Clinical trial

Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis

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SUMMARY The efficacy of methylprednisolone (1 g daily for three days), which is effective in reversing transplant rejection, was assessed in a randomised controlled trial of 55 patients with severe acute alcoholic hepatitis, 34 of whom had encephalopathy. The clinical progress, frequency of bleeding and sepsis, and cause of death were similar in the treatment (27 patients) and control groups (28 patients). There was no significant difference in mortality rate between the two groups: 57% of the control group and 63% of the treatment group died during the study. Patients' survival depended on the presence or absence of the following features: encephalopathy, serum bilirubin concentration more than 340 $\mu\text{mol/l}$, serum creatinine concentration more than 250 $\mu\text{mol/l}$, and histological evidence of cirrhosis as well as severe acute alcoholic hepatitis.

In addition to the direct toxic effects of alcohol, immunological mechanisms may also be involved in the pathogenesis of acute alcoholic hepatitis.¹⁻³ Thus patients are sometimes treated with corticosteroids, although the efficacy of this approach remains uncertain. Of a total of nine studies⁴⁻¹² only three^{4, 9, 11} have shown a significant improvement in survival with corticosteroids. One of the factors responsible for the conflicting results of these previous studies may be related to the wide range in severity of alcoholic hepatitis. Therefore in this study we have included only the most severely ill patients. In previous trials only standard doses of prednisolone (up to 100 mg/day or its equivalent corticosteroid) were given, usually for a four to six week period. Apart from their anti-inflammatory effects, corticosteroids, at least in high doses, also inhibit T cell function and, as cellular immune responses to autologous and homologous liver antigens have been found in alcoholic hepatitis,^{1,3} we have prescribed large doses of methylprednisolone for three days only, a regimen which is effective in reversing acute (cell-mediated) rejection of renal transplants.¹⁴

Methods**PATIENTS**

Sixty patients who had been referred from other

hospitals because of the severity of their illness were entered into the trial. For entry, patients had to satisfy the following criteria: a history of alcohol intake of about 80 g or more daily for at least five years, a serum bilirubin concentration greater than 80 $\mu\text{mol/l}$ (normal up to 20 $\mu\text{mol/l}$), a serum aspartate transaminase level at least twice the upper limit of normal (normal up to 40 IU/l), and a prothrombin time prolonged by at least nine seconds.

The presence of complications such as gastrointestinal bleeding, renal failure, and sepsis did not invalidate entry. However, patients with hepatoma and those with other diseases such as recent myocardial infarction, an accompanying cerebrovascular accident including evidence of subdural haematoma, and active tuberculosis were excluded. Informed consent for entry into the trial was obtained from the patient or more often from the next of kin.

Patients were allocated by random sealed envelope technique to a control or treatment group, the latter receiving intravenous methylprednisolone 1 g daily for three days. Of the 60 patients who satisfied the entry criteria, one in the treatment group and four in the control group were excluded from the final analysis because subsequent findings in four cases cast doubt on the initial diagnosis, and one patient was later found to have been given corticosteroids at the referring hospital. Thus there were 27 patients in the treatment and 28 in the control group.

Patients who were too ill to take the standard hospital diet received a minimum of 2000 calories as intravenous 20% glucose. Encephalopathy was treated with protein restriction (maximum of 20 g/day), lactulose (15–30 ml twice daily), and daily magnesium sulphate enemas.

Effects of treatment were assessed by comparing the survival times of treatment and control groups and by following changes in liver function tests carried out on entering the trial and weekly or twice weekly thereafter. Liver biopsy was performed after clinical improvement or immediately post mortem.

STATISTICAL ANALYSIS

Clinical differences on entry to the trial were assessed by Fisher's exact test. Differences in liver function and haematological tests between the two groups and within groups were assessed by *t* tests. To justify use of the *t* tests, each set of data was first converted to a symmetrical distribution by taking logarithms. Differences in survival between the two groups were assessed by the log rank test. Failure to recognise a beneficial effect of treatment is known as type II or B error.^{15 16} We assessed the likelihood of avoiding this error by drawing a graph relating the chance of detecting a difference between the two groups to the possible differences in survival between the two groups (Figure).

Results

On entry to the trial, patients in the two groups did not differ significantly in any of the nine clinical features analysed (Table 1). There was little difference between the groups in the mean length of stay in hospital (treatment group 24.2 days, and control group 28.1 days).

Assessment of survival by means of life table and log rank tests showed no significant difference between the two groups: 57% of the control group and 63% of the corticosteroid group died during the study.

There was no significant difference in biochemical and haematological findings between the two groups either on entry or at 10 days post-randomisation (Table 2). In addition, within each group, there was no significant change after 10 days in the liver function tests or prothrombin time. However, in the corticosteroid group the white blood cell count and in the control group the serum creatinine concentration value were significantly higher at 10 days than on entry to the trial.

FACTORS DETERMINING PROGNOSIS

Mortality was related to massive upper gastrointestinal bleeding in 41% of the corticosteroid group and

Figure Power curve relating the chance of detecting a difference in survival between the treatment and control groups to the possible differences in survival between the two groups.

Table 1 Clinical features of patients with acute alcoholic hepatitis on entry into trial

Feature	Methylprednisolone group (27)		Control group (28)	
	No.	%	No.	%
Sex				
Men	19	70	12	43
Women	8	30	16	57
Spider naevi	27	100	25	89
Palmar erythema	18	67	20	71
Pyrexia	7	26	4	14
Liver tenderness	4	15	6	21
Hepatomegaly	22	74	24	86
Ascites	25	93	21	71
Encephalopathy	20	74	14	50
Splenomegaly	9	33	6	21

21% of the control group. This was mostly variceal in origin, although five patients in the corticosteroid group and one in the control group had peptic ulceration shown either by endoscopy or at post mortem or both; these differences were not statistically significant. Seven corticosteroid patients and six control patients had septicaemia and two patients from each group had pancreatitis.

Table 2 Laboratory data (range and median)

	Methylprednisolone		Control group	
	On entry	At 10 days	On entry	At 10 days
Haemoglobin (13.4–17.3 g/dl) *	8.0–15.2 (11.5)	7.0–15.7 (11.6)	5.7–14.8 (12.5)	7.9–13.9 (11.3)
White cell count (2800–11 200)*	5.8–23.1 (10.7)	6.3–29.0 (14.3)	3.0–30.7 (15.2)	6.2–42.2 (17.0)
Prothrombin time (s prolonged)	9–20 (10)	4–80 (13)	5–20 (11)	3–27 (10)
Serum creatinine (45–105 μ mol/l) *	60–260 (100)	40–560 (115)	40–1080 (115)	40–1000 (197)
Albumin (35–50 g/l) *	19–38 (25)	18–39 (25)	22–46 (28)	19–40 (31)
Bilirubin (3–20 μ mol/l)*	83–700 (188)	72–630 (169)	84–900 (300)	45–880 (332)
Alkaline phosphatase (30–85 IU/l)*	68–480 (204)	85–144 (197)	106–424 (242)	104–413 (201)
Aspartate transaminase (10–50 IU/l)*	80–500 (177)	50–1600 (164)	85–1800 (149)	77–500 (118)

*Normal ranges.

Of the patients with encephalopathy, 94% of those in the corticosteroid group and 69% of those in the control group died, the difference not being statistically significant. However, when all patients with encephalopathy were considered, the mortality of those with this feature was significantly higher than the mortality of those without it (79% vs 29%, $P < 0.001$). Similarly, the mortality in those with renal failure (serum creatinine $> 250 \mu\text{mol/l}$) was not significantly different in the corticosteroid and control groups, but a significantly higher proportion of patients with renal failure died (96% with renal failure and 25% without, $P < 0.001$). The level of serum bilirubin also seemed to be an important prognostic factor. Thus 79% of those with a serum bilirubin greater than $340 \mu\text{mol/l}$ died compared with 36% of those with a value less than $340 \mu\text{mol/l}$, the difference being significant ($P < 0.01$).

Histological assessment in 24 patients in the corticosteroid and 26 in the control group showed that 74% of the corticosteroid patients and 81% of the controls had features strongly suggestive of cirrhosis in addition to those of a severe acute alcoholic hepatitis. The mortality rate in those with histological evidence of cirrhosis was significantly higher than the rate in those without such evidence (77% vs 27%, $P < 0.01$).

Discussion

The corticosteroid regimen adopted in this study is known to be effective in controlling acute rejection of renal transplants.¹³ If immune reactions to alcohol-

altered liver cell antigens are of major importance in the pathogenesis of liver cell damage in acute alcoholic hepatitis then survival should have improved. The lack of such an effect, with 57% of the control group and 63% of the corticosteroid group dying during the study, is in agreement with six of the nine previous controlled studies, although these are not strictly comparable with our study because of differences in the corticosteroid regimens. Some workers have found that, although corticosteroids do not improve survival, they do, nonetheless, improve the albumin level and hasten the fall in serum bilirubin^{11 12} but such changes were not seen in our patients.

Our results cannot be explained by differences in complications between the two groups. It can, however, be argued that the number of patients in each group was too small to provide a firm conclusion.

The Figure shows the likelihood of avoiding a B error. If we assume a mortality rate of about 60% in a population of patients similar to those in the trial, then with the number of patients studied there was a 43% chance of detecting a 20% difference in survival between the two groups.

Davidson¹⁷ considered that treatment with corticosteroids was most likely to be effective 'in a group of patients neither so ill that their fate is already sealed nor yet so well that they would recover anyway'. However, others have suggested that corticosteroids should be reserved for severely ill patients^{4 11 18} and our patients were in this category. Maddrey *et al.*¹¹ have described a discriminant function based on the initial serum bilirubin and prothrombin time: if

Table 3 Analysis of data in literature with respect to prognosis of patients with alcoholic hepatitis.

Author	With encephalopathy		Without encephalopathy		With cirrhosis		Without cirrhosis	
	No.	%	No.	%	No.	%	No.	%
Becket ²⁴	NS		NS		1/4	(25)	0/2	
Blitzer ⁸	3/5	(60)	8/23	(35)	NS		NS	
Campora ⁶	12/18	(67)	4/27	(15)	NS		NS	
Nepew ¹²	15/28	(54)	a		5/12	(42)	4/9	(44)
Edmondson ²⁶	NS		NS		12/14 Gr II	(86)	0	
					2/2 Gr I	(100)	1/3	(33)
Hardison ¹⁹	9/16	(56)	18/69	(26)	NS		NS	
Harinasata ²⁵ (b)	4/7	(57)	2/68	(3)	NS		NS	
Helman ⁴	7/15	(47)	0/10 Gr II		7/11	(64)	0/4	
			0/12 Gr III					
Lesessne ⁹	9/14	(64)	a		7/10	(70)	0/1	
Maddrey ¹⁰	7/15	(47)	0/40		NS		NS	
McClain ²⁷	25/42	(60)	NS		NS		NS	
Mikkelsen ²⁸ (c)	10/12	(83)	2/11	(18)	12/19	(63)	0/4	
Porter ⁵	13/16	(81)	NS		9/10	(90)	2/8	(25)
Shumaker ¹⁰	6/12	(50)	7/15	(47)	NS		NS	
Present series	27/34	(79)	6/21	(29)	30/39	(77)	3/11	(27)
Total	147/234d		47/286		85/121e		10/42e	
Percent mortality		(63%)		(16%)		(70%)		(24%)

NS: not stated.

a: all encephalopathic on admission.

b: liver biopsy group.

c: non-shunt group.

d and e: $P < 0.001$.

the value was greater than 93 or the prothrombin time prolonged more than eight seconds, the patient would almost certainly die. All the patients in our study had a discriminant value greater than 93 and a prothrombin time prolonged more than eight seconds, and yet 40% survived. We have found, as Maddrey and others have also found,^{6 11 12 19} that the serum creatinine level as well as that of the bilirubin, the presence of encephalopathy on admission, and the presence of an underlying cirrhosis are also important factors in determining prognosis.

A review of the results of several studies (Table 3) emphasises the importance of encephalopathy and/or underlying cirrhosis in determining prognosis. Certain important statistical considerations have to be taken into account when summarising results of different studies²⁰. For instance, the wide variation in mortality rates indicates that the study groups are not homogeneous and therefore should not really be assessed together. Nevertheless, when the calculations are repeated with data only from those studies with fairly consistent mortality rates, the overall conclusions can be drawn.

According to Boyer,²¹ patients with alcoholic hepatitis are most likely to benefit from corticosteroids before cirrhosis develops, but the identification of such patients may be difficult. Histological assessment showed that 78% of our patients and 57% of Depew's patients¹² had underlying cirrhosis in addition to alcoholic hepatitis. Although in most cases liver biopsy will identify those with alcoholic hepatitis who have not yet progressed to cirrhosis, we

and others have found^{22 23} that more than 95% of patients whose prothrombin time and platelet count are adequate enough to allow percutaneous liver biopsy are likely to improve with supportive care alone and do not require corticosteroids.

All available information suggests that patients with acute alcoholic hepatitis are by no means a homogeneous group, and further assessment is necessary to identify markers which can select those patients who could benefit from treatment with corticosteroids.

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