the effect is at odds with the basic purpose of active management of labour.[9] This suggests that observers who report a much higher incidence of fetal distress are recording evidence of distress caused by induction.

The current tendency to discount clinical methods of supervision of the fetus during labour is not well founded, partly because the importance of meconium is not always appreciated, and partly because insufficient attention is paid to the management of labour. In this series of 1000 primigravidae the concept of high risk was transferred from mother to child, where it belongs. Clear liquor gave reliable evidence that the fetus would survive normal labour and not suffer brain damage; meconium, or no liquor, distinguished the fetus who was vulnerable because placental function was already impaired. A single fetal blood sample was enough to identify infants affected by hypoxia, but fetal heart monitoring contributed nothing to the management of these cases. We conclude that obstetricians engaged in clinical practice can provide an excellent service for the fetus by ascertaining the colour of the liquor early in labour, by restricting the duration of exposure to stress, and by avoiding difficult forceps delivery. Special techniques may be restricted to a few cases. We confined the study to primigravidae because the problems of labour and delivery are concentrated in this group. The inclusion of multigravidae in studies of labour dilutes results. During the study 1911 multigravidae were delivered in this hospital; there was one death during labour, in a breech presentation, and one case of cerebral dysfunction, in a second twin.

We thank Dr Declan Meagher, Master of the National Maternity Hospital, for his advice; Dr Niall O'Brien for assessing the newborn infants; Dr Francis Geoghegan for performing the postmortem examinations; and the sisters in the delivery unit for their unfailing co-operation.

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CONDENSED REPORTS

Haemoperfusion with R-004 Amberlite resin for treating acute poisoning

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Summary

Eleven patients who had taken overdoses of barbiturates, glutethimide, tricyclic antidepressants, and chloroquine were treated by resin haemoperfusion using an R-004 haemoperfusion cartridge containing XAD-4 resin. All but one patient showed rapid clinical recovery and the drugs were cleared rapidly from the plasma. There were few complications.

Resin haemoperfusion is more effective than dialysis and other perfusion methods, especially in poisoning with tricyclic antidepressants. Although haemoperfusion is expensive, it greatly reduces the length of the patient's stay in an intensive care unit and hence is cost-effective.

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Introduction

Self-poisoning is a common cause of admission to hospital, and, although most patients recover with only minimal care, some need full ward care and a few need expensive intensive care.

The overall mortality from self-poisoning is 0·5 to 1%, but a survey in our intensive therapy unit (ITU) in 1973-6 showed a mortality of 10% among severely self-poisoned patients. Death may be caused by the drugs themselves or by complications of treatment—for example, with pressor agents. And prolonged coma and mechanical ventilation produce significant mortality. Therefore, although supportive treatment is adequate for most patients, it may be desirable to remove the toxin from the circulation in very severe cases.

A means of treating severe self-poisoning would also reduce the occupancy of ITU beds, which in this district cost £120 per day, and so reduce the overall cost of treatment.

Treatment has included forced diuresis, peritoneal dialysis, and haemodialysis,[1 2] but the usefulness of these measures is limited. More recently drugs have been absorbed by perfusion through activated charcoal,[3] hydrogel-coated charcoal,[4 5] and various exchange resins.[6] Unfortunately, these techniques need high-dose anticoagulation and can damage formed elements of blood, particularly platelets.

A new technique must be efficient, safe, cost-effective, and simple. We report here the use of the R-004 haemoperfusion cartridge (Extracorporeal Medical Specialties Incorporated),

which contains Amberlite XAD-4 resin,[7-10] for treating severely poisoned patients.

Patients and methods

The haemoperfusion system consists of an R-004 haemoperfusion cartridge comprising a Lexan cylinder containing 650 g of XAD-4 polycarbonate resin and two Swank IL 200 transfusion filters (Pioneer Filters, Beaverton, Oregon). On the venous side of the cartridge these filters are Dacron microembolism filters. Standard arteriovenous blood tubing is used to connect these elements of the circuit.

Three manometers, placed in the inflow (arterial) line, the outflow (venous) line immediately distal to the cartridge, and in the final outflow line beyond the filters (fig 1) were used to monitor pressures in the system. The arterial line passed through a conventional arterial pressure monitor.

We have treated 11 patients with the haemoperfusion cartridge. In the early cases the system was primed with heparinised dextran (1500 units of heparin in 500 ml of dextran 70 saline) after saline irrigation of the cartridge and lines. Subsequently priming with heparinised saline (1500 units of heparin in 500 ml of isotonic saline) was found to be satisfactory. In patients with systolic blood pressures below 90 mm Hg a plasma expander such as dextran or plasma for priming was used before haemoperfusion started.

Access to the patient's circulation was achieved with a conventional or modified form of forearm arteriovenous Scribner shunt or percutaneous arterial puncture using Argyll or Medicut cannulae. The patients were given 4000 to 10 000 units of heparin initially and the whole-blood clotting time was maintained at 30–45 minutes by the administration of further intermittent doses of heparin. Blood was passed through the system at 150 to 300 ml/min using a Sarnes roller pump, and haemoperfusion was continued until a satisfactory clinical or biochemical response was obtained. At various intervals during perfusion blood samples were obtained simultaneously from the inflow and outflow lines of the column for determining drug levels. Haemoglobin; total and differential white cell count; platelet count; and electrolyte, blood urea, calcium, glucose, cholesterol, creatinine, total protein, bilirubin, alkaline phosphatase, aspartate transaminase, lactate dehydrogenase, and urate concentrations were all estimated before and after haemoperfusion. During haemoperfusion the haemoglobin concentration and platelet count were measured frequently. In all cases of recent ingestion gastric aspiration was carried out with the appropriate safeguards to the airway. During perfusion the pulse rate, blood pressure, respiration rate, rectal temperature and the change in the level of consciousness or in neurological signs, pupil response, reflex activity, and response to voice or pain were recorded every half-hour.

Plasma barbiturate concentrations were estimated by ultraviolet spectrophotometry,[11] glutethimide concentrations by a modification of Curry's method,[12] chloroquine concentrations by ultraviolet spectrophotometry (after Hexane extraction), and nortriptyline and amitriptyline concentrations by gas chromatography.

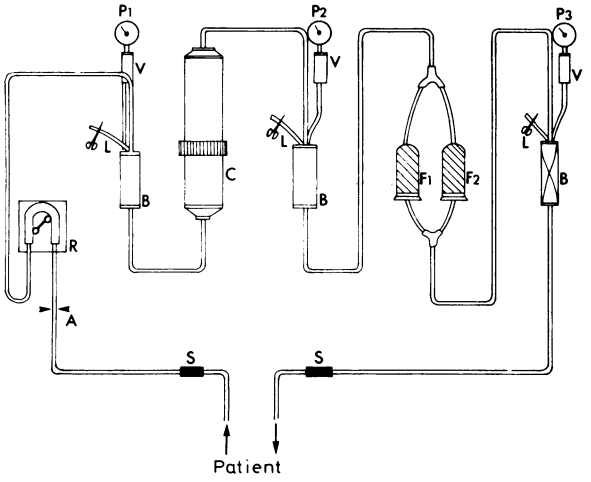

FIG 1—Haemoperfusion circuit. A = Arterial pressure monitor. B = Bubble chamber. C = DX 60 cartridge. F_1F_2 = Swank filters. L = Level control line. P_1,P_2,P_3 = Pressure monitors. R = Roller pump. S = Latex sampling sleeve. V = Venous pressure isolator.

TABLE II—*Total amount of drug removed*

Case No	Drug	Amount removed
1	Quinalbarbitone	240 mg
2	Amylobarbitone	720 mg
3	Glutethimide	3240 mg
	Glutethimide	2520 mg
4	Phenobarbitone	1620 mg
5	Quinalbarbitone and amylobarbitone	1215 mg
6	Chloroquine	Insufficient data
7	Clomipramine	Not assayed
8	Quinalbarbitone, amylobarbitone, and pentobarbitone	1200 mg
9	Amitriptyline	200 mg
	Nortriptyline	155 mg
10	Heptabarbitone	961 mg
11	Pentobarbitone	857 mg

Results

Clinical response—The clinical response of each patient is summarised in table I. The condition of nine of the 11 patients improved significantly during haemoperfusion; one patient (case 6) died after remaining in coma for three weeks; and the remaining patient showed considerable improvement four hours after the end of haemoperfusion.

Plasma drug concentrations—Table A* summarises the changes in blood concentrations of the drugs and the arteriovenous differences. Table II shows the total amount of drug removed. The clearance rates

* Copies of table A are available from the authors.

TABLE I—*Details of patients and their responses to treatment*

Case No	Age and sex	Drugs taken	Condition	Duration of perfusion (h)	Hours after start of perfusion: Spontaneous respiration	Withdrawal of circulatory support	Response to pain	Response to command	Fully alert
1	35 M	Quinalbarbitone	Hypotensive, grade III coma, respiratory arrest	3·5	1·25	2	1	3	16
2	76 F	Amylobarbitone		6	10	12	10	24	36
3	64 F	Glutethimide, trichloral, and diazepam	Hypotensive, grade III coma, no reflexes	6 (day 1), 6 (day 2)	4	24	6	24	30
4	28 M	Phenobarbitone	Grade IV coma	3	1		1	2	8
5	60 M	Alcohol, quinalbarbitone, amylobarbitone	Unrecordable blood pressure, grade IV coma	4·5	2	3	0·5	2·5	4
6	22 F	Chloroquine	Cardiorespiratory arrest	6 (day 1), 6 (day 2)		12	4		
7	19 F	Clomipramine	Hypotensive, grade IV coma, depressed reflexes	3	1·5		1	2	2·5
8	58 M	Quinalbarbitone, amylobarbitone, pentobarbitone	Hypertensive, grade IV coma	8	Did not need ventilation		8	12	20
9	40 F	Amitriptyline	Grade IV coma	2·5	2		0·75	1·25	2·15
10	44 F	Heptabarbitone, diazepam	Grade IV coma	4	3		2	3·5	6
11	34 M	Phenobarbitone, carbromal	Unrecordable blood pressure, grade IV coma	4	2		1	1·5	3.5

TABLE III—*Calculated maximum clearances on haemoperfusion and comparative clearances of some drugs with other techniques*[5 14]

Case No	Drug	Resin haemoperfusion		Peritoneal dialysis clearance (ml/min)	Haemodialysis		Charcoal haemoperfusion	
		Clearance (ml/min)	Flow rate (ml/min)		Clearance (ml/min)	Flow rate (ml/min)	Clearance (ml/min)	Flow rate (ml/min)
1	Quinalbarbitone	220	300	9·7	65	400	} 50–120	200
2	Amylobarbitone	132	170	10·2	95	400		
3	Glutethimide	280–300	300	Minimal	90	400	125	200
4	Phenobarbitone	280–300	300	6·3	110	400	90–120	200
5	Quinalbarbitone, amylobarbitone	300	300					
6	Chloroquine	76	200					
8	Quinalbarbitone, amylobarbitone, pentobarbitone	300	300					
9	Amitriptyline	240	300					
	Nortriptyline	280	300					
10	Heptabarbitone	300	300					
11	Pentobarbitone	300	300		85	400	50–120	200

of the drugs are compared with those obtained using other techniques in table III. In many patients absorption of drug in the gut would, of course, continue, and serum concentrations may therefore be a source of confusion. Rebound effects after haemoperfusion of drugs that are strongly tissue bound—for example, glutethimide—are well known.

Blood chemistry—There were no significant differences in the blood concentrations of electrolytes, urea, calcium, glucose, cholesterol, creatinine, protein, bilirubin, alkaline phosphatase, lactate dehydrogenase, and urate before and after haemoperfusion in any patient.

Haematology—In none of the patients did problems with the formed elements of the blood cause premature termination of haemoperfusion. Most patients showed a slight to moderate fall in total platelet count. The haemoglobin concentration also fell during haemoperfusion, although, as previously reported,[13] a rise in both haemoglobin level and platelet count occurred spontaneously either during or within hours of completing haemoperfusion. Haematological values in the three patients who showed the greatest changes during haemoperfusion are recorded in fig 2. Only one patient (case 3) showed a significant fall in total leucocyte count (from 9·5 · 10^9/l to 1·9 · 10^9/l); the count spontaneously returned to the preperfusion level within 24 hours.

Complications—One patient (case 2) developed troublesome haemorrhage from her oropharynx. This was related to heparin administration and intubation and was not associated with thrombocytopenia; it was treated actively and stopped after eight hours. A second patient (case 3) passed a melaena stool after haemoperfusion and was found at endoscopy to have a small erosion within a hiatus hernia. In neither patient did haemoperfusion itself cause the complication, and no other complications were observed. Haemoperfusion was subsequently used in a patient with liver failure, where bleeding problems are much more likely, and there were no apparent ill effects.

Discussion

The R-004 haemoperfusion cartridge contains Amberlite XAD-4, which is a macroreticular resin with a specific adsorptive attraction for lipid-soluble organic molecules. We have shown its efficiency in removing short-, medium-, and long-acting barbiturates, glutethimide, amitriptyline, nortriptyline, and chloroquine. Associated complications were few: bleeding in two patients, probably due to the heparinisation. Damage to formed elements of the blood was minimal. Access to the circulation by means of a Scribner arteriovenous shunt presents no problems in a unit experienced in its use in haemodialysis for renal failure. In later cases we avoided destroying the radial vessels by percutaneous puncture with an Argyll or Medicut cannula.

Since the mortality rate of poisoned patients treated by supportive measures alone is so low, the value of active treatment to remove the drug has to be considered carefully. Conventional haemodialysis is of little value in poisoning with short-acting barbiturates, glutethimide, and tricyclic antidepressants.[14] Charcoal haemoperfusion is effective in removing barbiturates and glutethimide,[5] though resin haemoperfusion is better, and for tricyclic antidepressants resin haemoperfusion is the only method that has been shown to achieve useful clearance. In both our patients who had taken tricyclic antidepressants the rapidity of the clinical response and the reversion of the electrocardiographic abnormalities were dramatic and in strong contrast to the outcome expected in patients treated conservatively. Further experience is needed, but resin haemoperfusion promises to be a valuable method for treating severe tricyclic poisoning. Patients poisoned with barbiturates and glutethimide are less at risk of developing sudden life-threatening complications and can be kept alive during long periods of coma with assisted ventilation and other supportive measures. But these measures can themselves produce serious complications and the patients remain at risk during prolonged intensive treatment. By contrast, patients treated with haemoperfusion recovered consciousness quickly and all but one could be transferred safely to a general ward within a few hours.

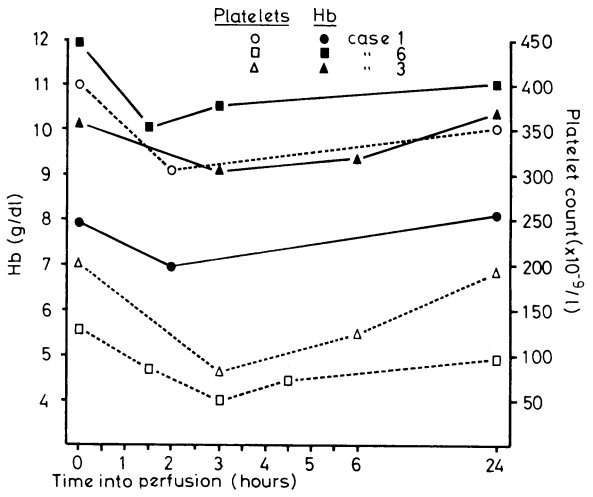

FIG 2—Haematological changes during perfusion in cases 1, 3, and 6.

We estimate that a resin haemoperfusion procedure costs £120, which is roughly the cost of 24 hours' treatment in our ITU. Since most patients selected for haemoperfusion would occupy the resources of the ITU for several days, the procedure is cost-effective. The technique is easily mastered by medical and nursing staff familiar with haemodialysis. The apparatus itself is quickly assembled and occupies less space than conventional haemodialysis equipment. Our preliminary impression is that Amberlite XAD-4 (R-004) resin haemoperfusion is a safe, efficient, and cost-effective method of treating selected patients severely poisoned with tricyclic antidepressants, barbiturates, and glutethimide. Further evaluation is needed in these and other cases of poisoning.

Copies of the unpublished table can be obtained from Dr A Trafford, Renal Unit, Royal Sussex County Hospital, Brighton BN2 5BE.

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SIDE EFFECTS OF DRUGS

Reversible malabsorption caused by methyldopa

We report a case in which a reversible histological abnormality of the small bowel with features of malabsorption was found to be related to treatment with methyldopa.

Case report

A man aged 58 years presented with a short history of diabetes mellitus, and after a right-sided hemiparesis he was found to be hypertensive. After 12 months' treatment with a thiazide diuretic, methyldopa 250 mg thrice daily was added to the regimen. Six months later he was admitted to hospital in hypoglycaemic coma (blood glucose 0·8 mmol/l (14·4 mg/100 ml)). He gave a three-month history of severe diarrhoea, and had lost 15 kg. Concentrations of both serum potassium (1·8 mmol(mEq)/l) and serum albumin (25 g/l (2·5 g/100 ml)) were greatly reduced. As his blood pressure rapidly settled, methyldopa was stopped, and after one month the diarrhoea ceased and the serum albumin (45 g/l) was normal.

Four months later his general practitioner restarted methyldopa in the same dosage and the patient again noticed slight diarrhoea which gradually increased in severity. Hypoglycaemic attacks recurred, and as a glucose tolerance test gave normal results, insulin treatment was stopped. After 10 months' treatment with methyldopa he was readmitted for investigation of diarrhoea and ankle oedema, having lost 32 kg in weight. Several of his blood values suggested malabsorption: serum calcium 1·76 mmol/l (7 mg/100 ml) (corrected for albumin of 21 g/l); serum magnesium 0·17 mmol/l; serum folate 2·4 μg/l; and serum iron 10·3 μmol/l (57·5 μg/100 ml. Xylose absorption was also abnormal (table), and barium follow-through examination showed gross dilatation of the small intestine consistent with malabsorption. The jejunal biopsy specimen, which was reviewed by three consultant pathologists, showed moderately severe partial villous atrophy, extensive inflammatory infiltrate of the mucosa and submucosa, and a giant-cell granuloma (fig).

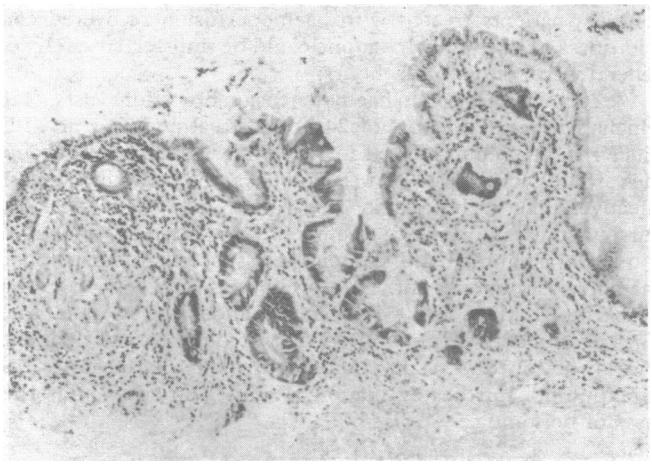
Methyldopa was again discontinued because of satisfactory blood-pressure control, and two months later the patient's malabsorption was reinvestigated. Initially he still produced up to a litre of stool per day but this settled during his admission. On this occasion most biochemical criteria, including serum albumin, serum calcium and magnesium, serum and red-cell folate, results of xylose absorption test (see table), results of ^{14}C-glycine glycocholic acid breath test, immunoglobulins, and faecal fats were normal. Results of barium-enema examination and rectal biopsy were normal, and a Coombs test and complete screen of tissue autoantibodies showed nothing abnormal. The erythrocyte sedimentation rate, however, was 35 mm in the first hour, the serum iron concentration was still reduced at 7·2 μmol/l (40·2 μg/100 ml), and a part 2 Schilling test showed a reduced absorption of vitamin B_{12} at 4·9% of the ingested dose excreted in 24 hours. His barium follow-through examination and the follow-up jejunal biopsy now gave normal results (fig). He was discharged completely fit having gained 20 kg in weight.

Results of xylose absorption test (five-hour urinary excretion of 156 mM dose) during and after methyldopa treatment

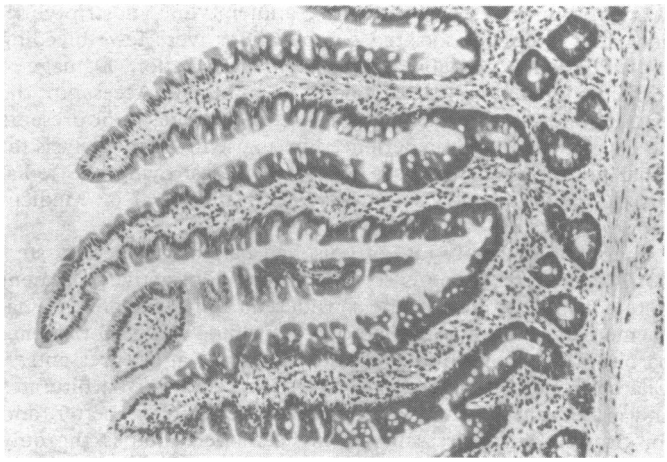
Date	Methyldopa treatment	Xylose absorption (mmol/l)*
October 1975	On treatment for 10 months	2·9
December 1975	Treatment withdrawn for 2 months	29·1
December 1976	On treatment for 3 months	2·2
February 1977	Treatment withdrawn for 2 months	21·1

*Normal range 25-30 mmol/l (375-450 mg/100 ml). *Conversion: SI to traditional units*—Xylose: 1 mmol/l ≈ 15 mg/100 ml.

Methyldopa was restarted three months later, and diarrhoea occurred within a few days. Xylose absorption (table) was again reduced. We reviewed the drug history carefully, and appreciated the relation between methyldopa treatment and the intermittent malabsorption syndrome. Methyldopa was stopped, and the patient remained in good health during 9 months' follow-up. All biochemical values, including xylose absorption (table), red-cell folate, and serum vitamin B_{12} were within the normal range, and he was having one formed motion daily.



Jejunal biopsy appearance while taking methyldopa (Haematoxylin and eosin. × 80.)



Jejunal biopsy appearance two months after drug had been withdrawn. (Haematoxylin and eosin. × 80.)