Controlled trial of cysteamine and dimercaprol after paracetamol overdose

Clinical studies indicate that compounds containing a sulphydryl group protect against paracetamol-induced hepatic necrosis,[1 2] but there are few data on their relative efficacy. We report the results of the first controlled clinical trial comparing two such compounds—namely, cysteamine (mercaptamine) and dimercaprol.

Patients, methods, and results

All 52 patients (34 women, 18 men) were seen within 10 hours after paracetamol overdose. Plasma paracetamol concentrations, measured by a rapid ether extraction method, fell above a line on a semilogarithmic graph joining values of 1·3 mmol/l (200 μg/ml) two hours after ingesting the tablets and 0·5 mmol/l (80 μg/ml) 12 hours after ingestion.

After gastric lavage and institution of supportive measures patients were allocated at random to treatment with cysteamine or dimercaprol, which was started within 12 hours of overdose. Infusions of cysteamine hydrochloride, freshly prepared for each patient, were administered intravenously through a Millipore filter (0·22 μm) in a dose of 2 g in 20 ml water. A further 1·2 g dissolved in 1500 ml 5% dextrose was given over the next 20 hours. Dimercaprol was administered by deep intramuscular injection in a dose of 4 mg/kg body weight four-hourly for 24 hours, then 3 mg/kg four-hourly for 24 hours.

In addition to serial liver function tests, liver biopsies were performed on 16 patients when their prothrombin times had returned to normal. The extent of hepatic necrosis was measured quantitatively by means of a morphometric technique[3] without knowledge of the clinical background, and the results were expressed as the hepatocyte volume fraction. In 15 patients the total erythrocyte sulphydryl group concentration was estimated[4] as an index of cellular stores. Estimations were made on admission and four- to eight-hourly over the next 24 hours.

In both treatment groups the mean interval between ingestion of tablets and admission was similar (cysteamine group 4·8±1 SE of mean 0·5 hours, dimercaprol group 6·0±0·6 hours), as was the mean time between overdose and treatment (7·7±0·5 hours and 7·9±0·6 hours). There was no significant difference in mean initial plasma paracetamol concentrations (cysteamine group 2·0±0·1 mmol/l (295±19 μg/ml), dimercaprol group 1·8±0·1 mmol/l (269±17 μg/ml)).

One patient, who received dimercaprol 12 hours after overdose, died after developing fulminant hepatic failure. None of the other patients developed hepatic encephalopathy.

Peak abnormalities in serum bilirubin concentrations and prothrombin times were significantly greater in patients treated with dimercaprol than in patients given cysteamine, and the severity of hepatic necrosis found on liver biopsy was also greater in the dimercaprol group (see table). The mean erythrocyte sulphydryl group concentration was not significantly different from normal in patients receiving cysteamine (cysteamine group 7·31±1 SE of mean 1·0 mmol/l; controls 8·04±0·28 mmol/l), but was significantly reduced in the dimercaprol group (6·73±0·3 mmol/l; $P<0·01$).

Of the patients given cysteamine, all developed severe nausea and vomiting, six became drowsy, and one developed meningism, although lumbar puncture showed nothing abnormal. Patients receiving dimercaprol found the injections painful, and nine developed severe abdominal pain, which persisted throughout treatment. No permanent ill effects were associated with either regimen, however.

Comment

These results show that cysteamine affords greater protection than dimercaprol against hepatocellular necrosis after paracetamol overdose. This may be due to a higher intracellular bioavailability for cysteamine, since recipients of this compound maintained a higher erythrocyte sulphydryl group concentration than those given dimercaprol. The only death in this series occurred in a patient given dimercaprol 12 hours after overdose. We have seen two other patients who died in fulminant hepatic failure when cysteamine was given at 15–16 hours, and this emphasises the inefficacy[1] and possible danger of treatment delayed beyond about 10 hours.

We gave patients a lower dose of cysteamine (equivalent to 2·17 g cysteamine base) than that used by other workers (equivalent to 3·6 g), which may explain why biochemical abnormalities in our patients were greater than those in patients treated by Prescott *et al.*[1] There was still a high incidence of unpleasant side effects, however, and we found cysteamine inconvenient to use. Methionine appears to be a promising substitute,[5] and a controlled clinical study of its use is urgently needed.

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[1] Prescott, L F, *et al*, *Lancet*, 1976, **2**, 109.
[2] Douglas, A P, Hamlyn, A N, and James, O, *Lancet*, 1976, **1**, 111.
[3] Weibel, E R, Kistler, G S, and Scherle, W F, *Journal of Cell Biology*, 1966, **30**, 23.
[4] Ellman, G L, *Archives of Biochemistry and Biophysics*, 1959, **82**, 70.
[5] Crome, P, *et al*, *Lancet*, 1976, **2**, 829.

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Liver Unit, King's College Hospital and Medical School, London SE5 9RS
R D HUGHES, BSC, PHD, lecturer
B G GAZZARD, MD, MRCP, research fellow (present address: St Bartholomew's Hospital, London EC1)
M A HANID, MB, MRCP, research fellow
P N TREWBY, MA, MRCP, registrar
I M MURRAY-LYON, MD, MRCP, senior lecturer (present address: Charing Cross Hospital, London W6)
M DAVIS, MD, MRCP, senior lecturer and honorary consultant physician
ROGER WILLIAMS, MD, FRCP, consultant physician and director of unit

Hull Royal Infirmary, Hull, Yorkshire
J R BENNETT, MD, FRCP, consultant physician

Direct addition of small doses of insulin to intravenous infusion in severe uncontrolled diabetes

Since 1973 various techniques of low-dose insulin administration in severe uncontrolled diabetes have been described, including intermittent intramuscular injection, continuous intravenous infusion using either a syringe pump or a separate paediatric giving set, and intermittent intravenous boluses.[1]

We describe here a simpler technique in which small insulin doses are added directly to the intravenous infusion bottle without the need for added albumin to prevent adsorption to the glass or polyethylene surfaces.

Patients, methods, and results

Twenty-one patients admitted with severe uncontrolled diabetes (20 with ketoacidosis and one with non-ketotic hyperglycaemia) were studied. They

Liver function values and proportion of surviving hepatocytes (expressed as % hepatocyte volume fraction; (HVF) in patients receiving cysteamine and dimercaprol. Values are means ±1 SE of mean

	Maximum serum bilirubin concentration (μmol/l)	Maximum prothrombin time ratio	Maximum SGOT concentration (IU/l)	HVF (%)
Cysteamine group (n = 26)	24 ± 3	1·5 ± 0·13	722 ± 177	81·0 ± 4·9
Dimercaprol group (n = 26)	54 ± 14	2·1 ± 0·35	754 ± 170	61·0 ± 2·4
P (Wilcoxon's rank sum test)	<0·05	<0·05	NS	<0·01

SGOT = Serum aspartate transaminase. NS = Not significant.
Conversion: SI to traditional units—Serum bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml.