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The metabolism and bioavailability of morphine in patients with severe liver cirrhosis

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1 The oral and intravenous kinetics of morphine were investigated in seven cirrhotic patients with a history of encephalopathy. The plasma concentrations of morphine and its metabolites morphine-3 (M3G) and morphine-6 (M6G) were measured by h.p.l.c.
2 The mean terminal elimination half-life of morphine was 4.2 h (95% CI 3.6–4.8) the mean volume of distribution was 4.1 l kg^{-1} (95% CI 2.9–5.4) and the mean plasma clearance was 11.4 ml min^{-1} kg^{-1} (95% CI 8.1–14.7). The mean oral bioavailability was 101% (95% CI 56–147).
3 The plasma clearance of morphine was significantly lower, its terminal elimination half-life longer and its oral bioavailability greater in the cirrhotic patients compared with patients with normal liver function. The metabolic ratio M3G/morphine was significantly lower in the cirrhotic patients than in control subjects after oral dosing, but did not differ after intravenous dosing.
4 The average urinary recoveries of morphine plus M3G and M6G were 49.9% after i.v. and 57.7% after oral administration. There were no statistically significant differences in the urinary recovery between the two routes of administration or between the cirrhotic patients and controls.
5 Specific changes in the EEG pattern could not be detected after intravenous dosage.
6 The metabolism of morphine is impaired significantly in patients with severe cirrhosis. Clinically important findings were a high oral bioavailability and a long elimination half-life. These findings call for cautious dosing of oral and intravenous morphine in patients with severe end stage liver disease.

Keywords morphine liver cirrhosis bioavailability pharmacokinetics EEG

Introduction

Patients with severe liver disease have an increased sensitivity to analgesics, sedatives and hypnotics, and the administration of such drugs could result in cerebral dysfunction (Conn & Lieberthal, 1979; Fraser & Arieff, 1985). It has been suggested that morphine, which is a first-line choice among opioids, can cause hepatic encephalopathy in patients with liver cirrhosis (Laidlaw *et al.*, 1961). Whether this is a result of altered drug response, impaired hepatic drug metabolizing capacity or both is not known.

Morphine is subject to extensive pre-systemic elimination and its oral bioavailability is low (Säwe *et al.*, 1981, 1985). In patients with cirrhosis and portal hypertension it is anticipated that a substantial fraction of an oral dose passes through portal systemic collaterals, leading to high oral bioavailability with clinically important implications.

In a study by Pathwardhan *et al.* (1981) the systemic clearance and elimination half-life of morphine were similar in cirrhotic patients and

in a group of healthy volunteers, while in two recent studies (Crotty *et al.*, 1989; Mazoit *et al.*, 1987) decreased systemic clearance and impaired extraction were found.

In 1961 Laidlaw *et al.* demonstrated dose dependent changes in the EEG pattern similar to those seen in hepatic encephalopathy in cirrhotic patients receiving single parenteral doses of morphine.

In the present study the kinetics of oral and intravenous morphine were investigated in patients with cirrhosis and severe liver dysfunction. The effect of morphine on the central nervous system was assessed by EEG recordings.

Methods

Patients and study design

Eight patients with alcoholic cirrhosis, six male and two female, aged 62 ± 3 years participated in the study (one of these patients was later excluded following a severe adverse reaction after the intravenous dose). The diagnoses, clinical data and concomitant medication are shown in Table 1. All patients had a history of hepatic encephalopathy, verified by EEG. Six of the patients had ascites. The control group comprised six male patients (aged 69 ± 3 years) with cancer and normal kidney and liver function. These patients were studied previously in our hospital using identical dosing, sampling and analytical procedures (Säwe *et al.*, 1985).

The patients were informed of the nature, purpose and possible risks involved in the study before giving their consent to participate. The protocol was reviewed and approved by the ethics committee of Huddinge University Hospital.

Single oral (10 mg) and intravenous (4 mg) doses of morphine hydrochloride were administered on two separate occasions with an interval of 48 h or more. The oral dose was given as an aqueous solution. Patient number 5 received by an oversight only 5 mg of oral morphine instead of 10 mg and patient number 1 did not take part in the oral part of the study. Patient number 7 did not receive the intravenous dose. The oral dose of morphine was 20 mg in the control group (Säwe *et al.*, 1985). The intravenous doses were administered slowly over 1 min into an antecubital vein. The patients remained in the supine position for 4 h after administration of morphine.

Sample collection

Venous blood samples were taken for the measurement of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The samples were drawn from an indwelling cannula into heparinized plastic tubes before and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 24 h after the oral dose and 2.5, 5, 15, 30, 60 and 90 min and then hourly up to 6 h and finally 8, 10 and 12 h after the intravenous dose. The samples were centrifuged and the plasma was frozen at −20° C until analysed.

Urine was collected for 24 h after the oral and intravenous doses. Aliquots of the urine were frozen at −20° C until assay for morphine, M3G and M6G.

EEG recordings were made in all patients 1 to 3 days prior to the study. During the intravenous part of the study, recordings were taken 20 min before and continuously for 2 h after the administration and thereafter every 15 min up to 3 h and finally at 6 h after the dose.

Analyses

Morphine, M3G and M6G concentrations were measured by reversed phase high performance liquid chromatography (Svensson *et al.*, 1982; Svensson, 1986) with an intra-assay coefficient of variation of 5.9% at a morphine concentration of 5 nmol l^{-1} and 4% at an M3G concentration of 100 nmol l^{-1}. The limit of detection was 1 nmol l^{-1} for morphine and M6G and 10 nmol l^{-1} for M3G.

Statistical analysis was by the Mann-Whitney U-test and the Wilcoxon matched pairs signed ranks test. In the text, data are presented as mean values with 95% confidence intervals in brackets (CI).

Kinetic calculations

The plasma half-life ($t_{½}$) was calculated from the regression line fitted to a semilogarithmic plot of the plasma concentration of morphine *vs* time by the method of least squares. The area under the plasma drug concentration *vs* time curve (AUC) was calculated by the linear trapezoidal rule with extrapolation to infinity. The residual areas were always less than 18% of the total AUC values (mean 10.5%) for morphine. For M3G and M6G the mean residual area was 21 and 22%, respectively. Clearance (CL) was calculated by dividing the dose by AUC. The apparent volume of distribution (V) was calculated from CL divided by the terminal elimination rate constant. The oral bioavailability (F) was calculated by dividing the AUC after the oral dose by the AUC after the intravenous dose with dose differences taken into account. Ratios of M3G/M and M6G/M were

Table 1 Clinical and laboratory data of the cirrhotic patients

Patient	*Sex / age / weight (years) (kg)*	*Diagnosis and clinical signs*	*Concomitant drugs*	*Child-Pugh classification (Pugh* et al., *1973)*	*Blood chemistry albumin* ($g\ l^{-1}$)*	*bilirubin* ($\mu mol\ l^{-1}$)*	*NT* (%)*	*ALAT* ($\mu kat\ l^{-1}$)*	*creatinine* ($\mu mol\ l^{-1}$)*
1	M/68/60	Ascites Oesophageal varices	a	C	33	52	58	0.56	100
2	F/58/50	Ascites	a, b, c, d	C	30	93	45	1.20	66
3	M/52/85	Ascites Diabetes mellitus	a, b, d, e, f	C	19	169	35	0.95	120
4	M/57/82	Ascites	a, b, g, h, d, i, k	B	31	29	73	0.77	141
5	M/56/85	Oesophageal varices	a, b, l, m, n	B	33	17	55	0.32	65
6	M/72/79	Ascites Diabetes mellitus	a, n, o	A	41	33	88	0.55	81
7	M/69/90	Ascites	a, d	C	24	79	73	0.73	102
Mean ± s.e. mean (95% CI)	62 ± 2.9/76 ± 5.6 (55–69)/(62–90)				30 ± 2.7 (24–37)	67 ± 19.9 (19–116)	61 ± 6.9 (44–78)	0.73 ± 0.113 (0.48–1.03)	96 ± 10.6 (70–122)

*Normal values: albumin: 35–46 g l^{-1}, bilirubin: < 26 $\mu mol\ l^{-1}$, NT**: 70–130%, ALAT**: < 0.7 $\mu kat\ l^{-1}$, creatinine: < 120 $\mu mol\ l^{-1}$
**NT = the %-age of normal prothrombin complex activity; ALAT = alanine aminotransferase (GPT)
Drugs: a = spironolactone; b = frusemide; c = dimethicone; d = vitamin B; e = potassium chloride; f = insulin; g = phenoxymethylpenicillin; h = dixyrazine; i = paracetamol; k = dextropropoxyphene; l = ranitidine; m = hyoscyamine; h = lactulose; o = glibenclamide

based on the AUC values of the respective compounds.

Results

Parent compound

(a) Intravenous dose The plasma concentrations of morphine in the individual patients after the i.v. dose are shown in Figure 1 and the mean curves for patients and controls in Figure 2a. The plasma concentrations of morphine declined more slowly in the cirrhotic patients as shown in Figure 2a. The $t_{½}$ was three times longer in the patients (4.2 h) than in the controls (1.7 h), ($P < 0.01$). Kinetic parameters for the individual patients and the controls are shown in Table 2. Plasma CL averaged 11.4 (8.1–14.7) ml min^{-1} kg^{-1} and the V was 4.1 (2.9–5.4) l kg^{-1}. Mean values of plasma CL and elimination $t_{½}$ differed significantly ($P < 0.01$) from those in the control group (Table 2).

(b) Oral dose Plasma morphine concentrations are shown for five of the patients in Figure 1 and the mean curve is presented in Figure 2b (data for patient 5 who received 5 mg are excluded from the figures). The average maximum plasma morphine concentration was 103 (70.2–136) nmol l^{-1} (28.3 (19.3–37.4) ng ml^{-1}) at 1.4 (0.4–2.3) h after dosage. The mean elimination $t_{½}$ was 5.5 h in the cirrhotic patients and 3.3 h in the control group ($P < 0.05$).

The mean oral bioavailability in the cirrhotic patients was 101 (56–147) %, which was signifi-

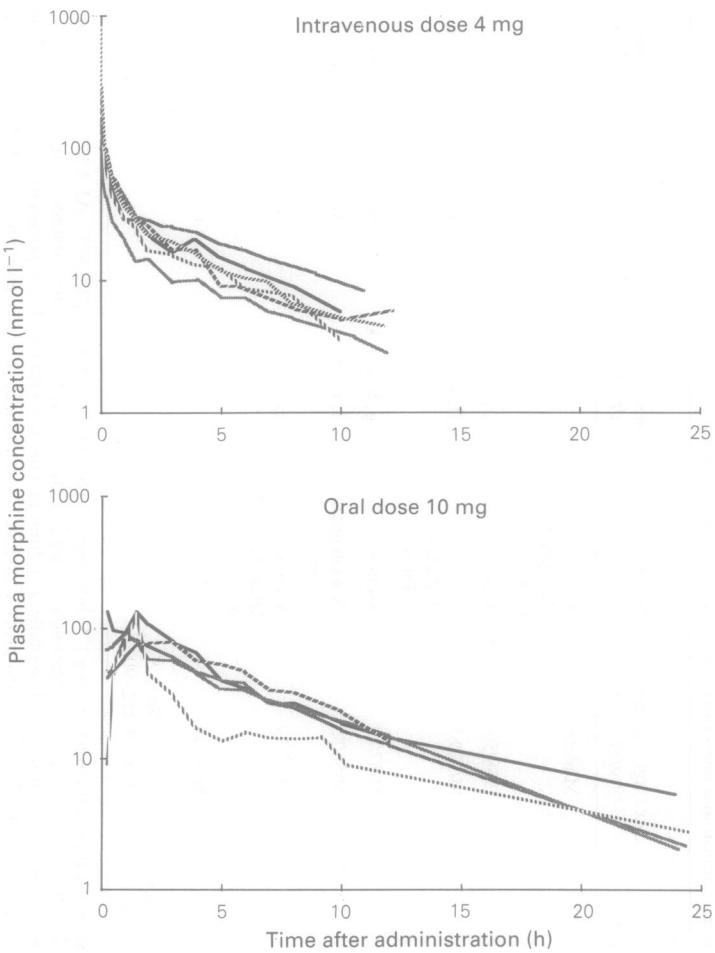

Figure 1 Individual plasma morphine concentration *vs* time curves after intravenous and oral administration of morphine hydrochloride to cirrhotic patients.

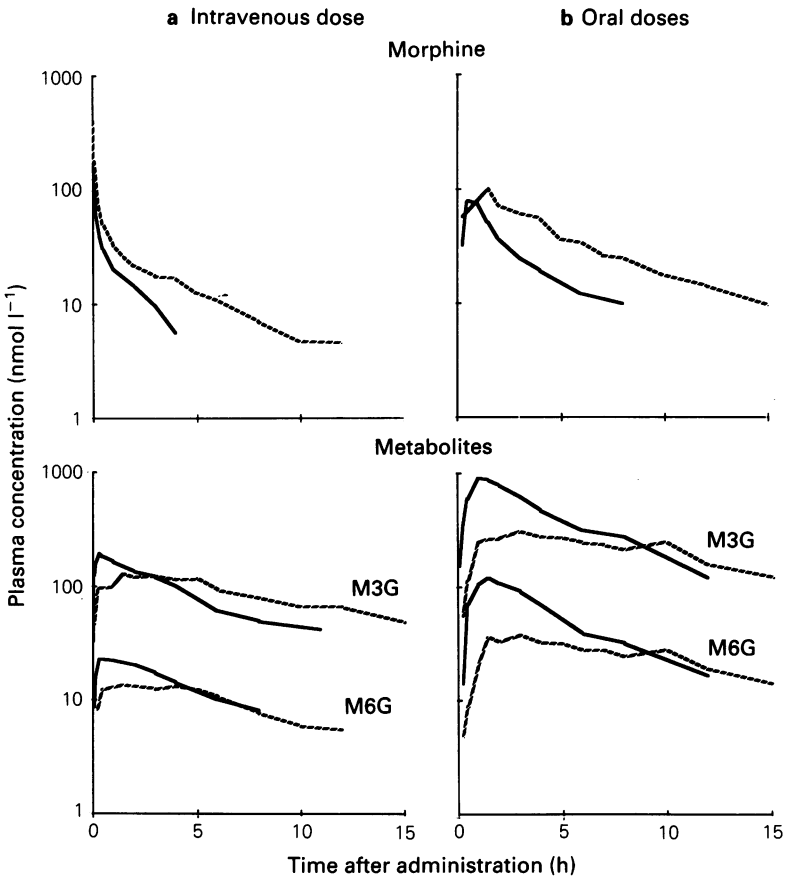

Figure 2 Mean plasma concentrations of morphine and its metabolites M3G and M6G after administration of intravenous (a) and oral (b) morphine to cirrhotic patients (---) and controls (——).

cantly ($P < 0.01$) different from that in the control group (Table 2).

Metabolites

(a) Intravenous dose The concentration *vs* time curves of the metabolites M3G and M6G are shown in Figure 2a). Mean M3G/morphine AUC ratios in cirrhotic patients and controls were 8.3 and 11.1, respectively and did not differ significantly (Figure 3). The corresponding ratios for M6G/morphine were 0.7 ($n = 6$) and 1.3 ($n = 2$). The M3G/morphine AUC ratios were more than 12-fold higher than the M6G/morphine ratios (Table 2).

(b) Oral dose The plasma concentrations of M3G exceeded those of the parent compound within 2.5 min after the oral dose (Figure 2b). The mean oral M3G/M plasma AUC ratio was 8.3, which was significantly ($P < 0.01$) lower than the corresponding ratio of 24.5 in the control group (Figure 3). The M3G/morphine AUC ratios were 11-fold higher than the M6G/morphine plasma AUC ratios. The mean M6G/morphine AUC ratios in cirrhotic patients and controls were 0.9 ($n = 6$) and 2.5 ($n = 4$), respectively.

Among the cirrhotic patients the M3G/M plasma AUC ratios were similar after intravenous and oral administration while the M3G/M plasma ratios were higher after oral compared to intravenous dosage in the controls (Figure 3).

Urine

The average 24 h urinary recovery of morphine plus M3G and M6G was 49.9% (32.0–67.8), ($n = 6$) in the cirrhotic patients after intravenous and 57.7% (41.6–73.9), ($n = 6$) after oral dosing.

Table 2 The kinetics of intravenous and oral morphine in seven patients with severe liver cirrhosis

	Intravenous dose					*Oral dose*			
Patient	$\frac{M3G^c}{morphine}$	$\frac{M6G^c}{morphine}$	*clearance* (*ml* min^{-1} kg^{-1})	V (*l* kg^{-1})	$t_{1/2}$ (*h*)	$\frac{M3G^c}{morphine}$	$\frac{M6G^c}{morphine}$	$t_{1/2}$ (*h*)	F (%)
1	8.6	0.8	11.9	4.2	4.2	—	—	—	—
2	9.9	0.7	15.0	5.3	4.1	9.2	0.9	4.9	124
3	10.3	1.0	7.4	3.3	5.1	10.2	1.2	4.3	80
4	10.3	0.8	14.6	5.8	4.6	10.3	0.9	4.5	154
5	3.1	0.2	8.2	2.9	4.0	3.7	0.2	9.2	65
6	7.3	0.9	11.4	3.3	3.4	9.0	1.1	6.4	84
7	—	—	—	—	—	7.3	0.8	3.7	—
Mean ± s.e. mean (95% CI)	8.3 ± 1.1^{NS}	0.7 ± 0.1	11.4 ± 1.3** (8.1–14.7)	4.1 ± 0.5^{NS} (2.9–5.4)	4.2 ± 0.2** (3.6–4.8)	8.3 ± 1.1**	0.9 ± 0.1	5.5 ± 0.8* (3.4–7.6)	101 ± 16.4** (56–147)
Control group mean ± s.e. mean (95% CI)	11.1 ± 1.7	1.3[a]	28.0 ± 2.3 (22.1–34.0)	4.0 ± 1.0 (1.6–6.5)	1.7 ± 0.3 (0.9–2.5)	24.5 ± 3.4	2.5 ± 1.3[b]	3.3 ± 0.6 (1.9–4.8)	47 ± 5.8 (32–62)

*$P < 0.05$, **$P < 0.01$ as compared with the healthy controls; NS not significantly different
a $n = 2$, b $n = 4$, c plasma AUC ratio.

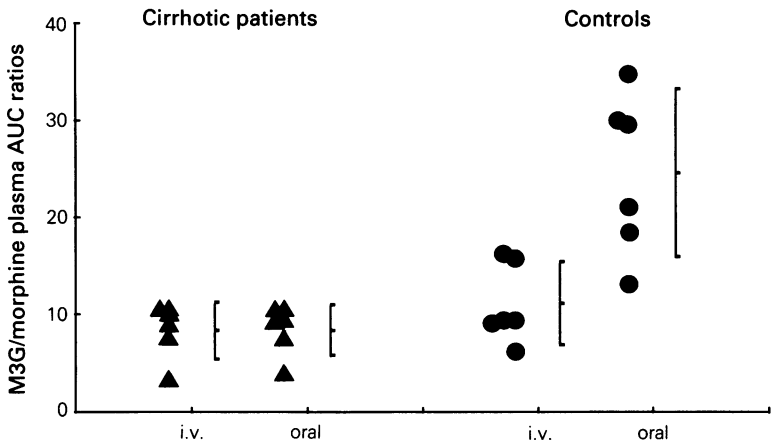

Figure 3 Comparison of M3G/morphine plasma AUC ratios after morphine administration in cirrhotic patients and controls. Bars indicate mean ± confidence interval.

The corresponding 12 h values for the control group were 55.3% (n = 4) after intravenous and 56.4% (n = 5) after oral administration. The difference between the two routes of administration was not significant. M3G was the major excretion product after both intravenous (77.8%) and oral (78.6%) dosing.

EEG

The EEG was recorded during the intravenous part of the study. The initial pattern showed diffuse abnormality in four patients (numbers 1, 3, 4 and 6) consistent with encephalopathy. The other two (numbers 2 and 5) had normal EEGs. Three patients (numbers 3, 5 and 6) had a previous history of an EEG with frontal rhythmic slow waves typical of liver pre-coma. No consistent changes in the EEG-pattern could be detected in any of the patients up to 6 h after the intravenous dose. However, patient 1 showed a slightly increased amount of low frequency activity during the first hour after administration of the intravenous dose, probably due to drowsiness.

Clinical observations

Patients 2 and 6 reported nausea after the oral dose. Patient 3 was sedated and slightly disorientated 3 to 8 h after the oral dose. Patient 7 did not have any remarkable symptoms during the first 12 h after oral dose but later became confused. The excluded patient complained of nausea, chest pain and was in a cold sweat within 10 to 20 s after the intravenous dose. These symptoms disappeared after 10 to 20 min but nausea was also reported 90 min after the dose was administered.

Discussion

The present study demonstrates that patients with severe cirrhosis have a decreased plasma clearance and a prolonged elimination half-life of morphine as compared with historical control patients without liver disease. These findings agree with those of Mazoit *et al.* (1987) and Crotty *et al.* (1989). In contrast, Pathwardhan and coworkers (1981) found normal morphine metabolism in their patients with hepatic cirrhosis. These contradictory findings may be explained by differences in the severity of liver disease in the patients included in the studies. Thus the clinical data presented by Pathwardhan *et al.* (1981) suggest that their patients had less severe hepatic failure compared with other studies (Crotty *et al.*, 1989; Mazoit *et al.*, 1987). Likewise, four of the present patients were in Child-Pugh class C and one of the inclusion criteria was a history of encephalopathy.

The cirrhotic liver displays many pathologic features among which a decreased enzyme content or decreased intrinsic clearance and intra- and extrahepatic shunting of blood must be considered important for drug elimination. Accordingly, Pessayre *et al.* (1978) found that a lowered clearance of (+)-propranolol could be explained mainly by a decrease in the intrinsic clearance. Huet *et al.* (1983) showed the same for lignocaine. Thus, the overall characteristics of these high clearance drugs were changed to those of low clearance drugs. The methodology

of these investigations could, however, not distinguish between a low enzyme content and intra-hepatic shunting of the blood. This is of importance since the fibrotic process in the cirrhotic liver is suspected to have an influence on the clearance of these drugs (Sotaniemi *et al.*, 1986). The decreased intrinsic clearance could explain why the findings of increased liver blood flow in patients with liver cirrhosis (Ohnishi *et al.*, 1987; Sato *et al.*, 1983) do not seem to influence the pharmacokinetics of high clearance drugs.

The eliminating enzymes for drugs subject to glucuronidation such as morphine have, contrary to the above mentioned findings of decreased intrinsic clearance in liver cirrhosis, been shown to be well preserved during the pathological process. This has been indicated in several studies of low clearance drugs which are glucuronidated where no significant changes were seen in systemic clearance in cirrhotic patients compared with controls (Crom *et al.*, 1987; Ghabrail *et al.*, 1986; Kraus *et al.*, 1979; Shull *et al.*, 1976). Extrahepatic clearance by glucuronidation has been shown for many drugs. Recent estimations by Crotty *et al.* (1989) indicate that as much as 30% of the total clearance of morphine is attributed to extrahepatic glucuronidation in cirrhotic patients compared with 10% in controls with normal liver function. Thus, extrahepatic glucuronidation might contribute substantially to the overall clearance of morphine in liver cirrhosis. This is substantiated further by Pacifici *et al.* (1986) and Yue *et al.* (1988) who found that M3G and M6G are formed in microsomes isolated from human intestine and human kidney. The fibrotic process in itself could be a possible additive factor presenting diffusional barriers between enzyme and blood as suggested by Sotaniemi *et al.* (1986), thus creating intrahepatic shunting of the blood.

The high bioavailability of morphine found in the present study has not previously been shown but agrees well with the low extraction of morphine demonstrated by Crotty *et al.* (1989) as well as findings of increased oral bioavailability of other high to intermediate extraction drugs in cirrhotic patients, such as pentazocine (Neal *et al.*, 1979), pethidine (Neal *et al.*, 1979) and chlormethiazole (Pentikainen *et al.*, 1978). The relative contributions of a lowered intrinsic clearance and intra- or extrahepatic shunts to the increased bioavailability are unclear.

The metabolic ratios after intravenous and oral administration were similar in the patients. However, in the control group, they were much higher after oral intake (Figure 3), indicating higher enzyme activity in the controls. In patients without liver disease the oral M3G/M ratio *in vivo* correlated with M3G formation in liver microsomes isolated from the same patients (Säwe *et al.*, 1985).

The volume of distribution of morphine was not significantly different in the patients compared to the controls. The extent of plasma binding of morphine has been reported to be only 20–30% (Olsen, 1975; Pathwardhan *et al.*, 1981). Therefore an increased unbound fraction in plasma is unlikely to influence distribution of morphine significantly. Moreover Pathwardhan and co-workers (1981) measured plasma binding of morphine in cirrhotic patients and controls and did not find any differences.

The amount of morphine given intravenously in the present study did not cause EEG changes typical of liver encephalopathy. In one of our patients (number 1) a slowing in the EEG pattern similar to that seen when administering any sedative drug was observed. Most of the side effects were reported after the oral dose, in agreement with the higher concentrations of both morphine and the active metabolite M6G. No EEG-recording was performed after administration of the oral dose. However, in three of our patients two psychometric tests (Conn, 1977; Mirsky & Kornetsky 1964) were performed before and after administration of the oral dose and the results were unchanged during the 3 h observation period as compared with predose values, which might indicate that the encephalopathy was not deteriorating. However, higher doses could result in specific changes in the EEG or a worsening of the encephalopathy, as reported previously by Laidlaw *et al.* (1961).

Interaction with other drugs, e.g. spironolactone, must also be taken into account when evaluating the results of our study. There are no data in the literature to suggest such an interaction in humans although conflicting evidence of pharmacodynamic reactions in rats has been presented (Chu *et al.*, 1978; Selye *et al.*, 1969).

In conclusion we have found a significantly lower plasma clearance, a longer elimination half-life and a higher oral bioavailability of morphine in a group of seven cirrhotic patients compared with a group of patients with normal hepatic function. These data clearly indicate the need for dosage reduction in cirrhotic patients to avoid toxicity. To what extent the lower formation of M6G after the oral dose in cirrhotic patients is associated with a lower pharmacological effect has not been evaluated. The decreased clearance and high oral bioavailability of morphine will have a marked influence on blood drug concentrations after oral dose. Thus,

if an altered response is seen after an intravenous dose this will be even more pronounced after oral intake if the same doses are used in cirrhotic patients and patients with normal liver function.

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