Gut, 1980, **21**, 52-56

Impaired conversion of prednisone to prednisolone in patients with liver cirrhosis

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SUMMARY Fourteen patients with liver cirrhosis received oral prednisone or prednisolone (0·3 mg per kg) randomised on two consecutive days. Serum prednisone and prednisolone were measured over the following four hours. Mean serum prednisolone concentration after oral prednisone decreased with impaired liver function estimated by galactose elimination capacity ($r=0·64$, $P<0·03$). Mean serum prednisolone concentration after oral prednisone in the seven patients with severely impaired liver function was only 53% ($P<0·05$) of that observed in the seven patients with slightly impaired liver function. Conversely, mean serum prednisone concentration after oral prednisone in the patients with severely impaired liver function was 74% higher ($P=0·05$) than in patients with slightly impaired liver function. Mean serum prednisolone after oral prednisolone was independent of liver function. As only prednisolone exerts glucocorticoid activity, our results indicate that prednisolone should be preferred to prednisone in the treatment of patients with impaired liver function.

Controlled investigations of the effect of prednisone treatment in chronic liver disease have demonstrated a favourable effect in the majority of patients with non-alcoholic cirrhosis and patients with chronic active hepatitis (Murray-Lyon *et al.*, 1973; Copenhagen Study Group for Liver Diseases, 1974; Summerskill *et al.*, 1975). It is not clear why some patients with these liver disorders do not respond to prednisone treatment. In itself, prednisone has no glucocorticoid effect (Sarett and Patchett, 1963) but must first be converted into prednisolone by 11-hydroxylation, chiefly performed in the liver. A possible explanation of the failure of prednisone treatment, therefore, could be the inability of patients with impaired liver function to carry out the conversion of prednisone to prednisolone. Previous studies on the conversion of prednisone to prednisolone in patients with liver disease are contradictory (Jenkins and Sampson, 1967; Powell and Axelsen, 1972; Uribe *et al.*, 1976; Davis *et al.*, 1978), but in none of these studies was the liver function evaluated by a quantitative test. The purpose of our study therefore has been to examine the conversion of prednisone to prednisolone with regard to liver function in patients with cirrhosis.

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Received for publication 8 August 1979

Methods

PATIENTS

Thirteen men and one woman with liver cirrhosis, verified by biopsy within the past six months, were examined. None of the patients had previously been treated with glucocorticoids. No medications other than diuretics and possibly lactulose, magnesium sulphate, and neomycin were given for three weeks before the start of the investigation. None of the patients had any serious illness but cirrhosis of the liver. Informed consent to taking part was obtained in all instances in accordance with the Helsinki declaration. On two consecutive days at 0730 hours, after fasting overnight, an indwelling plastic cannula was inserted into a cubital vein. In random order the patients were given orally either 0·30 mg prednisone (Deltasone) or prednisolone (Delta-cortef) per kg body weight at 0800 hours, together with 125 ml of water. The exact amount of steroid administered was calculated by dividing and weighing the tablets. Blood samples were drawn

Table *Clinical data in patients with slightly impaired liver function and patients with severely impaired liver function*

	Slightly impaired liver function n=7		*Slightly impaired liver function n=7*		*Difference*
	Mean	*Range*	*Mean*	*Range*	
Age (yr)	51·3	36–57	49·6	40–55	NS
Weight (kg)	76·5	70·0–81·8	78·2	65–91·2	NS
Aspartate aminotransferase (10–25 u/l)	37·0	22–63	57·4	28–104	NS
Alkaline phosphatase	87·1	58–142	113·6	82–130	NS
S-prothrombin (60–130%)	77·5	46–105	42·6	30–66	$P<0.05$
S-total bilirubin (7–14·1 μmol/l)	17·3	6·8–35·9	62·3	17·1–126·5	$P=0.05$
S-albumin (510–740 μmol/l)	434·7	303·9–578·8	386·4	247·8–549·9	NS
Protein (g/l) (60–80 g/l)	72·1	61–82	69·0	59–85	NS
Creatinine (50–120 μmol/l)	102·5	88·4–114·9	108·7	88·4–123·8	NS

after 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes, during which time the patients remained fasting. The sera were cooled to —28°C until analysis. Prednisone and prednisolone were determined by radioimmunoassay (Colburn and Buller, 1973; Colburn, 1974) on coded samples. On the first day of investigation additional analyses were made of serum aspartate aminotransferase, alkaline phosphatase, prothrombin, albumin, and creatinine. On the third day of investigation, galactose elimination capacity (GEC) was measured after intravenous injection of 0·5 g galactose per kg body weight as described by Tygstrup (1963). According to the results of the GEC the 14 patients were arbitrarily divided into two groups. One group with slightly impaired liver function, mean GEC 2·14 mmol/min, range 1·80–2·54 mmol/min (no.=7). The second group with severely impaired liver function, mean GEC 1·35 mmol/min, range 1·05–1·58 mmol/min (no.=7). The remaining laboratory values of the two groups are shown in the Table.

As the time course of serum concentrations of prednisone and prednisolone was followed for only four hours, half-life values were not calculated. As an expression of the mean concentration of the two compounds during the four-hour period, the area under the respective curves was used.

For statistical estimations the Mann-Whitney rank sum test or Wilcoxon's test was used to compare mean concentrations of prednisone and prednisolone. Spearman's test was used to compare GEC and mean plasma prednisolone concentration

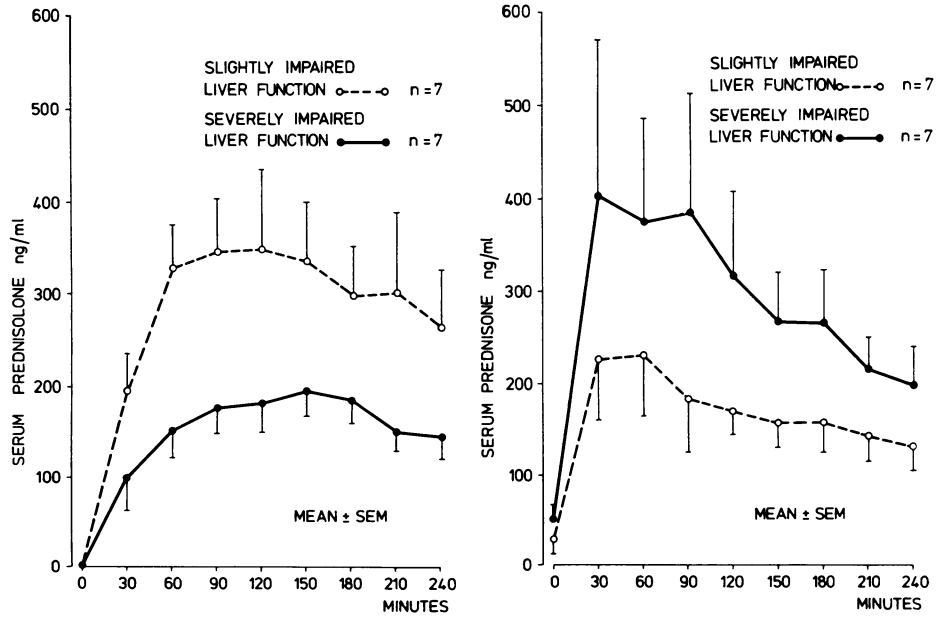

Fig. 1 *Serum concentration of prednisolone and prednisone after oral prednisone in patients with slightly impaired liver function and patients with severely impaired liver function. Conversion to SI units: 100 ng prednisone=0·277 nmol, 100 ng prednisolone=0·279 nmol.*

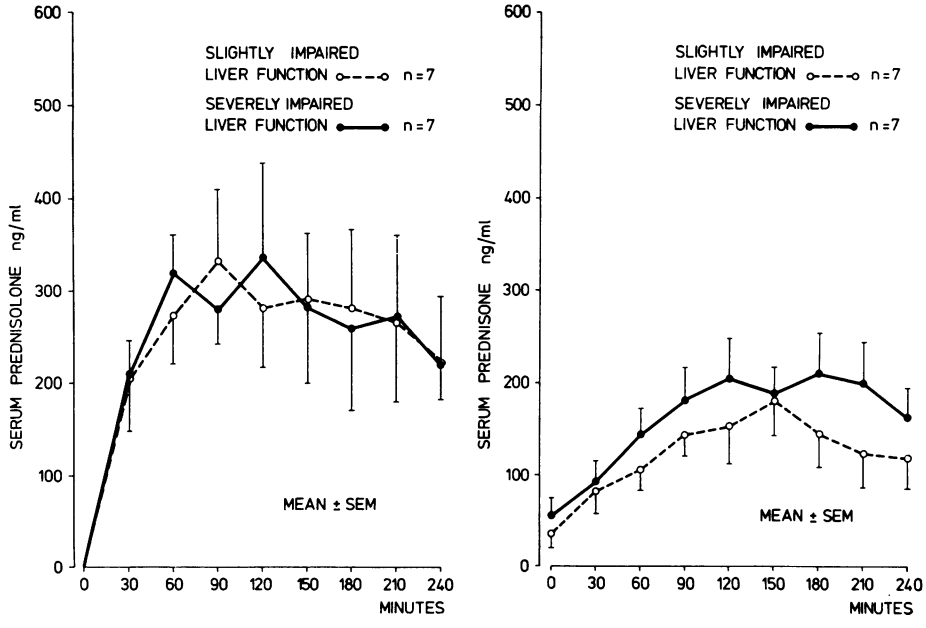

Fig. 2 *Serum concentration of prednisolone and prednisone after oral prednisolone in patients with slightly impaired liver function and patients with severely impaired liver function. Conversion to SI units: 100 ng prednisone = 0·277 nmol, 100 ng prednisolone = 0·279 nmol.*

after prednisone. The level of statistical significance was $2\alpha = 0{\cdot}05$.

Results

The serum concentrations of prednisone and prednisolone after oral administration of prednisone are shown in Fig. 1. The area under the prednisolone curve of the group with severely impaired liver function constituted only 53% of the area under the prednisolone curve of the group with slightly impaired liver function ($P < 0{\cdot}05$). The average maximal concentrations of prednisolone after oral prednisone were 348 ng/ml and 195 ng/ml in the group with slightly and severely impaired liver function respectively. Conversely, the area under the prednisone curve (Fig. 1) of the group with severely impaired liver function was found to be 74% higher than the area under the prednisone curve of the group with slightly impaired liver function ($P = 0{\cdot}05$). The average maximal concentrations of prednisone were 403 ng/ml and 230 ng/ml in the group with severe and slight liver function impairment, respectively.

Figure 2 shows the serum concentrations of prednisone and prednisolone after oral administration of prednisolone. There was no significant difference between the two groups with respect to the time course of concentrations or to the maximal concentrations of prednisone and prednisolone.

In the group with slightly impaired liver function there was no significant difference in the area under the serum prednisolone curves after oral prednisone (Fig. 1) or prednisolone (Fig. 2).

In the group with severely impaired liver function the area under the prednisolone curve (Fig. 1) after intake of prednisone constituted 59% of the area under the prednisolone curve (Fig. 2) after intake of prednisolone ($P < 0{\cdot}05$).

After intake of prednisone, the correlation between the mean serum prednisolone concentration and the GEC during the four-hour observation period in individual patients is plotted in Fig. 3. It can be seen that declining liver function was accompanied by lower serum prednisolone values after oral administration of prednisone ($r = 0{\cdot}64$, $P < 0{\cdot}03$).

Discussion

In 1967 Jenkins and Sampson (1967) reported an almost unchanged conversion of prednisone to prednisolone in two patients with not clearly defined liver function. Powell and Axelsen (1972) studied six patients with acute hepatitis and 16 patients with chronic liver disease of whom nine had 'active' liver disease. In the groups with 'active' liver disease and acute hepatitis peak plasma prednisolone was found to be about 15% higher after oral prednisolone than after prednisone. On the other hand, there was no difference in the prednisolone concentrations after oral prednisone or prednisolone in the group with chronic inactive liver disease. In two other studies (Uribe *et al.*, 1976; Davis *et al.*, 1978), in which the liver function was not defined, no

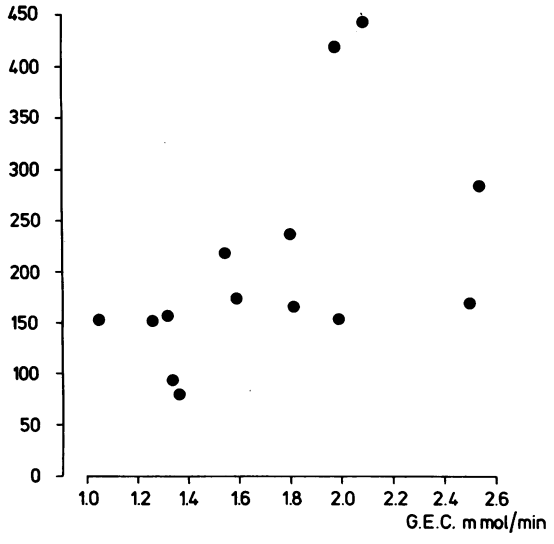

Fig. 3 *Correlation between mean serum concentration of prednisolone (ng/ml) after oral prednisone (03·0 mg/kg) and liver function as expressed by galactose elimination capacity (GEC) ($r=0·64$, $P<0·03$). Conversion to SI units: 100 ng prednisone=0·277 nmol, 100 ng prednisolone=0·279 nmol.*

major difference in plasma prednisolone was found after oral prednisone between patients with chronic active liver disease and normal individuals, although patients with liver disease showed a delayed appearance of plasma prednisolone peak concentration; however, plasma half-life of prednisolone was slightly prolonged making the plasma concentration-time curve similar to normal subjects (Davis *et al.*, 1978).

Our study differs from the above-mentioned studies in that we have attempted a quantitative estimation of liver function. Among the numerous laboratory analyses (Table) available for evaluation of liver function, the maximal uptake rate of galactose by the liver (GEC) is presumably one of the best methods for evaluation of liver function (functional liver cell mass, Tygstrup, 1973). From a biochemical point of view, GEC measures the maximal rate of phosphorylation, and thus is an indicator of one of the basic liver functions. In rats receiving carbon tetrachloride, GEC was reduced parallel to the damage of the liver (Vilstrup, 1978), and, in the isolated perfused pig liver, GEC and ATP were both reduced parallel to the degree of hypoxia (Rabøl *et al.*, 1974). Furthermore, in man, GEC shows a positive correlation with other hepatic tolerance tests as antipyrin clearance and Tm of bromsulphalein (Andreasen *et al.*, 1974). In patients with fulminant hepatic failure, GEC is significantly higher in patients who survive compared with those with a fatal outcome (Ranek *et al.*, 1976). In patients with hepatic cirrhosis, GEC shows a good correlation with prognosis (Tygstrup, 1964). A positive correlation was found between the mean prednisolone concentration after oral prednisone and the galactose elimination capacity. After intake of prednisone mean prednisolone concentration in patients with severely impaired liver function was only 53% of that observed in patients with slightly impaired liver function. Conversely, mean prednisone concentration in patients with severely impaired function was 74% higher than in patients with slightly impaired liver function. As the total glucocorticoid level (prednisone plus prednisolone) after oral prednisone was similar in patients with severely and slightly impaired liver function the observed differences cannot be explained by differences in absorption between the two patient groups. The differences in prednisolone values after oral prednisone might be expected to be equalised if prednisolone metabolism was deficient in the patients with severely impaired liver function. However, this is unlikely, as plasma prednisolone values were similar in patients with slightly and severely impaired liver function after oral prednisolone (Fig. 2). The low values of prednisone detectable even before steroid administration may be due to cross-reactivity from endogenous cortisone and cortisol (Colburn, 1974).

Our results indicate that the liver function must be considerably impaired before a difference can be detected in the serum prednisolone concentrations after oral administration of prednisone and prednisolone, respectively.

The practical clinical significance of the demonstrated impaired conversion of prednisone to prednisolone is not yet clear. In a recently published study (Schalm *et al.*, 1977), in which patients with chronic active liver disease were divided into one group which responded to prednisone treatment and into another which did not respond, the serum concentrations of prednisolone after intravenous administration of 10 mg prednisone were found to be only 15% lower in the group which did not respond than in the group which did respond. From these results the authors concluded that the therapeutic ineffectiveness of prednisone must be considered to be caused by factors other than an impaired conversion to prednisolone.

On the basis of our results we conclude that in relation to the amount of prednisone administered the level of serum prednisolone in patients with severely impaired liver function is less than expected. As prednisolone, unlike prednisone, exerts biological glucocorticoid activity without undergoing metabolic

conversion, prednisolone should be preferred to prednisone in glucocorticoid treatment of patients suffering from liver diseases.

We are grateful to Upjohn Company, Kalamazoo, Michigan, USA for performing the serum analyses of prednisone and prednisolone.

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