Title : SUFENTANIL PHARMACOKINETICS IN PATIENTS WITH CIRRHOSIS

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Introduction. Sufentanil like other central analgesics, undergoes extensive hepatic biotransformation prior to its excretion. Therefore liver dysfunction would be expected to alter its elimination kinetics. In the present study the pharmacokinetics of sufentanil were evaluated in patients with cirrhosis and in patients with normal liver function.

Methods. After Institutional approval and informed consent were obtained, 12 patients with histologically proven cirrhosis, aged (mean ± SD) 52 ± 12 yr and weighing 70 ± 12 kg and 9 patients ASA status 1-2 aged 50 ± 14 yr and weighing 68 ± 16 kg were studied. All patients underwent elective surgery or endoscopy under general anesthesia. None of the patients with cirrhosis had ascites, oedema or encephalopathy at the time of the study. Patients were premedicated with lorazepam orally (1.5 mg) and anesthetized with thiopental 5 $mg.kg^{-1}$ IV and nitrous oxide 70 percent in oxygen. Endotracheal intubation was carried out following an IV injection of 0.1 $mg.kg^{-1}$ vecuronium. Ventilation was controlled in order to maintain an end-tidal CO_2 of 5 %. A single dose of sufentanil of 3 $\mu g.kg^{-1}$ was administered over 30 s. Serum samples were obtained from a peripheral venous catheter at 2, 5, 10, 15, 30, 45 min and at 1, 1.5, 2, 3, 4, 6, 8 and 10 hours after sufentanil injection and sufentanil concentrations were determined by radioimmunoassay sensitive to 50 $pg.ml^{-1}$ (1). The following pharmacokinetic parameters were calculated : plasma clearance (Cl) by dividing the dose by the area under the curve of plasma concentration vs. time, terminal elimination half-life (t1/2 beta) by least squares regression analysis of Cp vs. time and total apparent volume of distribution (Vd beta) according to the following equation : Vd beta = Cl x 1.44 t1/2 beta. The unbound fraction of sufentanil was measured by equilibrium dialysis using serum collected preoperatively. Serum albumin (SA), α1-acid glycoprotein (α1GP), bilirubin (Bi) plasma concentrations and prothrombin time (PT) were measured preoperatively.

Results. Preoperative biochemical data are reported in Table 1. No significant difference was found in pharmacokinetic parameters between patients with cirrhosis and control patients (Table 2). The free fraction (FF) of sufentanil was not different between the two groups (Table 2). No correlation was observed between sufentanil FF and α1GP or SA concentration. The delay of recovery from anesthesia was the same in the two groups.

Discussion. The elimination of lipophilic drugs is generally delayed in patients with liver disease because the capacities for drug hepatic uptake, biotransformation and biliary elimination are diminished. In the present study however, the elimination kinetics of sufentanil remained unchanged in patients with cirrhosis. There could be several explanations for these findings. The patients with cirrhosis studied here could have eliminated sufentanil at the same rate as normal patients because their hepatic function was moderatly alterated. However a prolonged prothrombin time which is an index of decreased liver parenchymal function was observed in patients with cirrhosis. An other explanation is that owing to the potency of sufentanil and to its large volume of distribution, the plasma concentration of sufentanil becomes rapidly undetectable even after a dose of 3 $\mu g.kg^{-1}$. Then it is conceivable that in cirrhotic patients with moderate degree of hepatic insufficiency, the elimination kinetics appears unaltered over the first ten hours despite the hepatic dependent elimination of this drug. Thus the absence of detectable change in elimination kinetics together with unchanged unbound fraction of sufentanil presently observed suggests that sufentanil in a single dose will not exert a prolonged effect in uncomplicated cirrhosis.

Table 1. Biochemical data (mean ± SD)

	SA ($g.l^{-1}$)	α1GP ($g.l^{-1}$)	Bi ($mg.dl^{-1}$)	PT (sec)
Controls	36 ± 5	0.77 ±0.60	0.9 ± 0.7	12.7 ± 0.7
Cirrhosis	37 ± 4	1.07 ±1.19	2.1* ±1.1	15.7* ± 1.3

* $p < 0.05$ vs. controls

Table 2. Pharmacokinetics parameters (mean ± SD)

	T1/2 beta (h)	Vd beta ($l.kg^{-1}$)	Cl ($ml.min^{-1}.kg^{-1}$)	FF (%)
Controls	3.51 ±0.90	3.34 ±0.74	11.25 ± 2.46	8.3 ±1.5
Cirrhosis	4.09 ±0.57	3.98 ±1.59	10.83 ± 4.57	9.6 ±1.8

References.
1. Michiels M, Hendriks R, Heykants J : Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. J Pharm Pharmacol 33:86-93,1983