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PREDNISONE OR PREDNISOLONE FOR THE TREATMENT OF CHRONIC ACTIVE HEPATITIS? A COMPARISON OF PLASMA AVAILABILITY

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1 The plasma availability of prednisolone after oral doses of prednisolone and its precursor, prednisone, were compared in ten normal controls and twenty-five patients with chronic active hepatitis by estimation of the area under the plasma concentration–time curve for the drug (AUC).

2 In controls, values for AUC were significantly more variable after prednisone than prednisolone, and two subjects showed markedly inefficient conversion of prednisone to prednisolone. In patients, variability was similarly wide after both preparations, but overall bioavailability after both prednisone and prednisolone was similar to that found in controls, although three patients showed subnormal values after both preparations, possibly as a result of impaired intestinal absorption.

3 Patients with biochemical and histological evidence of active hepatocellular necrosis showed evidence of impaired activation of prednisone, but this was compensated for by a decreased rate of elimination of prednisolone from the plasma.

4 It is concluded that plasma prednisolone levels will be more predictable after prednisolone than after prednisone in subjects without hepatic dysfunction. In the presence of liver disease, because of the marked variability in plasma prednisolone levels after either drug, estimation of these could be of value in those patients whose disease cannot be controlled by normal maintenance doses.

Introduction

Despite the widespread use of prednisone in the treatment of chronic active hepatitis (Mistilis & Lam, 1972), there is uncertainty as to whether conversion of the drug to its biologically active metabolite prednisolone, a process mediated by the hepatic enzyme 11β-hydroxy-dehydrogenase, occurs normally in patients with hepatic dysfunction. Powell & Axelson (1972) compared peak plasma levels of prednisolone after oral administration of prednisone and prednisolone in patients with liver disease and concluded that prednisolone rather than the parent compound should be used in this situation. In contrast, Jenkins & Sampson (1967) found normal conversion of prednisone to prednisolone, and suggested that these two compounds would be equally therapeutically effective in liver disease. However, in the latter studies, only two patients were investigated while in the former only peak plasma levels, rather than the overall plasma availability of prednisolone, were measured. The present study was therefore undertaken to compare the plasma availability of prednisolone after therapeutic doses of this drug with that obtained after its precursor prednisone in patients with chronic active hepatitis of varying activity and severity.

Methods

The twenty-five patients investigated (fifteen females, ten males; mean age 32.6, range 24–39 years) all had histologically proven chronic active hepatitis (De Groote, Desmet, Gedigk, Korb, Popper, Poulsen, Scheuer, Schmid, Thaler, Vehlinger & Wepler, 1968), and presented either to the Liver Unit, King's College Hospital or the Instituto di Patologia Medica in Milan. Smooth muscle antibodies were present in the serum of twenty-two patients. In ten, the disease was classified as 'active', on the basis of marked inflammatory cell infiltration in portal tracts on liver biopsy, serum aspartate aminotransferase levels of greater than 200 i.u./l (upper limit of normal 50 i.u./l), and levels of serum bilirubin above three times normal. In the remaining fifteen patients, classified as 'well controlled', inflammatory cell infiltration was mild, and the biochemical features mentioned above were absent. Mean $\pm$ s.e. mean serum globulin levels were

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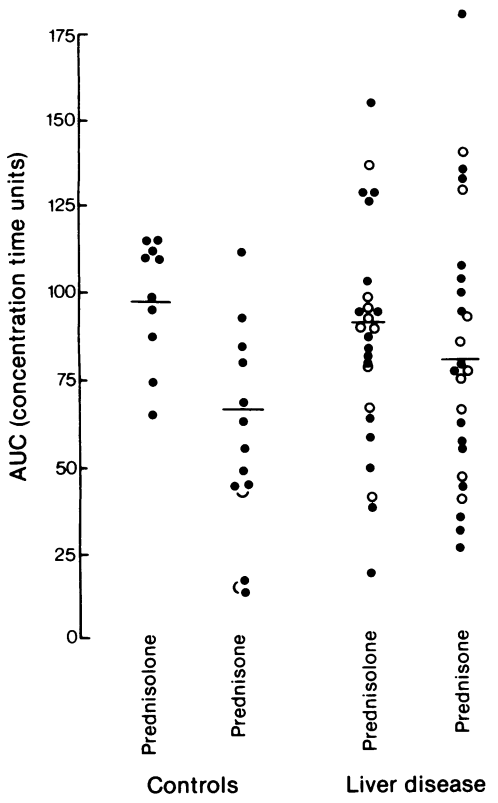

Figure 1 Values for the area under the plasma concentration time curves for prednisolone after oral administration of prednisolone and prednisone to controls and patients with chronic active hepatitis (● serum albumin > 30 g/l), (○ serum albumin < 29 g/l). Bracketed points indicate values from duplicate studies.

lower in those classified as 'well controlled', than those with 'active' disease (32.5 ± 3.2 g/l and 45.0 ± 5.1 respectively). Nine patients (five 'active' and four 'well controlled') had evidence of chronically impaired hepatic synthetic function, as judged by a plasma albumin of 29 g/l or less (normal range 35–50 g/l).

Ten patients, all 'active', were studied at the time of their first presentation, while the remaining fifteen had been receiving maintenance corticosteroid therapy (prednisone or prednisolone 10–20 mg daily) for up to 3 years before the investigation. Eight of these, including the four in the 'well controlled' group with low serum albumin levels, were taking spironolactone (100–200 mg daily for 6–24 months), but none had clinical evidence of peripheral oedema or ascites at the time of study.

Ten volunteer subjects (two females, eight males; mean age 27.2, range 23–40 years), all laboratory staff at King's College Hospital, with no clinical evidence of liver disease, normal standard liver function tests, and no history of excessive alcohol consumption, served as controls. Mean ± s.e. mean body weight was similar in the patients and the controls (66.2 ± 6.3 kg and 69.5 ± 5.8 respectively). Informed consent was obtained from both patients and controls.

After an overnight fast, oral doses of prednisone acetate (10 mg) or prednisolone phosphate (10 mg) were given, on separate occasions. The two drugs were given in random order, and the interval between the two studies was at least 3 days. In the patients receiving maintenance corticosteroids, therapy was withheld for 24 h before each study. Venous blood samples were collected before administration of the tablets, and 1, 2, 3, 4, 6 and 8 h afterwards. After centrifugation of the heparinized samples, the supernatant plasma was stored at −20°C until assayed for prednisolone (by J.E.), using a competitive protein-binding technique, the drug having been separated from cortisol by thin layer chromatography (English, Chakraborty & Marks, 1974).

The areas under the curves of plasma prednisolone versus time were measured by planimetry for each patient after prednisone and prednisolone. The results, expressed in concentration time units, provide an index of the overall availability of prednisolone in the plasma after each drug (Disanto & Desante, 1975) and the ratio of these two values allowed comparison in individual subjects. In addition, half lives of prednisolone in plasma were calculated from semi-logarithmic plots of the plasma concentration time curve, provided that at least four points on the decay portion were log-linear, with a regression coefficient of > 0.97, as calculated by the method of least squares. In practice, it proved possible to do this only for the values obtained after prednisolone, because of the delay in achieving peak plasma concentrations after prednisone.

Results

In control subjects, peak prednisolone levels were slightly but significantly higher following prednisolone than after prednisone (Table 1) and these values were achieved at a similar time after ingestion of the two preparations. In contrast, in patients with chronic active hepatitis peak values occurred significantly later after prednisone than after prednisolone. Compared with controls, however, this delay was only significant in patients with 'active' liver disease.

In control subjects, mean values for the plasma availability of prednisolone were greater after prednisone than prednisolone (Table 1), although the difference failed to reach statistical significance (Wilcoxon sum of ranks test) due to the wide scatter of

Table 1 Prednisolone pharmacokinetics in controls and patients with chronic active hepatitis. Values given are mean ± 1s.e. mean

	Peak plasma prednisolone concentration (ng/ml)		*Time between ingestion and peak level (h)*		*Area under plasma concentration–time curve (concentration–time units)*		$T_{\frac{1}{2}}$ *(h)*[‡]
	After prednisone	*After prednisolone*	*After prednisone*	*After prednisolone*	*After prednisone*	*After prednisolone*	
Controls ($n=10$)	95.9 ± 8.62	115.8 ± 7.2[1]	1.6 ± 0.21 N.S.	1.4 ± 0.16	70.1 ± 8.54	98.2 ± 15.49	2.13 ± 0.12
Liver disease							
'Well controlled' Serum albumin ⩾30 g/l ($n=11$)	96.54 ± 13.98	125.54 ± 15.35	1.81 ± 0.29	1.27 ± 0.14[2]	80.09 ± 13.08	95.36 ± 11.33	2.49 ± 0.25
'Well controlled' Serum albumin <30 g/l ($n=4$)	88.25 ± 12.0	104.0 ± 14.98[2]	1.95 ± 0.15	1.5 ± 0.35[3]	76.5 ± 12.1	85.5 ± 12.9	2.7 ± 0.36
'Active' Serum albumin ⩾30 g/l ($n=5$)	98.3 ± 14.5	94.0 ± 9.98	2.6 ± 0.31[4]	1.75 ± 0.25[1]	85.6 ± 15.19	89.0 ± 12.01	3.27 ± 0.33[5]
'Active' Serum albumin <30 g/l ($n=5$)	114.6 ± 16.45	120.75 ± 9.75	2.4 ± 0.24[6]	1.8 ± 0.2[3]	87.2 ± 18.2	92.76 ± 16.67	3.73 ± 0.56[4]

1 $P<0.01$ compared with values
2 $P<0.02$ after prednisone
3 $P<0.05$ (Wilcoxon sum of ranks test)

4 $P<0.001$ compared with values
5 $P<0.005$ in normal controls
6 $P<0.01$ (Student's *t*-test)

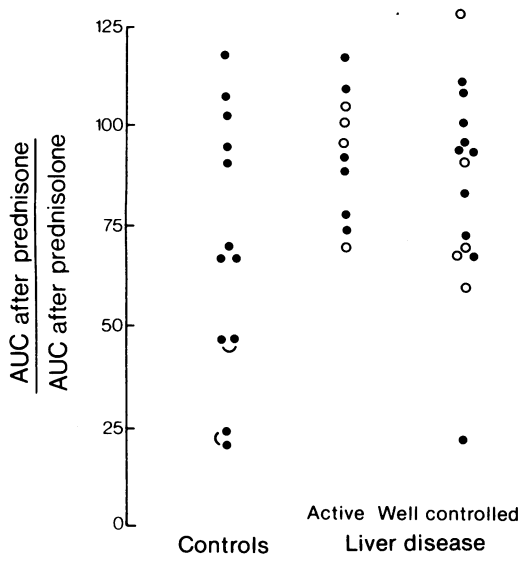

Figure 2 Ratios of the area under the plasma concentration–time curves (AUC) for prednisone: prednisolone in controls and patients (● serum albumin >30 g/l), (○ serum albumin <29 g/l). Bracketed points indicate values from duplicate studies.

values after prednisone (Figure 1). Two subjects showed particularly low levels after prednisone (17 and 45 units), and these were reproduced in a subsequent study, while corresponding values after prednisolone were within the normal range at 64 and 96 units respectively. Analysis of variance showed that significantly greater variations occurred in prednisolone plasma availability after prednisone than after prednisolone itself was given ($F=5.48$, $P<0.01$).

In patients with chronic active hepatitis mean plasma availability of prednisolone after prednisone did not differ significantly from that observed after prednisolone, but as in the control subjects there were wide individual variations (Figure 1). In contrast to the controls, variability after prednisone was not significantly greater than that observed after prednisolone. When patients were classified according to the activity of their liver disease, as assessed by hepatic histology and biochemical liver function tests, including serum albumin levels, no significant differences could be found in values for plasma availability of prednisolone after either preparation when compared with normal controls (Table 1).

Comparison of prednisolone availability after prednisone and prednisolone in normal controls showed values after prednisone ranging from 22–127% (mean 78%) of those observed after prednisolone itself was given (Figure 2). In patients comparable values were obtained after prednisone (mean 84.8%, range 22–127% of availability after prednisolone). However, three patients showed markedly subnormal plasma availability after both prednisone and prednisolone (> 2 s.d. below mean for normal controls), although the relative availability was similar after both preparations.

Plasma half lives of prednisolone were longer in patients with liver disease than in controls but this difference only achieved statistical significance for patients with 'active' disease (Table 1). Impaired elimination of prednisolone from the plasma appeared to contribute to the normal plasma availability of the drug in the patients, since in those with normal values after prednisone (i.e. within 2 s.d. of mean for controls), plasma half lives were significantly longer (2.83 ± 0.2 h) than in controls (2.13 ± 0.12 h) ($P<0.05$).

Four patients with 'well controlled' disease and normal values for serum albumin had received prior treatment with spironolactone in addition to prednisolone, while an additional seven had not been given this enzyme inducing diuretic. However, comparison of the various pharmacokinetic parameters revealed no significant differences between these two groups.

Discussion

The area under the plasma concentration–time curve after oral administration of a drug provides an index of its availability in the plasma (Disanto & Desante, 1975). For prednisone, this will be governed by its absorption, distribution, activation and elimination. The results of the present study have shown that in patients with chronic active hepatitis with florid histological and biochemical evidence of hepatic necrosis, there is delayed conversion of prednisone to prednisolone, as evidenced by delayed appearance of the plasma peak concentration. This suggests that in this situation there is impairment of the hepatic enzyme 11-β-hydroxy-dehydrogenase which renders prednisone, as well as cortisone, biologically active. Similar results were obtained by Powell & Axelsen (1972), who suggested that prednisolone rather than prednisone should be used if normal availability of the biologically active metabolite in the plasma was to be obtained in patients with liver disease. However, in our patients showing this abnormality the elimination of prednisolone from the plasma was also impaired, indicating impaired hepatic A ring reduction of this compound, so that the overall plasma availability of prednisolone after prednisone was no different from that in normal controls. This suggests that impaired conversion of prednisone to prednisolone was compensated for by a decreased rate of elimination of the active metabolite. Protein-binding of prednisolone was not investigated in the present study, but other workers have shown that when levels of serum

albumin are low, a higher than normal proportion of the drug circulates as the free biologically active form (Powell & Axelsen, 1972). This would also tend to decrease the effect of impaired conversion of prednisone to prednisolone.

A striking feature of the present study was the observation that a proportion of the patients, and also of the controls, showed abnormally low plasma levels of prednisolone after prednisone. The most likely explanation for these findings in the controls is a differing rate of hepatic conversion of prednisone to prednisolone, and both genetic and environmental factors have been implicated as the basis of similarly wide individual variations in the metabolism of other drugs (Vesell, 1974). Comparable individual variations, as well as hepatic dysfunction itself, are likely to modify the metabolism of prednisone in patients with chronic active hepatitis. Previous workers have suggested that some patients with liver disease are able to metabolize drugs normally because other compounds taken concurrently have produced enzyme induction (Levi, Sherlock & Walker, 1968). However, in the present study previous treatment with spironolactone, which induces microsomal enzymes in rats (Solymoss, Classen & Varga, 1969), had no effect on the kinetics of prednisone or prednisolone.

The observed variations in plasma prednisolone levels after prednisone could also be due in some measure to differences in the intestinal absorption of the drug, possibly as a result of variations in the hydrolysis of prednisone acetate by intestinal acetylases. Furthermore, it is of potential therapeutic importance that in three of our patients, plasma prednisolone levels were below the range for normal controls after prednisolone as well as prednisone. Impaired drug absorption seems a likely basis for this abnormality, but little is known of the effect of hepatic dysfunction on the intestinal absorption of therapeutic agents.

Although prednisone and prednisolone are commonly used interchangeably, our results in control subjects without Liver disease would indicate that if predictable plasma concentrations are to be achieved, prednisolone is the drug of choice. In the presence of liver disease, however, wide variations were observed after both preparations, and these could not be predicted by clinical or biochemical indices of hepatic function. Because of this, estimation of plasma prednisolone levels could be of value in those patients whose disease cannot be controlled by normal maintenance doses.

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