MEDICAL PRACTICE

Occasional Review

Factors contributing to mortality in paracetamol-induced hepatic failure

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Abstract

Fifty patients with fulminant hepatic failure from paracetamol overdose were reviewed retrospectively to determine whether there had been any avoidable delays in treatment with protective agents, or other preventable factors which could contribute to the high mortality. Only nine were admitted to the local hospital early enough (within 12 hours) to benefit from protective agents, and only three of these were treated. Treatment was delayed in two patients while the results of plasma paracetamol concentrations were awaited. Signs of grade 3 hepatic encephalopathy were never found until 72 hours after the overdose, and sudden deterioration in consciousness at an earlier stage was due either to the sedative effects of drugs or to hypoglycaemia, which in one patient went unrecognised for 24 hours. A rapid deterioration in prothrombin time, which became prolonged by at least 25 seconds at 48 hours, preceded the onset of grade 3 encephalopathy, and this is the time at which transfer should be arranged to avoid the danger of brain-stem coning. This occurred more rapidly in those transferred at a later stage of their illness.

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Introduction

Since 1966, when the first cases of paracetamol overdose leading to fulminant hepatic failure (FHF) were reported,[1 2] much has been learnt about the clinical course, the mechanism of toxicity,[3 4] and the efficacy of the protective agents cysteamine, methionine,[5] and the more recently introduced N-acetyl cysteine.[6] Despite this, the number of deaths due to paracetamol overdose has not fallen, with 146 in 1977[7] and 190 in 1978,[8] the last year for which figures are available. Furthermore, the popularity of paracetamol as a suicidal agent has spread to other parts of the world, with instances being reported from the USA,[9] Europe,[10] and Australia.[11]

In the present study case histories of 50 consecutive patients with severe liver damage from paracetamol were analysed retrospectively to determine whether there had been any avoidable delays in treatment or other possible preventable factors in the early course that could have contributed to the high mortality.

Patients and methods

The 50 patients were admitted over the two-year period January 1978-December 1979. All had severe hepatic necrosis, as shown by considerably raised serum aspartate transaminase (5200±4100 IU/l) and serum bilirubin concentrations (95±40 μmol/l) on the third day after ingestion and by the development of grade 4 hepatic encephalopathy.[12] There were 17 men and 33 women with a mean age of 30±9 years (SD). This was the first suicidal gesture in 42 patients, while eight had taken a previous overdose, and three of these were still under psychiatric care. The reported quantity of paracetamol ingested ranged from 10-100 g, and 11 patients had taken 50 g or more (table I). Plasma paracetamol concentrations were measured in 27 patients and in all instances fell above a line on a semilogarithmic plot joining the values of 200 μg/ml at four hours and 50 μg/ml at 12

hours, the "high-risk" category of Prescot *et al.*[13] All patients had been admitted initially to local district or regional hospitals.

After admission to the liver unit, patients received full supportive care,[14] with additional use in 45 patients of daily periods of liver support, using either haemodialysis (polyacrylonitrile), or, in the more recently treated patients, charcoal haemoperfusion (Haemacol 100) together with prostacyclin as a platelet protective agent.[15]

TABLE I—*Clinical data of 50 patients*

	Survivors	Patients who died
Men	5	12
Women	11	22
Age (years)	32±9	27±9
Paracetamol dose (g)		
10-25	3	12
25-50	6	6
50-100	4	11
Not known	3	5

TABLE II—*Effects of travel in relation to degree of encephalopathy at start of journey*

	Grade of encephalopathy 0-2	3-4
No of patients	28	22
Median and range of distances travelled (miles	80 (5-210)	80 (5-200)
Deterioration in level of consciousness during travel	4	14*
Median time from signs of grade 3 encephalopathy to brainstem coning (hr)	96 (24-110)	48** (10-96)
No of survivors	12 (43%)	4 (18%)

*$p \leq 0.001$.
**$p \leq 0.05$ (Chi-square).

Results

The time between ingestion of paracetamol (assessed from evidence by patients or their relatives) and admission to the local hospital varied widely between three and 72 hours. Only nine patients were admitted within the first 12 hours, the period during which protective agents need to be administered. Of the remainder, nine were admitted between 16 and 24 hours, 28 between 24 and 48 hours, and four as long as 48-72 hours after the overdose. Plasma paracetamol concentrations were measured in all nine patients presenting in the first 12 hours and were in the high-risk category, yet only three were given a protective agent (methionine). In two other patients methionine was given at 24 and 30 hours respectively, apparently due to a delay in obtaining the results of plasma paracetamol concentrations. No protective agents were given to the other four for reasons that were not apparent. Methionine was given to four additional patients who were admitted very much later after the overdose—three of them at 20 hours and the other at 48 hours.

In two instances case records indicated denial of a drug overdose at the time of admission, although evidence for this was later obtained from relatives in one patient and from a suicide note left by the other. Both had complained of abdominal pain and were admitted to surgical wards with a provisional diagnosis of an acute abdominal emergency. One patient underwent a laparotomy and failed to regain consciousness, dying five days later; blood taken preoperatively subsequently showed a high paracetamol concentration.

Deterioration in the level of consciousness was the commonest reason for referral to King's College Hospital. This was not always due to progression of hepatic encephalopathy. In two patients it was related to the effect of diazepam and dextropropoxyphene (in Distalgesic) respectively taken at the same time as the paracetamol and occurred within the first 12 hours. Sudden deterioration in consciousness occurred between 24 and 72 hours in six patients and was due to hypoglycaemia. In each instance conscious level improved after treatment with intravenous glucose, although hypoglycaemia went unrecognised for 24 hours in one patient. Evidence of grade 3 hepatic encephalopathy (when the patient sleeps most of the time, may show aggressive behaviour, but still responds to vocal commands) was never found before 72 hours (33 patients between 72 and 96 hours, 16 between 96 and 120 hours, and one between 120-144 hours). Deterioration to grade 4 hepatic encephalopathy (when patient becomes unresponsive to vocal commands but may respond to painful stimuli) occurred over the subsequent 24-48 hours.

A considerably higher number of patients transferred at a time when signs of grades 3-4 encephalopathy were already evident appeared to have been adversely affected by the journey than those transferred at the earlier stage of grades 0-2 encephalopathy (table II). Five patients with grade 4 hepatic encephalopathy suffered brain-stem coning (with sudden respiratory arrest and fixed dilated pupils) during or immediately after transfer. A further patient needed endotracheal intubation in the ambulance because of respiratory difficulty. To determine whether deterioration was due to rapid progression of the illness or to movement of the patient, the time from the appearance of first signs of grade 3 hepatic encephalopathy to the episode of brain-stem coning was compared. This was significantly shorter when patients were transferred later (table 2). The severity of hepatic necrosis, assessed by the maximum rise in prothrombin time, and the distance travelled were the same in both groups. Only 18% of those referred late survived, as compared with 43% of those transferred in grades 1-2 hepatic encephalopathy (table II). The prothrombin time became prolonged by at least 25 seconds at 48 hours and 39 seconds at 72 hours in all patients who progressed to grade 4 encephalopathy.

Discussion

Most (82%) of these patients with severe liver damage arrived too late—that is, after 12 hours—at the local hospital for protective agents to be of benefit. The delay in seeking help may reflect a more determined suicidal intent, although in studies of self-poisoning with other drugs no correlation has been found between the seriousness of suicidal intent and the severity of the resulting illness.[16] Furthermore, in a previous study from our unit,[17] most of the patients who took a paracetamol overdose did so as an impulsive act.

More serious is the fact that over half the patients seen early enough to benefit from protective agents did not receive them, or received them too late to benefit. Further evidence for lack of awareness of the proper use of these compounds was the administration of methionine to four patients who presented after 16 hours. The efficacy of protective agents diminishes when administered later than 10-12 hours after the overdose,[5,6] and the giving of oral methionine to patients with established hepatic damage may precipitate encephalopathy.[18]

Protective agents are currently recommended only for patients falling in the high-risk category. The delay in their administration to two patients, however, highlights the undesirability of withholding treatment while waiting for the results of the plasma paracetamol concentration. This applies especially to patients presenting six to eight hours after overdose, and it is safer to administer protective agents immediately, and to stop them if plasma paracetamol concentrations are below the high-risk values (table III). If an emergency laboratory service is not available a guide to the paracetamol concentration may be obtained in the casualty department using a simple test kit.[19,20] N-acetyl cysteine given intravenously is probably preferable to oral methionine, although more expensive, as vomiting is common during the early hours of the overdose.

It is also important to differentiate between stupor due to grade 3 hepatic encephalopathy, which occurred in all patients after 72 hours from the overdose, and sudden deterioration of consciousness, which was seen at an earlier stage. Within 12

TABLE III—*Management of patient suspected of severe paracetamol poisoning*

Time from overdose	
	1 Give protective agent at once
<12 hours	2 Await blood paracetamol concentration
	3 Watch for depressed consciousness due to other drugs
>12 hours	Full supportive care[14]
>24 hours	Monitor for hypoglycaemia
48 hours	If prothrombin time prolonged >25 secs consider transfer to special unit

hours this was due to the sedative effect of other drugs taken at the same time. With the increasing use of dextropropoxyphene/paracetamol (Distalgesic) in suicide attempts, the early onset of coma and respiratory depression from propoxyphene represents a greater threat than the later onset of hepatic damage from paracetamol. At a later stage (24-72 hours after overdose) hypoglycaemia may cause sudden deterioration in consciousness; its occurrence in six patients emphasises the need for prophylactic infusions of dextrose and four to six hourly monitoring of blood glucose concentrations by Dextrostix.

The timing of transfer for further treatment of fulminant hepatic failure is clearly important in view of the more rapid deterioration and earlier onset of brain-stem coning in those patients who were transferred late in the course of their illness. Cerebral oedema is a frequent development in hepatic encephalopathy, being found at necropsy in 80% of those who die.[21] In neurosurgical patients with cerebral oedema, procedures such as physiotherapy and movement of the patient have been shown to cause a rise in intracranial pressure[22]; a similar mechanism may account for the deleterious effect of travel in patients with grade 4 hepatic encephalopathy, in whom cerebral oedema is likely to be already established. We have recently shown that institution of charcoal haemoperfusion at signs of grade 3 rather than grade 4 encephalopathy gives a better survival rate.[23]

If safe transfer is to be achieved for those patients likely to develop severe liver damage reliable techniques for their recognition at an early stage are needed. Various methods have been used, including the height of serum bilirubin at 72 hours,[24] plasma paracetamol half-life,[13] and the ^{14}C aminopyrine breath test.[25] The latter investigation appears to have good predictive value but is not readily available at most hospitals. The prothrombin time is simple, inexpensive, and readily available, and in our experience provides a good guide to those who are at risk of developing grades 3-4 encephalopathy. In the present patients with severe liver damage it was prolonged by at least 25 seconds at 48 hours, and this is when transfer should be arranged.

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References

1 Davidson DGD, Eastham WN. Acute liver necrosis following overdose of paracetamol. *Br Med J* 1976;ii:497-9.
2 Thomson JS, Prescott RF. Liver damage and impaired glucose tolerance after paracetamol overdosage. *Br Med J* 1966;ii:506-7.
3 Mitchell JR, Jollow DJ, Potter WZ, *et al.* Acetaminophen-induced hepatic necrosis. I Role of drug metabolism. *J Pharmacol Exp Ther* 1973; **187**:185-94.
4 Jollow DJ, Mitchell JR, Potter WZ, *et al.* Acetaminophen-induced hepatic necrosis. II Role of covalent binding in vivo. *J Pharmacol Exp Ther* 1973;**187**:195-202.
5 Crome P, Volans GN, Vale JA, *et al.* Oral methionine in the treatment of severe paracetamol (acetaminophen) overdose. *Lancet* 1976;ii:829-30.
6 Prescott LF, Illingworth RN, Critchley JAJH. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *Br Med J* 1979;ii:1097-1100.
7 Office of Population Censuses and Surveys. *Mortality statistics No 4.* London: HMSO, 1977. (Series DH2.)
8 Office of Population Censuses and Surveys. *Mortality statistics No 5.* London: HMSO, 1978. (Series DH2.)
9 Black M. Acetaminophen hepatotoxicity. *Gastroenterology* 1980;**78**: 382-92.
10 Spooner JB. Paracetamol-induced hepatic damage—worldwide extent of the problem. In: Davis M, Tredger JM, Williams R, eds. *Drug reactions and the liver.* London: Pitman Medical (in press).
11 Gilligan JE, Kemp R, Pain R, *et al.* Paracetamol concentrations, hepatotoxicity, and antidotes. *Br Med J* 1980;**280**:114.
12 Trey C, Davidson CC. The management of fulminant hepatic failure. In: Popper H, Schaffner F, eds. *Progress in liver disease.* Vol III. New York: Grune and Stratton, 1970:282-98.
13 Prescott LF, Wright J, Roscoe P, *et al.* Plasma paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. *Lancet* 1971; i:579-622.
14 Trewby PN, Williams R. In: Hanson GC, Wright PL, eds. *Medical management of the critically ill.* New York: Academic Press, 1978: 99-115.
15 Gimson AES, Langley PG, Hughes PD, *et al.* Prostacyclin to prevent platelet activation during charcoal haemoperfusion in fulminant hepatic failure. *Lancet* 1980;i:173-5.
16 Kreitman N. Psychiatric aspects of the problem of drug overdosage. In: Breckenridge AM, ed. *Topics in therapeutics.* London: Pitman, 1975: 32-4.
17 Gazzard BG, Davis M, Spooner J, *et al.* Why do people use paracetamol for suicide? *Br Med J* 1976;i:212-3.
18 Phear EA, Ruebner B, Sherlock S, *et al.* Methionine toxicity in liver disease and its prevention by chlortetracycline. *J Clin Sci* 1956;**15**:93-117.
19 Kendal SE, Lloyd-Jones G, Smith CF. The development of a blood paracetamol estimation kit. *J Int Med Res* 1976;**4**, suppl 4:83-8.
20 Widdop B. The paracetamol test kit in practice. *J Int Med Res* 1976; **4**,Suppl 4:89-92.
21 Silk DBA, Trewby PN, Chase RA, *et al.* Treatment of fulminant hepatic failure by polyacrylonitrile membrane haemodialysis. *Lancet* 1977; ii:1-3.
22 Lundberg N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta Psychiatr Neurol Scand* 1960; **38**,Suppl 149:1.
23 Gimson AES, Canalese J, Langley PG, *et al. Charcoal haemoperfusion with PGI_2 in the treatment of patients with fulminant hepatic failure.* Proceedings of CELLA meeting. Berlin: Springr-Verlag, (in press).
24 Clark R, Borirakchanyavat V, Davidson AR, *et al.* Hepatic damage and death from overdose of paracetamol. *Lancet* 1973;i:66-70.
25 Saunders JB, Wright N, Lewis KO. Predicting outcome of paracetamol poisoning by using ^{14}C-aminopyrine breath test. *Br Med J* 1980; **280**:279-80.

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Should young European children living in a tropical forest environment be given anticholera vaccine?

Cholera vaccine was the first antibacterial vaccine to be introduced, yet current vaccines reduce the risk of clinical cholera by only about half and protection lasts for only three to six months. If a child does suffer from cholera despite immunisation the attack is likely to be no less severe than if he were not immunised.[1] Parents should understand that high standards of hygiene and a good water supply are more important than immunisation in preventing cholera. Nevertheless, the degree of protection obtained from cholera vaccine is still worth while for children living in an endemic area. The first dose of the vaccine should be given subcutaneously, but second and subsequent doses may be given intradermally as this often provokes less reaction. The best interval between the first and second doses is one month or more but an interval of seven days may be used if necessary. Cholera vaccine is not usually recommended for children under 1 year of age. Use the doses recommended by the manufacturer; a commonly used schedule is as in the table.

	First dose	Subsequent doses	
Age (yr)	Subcutaneous	Subcutaneous	Intradermal
1-5	0·1 ml	0·3 ml	0·1 ml
6-10	0·3 ml	0·5 ml	0·1 ml
>10	0·5 ml	1·0 ml	0·2 ml

If the child continues to live in an endemic area vaccine should be repeated at six monthly intervals; longer gaps, however, do not necessitate repetition of full primary immunisation. Very few countries now require cholera immunisation of all travellers as a condition of entry, but some still insist on an international certificate if the traveller comes from an infected area. It is entirely possible that more effective cholera vaccines will become available within the next few years.[2]

1 Joó I. *Cholera vaccines.* In: Barua D, Burrows W, eds. *Cholera.* Philadelphia: W B Saunders, 1974.
2 World Health Organisation Scientific Working Group. Cholera and other vibrio associated diarrhoeas. *Bull WHO* 1980;**58**:353-74.