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CHARCOAL HAEMOPERFUSION FOR PARACETAMOL OVERDOSE

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1 A controlled trial of charcoal haemoperfusion as an early treatment for paracetamol overdose showed no benefit.

2 The plasma clearances of paracetamol by the charcoal column were variable and disappointingly small (range 4-119 ml/minute). The cumulative amounts removed were also low, mean 1.4 g (range 0.2-5.2 g).

3 No clinical problems were encountered with the technique of haemoperfusion and in particular the drop in blood platelet counts was small (mean fall 16%).

Introduction

Since the first description in 1966 of hepatotoxicity due to paracetamol (*N*-acetyl-*p*-aminophenol) overdosage, there has been rapid increase in the use of this drug as a self-poisoning agent (Clark, Thompson, Borirakchanyavat, Widdop, Davidson, Goulding & Williams, 1973). We have previously reported studies in the pig which showed that haemoperfusion through a column of charcoal particles removed paracetamol rapidly and efficiently from the blood stream (Willson, Winch, Thompson & Williams, 1973). This paper describes eight patients treated in this way as part of a prospective controlled trial. The other eight patients received supportive therapy alone.

Methods

All patients seen in the Liver Unit with a plasma paracetamol level of greater than 200 μg/ml at any time in the first 12 h after overdosage were allocated by a system of sealed envelopes to either charcoal haemoperfusion or standard supportive treatment. All patients were treated by gastric lavage when first seen and fluid and fresh frozen plasma was administered as clinically indicated. Paracetamol was measured in the plasma by the method of Dordoni, Willson, Thompson & Williams (1973) which enabled a result to be obtained within 15 minutes. With one exception, all the patients were conscious when first seen, and the nature of the procedure was explained to them, informed consent also being obtained from a close relative.

Method of haemoperfusion

Two catheters (14 French gauge 50 cm in length) were inserted under local anaesthesia into the saphenous vein, positioned in the inferior vena cava under X-ray control and attached to a pre-packed sterilized perfusion column. This had been prepared as follows: Speakman coconut charcoal was washed with sterile 0.9% w/v NaCl (saline; 6 litres) and sieved to remove particles smaller than 600 μm in diameter. Aliquots (200 g) were then steam sterilized and transferred to plastic chromatography columns (Wright Scientific Ltd) 12 x $1\frac{3}{4}$ inch which had been sterilized with ethylene oxide. Nylon filters (pore size 600 μm) were fitted at both ends. After assembly the column was washed through with 6 litres of sterile heparinized saline (1 unit heparin/ml). Blood was pumped upwards through the column at 150 ml/min using a Watson-Marlow roller pump (MHRE 88), and was returned to the patient via the inferior vena cava catheter situated nearer the heart.

In all cases the charcoal used was covered with a thin coating of poly(hydroxyethylmethacrylate). In the first two patients studied (1 and 2) this increased the weight of the uncoated granules by 10% and in the other six patients by 11%.

The patient was heparinized by an i.v. loading dose of 2,000 units 10 min before the procedure, and thereafter a constant infusion pump delivered (1,500-2,000 heparin units)/hour. This maintained the blood heparin level at 0.5 mg/100 ml, measured each hour by protamine sulphate dilution (O'Shea, Flute & Pannell, 1971). Haemoperfusion was continued until the patient's paracetamol level was less than 30 μg/ml.

Calculation of paracetamol removal and half-life

Immediately following gastric lavage two venous blood samples were removed at timed intervals (30-60 min apart) to calculate the plasma time of disappearance of paracetamol. A third sample was taken at the start of the perfusion and further specimens were taken simultaneously from the input and output tubing at 30 and 60 min, and then hourly throughout the procedure. In three pateints further timed samples were also obtained following perfusion. A plot of these values on semi-logarithmic paper allowed calculation of plasma paracetamol half-time of disappearance before and during column haemoperfusion. It was recognized that the half-time of disappearance both before and during haemoperfusion might be affected by continuing absorption of the drug as all these samples were obtained within 12 h of ingestion. The arterio-venous differences across the column together with the flow rate were used to calculate clearances of the drug, and the total amount of paracetamol removed.

Results

Although the two groups were randomly allocated those receiving supportive therapy alone had ingested fewer tablets, were first seen earlier following the overdose, had a lower mean level of plasma paracetamol and a shorter initial drug half-life (Table 1). The mean ages and weights of the patients in the control group were 35 years (range 16-47) and 56 kg (range 45-65) and for the treatment group 31 years (range 18-44) and 63 kg (range 52-83). None of these differences reached statistical significance.

The ensuing liver damage in most patients was mild but the treated group had more evidence of hepatic dysfunction with a higher mean bilirubin level. The difference in the aspartate amino transferase levels between the treated and control group was significant ($P < 0.05$). Two patients in the treatment group had a protracted clinical course and were in hospital for more than 3 weeks, all the other patients being discharged in a few days.

The one death in the series also occurred in the treatment group (case No. 8). This patient took a large overdose (135 g) and the plasma paracetamol level was 600 μg/ml 9 h after ingestion (Figure 1).

No serious clinical problems were encountered during periods of haemoperfusion from 2 to 9 hours. There was a variable extraction of paracetamol from the blood stream causing a considerable range of calculated plasma clearances of the drug (Table 2). There was also some

Table 1 Clinical and biochemical data on the two groups of patients (mean ± s.e. mean)

	Time first seen after overdose (h)	*Estimated amount taken (g)*	*Paracetamol Initial plasma level (μg/ml)*	*Plasma half life (h)*	*Plasma bilirubin (mg/100 ml)*	*Prothrombin time (s prolonged)*	*AST* (iu/litre)*
Supportive therapy ($n = 8$)	3 ± 0.4	34 ± 4	238 ± 12	5 ± 0.5	1.27 ± 0.7	2.2 ± 3	142 ± 55
Column haemoperfusion ($n = 8$)	5 ± 0.8	56 ± 14	305 ± 46	7 ± 0.6	1.85 ± 1.23	12 ± 15	827 ± 430

* AST, aspartate amino transferase.

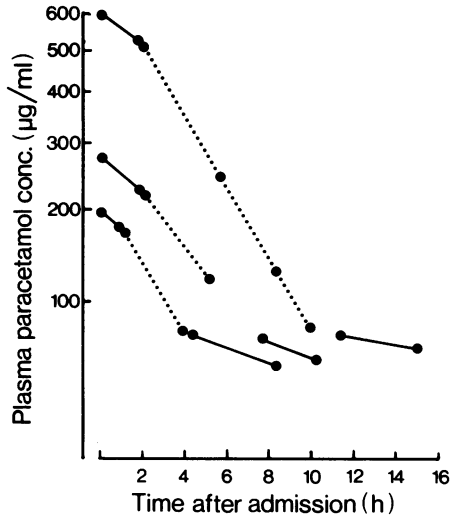

Fig. 1 Plasma half-lives of paracetamol before, during (dotted line) and after haemoperfusion in three patients with paracetamol overdose.

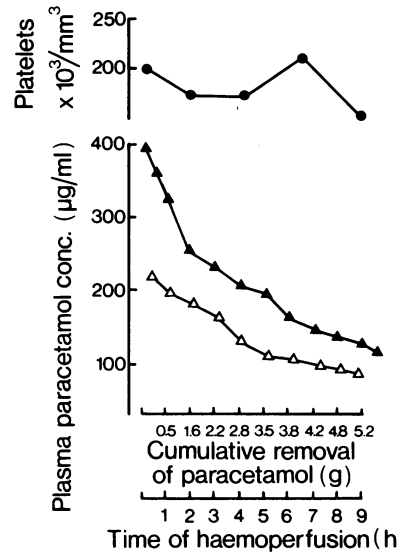

Fig. 2 Platelet counts, concentrations of paracetamol in input (arterial line; ▲) and output (venous line; △) tubing, and cumulative removal of paracetamol in one patient who died from overdose of the drug.

variation in clearance during the course of a single perfusion (Table 2) and in one instance there was a sudden fall in the pressure across the column, when both extraction and clearance decreased. The total amounts of paracetamol removed were small, the maximum being 5.2 g, but in each case haemoperfusion was associated with a marked fall in plasma disappearance time of the drug. Following perfusion the plasma disappearance time of the drug became more prolonged in three patients (Figure 2).

The blood platelets fell during perfusion, but in no case to below 100,000/mm^3. Most of the fall occurred during the first hour of perfusion and following perfusion the level returned rapidly to normal. There was a parallel drop in the white cell count, but 4-6 h after perfusion it increased to slightly above normal levels. Blood electrolyte levels measured pre- and post-perfusion were unchanged, except in one patient in whom a transient fall in the serum calcium was noted.

Discussion

Paracetamol is a water soluble drug which is protein bound to only a small extent, (Gazzard, Ford-Hutchinson, Williams & Smith, 1974) and it might therefore be removed by haemodialysis. Charcoal haemoperfusion has two theoretical

Table 2 Data relating to charcoal haemoperfusion in eight patients

Patient number	*Duration of perfusion (h)*	*Paracetamol*				*Platelet count (% drop)*
		Amount removed (g)	*Plasma clearance (mean & range) (ml/min)*	*Plasma half-life Before perfusion (h)*	*During*	
1	2	0.4	40 (32-45)	8.0	3.0	4
2	4	1.2	103 (92-119)	5.0	2.5	29
3	6	1.6	44 (28-69)	6.0	2.0	19
4	4	1.5	28 (24-37)	8.0	1.75	19
5	5	1.2	40 (12-61)	5.5	2.5	10
6	3	0.2	60 (37-77)	6.0	1.5	32
7	4	0.2	14 (4-25)	7.5	2.0	7
8	9	5.2	50 (39-60)	9.0	4.0	12

advantages over haemodialysis. Firstly, the membrane coating of the charcoal is thinner (0.05 μm) than that of a conventional dialysis membrane (5 μm), and secondly, the total area available for exchange is much greater (Chang, 1972). Both should allow more rapid removal of the drug. In our previous pig experiments (Willson *et al.*, 1973) we found that the extraction of paracetamol across the columns of charcoal was greater than 90%. However, in the present patients the extractions obtained were lower. This may be related to the thickness of the 'polyhema' coating of the charcoal for in the patient perfusion with the best extractions (over 70%) and in the pig experiments a thinner 'polyhema' coating was used. Subsequently the thickness of coating was increased by 1% and the technique of application was changed. These factors may be of critical importance in the rate of removal of paracetamol by coated charcoal (Gazzard, Langley, Dunlop, Weston & Williams, 1974). Channelling of blood in the column with by-passing of the absorptive surface may have been the cause of the variation in clearance during individual perfusions.

Unconjugated paracetamol circulates in the plasma for some hours following ingestion, and removal of the drug might be expected to reduce the amount entering and damaging the liver. We did not demonstrate any benefit of charcoal haemoperfusion on the clinical course of patients. Indeed the control group suffered from less liver damage and it is possible that the treatment was actually harmful. This is unlikely and the most reasonable explanation for the differences in the two groups would be the difference in number of tablets ingested. The lack of benefit of haemoperfusion may be related to the small total amounts of paracetamol removed by the column; these ranged from as little as 0.2 g-5.2 g, the mean removal being 1.4 g, which is less than three tablets. Alternatively the patients may have been treated too late, as it has been shown that paracetamol becomes bound in the liver within 2 h of an i.p. injection in the mouse (Jollow, Mitchell, Potter, Davis, Gillette & Brodie, 1973).

All the patients in the control group did well and the selection of patients for treatment presents a real problem. It is difficult to predict the severity of subsequent hepatic damage during the first few hours after overdosage. Prescott, Wright, Roscoe & Brown (1971) showed that the mean plasma level of paracetamol 4 h after ingestion of the drug was 288 μg/ml in those patients who developed severe hepatic damage. We selected patients with a level above 200 μg/ml within 12 h, in the belief that most of our patients would not be seen until after the first 4 hours.

The coating of the activated charcoal used in the haemoperfusion columns has now been modified to produce a thinner coating which is still biocompatible (Gazzard *et al.*, 1974). Activated charcoal coated in this way has been shown to remove paracetamol more efficient *in vitro*. If this is confirmed *in vivo* and adequate amounts of the drug can be removed then it would be worthwhile setting up a controlled trial to re-evaluate this technique. This should include only those cases seen early following a massive overdose who have very high plasma paracetamol levels, and are liable to develop extensive hepatic necrosis.

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