Controlled trial of cysteamine and dimercaprol after paracetamol overdose

Clinical studies indicate that compounds containing a sulphhydryl 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 technique³ without knowledge of the clinical background, and the results were expressed as the hepatocyte volume fraction. In 15 patients the total erythrocyte sulphhydryl group concentration was estimated⁴ 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 sulphhydryl 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 sulphhydryl 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 inefficacy¹ 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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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.

were aged 10 to 83 years (mean 37 ± 5) and four were newly diagnosed. Four had moderately impaired consciousness and three severely impaired consciousness. Thirteen had clinical evidence of precipitating infection. The initial plasma concentrations were as follows: glucose ranged from 17.5 to 65.0 mmol/l ($315-1171$ mg/100 ml) (mean 39.0 ± 2.9 mmol/l (702 ± 52 mg/100 ml)); plasma bicarbonate $2.0-13.0$ mmol (mEq) l (7.1 ± 0.6 mmol/l); blood urea $3.5-25.9$ mmol/l ($127-156$ mg/100 ml) (13.3 ± 1.5 mmol/l (80.1 ± 9 mg/100 ml)); plasma potassium $3.2-7.2$ mmol (mEq) l (5.0 ± 0.2 mmol/l); and plasma sodium $113-142$ mmol (mEq) l (130.4 ± 1.7 mmol/l). The arterial H⁺ concentration measured in eight patients was 69 to 118 nmol (mEq) l (95.3 ± 6.2 mmol/l).

The regimen—A loading dose of 2 units of soluble insulin was given intravenously. Soluble insulin was added direct to the drip bottle (or polyethylene container) to achieve an infusion rate of six units/h. Initial fluid replacement was given as saline (0.154 mol/l), the infusion rate of 1.0 l or 0.5 l per hour depending on the degree of dehydration. This continued until the plasma glucose concentration had fallen to an arbitrary correction level less than 15 mmol/l (270 mg/100 ml). Dextrose (50 g/l) was then substituted and the rate of insulin infusion halved to three units/h to prevent any further fall. Potassium chloride replacement was started immediately unless the initial plasma potassium was greater than 5.0 mmol/l. No patient needed treatment with sodium bicarbonate. Plasma insulin was measured in three of the newly diagnosed diabetics by specific radioimmunoassay.

The mean hourly plasma glucose concentration fall ($\pm$ SE of mean) was 5.8 ± 0.6 mmol/l (105 ± 11 mg/100 ml). It took an average of 5.2 ± 0.6 hours for the concentration to reach less than 15 mmol/l. The mean insulin dose given over this period was 32 ± 4 units (range 8–71). The mean time for correcting plasma bicarbonate (18 mmol/l or greater) was 15.2 ± 1.2 hours. The amounts of intravenous fluid given during correction of the plasma glucose and bicarbonate in the ketoacidotic patients were 3.7 ± 0.4 l and 5.8 ± 0.4 l respectively. The plasma potassium concentration was well maintained during treatment and the infusion concentration did not have to be increased above 20 mmol per 0.5 l. The cumulative amounts of potassium given at 6, 12, and 24 hours were 60 ± 5 , 85 ± 5 , and 114 ± 7 mmol, respectively. Plasma insulin in the three patients not previously treated with insulin showed an initial concentration of 10 ± 4 mU/l (range 6 to 18) with a rise to 76 ± 24 mU/l (range 45 to 124) at 2 hours and 59 ± 8 mU/l (range 46 to 72) after 4 hours. No complications occurred during treatment and all patients survived.

Comment

For several years we have treated diabetic ketoacidosis by adding insulin direct to the intravenous infusion drip bottle.² The technique has been discouraged by reports that insulin is variably adsorbed to glass or polyethylene surfaces, although this effect is offset if albumin or other protein carrier is added.³ These additives are considered unnecessary if excessively dilute insulin solution—such as results when small amounts are added to the drip bottle—are avoided and the insulin is used in concentrated solution as with a syringe pump.¹ We have shown, however, that when low-dose insulin was administered in dilute solution without the addition of albumin it was effective and insulin adsorption was not clinically important.

The rate of fall in plasma glucose concentration, the time to achieve correction of the plasma glucose, and the total amount of insulin given with our method were comparable with those with more elaborate techniques of low-dose insulin administration. In the three patients not previously treated with insulin the plasma insulin concentrations achieved were within the accepted physiological range⁴

and comparable with those obtained with the other techniques (see table).

Requests for reprints should be addressed to Dr B F Clarke.

¹ *British Medical Journal*, 1977, **1**, 405.

² Duncan, L J P, in *Textbook of Medical Treatment*, 13th edn, ed S Alstead and R H Girdwood, p 363. Edinburgh and London, Churchill Livingstone, 1971.

³ Kraggen, E W, et al, *British Medical Journal*, 1975, **3**, 464.

⁴ Sönksen, P H, et al, *Clinical Science and Molecular Medicine*, 1973, **45**, 633.

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Lithium intoxication induced by dieting and saunas

Lithium is being increasingly used for long periods in the prophylaxis of recurrent affective illnesses. It has only a small margin of safety. Serum lithium concentrations between 0.7 and 1.2 mmol/l are aimed at, yet neurological toxic effects occur with concentrations around 2 mmol/l.¹ Irreversible neurological damage has been reported after serum concentrations of 2.3 mmol/l,² and with concentrations of 4 mmol/l patients are comatose and very ill.³

Lithium may cause weight gain of 5 kg or more.¹ This is often worsened by concurrent antidepressant drugs, which also cause weight gain. When this occurs patients may be tempted to diet drastically. This may be dangerous as fluid and salt restriction cause increases in serum lithium concentrations.³ The following case illustrates this danger.

Case report

A 60-year-old man was being maintained on phenelzine, 15 mg three times daily; tryptophan, 500 mg at night; nitrazepam, 10 mg at night; and a delayed release preparation of lithium carbonate, 1 g a day. The results of serum lithium estimations seemed stable around 1.1 mmol/l. He was psychiatrically well but mildly obese.

He asked his psychiatrist if he could have treatment at a health farm for one week to lose weight. He was advised not to diet too vigorously and to

Comparison of previous low-dose insulin techniques 1973–76 with that of present study

Author ¹	Low-dose insulin technique ²	No of ketoacidotic patients	No of non-ketotic hyperglycaemic patients	Mean plasma glucose (mmol/l)	Insulin loading dose (U)	Insulin hourly dose (U)	Criterion for plasma glucose correction (<mmol/l)	Mean plasma glucose fall (mmol/l/h)	Mean time for plasma glucose correction (h)	Mean insulin dose for plasma glucose correction (U)	Plasma insulin (mU/l)
Alberti et al 1973	1	14		34.8 ± 2.8	16	5–10	16.6	5.1	6.5	43	33–92
Moseley 1975*	1	12		35.0 ± 4.1	8	3–5	11.1	5.3†	5.3†	23	§
Kitabachi et al 1976	1	24		40.2 ± 3.4	13.5	5	13.8	4.0†	6.7	45 ± 5	82 ± 13
Kidson et al 1974	2,3	7	4	28.6 ± 3.7	0.5	2.4	11.0	4.2	4.0†	10†	36–143
Page et al 1974	2	31	7	44.9 ± 3.2	0	7.2	13.8	§	§	§	50–100
Semple et al 1974	2	13		40.3 ± 4.4	6.5	6.5	16.6	5.6	6.5†	39 ± 7	75 ± 8
Soler et al 1975	2	18		37.8	0	8	13.8	§	5.9	54 ± 19	§
Campbell et al 1976	3	46	8	37.2 ± 16.1	0	2.4	11.1	3.4	8.1	§	§
Clumbeck et al 1976	4	19	4	44.5 ± 4.4	0	5	13.8	4.3	§	§	0–>600
Malleson 1976*	4	4		35.4 ± 7.5	10	4	16.6	3.4†	8.3†	35 ± 6†	68–188
Present study	5	20	1	39.0 ± 2.9	2	6	15.0	5.8	5.2	32 ± 4	45–124

*Studies in children.

†1 = Intermittent intramuscular injection. 2 = Continuous intravenous infusion with syringe pump. 3 = Continuous intravenous infusion with paediatric set. 4 = Intermittent intravenous boluses. 5 = Direct addition to infusion bottle.

†Calculated from authors' data.

§No data.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg 100 ml.