caused by measles but without a rash is generally fatal,⁷ but early diagnosis and stopping cytotoxic treatment may allow some return of immune function. Since the UKALL III regimen was modified³ fewer deaths have occurred during remissions attributable to immunosuppression. Moreover, large doses of pooled gammaglobulin may benefit children with leukaemia who have established measles.¹

The clinical and radiological features in case 3 together with the response to treatment were consistent with methotrexate pneumonia, which is characterised by fever, cough, dyspnoea and cyanosis, scattered pulmonary opacities in chest x-ray films,⁴ and usually a prompt response to steroids.⁸⁻¹⁶ Reported pathological features were also consistent.^{4, 11-14} There is no clear relation between this syndrome and methotrexate, however, as some patients improve while still taking the drug⁴ and others do not react to further challenge.⁸⁻¹⁰ Allergy¹ or a direct toxic reaction¹¹ to methotrexate has been blamed; a virus has not previously been implicated. Whether the illness in case 3 was due to primary measles infection or an abnormal reaction induced by methotrexate to latent virus is uncertain. The response to steroids implicates methotrexate.

The isolation of measles virus from case 4 one year after the initial episode of pneumonia was unexpected. Since the virus evoked no antibody response, it had possibly remained latent from the original illness. Persistence of measles virus occurs in leukaemic children⁹ and is a feature of measles inclusion-body encephalitis.¹⁵

Our findings suggest that children receiving immuno-

suppressive agents and methotrexate and infected by measles virus may develop either fulminating giant-cell pneumonia or a condition indistinguishable from methotrexate pneumonia, which responds to steroids and gammaglobulin. The factors governing the particular response are not clear.

References

- ¹ Pullan, C R, *et al*, *British Medical Journal*, 1976, **1**, 1562.
- ² Enders, J F, *et al*, *New England Journal of Medicine*, 1959, **261**, 875.
- ³ Mitus, A, *et al*, *New England Journal of Medicine*, 1959, **261**, 882.
- ⁴ Clarysse, A M, *et al*, *Journal of the American Medical Association*, 1969, **209**, 1861.
- ⁵ McLennan, I C, Peto, J, and Kay, H E M, *British Journal of Cancer*. In press.
- ⁶ Shah, K J, *et al*, *Annales de Radiologie*, 1977, **20**, 79.
- ⁷ Williams, H E, and Phelan, P D, *Respiratory Diseases in Children*. Oxford, Blackwell Scientific Publications, 1975.
- ⁸ Robertson, J H, *British Medical Journal*, 1970, **2**, 156.
- ⁹ Whitcomb, M, *et al*, *Thorax*, 1972, **27**, 636.
- ¹⁰ Schwartz, I R, and Kajani, M K, *Journal of the American Medical Association*, 1969, **210**, 1924.
- ¹¹ Filip, D J, *et al*, *Journal of the American Medical Association*, 1971, **216**, 881.
- ¹² Goldman, G C, and Moschella, S L, *Archives of Dermatology*, 1973, **103**, 194.
- ¹³ Rawbone, R G, *et al*, *British Medical Journal*, 1971, **4**, 467.
- ¹⁴ Gutin, P H, *et al*, *Cancer (Philadelphia)*, 1976, **38**, 1529.
- ¹⁵ Drysdale, H C, *et al*, *Journal of Clinical Pathology*, 1976, **29**, 865.

(Accepted 23 November 1977)

Late treatment of paracetamol poisoning with mercaptamine

JENNIFER M SMITH, W O ROBERTS, SYBIL M HALL, T A WHITE, A A GILBERTSON

British Medical Journal, 1978, **1**, 331-333

Summary and conclusions

Forty patients who had taken overdoses of paracetamol were treated with mercaptamine. Twenty-three patients given mercaptamine within 10 hours of poisoning had normal liver function tests at follow-up, and one could not be traced. In 16 patients mercaptamine was begun more than 10 hours after ingestion of paracetamol ("late" mercaptamine). Eight of these patients developed severe liver damage, which in six was moderate or severe before mercaptamine administration. Acute renal failure occurred in two patients; in one other renal function was temporarily severely impaired. At follow-up two patients were not available, and one admitted moribund had died soon after admission. The remaining 13 all had normal liver function tests.

It is concluded that late mercaptamine is not dangerous and may prevent further liver damage.

Introduction

Mercaptamine (cysteamine) appears to be highly effective in preventing liver damage after paracetamol poisoning.¹⁻³ There is evidence, however, that it may be ineffective³ or even harmful⁴⁻⁶ if started more than 10 hours after an overdose. Nevertheless, in view of the high mortality rate associated with liver failure due to paracetamol poisoning, we did not feel justified in withholding mercaptamine from patients seen more than 10 hours after they had taken a toxic dose; and we report here the results of treating 16 patients presenting 10-72 hours after the overdose.

Patients and methods

THE PATIENTS

We included 51 unselected patients in the study—34 women aged 13-60 (mean 26), and 17 men aged 19-67 (mean 29).

Gastric lavage was performed on all patients admitted from the casualty department and blood was taken for estimating the paracetamol concentration. We gave mercaptamine to 40 patients whose paracetamol concentrations fell on or above the danger line in the graph of Prescott *et al*,¹ extrapolating for those admitted more than 12 hours after taking paracetamol. The others had only general supportive treatment, and all of these recovered uneventfully. The 40 patients treated with mercaptamine were divided into two groups (see table)—

General Intensive Therapy Unit, Sefton General Hospital, Liverpool L15 2HE

JENNIFER M SMITH, FFARCS, senior anaesthetic registrar

SYBIL M HALL, BSC, FRIC, principal biochemist

T A WHITE, MSC, FRIC, senior biochemist

A A GILBERTSON, FFARCS, director of unit and consultant anaesthetist

Caernarvonshire and Anglesey General Hospital, Bangor, Gwynedd

W O ROBERTS, FFARCS, consultant anaesthetist

Details of 40 patients treated with mercaptamine for paracetamol poisoning

Case No	Dose of paracetamol (g)	Initial plasma paracetamol (mg/l) (hours after ingestion)	Mercaptamine treatment – hours after paracetamol ingestion	Maximum prothrombin time ratio	Maximum serum bilirubin (μmol/l)	SGPT (IU/l)			Complications	Other drugs taken
						On admission	Maximum	At follow-up (time after admission)		
Early mercaptamine group: patients with severe liver damage										
1	15–25	367 (3)	7.5	1.5	36		2578	12 (35 m)		
2	12.5	197 (>3)	>3	1.7	27		1616	19 (3 w)		
3	>8.13	407 (2)	5.25	2.1	16		1168	8 (16 m)		Dextropropoxyphene
Late mercaptamine group: patients with severe liver damage										
4*	7–25	290 (10)	17.5	3.9	142	275	783		Grade I hepatic encephalopathy	
5	23–35	154 (16.5)	18	3.2	72		6250	8 (25 m)		Trimipramine
6	“Bottleful”	0 (>60)	>60	1.5	27	2570	3940	17 (34 m)		Chlordiazepoxide
7	25	316 (14)	16.5	7.5	67	5697	8100	18 (4 w)	Acute renal failure	
8†	≈ 12.5	71.5 (25.5)	30	1.8	22		2026	16 (5 m)		
9	Not known	108 (10.5)	16	1.6	21	276	1958	16 (11 m)		
10	≈ 25	138 (15.5)	17.5	1.5	46	707	7935	21 (3 w)	Acute renal failure	Alcohol
11	≈ 50	208 (14)	16	10.0	110	1534	5145	22 (4 w)	Grade II hepatic encephalopathy; temporary severe renal impairment	Salicylate
Early mercaptamine group: patients without severe liver damage										
12	25	369 (3)	8	1.2	24	16	18	15 (discharge§)		
13	25	170 (7)	9	1.6	27		493	18 (4 m)		
14	14	140 (2.5)	6	2.0	9	22	22	22 (discharge)		Dextropropoxyphene
15	Not known	178 (4)	7	1.1	14		36	26 (discharge)		Dihydrocodeine
16	23.5	279 (1)	4	1.0	15	15	24	24 (discharge)		
17	14	161 (6)	9	1.3	7		12	16 (20 m)		Dextropropoxyphene
18	1–9.5	116 (6.5)	9.5	1.3	7	19	19	11 (discharge)		Salicylate
19	20	377 (1.75)	5.5	1.0	10		17	12 (discharge)		
20	≈ 25	287 (1)	9	1.3	9	53	53	19 (discharge)		
21	8–13	186 (7)	9	1.0	7		26	26 (discharge)		Dextropropoxyphene, isoxsuprine
22	≈ 50	314 (2)	6.5	1.1	9		270	17 (18 m)		Dextropropoxyphene
23	Not known	239 (3)	5	1.0	10	35	40	(Defaulted)		
24	≈ 25	200 (1)	4	1.0	14		270	18 (discharge)		Diazepam
25	Not known	204 (4)	8.5	1.1	15	36	37	11 (discharge)		
26	Not known	200 (4)	9.5	1.2	11	14	26	20 (discharge)		
27	Not known	274 (4)	9	1.1	9		22	17 (discharge)		
28	12.5	220 (4)	6.75	1.2	16	10	32	26 (discharge)		
29	30	231 (7)	9	1.3	23	14	696	23 (3 w)		
30	Not known	454 (3.5)	6.25	1.3	17	88	549	20 (4 w)		
31	Not known	357 (4)	5.75	1.0	8		117	22 (discharge)		Chlordiazepoxide
32	Not known	259 (3)	5.75	1.2	20	8	10	10 (discharge)		
Late mercaptamine group: patients without severe liver damage										
33	Not known	131 (10)	12	1.0	15		35	20 (discharge)		
34	Not known	160 (12)	15	1.0	14	14	24	24 (discharge)		
35‡	Not known	1076 (24–72)	24–72	2.9	22	289	289		Comatose, hypothermic, hypotensive on admission	
36	6.83	379 (15.5)	17.5	1.1	5	14	14	8 (discharge)		Dextropropoxyphene
37	27.5	78 (30.5)	30.5	1.3	9		56	12 (3 m)		Nitrazepam, ? amitriptyline
38	13	184 (2)	16	1.1	15	8	19	19 (discharge)		Alcohol, haloperidol
39	25	54 (12.5)	13.5	1.5	14	116	380	25 (4 w)		
40	Not known	116 (9)	11	1.1	13		29	29 (discharge)		

*Follow-up not possible. Died (from unrelated causes?) 18 months after discharge.

†Died 17 months after discharge from further overdose: SGOT still raised (39 IU/l) when last seen at 5 m.

‡Died 22 hours after admission.

§"Discharge" refers only to patients discharged within two weeks of admission.

Conversion: SI to traditional units—Bilirubin: 1 $\mu\text{mol/l}$ $\approx$ 5.85 mg/100 ml.

an "early" mercaptamine group (24 patients starting mercaptamine treatment up to 10 hours after taking paracetamol); and a "late" mercaptamine group (16 patients starting treatment more than 10 hours after taking paracetamol).

TREATMENT

Patients treated with mercaptamine had a total dose of 3.2 g (as mercaptamine base, freshly prepared) over 20 hours. They received an initial loading dose of 2 g (in 10 ml sterile water), injected intravenously over 10 minutes through a disposable bacterial filter. This was followed by three doses of mercaptamine, 400 mg in 500 ml 5% dextrose, each infused over four hours. Metoclopramide, 10 mg intramuscularly, was prescribed six-hourly for the relief of vomiting.

INVESTIGATIONS

Total plasma paracetamol concentrations were estimated in all patients by a modification of the method of Welch and Conney,⁷ which is highly specific for paracetamol.

Measurements of the total plasma paracetamol concentration were made four-hourly after admission until it had fallen to zero. Blood was taken initially for estimation of haemoglobin concentration,

packed cell volume, white cell and platelet counts, plasma urea and electrolyte concentrations, prothrombin time ratio, and (for most patients) liver function tests. These estimations were repeated daily for four days.

Results

Serum alanine aminotransferase (SGPT) concentrations over 1000 IU/l were taken to denote severe liver damage, and from 30 to 1000 IU/l mild to moderate liver damage. Nevertheless, one patient who developed a serum bilirubin concentration of 142 $\mu\text{mol/l}$ (8.3 mg/100 ml) and a prothrombin time ratio of 3.9 was considered to have severe liver damage even though her maximum SGPT was only 783 IU/l. In the late mercaptamine group liver damage was severe in eight patients and mild to moderate in four, while in the early mercaptamine group it was severe in three and mild to moderate in 11. The only death occurred in the late mercaptamine group. The patient was admitted moribund and died 22 hours later with failure of multiple systems but with only moderate liver damage.

Two patients treated with mercaptamine 16½ and 17½ hours after taking paracetamol developed acute renal failure. Their amino-transferase concentrations were the highest in the series. One was an 18-year-old girl who developed renal failure three days after the

overdose. The renal failure was treated with haemodialysis. Her SGPT on admission, before mercaptamine therapy, was 5697 IU/l, rising to a maximum of 8100 IU/l on the second day with a prothrombin time ratio of 7.5. She was discharged home four weeks after admission with normal liver and renal function tests.

The other patient, a 21-year-old woman who had evidence of moderate liver damage on admission, developed a maximum SGPT of 7935 IU/l and renal failure three days after taking an overdose of paracetamol in conjunction with alcohol. She was treated with peritoneal dialysis. Liver and renal function tests had returned to normal three weeks later when she was discharged, but an intravenous pyelogram at the time showed an abnormal caliceal pattern suggesting renal papillary necrosis.⁸ The pyelogram was normal, however, when repeated later. This patient was back at work within a month of discharge.

One patient who developed severe liver damage that led to grade III hepatic encephalopathy⁹ also had severe renal impairment but did not need dialysis. Twelve patients whose liver function had not returned to normal by the time they were discharged were recalled for follow-up. One patient (in the early mercaptamine group) could not be traced, one had died from a subsequent overdose, and a third had died in unknown circumstances. The other nine had normal liver function tests and all were clinically well.

As in other series,^{1-2,10} mercaptamine caused nausea, vomiting, and drowsiness; but these were transient. Electrocardiogram tracings showed no serious abnormalities.

Discussion

Fully developed hepatic failure still carries a bad prognosis. Sixty-six patients died in fulminant hepatic failure due to paracetamol poisoning in England and Wales in 1975.¹¹ In one series of 24 cases of fulminant hepatic failure,¹² of which 16 were due to an overdose of paracetamol, the survival rate was only 33%. In a series of 60 patients poisoned with paracetamol before the advent of mercaptamine, 49 developed liver damage and 12 died in fulminant hepatic failure.¹³

Early treatment with mercaptamine seems to be highly effective in preventing liver damage after paracetamol poisoning or reducing its severity.¹⁻³ But the risk of liver damage and the need for mercaptamine are difficult to assess in the individual case.¹¹ About 15 g of paracetamol is probably a toxic dose for normal people,¹⁴ and 10 g in those whose drug-metabolising enzymes have been subject to enzyme induction¹⁵; but liver damage has been reported after as little as 5.8 g.¹⁶ Moreover, the dose cannot be reliably assessed from the history in poisoned patients¹⁷; we could get no idea of the dose in 13 cases.

Prescott and his colleagues¹ therefore proposed a graph relating plasma concentrations of unconjugated paracetamol to the time after the overdose as a basis for predicting liver damage. We used their danger line in selecting patients for mercaptamine treatment. But as we measured total rather than unconjugated plasma paracetamol we probably included some who were not at risk. In view of the high mortality resulting from liver failure, however, we preferred to overestimate the need for treatment.

Mercaptamine given more than 10 hours after an overdose of paracetamol has been suggested to be not only valueless³ but potentially harmful.⁴⁻⁶ During metabolism of a toxic dose, the reactive intermediate compound, formed as a result of microsomal oxidation of the drug by cytochrome P-450 mixed function oxidase, is conjugated initially with hepatic reduced glutathione. Once 70-80% of the glutathione has been used up, any intermediate metabolite that remains becomes covalently bound to liver cell proteins. The extent of the ensuing hepatic cell necrosis is commensurate with the degree of binding.¹⁸⁻²¹

Mercaptamine appears to act either by inhibiting the microsomal oxidation of paracetamol,²²⁻²³ thereby preventing the formation of the reactive intermediate compound, or by combining with the reactive metabolite¹⁴ and rendering it non-toxic. Unconjugated paracetamol in the plasma many hours after ingestion²⁴ could be expected to act as a continuing source of the toxic intermediate metabolite, which in the absence of available glutathione would bind to liver cell proteins and cause further

damage to liver cells. If this hypothesis is correct, mercaptamine should prevent or reduce the severity of further liver damage from any remaining unconjugated paracetamol however long after the overdose it is started.

We treated 16 patients with mercaptamine more than 10 hours after the overdose. Six had biochemical evidence of moderate or severe hepatic damage when admitted to hospital, before mercaptamine was started; two of these developed acute renal failure and one grade III hepatic encephalopathy. Nevertheless, there were no deaths from hepatic failure, and 13 of the 16 patients now have normal liver function tests and are clinically well—though we cannot, of course, be certain that the late mercaptamine treatment protected this group of patients to any extent against the hepatotoxic effects of paracetamol.

Diuretics might have improved urine output in the three patients whose renal function was impaired. Such treatment, however, is not without risk. For example, in animals frusemide in large doses produces histological changes in the liver similar to those caused by paracetamol,²⁵⁻²⁸ and it may enhance any nephrotoxic effect of paracetamol. We have therefore attempted to improve renal output by plasma expansion using dextrose and electrolyte solutions, although circulatory overload may be a hazard owing to the antidiuretic effect of paracetamol.²⁹

Although this study does not show conclusively that mercaptamine prevents liver damage when given more than 10 hours after a toxic dose of paracetamol, it does indicate that late mercaptamine treatment is safe and is justified whenever there is a risk of liver damage.

We thank Mr P G W Jones and his staff in the pharmacy for preparing the mercaptamine, the renal unit's physicians for invaluable help with renal problems, the department of pathology for laboratory investigations, and the junior medical staff for help in following up the patients. We are also greatly indebted to Miss Eileen Creaby for her expert and very patient secretarial assistance.

Requests for reprints should be addressed to AAG.

References

- Prescott, L F, *et al*, *Lancet*, 1974, **1**, 588.
- Hughes, R D, Trewby, P, and Williams, R, *Lancet*, 1976, **1**, 536.
- Prescott, L F, *et al*, *Lancet*, 1976, **2**, 109.
- Labadarios, D, Davis, M, and Williams, R S, *Journal of International Medical Research*, 1976, **4**, suppl (4), 145.
- Lancet*, 1975, **2**, 1189.
- British Medical Journal*, 1977, **2**, 481.
- Welch, R M, and Conney, A H, *Clinical Chemistry*, 1965, **11**, 1064.
- Krikler, D M, *British Medical Journal*, 1967, **2**, 615.
- Trey, C, Burns, D G, and Saunders, S J, *New England Journal of Medicine*, 1966, **274**, 473.
- Douglas, A P, Hamlyn, A N, and James, O, *Lancet*, 1976, **1**, 111.
- Gazzard, B G, *et al*, *Postgraduate Medical Journal*, 1977, **53**, 243.
- Silk, D B A, *et al*, *Lancet*, 1977, **2**, 1.
- Clark, R, *et al*, *Lancet*, 1973, **1**, 66.
- Mitchell, J R, *Clinical Pharmacology and Therapeutics*, 1974, **16**, 676.
- Emby, D J, and Fraser, B N, *South African Medical Journal*, 1977, **51**, 208.
- Fernandez, E, and Fernandez-Brito, A C, *New England Journal of Medicine*, 1977, **296**, 577.
- Matthew, H, *British Medical Journal*, 1971, **1**, 519.
- Mitchell, J R, *et al*, *Journal of Pharmacology and Experimental Therapeutics*, 1973, **187**, 185.
- Jollow, D J, *et al*, *Journal of Pharmacology and Experimental Therapeutics*, 1973, **187**, 195.
- Potter, W Z, *et al*, *Journal of Pharmacology and Experimental Therapeutics*, 1973, **187**, 203.
- Mitchell, J R, *et al*, *Journal of Pharmacology and Experimental Therapeutics*, 1973, **187**, 211.
- Harvey, F, and Goulding, R, *Lancet*, 1974, **2**, 1082.
- Harvey, F D, and Levitt, T E, *Journal of International Medical Research*, 1976, **4**, suppl (4), 130.
- Prescott, L F, *et al*, *Lancet*, 1971, **1**, 519.
- Mitchell, J R, *et al*, *Nature (London)*, 1974, **251**, 508.
- Mitchell, J R, Potter, W Z, and Jollow, D J, *Federation Proceedings*, 1973, **32**, 305.
- Potter, W Z, *et al*, *Federation Proceedings*, 1973, **32**, 305.
- Thorgeirsson, S S, *et al*, *Federation Proceedings*, 1973, **32**, 305.
- Nusynowitz, M L, and Forsham, P H, *American Journal of the Medical Sciences*, 1966, **252**, 429.

(Accepted 21 November 1977)