Tittle : FENTANYL PHARMACOKINETICS IN SURGICAL PATIENTS WITH CIRRHOSIS

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Introduction. To date, the pharmacokinetics of fentanyl (F) have been examined in several physiological and pathological situations in humans. There is however no data available concerning the pharmacokinetics of F in patients with liver disease, this despite its hepatic dependent route of elimination. The purpose of this study was to examine the disposition of F in patients with cirrhosis (Ci) undergoing surgery.

Methods. After obtaining informed consent and institutional approval, 8 patients with Ci aged (mean±SEM) 50±3 yrs and 13 normal patients (Nl) aged 41±2 yrs were studied. The diagnosis of Ci was established previously by a liver biopsy. All patients underwent elective surgery under general anesthesia. Patients were premedicated with diazepam (10-15 mg PO) and anesthetized with thiopental and nitrous oxide 70% in oxygen. A single bolus IV dose of F (5 µg/kg) was administered. Venous blood samples were obtained at 5, 10, 15, 30, 45 min and at 1, 2, 3, 4, 6, 8 and 10 hours after F injection. All samples were assayed for plasma concentration (Cp) of F by radioimmunoassay. The following pharmacokinetic parameters were calculated: the plasma clearance (Cl) was determined by dividing the dose by the area under the curve, the terminal elimination half-life (t 1/2 β) by linear regression of log Cp vs. time and the total apparent volume of distribution (Vd) according to the following equation: Vd=Clxt1/2β/log 2. F protein binding was performed by equilibrium dialysis at Cp of 1 and 10 ng/ml using purified ^{3}H-fentanyl. The values were compared between the two groups according to the Mann and Whitney U-test.

Results. The pharmacokinetic parameters summarized in Table 1, were not significantly different between the two groups. The free fraction of F was of 5.9±0.9 and 5.8±0.9 % and was significantly increased ($p < 0.05$) in Ci: 10.0±1.4 and 11.1±1.5 %, at Cp of 1 and 10 ng/ml respectively.

Discussion. It is generally accepted that the elimination of lipophilic drugs is delayed in patients with liver disease because the capacities for hepatic uptake and biotransformation are diminished. However in the present study, Cl and t 1/2 β were similar in Ci and Nl patients. This absence of significant change in total Cl in patients with Ci may receive several explanations. The increase protein free fraction presently observed may counter balance a decrease in hepatic intrinsic capacity of elimination. However F hepatic uptake is probably not restricted to the free fraction because of its elevated Cl suggesting a high extraction coefficient. F elimination may also be influenced by change in liver blood flow because of its high Cl. However when a highly extractable drug is administered intravenously, the systemic clerance may be maintained in patients with Ci because of the dual blood supply of the liver.[1] Assuming no difference in brain sensitivity to F in patients with Ci, our data predicts that the duration of action of F in Ci patients may be similar to that of Nl patients.

Table 1. Pharmacokinetic parameters

	T 1/2 β (min)	Cl (ml/kg/min)	Vd (l/kg)
Nl	384±71	10.7±1.3	5.29±0.86
Ci	545±183	10.1±1.9	5.62±0.74

Mean±SEM

Reference.

1. Neal EA, Meffin PJ, Gregory PB and Blaschke TF: Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis, Gastroenterology 77:96-102, 1979