TITLE : PHARMACOKINETICS OF MORPHINE IN NORMAL AND CIRRHOTIC SUBJECTS.

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INTRODUCTION. Cirrhosis of the liver usually decreases the rate of elimination of drugs which are actively metabolized by the liver. Morphine (M) is assumed to have a prolonged elimination half-life (t 1/2 β) in cirrhotic (Ci) patients when compared with normal (N) subjects (1). Surprisingly, Patwardhan et al (2) did not find any difference in M kinetics between N and Ci. Therefore, we used a highly specific radioimmunoassay in order to compare M kinetics in N and Ci subjects.

METHODS. After institutional approval, informed consent was given by 5 N subjects, aged (mean ± SD) 60 ± 8 years and weighing 65 ± 21 kg, and 7 alcoholic Ci patients aged 64 ± 6 years and weighing 71 ± 14 kg. Neither surgical portocaval shunt or clinical evidence of ascites was found in any. All had normal renal function. Major biochemical data (prothrombin time (PT), serum albumin (SA) and serum bilirubin (SBi)) levels are reported in table 1. All subjects received a single IV bolus of M hydrochloryde (0.1 mg/kg = 0.076 mg/kg M base). Peripheral venous samples were collected at frequent intervals from 2 min to 36 hours after injection. Dosage of unchanged M (M unc) in plasma was determined using a highly radioimmunoassay with a sensitivity of 0.2 ng/ml. Dosage of total M in plasma was determined using a standard radioimmunoassay (Abuscreen*). M metabolites (M met) were calculated (total M - M unc). Pharmacokinetic analysis was performed using a non-linear least-squares regression program. The following parameters were calculated : Terminal half-life (t 1/2 β), apparent volume of distribution (Vdβ), total body clearance (Clt), invasion half-life (t 1/2 α). Statistical analysis was performed using the non-parametric Mann-Witney U-test.

RESULTS. The prolonged t 1/2 β of free M in Ci patients was associated with a decreased Clt. Vdβ was similar in both groups. There was a prolonged t 1/2α and a shorter t 1/2 β of Mmet in the Ci group (table 2). A second peak of Mmet was observed in both groups (fig. 1).

DISCUSSION.

Unchanged M kinetics : Elimination of unchanged M is longer in Ci than in N subjects. The main cause of this prolonged t 1/2β is a slower Clt. Decrease in protein binding (increase in free fraction) due to the lower SA and higher SBi levels may occur in Ci patients (1). Nevertheless, in our study (patients without ascites) Vdβ does not significantly differ in the two groups.

Kinetics of M Metabolites : Production of metabolites (even actives (3)) did decrease in Ci patients, whereas elimination was shorter. This may be due to the lower SA and higher SBi levels in these Ci patients with normal renal function. The concentration-time curves show a second peak which may be due to late production of some metabolites and/or enterohepatic recirculation (4).

TABLE 1. Major biochemical data (mean ± SD)

	PT (per cent of normal)	SA (mmol/l)	SBi (umol/l)
N	100 per cent	491 ± 38	6 ± 2.3
Ci	52 ± 10 per cent	343 ± 56	45 ± 24
		p<0.01	p<0.01

TABLE 2. Pharmacokinetic parameters (mean ± SD)

	N	Ci	
M unc			
t 1/2β (min)	104 ± 44	168 ± 39	p<0.05
Vdβ (l.kg-1)	5.18 ± 1.9	4.58 ± 0.9	NS
Clt (ml.min-1.kg-1)	36 ± 18	19.5 ± 4.0	p<0.01
M met			
t 1/2α (min)	6.05 ± 1.7	24 ± 19	p<0.01
t 1/2β (min)	808 ± 228	166 ± 69	p<0.01

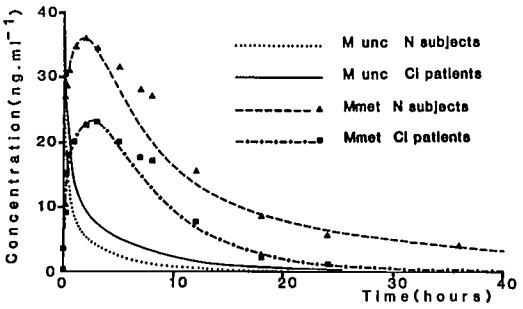

Fig. 1. Plasma levels of unchanged morphine and of metabolites. Curves were fitted to the mean data points for all patients in each group.

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