0.83	0.22	300	5.16	63
3	1.01	0.77	0.24	300	9.48	71
4	0.97	0.58	0.39	300	16.5	121
5	0.84	0.86	—	300	—	—
6	1.03	0.95	0.08	300	17.94	23

Clearance was calculated on the assumption that the concentration difference during the preceding hour remained constant. No metabolites were detected in any sample.

TABLE 2. Plasma levels of dothiepin and its chief metabolite in case 1

Hours post-ingestion	Plasma concentration ($\mu\text{g/ml}$)	
	Dothiepin	Northiaden
4.5	2.51	None detected
6.0	1.88	0.13
17.5	1.07	0.32
57.5*	4.54	1.28

*Post-mortem.

Plasma concentration of dothiepin = 1.49 $\mu\text{g/ml}$ at start of haemoperfusion 6.5 hr post-overdose.

TABLE 3. Concentrations of dothiepin and northiaden in plasma and urine in case 2

	Concentration ($\mu\text{g/ml}$)	
	Dothiepin	Northiaden
Plasma (hr post-ingestion)		
5 hr	4.67	1.2
14.75 hr	1.45*	0.32
25 hr	1.46	0.35
49 hr	0.68	0.23
74 hr	0.043	0.054
Urine		
Day 1: vol = 583 ml	4.64	3.17
Day 2: vol = 865 ml	1.23	1.44
Day 3: vol = 1460 ml	0.019	0.069

*Pre-exchange transfusion.

perfectly well. Levels of dothiepin and its desmethylated metabolite (northiaden) in plasma and urine for the duration of the illness are shown in Table 3. In both cases assays were carried out using high performance liquid chromatography (Brodie *et al.*, 1977).

Discussion

Dothiepin hydrochloride is a tricyclic antidepressant with similar pharmacokinetics and pharmacodynamics to other members of this group and, in overdosage, appears to have similar effects. Metabolites of dothiepin which have been identified in the circulation are dothiepin-s-oxide, northiaden and northiaden-s-oxide. Northiaden has similar activity to dothiepin but the sulphoxides are relatively less potent (Rees, 1981). Studies in man have shown that whilst dothiepin alone has an elimination half-life of about 24 hr, the elimination half-life of drug and metabolites is much longer. The elimination of radioactive labelled drug (^{14}C -dothiepin) appears to be biphasic with half-lives of 16 and 56 hr for phase I and II respectively. The major route of excretion is via the kidney, with a smaller fraction recoverable from the faeces. Biliary recycling probably accounts for the secondary peaks (Rees, 1981).

ted to hospital having accidentally ingested 900 mg of dothiepin 1½ hr previously. On arrival she was in status epilepticus with an irregular pulse and peripheral circulatory shutdown. On intubation she suffered an asystolic cardiac arrest which responded rapidly to external cardiac massage and intravenous adrenaline and calcium gluconate. Gastric lavage did not affect the immediate clinical state, but in this patient activated charcoal was instilled into the stomach following the procedure. Initial arterial acid-base analysis prior to ventilation revealed a metabolic acidosis with respiratory compensation (pH 7.30, base deficit 13.7, P_{CO_2} 20.8 mmHg; 2.8 kp) and this was partially corrected with a bicarbonate infusion. The patient subsequently required IPPV. Hypoperfusion and hypotension (systolic pressure of 55 mmHg) was treated with a dobutamine infusion. ECG monitoring revealed a series of tachyarrhythmias and bundle branch block which responded well to intravenous phenytoin and physostigmine (0.03 mg/kg). The patient's cardiovascular condition stabilized and dobutamine was discontinued 8.75 hr after its commencement. Resin column haemoperfusion (XAD4—'Amberlite') was attempted but discontinued after 10 min owing to blood pump failure. An exchange transfusion was performed. Over the next 9 hr a progressive improvement in the patient's condition was observed and IPPV was discontinued. The patient made a complete and otherwise uneventful recovery and on follow-up 1 month later appeared

In case 1, there appears to have been a very small clearance of dothiepin (totalling 18 mg) during the charcoal column haemoperfusion. In spite of this, a gratifying change in clinical state was observed during the course of this procedure and maintained for some considerable time afterwards. This confirms observations by others (Diaz-Buxo, Farmer and Chandler, 1978; Pond *et al.*, 1979) to the effect that haemoperfusion as adjunctive therapy in advanced comatose states of tricyclic intoxication may be beneficial. It remains a possibility that removal of alcohol from the blood by activated charcoal could, at least in part, have been responsible for some of the clinical improvement noted during the course of the haemoperfusion but we do not believe the contribution to be large in this patient as the quantity of alcohol ingested at the time of overdosage was comparatively small. No estimations of blood alcohol are available.

In the case of dothiepin, the signs and symptoms of 'rebound' toxicity may not appear for some considerable time following the initial haemoperfusion. Enterally administered activated charcoal, recommended by Crome *et al.* (1977) to prevent delayed gastro-intestinal absorption, might possibly have helped to prevent the fatal 'rebound' to toxic levels seen in this patient by blocking biliary recycling.

In case 2, where activated charcoal was given, no similar 'rebound' phenomenon was observed. The total urinary excretion of dothiepin and northiaden amounted to 3.8 mg and 3.2 mg in 72 hr, accounting for a fraction of the ingested quantity.

In neither case did the clinical state correlate closely with the serum levels of dothiepin, an observation similar to that of amitriptyline in overdosage (Hallstrom and Gifford, 1976). The serum levels of dothiepin in case 1 were seen to be falling before the initiation of the charcoal column haemoperfusion, at a time when the patient's clinical condition was, in fact, deteriorating. The serum level at 17.5 hr post-ingestion differs very little from the level obtained at the commencement of haemoperfusion, yet at this time the patient was conscious and orientated. Similar observations were made in case 2 when serum levels of dothiepin at 25 hr were identical to those prior to the exchange transfusion performed 10 hr before, despite marked differences in the patients' clinical condition at these times.

Temporary reduction in the concentration of tricyclic antidepressants in the brain or heart or removal of active metabolites have been the reasons suggested to account for the discrepancy between the quantity of drug removed by haemoperfusion and the clinical response observed in some of these patients (Pond *et al.*, 1979). The latter suggestion is

not upheld, however, by our data available on the plasma levels of northiaden, the principal metabolite of dothiepin. We do agree with the proposal of Trafford, Sharpstone and O'Neal (1980) that significant drug activity is likely to be more closely related to a much narrower volume distribution than the pharmacokinetics would suggest.

Conclusion

Dothiepin in severe intoxication behaves in a similar way to other members of the tricyclic group of antidepressants. The severity of cardiopulmonary and neurological sequelae is diminished by prompt detection and correction of acidosis and hypoxia. Haemoperfusion, either over charcoal, or resin columns, may, after all, have a place in the immediate prevention of life-threatening complications. Drug persistence in the bowel and biliary recycling may be prevented by the administration of activated charcoal. We draw attention to the long elimination half-life of the drug and its metabolites and the propensity to 'rebound', with little warning, to potentially fatal serum levels some considerable time following the initial ingestion.

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