

*Clinical trial*

# Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure

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**SUMMARY** A controlled trial of 44 patients was undertaken to evaluate the use of dexamethasone (32 mg stat, 8 mg qds) in preventing, and intravenous mannitol (1 g/kg) in reversing the cerebral oedema of fulminant hepatic failure. Diagnosis of cerebral oedema was based on intracranial pressure recordings or the presence of defined clinical signs. Cerebral oedema developed in 34 patients with similar frequency in those treated with and without dexamethasone (16 of 21 and 18 of 23 respectively). In those 34 patients episodes of cerebral oedema resolved significantly more frequently in the 17 patients who received mannitol than in the 17 patients who did not (44 of 53 and 16 of 17 respectively,  $p < 0.001$ ). Dexamethasone did not affect survival but among patients who developed cerebral oedema those who received mannitol had a significantly better survival than those who did not receive it (47.1% and 5.9% respectively,  $p = 0.008$ , Fisher's one-tail test).

Cerebral oedema is well documented as a significant cause of death in patients with fulminant hepatic failure<sup>1 2</sup> and in a series from this unit was found in 80% of cases at necropsy.<sup>3</sup> The exact relation between cerebral oedema and the metabolic derangements underlying encephalopathy in hepatic failure is uncertain, but in an experimental devascularisation model of acute liver failure in the pig we found a progressive rise in intracranial pressure after surgery which was attenuated by the early administration of methylprednisolone in high doses.<sup>4</sup> Since the introduction of continuous monitoring of intracranial pressure in patients with fulminant hepatic failure we have also found that bolus doses of mannitol intravenously can lead to a temporary lowering of intracranial pressure.<sup>5</sup>

In a randomised controlled clinical trial of patients with fulminant hepatic failure and grade IV encephalopathy we have assessed the value of both dexamethasone given prophylactically and mannitol to reverse such cerebral oedema. We have also evaluated the effect on survival of these specific treatments.

## Methods

### PATIENTS

Forty-four patients were studied (17 men and 27

women; age range 16-67 years) all of whom fulfilled criteria for the diagnosis of fulminant hepatic failure.<sup>6</sup> In all patients serum aspartate aminotransferase levels were raised (mean  $\pm$  SEM =  $3900 \pm 625$ ) and the prothrombin time was prolonged (by  $97.8 \pm 7.5$  seconds). Fulminant hepatic failure was due to paracetamol-overdose in 26 patients, acute viral hepatitis in 14 (hepatitis A virus, four; hepatitis B virus, six; presumed non-A non-B hepatitis, four, and halothane-associated hepatitis in four patients (Table 1). All patients deteriorated to grade IV encephalopathy (unrousable to commands but may be responsive to painful stimuli) at differing times after admission to the Liver Failure Unit. Seven patients with evidence on admission of irreversible brain-stem damage (shown by fixed dilated pupils; absent gag, oculocephalic and oculovestibular reflexes, and no spontaneous respiration) were not included in the trial.

Treatment was based on a full supportive regimen as described elsewhere<sup>7</sup> including daily haemodialysis with a polyacrylonitrile membrane (10 patients) or haemoperfusion using a Haemocoll 100 charcoal column (Smith and Nephew Research Ltd) together with prostacyclin (PGI<sub>2</sub>) as a platelet protective agent.<sup>8</sup> Eight of the 34 patients given haemoperfusion also required haemodialysis after the development of renal failure (urine output  $< 300$  ml/24 h plasma creatinine  $> 400$   $\mu$ mol/l with a normal central venous pressure). Blood gases were

Table 1 Clinical data in different treatment groups on admission to trial (mean±SEM)

Clinical data	Dexamethasone	Dexamethasone and mannitol	Mannitol	Control
No.	11	10	10	13
Age (yr)	41±4.4	32.4±5.1	36.5±4.3	31.3±2.5
Sex M:F	3:8	5:5	4:6	5:8
Aetiology				
Paracetamol	4	5	8	9
Viral hepatitis	5	4	2	3
Halothane	2	1	—	1
SGOT (IU/l)	3600±625	3100±1200	3000±460	5700±1750
Maximum increase in prothrombin time (seconds prolonged)	123±16.5	82±15.8	107.5±19.7	87.4±13.2
Renal failure	4	6	4	6

estimated four times a day or more often when indicated, and the patient was intubated when necessary to maintain adequate oxygenation and hypocapnia with a  $p\text{CO}_2 < 4.5$  Kpa. Plasma osmolality was measured daily, before and half an hour after receiving mannitol.

#### RANDOMISATION AND TREATMENT GROUPS

Patients were randomised to four groups: dexamethasone (group 1); mannitol (group 2); dexamethasone and mannitol (group 3); neither drug (group 4). Dexamethasone (32 mg intravenously and 8 mg every six hours thereafter) was given as soon as the first signs of grade III encephalopathy (sleeping most of the time, with incoherent speech and confusion) became apparent, or on arrival if these signs were already established. It was continued until the patient regained consciousness or signs of irreversible brain-stem coning appeared. Mannitol (1 g/kg body weight) was given as a rapid intravenous infusion of a 20% solution whenever the intracranial pressure rose above 30 mmHg for more than five minutes. Transient non-sustained rises during procedures such as chest physiotherapy, medical examination, or when the position of the patient was changed were not considered an indication for mannitol administration. In the absence of intracranial pressure monitoring mannitol was given on the appearance of one or more of the following clinical signs: unequal or abnormally reacting pupils; localised or generalised myoclonus or focal fitting; progressive hyperventilation with decerebrate posturing (opisthotonus, clenched teeth, profuse sweating, adducted hyperpronated extended arms and extended legs with plantar flexed feet); fixed pupils and/or absent caloric responses but spontaneous respiration. Doses of mannitol were repeated while renal function was unimpaired but in patients in whom renal failure had developed only one dose was given.

#### INTRACRANIAL PRESSURE MONITORING

This was performed in 17 patients using either a stable drift-free subdural monitor (Gaeltec Ltd, Skye) or, in more recent cases, an extradural pressure transducer (Ladd ICP Monitor, SLE, Croydon). The monitor was inserted through either a parietal or temporal burr hole in the non-dominant hemisphere. Nitrous oxide or halothane and oxygen anaesthesia was used except for those patients in whom halothane was a possible cause of the fulminant hepatic failure, who were given a halothane-free anaesthetic. Fresh frozen plasma was administered preoperatively to minimise the chances of bleeding. In all cases informed consent was obtained from the patients' relatives; the study received the approval of the local ethical committee. Intracranial pressure was not monitored in very restless patients or in those with fulminant hepatic failure caused by hepatitis B virus.

#### STATISTICS

All results are given as mean±SEM. Comparisons were by Student's *t* test, Chi square test with Yates's correction, and Fisher's one-tailed test where appropriate.

#### Results

There was no significant difference between the four treatment groups in age, sex, and cause, or severity of the liver disease as assessed by the maximum serum transaminase levels and prolongation of the prothrombin time (Table 1). There was no statistical difference in the frequency with which renal failure developed in the four groups (Table 1). No clinical evidence of cerebral oedema was found in seven patients, and in a further three patients, in whom a monitor was inserted, no significant rises in intracranial pressure were seen during their illness. Evidence of cerebral oedema in the other 34 patients was based on continuous monitoring of

intracranial pressure in 14 and the appearance of the defined clinical signs in 20. Cerebral oedema was significantly more common in the patients randomised to the mannitol group than in the group receiving neither dexamethasone or mannitol. However, the frequency with which cerebral oedema developed showed no correlation with the cause of the fulminant hepatic failure (21 of 26 patients with paracetamol-induced hepatic necrosis and nine of 14 with fulminant viral hepatitis) or with the severity of the underlying liver disease, the mean prolongation of the prothrombin time in those with and without cerebral oedema being  $76.0 \pm 15.7$  and  $103.0 \pm 8.2$  seconds prolonged, respectively. Comparison of the figures for cerebral oedema as evidenced by a rise in the intracranial pressure or appearance of clinical signs showed no significant difference (14 of 17 patients with and 20 of 27 without intracranial pressure monitoring). In 18 patients, with either clinical signs of cerebral oedema or a raised intracranial pressure, there was a close correlation between evidence of cerebral oedema in life and findings at necropsy (swollen gyri macroscopically and tentorial or uncal herniation), whereas there was no evidence of this in the four other patients whose intracranial pressure was not raised and who had no clinical features of cerebral oedema.

DEXAMETHASONE IN PROPHYLAXIS

Of the 21 patients given dexamethasone, it had been started in seven at the stage of grade III encephalopathy and in 14 patients when grade IV encephalopathy was present but before clinical signs of cerebral oedema or a raised intracranial pressure were evident. Comparison of groups 1 and 3 (receiving dexamethasone) with groups 2 and 4 (not receiving dexamethasone) showed no significant difference in the frequency with which cerebral oedema developed (16 of 21 and 18 of 23 patients respectively) (Table 2). Episodes of raised intracranial pressure occurring in patients given dexamethasone were indistinguishable with respect to baseline pressure, rapidity of onset, or level to which the pressure rose, from episodes in those not given it.

Table 2 Development of cerebral oedema in patients treated with and without dexamethasone

	Dexamethasone (no.)	No dexamethasone (no.)
Patients	21	23
Developing cerebral oedema	16	18

EFFECTS OF MANNITOL

As dexamethasone produced no observable difference in the incidence or pattern of rises in intracranial pressure, patients in groups 2 and 3 (receiving mannitol or dexamethasone and mannitol) have been combined for analysis. Among the group 2 and 3 patients who received mannitol, cerebral oedema was considered to have developed in 17 patients; in nine on evidence from continuous intracranial monitoring and in eight on the basis of the clinical signs (Table 3).

In the nine monitored patients, mannitol caused a fall in the intracranial pressure on 27 of 33 occasions (mean pre-mannitol intracranial pressure  $44.1 \pm 1.7$  mmHg; post-mannitol intracranial pressure  $21.5 \pm 2.2$  mmHg,  $p < 0.001$  paired *t* test). Pressures fell to less than 30 mmHg on 21 of these 27 occasions; on the other occasions the degree of reduction was less (30–35 mmHg). On average three doses were effective in each patient (range one to seven doses). On the six occasions (one episode in six monitored patients) when mannitol was not effective the intracranial pressure continued to rise to a mean level of  $92.5 \pm 18.9$  mmHg when in each case clinical signs of brain-stem coning appeared in association with a respiratory arrest. In these six patients mannitol had previously been effective (on average more than two times, range one to seven times) in five, but in the other patient it was not effective on the only occasion it was given.

The administration of mannitol to the eight patients in whom intracranial pressure was not monitored was followed by reversal of the clinical signs on 17 of 20 occasions (Table 3). Before mannitol administration all patients had developed unequal or abnormally reactive pupils, with sweating, opisthotonus, and hyperventilation. On average 2.1 doses (range one to four doses) were effective in these patients. On three occasions when mannitol was ineffective the patient had a respiratory arrest with signs of brain-stem coning, although mannitol had been effective on at least two

Table 3 Effect of mannitol on resolution of cerebral oedema

	Mannitol		No mannitol	
	ICP monitor (no.)	No monitor (no.)	ICP monitor (no.)	No monitor (no.)
Patients	9	8	5	12
Episodes of cerebral oedema	33	20	5	12
Resolution	27	17	0	1
Survival	3	5	0	1

earlier occasions in each of these three patients. On the nine occasions when mannitol was not effective (in six patients with and three patients without intracranial monitoring) renal failure had developed in each of the patients concerned. This had not been present earlier in these patients at a time when mannitol was effective.

In the groups 1 and 4 not receiving mannitol infusions cerebral oedema developed in 17 of the patients. In the five monitored patients the intracranial pressure continued to rise and signs of brain-stem coning appeared. In the other 12 patients clinical signs of cerebral oedema progressed to brain-stem coning on 11 occasions. Thus spontaneous improvement was observed on only one of 17 occasions compared with 44 of 53 occasions when the mannitol was given ( $p < 0.001$  Yates's correction) (Table 3).

On all occasions when mannitol was used, serum osmolality rose (mean  $+14.8 \pm 1.32$  mosmol/l) irrespective of the effect of mannitol on the intracranial pressure or clinical signs of cerebral oedema.

#### ANALYSIS OF SURVIVAL

In the overall series, 15 (34%) of the 44 patients survived to leave hospital. Of the 10 patients with no evidence of cerebral oedema, six survived to leave hospital, whereas there were no survivors among those in whom cerebral oedema did develop and who received no treatment ( $p < 0.01$ , Fisher's one-tail test). There was no significant difference in survival rate between patients in group 1 receiving dexamethasone and those in group 4 receiving neither dexamethasone nor mannitol when either all patients or only those with cerebral oedema were considered (Table 4).

With no evidence that dexamethasone influenced rises in intracranial pressure or survival, it is possible to combine the results of group 3 patients (dexamethasone and mannitol) with those of group 2 patients (mannitol alone). Survival of patients who developed cerebral oedema in this combined group was significantly better than in the patients in the

other two groups with cerebral oedema who did not receive mannitol (eight of 17 (47.1%) and one of 17 (5.9%) patients respectively,  $p < 0.008$ , Fisher's one-tail test).

#### Discussion

This study has further demonstrated the frequency and importance of cerebral oedema as a major factor in the mortality of fulminant hepatic failure. It might be questioned whether the rises in intracranial pressure as described can be extrapolated directly to cerebral oedema, because two different methods of diagnosis were used. As the frequency of cerebral oedema based on intracranial pressure monitoring was similar to that diagnosed as a result of changes in clinical signs, this is unlikely to have affected the results. Furthermore, in our patients, a rise in intracranial pressure above 30 mmHg was always followed by clinical manifestation of cerebral oedema, albeit at differing levels of intracranial pressure. The different levels of intracranial pressure at which these clinical features develop may also depend on other parameters such as blood pressure, cerebral perfusion pressure, and cerebral blood flow.<sup>9</sup>

The beneficial effects of mannitol are evident in these patients in reducing the intracranial pressure and reversing clinical features of cerebral oedema. Mannitol acts by increasing blood osmolality, drawing fluid along an osmotic gradient from brain to blood.<sup>10</sup> As mannitol depends on an intact blood brain barrier, its efficacy in these patients suggests that the cerebral oedema of fulminant hepatic failure is predominantly of the cytotoxic type<sup>11</sup> with accumulation of fluid and water in the intracellular space rather than the vasogenic variety resulting from damage to the blood brain barrier. Although Livingstone *et al*<sup>12</sup> have shown evidence of the latter in hepatectomised rats, post mortem studies in the pig model of fulminant hepatic failure<sup>4</sup> and in a patient with Reyes syndrome<sup>13</sup> would suggest the former. The lack of effect in our patients with renal failure remains unexplained. Uraemic toxins *per se* are damaging to the blood brain barrier<sup>14</sup> and together with those found in liver failure may prevent the development of an effective osmotic gradient down which water will pass. Furthermore, in these patients the absence of an osmotic diuresis may result in an increase in intravascular (and thus intracranial) blood volume after mannitol infusion sufficient to counteract any removal of fluid from the brain tissue.

Although in an animal model of liver failure methylprednisolone was effective in slowing the rate of rise in intracranial pressure<sup>4</sup> and dexamethasone

Table 4 Survival of patients with and without cerebral oedema in different treatment groups

Treatment group	Cerebral oedema	No cerebral oedema
Control	0/8	4/5
Dexamethasone	1/9	1/2
	p 0.008	
Dexamethasone and mannitol	3/7	1/3
Mannitol	5/10	—

has been shown to be effective in reducing peritumoural cerebral oedema of the vasogenic type,<sup>9</sup> we have been unable to show any benefit in this trial. The mechanism by which glucocorticoids reduce or prevent cerebral oedema is unknown, although they are known to be more effective in oedema that is focal and chronic than the more diffuse and acute varieties<sup>9</sup> that are found in fulminant hepatic failure. Furthermore, the disparity between the sudden precipitate rises which occur in the clinical situation and the slow almost linear rises seen in the animal model was well shown in the present study. Methylprednisolone was also given just before or immediately after surgery in the animal model and the timing in the clinical situation cannot be considered to be comparable. The failure of dexamethasone to influence survival is in keeping with the three controlled clinical studies of corticosteroids which have been carried out in patients with fulminant hepatic failure<sup>15-17</sup> in which no beneficial effect could be demonstrated.

The fact that reversal of cerebral oedema was associated with an improved survival rate does not imply that mannitol when given alone would give results similar to those obtained in this study in conjunction with the other treatments used such as haemoperfusion. Furthermore, the treatment over a period of days of other less acute complications – for example, fluid balance, renal failure and sepsis – the effects of which are not apparent in the control group owing to the development of cerebral oedema, may be revealed only when the acute and usually irreversible effects of sudden changes in intracranial pressure are prevented.

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