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Alfentanil Pharmacokinetics in Patients with Cirrhosis

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The pharmacokinetics of alfentanil were studied in 11 patients with alcoholic cirrhosis and 10 control patients during general anesthesia. All patients received 50 $\mu g \cdot kg^{-1}$ alfentanil as an intravenous bolus injection. Plasma concentrations were measured at intervals up to 10 h, using a specific radioimmunoassay technique. Protein binding was measured by equilibrium dialysis. Patients with cirrhosis had a significantly lower ($P < 0.01$) plasma clearance of alfentanil of 1.6 ± 1.0 $ml \cdot min^{-1} \cdot kg^{-1}$ (mean ± SD) instead of 3.1 ± 1.6 $ml \cdot min^{-1} \cdot kg^{-1}$ in the controls. The total apparent volume of distribution was similar in the two groups. The elimination half-life was prolonged from 90 ± 18 min in the controls to 219 ± 128 min in the cirrhotics ($P < 0.01$). Patients with cirrhosis had a higher ($P < 0.01$) alfentanil plasma-free fraction (18.6 ± 9.4%) compared with the control patients (11.5 ± 3.9%). When kinetic parameters were corrected for protein binding, the unbound volume of distribution and the free drug clearance were decreased significantly in patients with cirrhosis. Since the concentration α1-glycoprotein to which alfentanil mainly is bound in plasma did not differ in the two groups, it is suggested that the increase in the free fraction is caused by an alteration of binding sites of this protein in patients with cirrhosis. Owing to its delayed elimination and increased free fraction, alfentanil will exert a prolonged and pronounced effect in patients with cirrhosis. (Key words: Analgesics: alfentanil. Intravenous anesthetics: alfentanil. Liver: cirrhosis. Pharmacokinetics: alfentanil.)

ALFENTANIL IS a new short-acting central analgesic that is highly bound to plasma proteins[1] and almost exclusively eliminated by the liver, since only 1% of the administered dose is excreted unchanged in urine in various animal species.[2] Alfentanil undergoes oxidative N-dealkylation catalyzed by the liver monooxygenase system into inactive metabolites.[3] Owing to its hepatic-dependent elimination, it would be anticipated that alfentanil clearance should be decreased in cirrhosis. We therefore studied the pharmacokinetics of alfentanil intravenously administered in patients with cirrhosis to assess the influence of liver dysfunction upon its disposition.

Materials and Methods

Eleven patients with cirrhosis, between the age of 39 and 69 yr (56 ± 13 yr, mean ± SD) and weighing 43 to 73 kg (60 ± 9 kg), and 10 patients with normal hepatic and renal function, between the ages of 24 and 66 yr (45 ± 13 yr), weighing between 34 and 84 kg (59 ± 14 kg), took part in the study after giving their informed consent. The study was approved by the Institutional Board of Paris 5 University. Table 1 summarizes the clinical features of the patients with cirrhosis. Alcoholism was the cause of liver disease in all the patients, and cirrhosis was diagnosed by the histologic examination of a liver biopsy. At the time of the study, none of the patients had ingested alcohol for at least 1 week and none had ascites. All of the control patients underwent abdominal surgery, which consisted of colectomy in three patients, gastrectomy in two patients, hysterectomy in three patients, and repair of abdominal hernias in two patients. The cirrhotic patients underwent abdominal surgery in six cases and endoscopic sclerosis of esophageal varices under general anesthesia in five cases (table 1). Premedication consisted of atropine 0.5 mg intramuscularly and 10 mg diazepam, given orally 1 h before anesthesia. Anesthesia was induced with thiopental 5 to 8 $mg \cdot kg^{-1}$ intravenously; succinylcholine, 0.8 $mg \cdot kg^{-1}$, was given to facilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen delivered by mechanical ventilation. Ventilation was adjusted in order to maintain end-tidal CO_2 approximately to 5% (Datascope® 500 CO_2 analyzer). Pancuronium, 80 $\mu g \cdot kg^{-1}$, followed by repeated doses of 20 $\mu g \cdot kg^{-1}$ was given to provide adequate muscle relaxation.

A single bolus dose of 50 $\mu g \cdot kg^{-1}$ of alfentanil was given intravenously, 5–10 min after thiopental was administered. In some cases, when the level of analgesia was insufficient, fentanyl in repeated doses of 0.1 mg was administered. Multiple blood samples were obtained

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TABLE 1. Characteristics and Liver Function Tests of Cirrhotic Patients

Patient Number	Sex	Age (yr)	Surgical Procedure	SGPT* (IU/ml)	Serum Alkaline Phosphatase† (IU/ml)	Serum‡ Bilirubin (mg/dl)	Prothrombin§ (per cent of normal)
1	F	39	Portocaval shunt	15	228	1.58	62
2	F	55	Splenorenal shunt	19	159	1.40	79
3	F	68	Hysterectomy	21	161	2.40	50
4	M	60	Abdominal hernias	19	109	1.40	64
5	M	70	Cholecystectomy	27	77	3.00	78
6	F	52	Splenorenal shunt	27	177	0.95	81
7	M	40	Sclerosis of esophageal varices	85	176	0.33	65
8	M	72	Sclerosis of esophageal varices	19	92	1.75	63
9	F	48	Sclerosis of esophageal varices	63	130	1.05	100
10	M	40	Sclerosis of esophageal varices	23	77	2.27	87
11	M	69	Sclerosis of esophageal varices	44	66	2.51	73

Normal values: * <20 IU/ml; † <30 IU/ml; ‡<1.0 mg/dl; §>80%.

over the next 10 h after alfentanil administration. Sampling times were 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, and 600 min after drug administration.

Alfentanil plasma concentration was determined by radioimmunoassay with a sensitivity of 0.1 $ng \cdot ml^{-1}$.[4] It was verified in our laboratory that the antibody used for alfentanil radioimmunoassay did not cross-react with fentanyl.

The free fraction (unbound fraction) of alfentanil was measured by equilibrium dialysis at 37° C, using purified tritium labeled alfentanil at two concentrations of 50 and 500 $ng \cdot ml^{-1}$ and using serum collected preoperatively from each patient. An equilibrium dialyser (Dianorm®, Diachema AG, Rüschlikon, Switzerland) composed of 1.3 ml Teflon® cells and of dialysis membranes (Spectrapor® 2, Spectrum, Los Angeles, California) was used. Serum samples of 1 ml to which the desired concentration of alfentanil had been added were dialyzed against 1 ml of 0.067 M phosphate buffer *p*H 7.3. The cells were rotated at 20 rpm in a drive system in a thermostat bath at 37° C. A dialysis time of 4 h was chosen. The drug in the buffer compartment was equal to the concentration of free drug (C unbound), whereas the concentration in the protein compartment (C) was equal to the sum of the concentrations of both free and bound drug (C bound). Then, the per cent-free drug was C unbound ×100/C. The concentration of albumin and of α1-glycoprotein also were measured[5] on preoperative serum samples.

The plasma concentration curves obtained for individual patients were fitted to a biexponential equation, interpreted as a two-compartment open model, using nonlinear least-squares regression analysis. The following pharmacokinetic parameters were derived: distribution half-life ($t_{1/2}\alpha$); elimination half-life ($t_{1/2}\beta$); volume of the central compartment (V_1); volume of distribution at steady state (Vd_{ss})[6]; and plasma clearance. The total apparent volume of distribution measured by the area method ($Vd\beta$) as determined by the trapezoidal rule also was obtained. Pharmacokinetic parameters based upon free alfentanil also were determined. The unbound clearance was determined by dividing the total drug clearance by the free fraction. The volume of distribution at steady state for unbound alfentanil was determined by dividing the Vd_{ss} by the free fraction. Statistical differences between the data obtained in the patients with cirrhosis and in the control patients were analyzed by the two-tailed nonparametric Mann-Whitney U-test, and linear regression was used to examine the relationship between alfentanil protein binding and plasma protein levels, with $P < 0.05$ taken as the minimum level of statistical significance.

Results

The duration of anesthesia was 2.1 ± 1.5 h in the control patients and 2.4 ± 1.6 h in the patients with cirrhosis. Additional doses of fentanyl were administered in seven control patients and in five cirrhotics. The plasma concentration curve was biexponential in all patients, as shown in figure 1. The distribution half-life and the volume of the central compartment were not significantly different between the two groups of patients (table 2). The total plasma clearance was diminished significantly ($P < 0.01$) in patients with cirrhosis from 3.1 ± 1.6 to 1.6 ± 1.0 $ml \cdot min^{-1} \cdot kg^{-1}$, leading to a prolonged elimination half-life from 90 ± 18 min in the

controls to 219 ± 128 min in the patients with cirrhosis. The total apparent volume of distribution was unchanged in cirrhotics. The extent of alfentanil protein binding was similar in the controls at the two alfentanil concentrations studied and the free fraction averaged 11.5% (table 3). Protein binding was decreased significantly in patients with cirrhosis. After correction for the individual differences in binding, the total apparent volume of distribution and the plasma clearance for the unbound drug were significantly different between the two groups. The unbound volume of distribution was of 1.71 ± 0.74 $l \cdot kg^{-1}$ in patients with cirrhosis instead of 2.58 ± 0.57 $l \cdot kg^{-1}$ in controls. In patients with cirrhosis the unbound clearance was decreased to 8.33 ± 4.61 $ml \cdot min^{-1} \cdot kg^{-1}$ instead of 26.31 ± 8.93 $ml \cdot min^{-1} \cdot kg^{-1}$ in controls. The plasma concentration of albumin was decreased significantly in patients with cirrhosis ($P < 0.05$), whereas the concentration of α1-glycoprotein did not differ between the two groups (table 3).

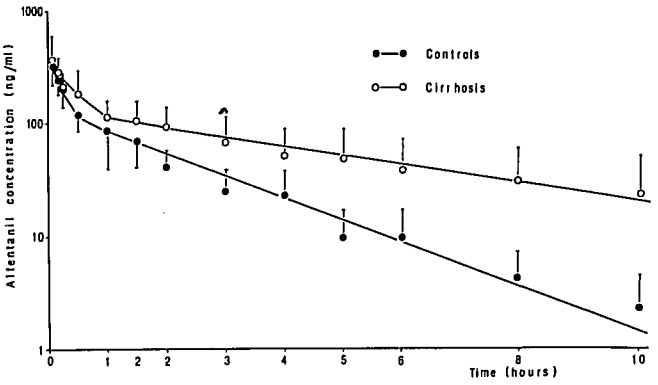

FIG. 1. Disappearance of alfentanil from the plasma following a single intravenous injection. Semilogarithmic plot of alfentanil plasma concentration (±SD) for control patients (black circles) and patients with cirrhosis (open circles).

Discussion

The decrease in drug plasma clearance in patients with cirrhosis may be caused by a combination of disordered hepatocyte function and decreased hepatic blood flow.[7] The relative importance of these two factors depends upon the hepatic extraction coefficient of the drug considered.

The hepatic extraction coefficient of alfentanil can be estimated by dividing the plasma clearance by the hepatic plasma flow, since alfentanil hardly crosses the red blood cell membrane.[1,8] According to the plasma clearance

TABLE 2. Body Weight and Pharmacokinetics of Alfentanil in Cirrhotics and Normal Patients

Subject	Body Weight (kg)	V_i* ($ml \cdot kg^{-1}$)	Vd_{ss}† ($ml \cdot kg^{-1}$)	$Vd\beta$‡ ($ml \cdot kg^{-1}$)	Cl§ ($ml \cdot min^{-1} \cdot kg^{-1}$)	$T_{1/2}\alpha$¶ (min)	$T_{1/2}\beta$** (min)
Patient with cirrhosis							
1	43	98	282	332	2.2	5	104
2	58	128	232	238	1.6	2	105
3	63	98	380	475	0.9	25	350
4	70	140	228	231	0.3	14	497
5	60	335	907	1,010	3.7	8	189
6	56	31	178	220	1.4	5	172
7	54	140	433	529	1.4	3	217
8	73	106	456	486	1.0	2	313
9	56	104	215	227	0.6	12	259
10	59	134	292	357	2.9	8	85
11	72	82	260	338	2.1	8	114
Mean ± SD	60 ± 9	128 ± 76	351 ± 206	404 ± 230	1.6 ± 1.0††	8 ± 7	219 ± 128††
Control							
1	34	215	251	280	3.3	22	67
2	73	169	484	778	7.3	9	83
3	68	97	237	344	2.7	12	97
4	84	149	236	276	2.2	16	94
5	55	141	159	161	1.1	9	100
6	40	80	253	312	2.1	7	113
7	60	125	237	277	2.8	9	71
8	63	118	326	376	2.8	6	94
9	61	135	403	460	2.8	6	114
10	50	69	224	294	3.5	5	64
Mean ± SD	59 ± 14	130 ± 43	281 ± 97	356 ± 167	3.1 ± 1.6	10 ± 6	90 ± 18

* Initial volume of distribution.
† Total apparent volume of distribution at steady state.
‡ Total apparent volume of distribution measured by the method of the area under the curve.
§ Plasma clearance.
¶ Distribution (alpha) half-life.
** Distribution (beta) half-life.
†† $P < 0.01$.

TABLE 3. Plasma Protein Concentration and Alfentanil Pharmacokinetic Parameters in Cirrhotic and Normal Patients

Subject	Albumin* Plasma ($g \cdot l^{-1}$)	α1-glycoprotein† Plasma ($g \cdot l^{-1}$)	Free Fraction Plasma (%) Alfentanil Concentration		Unbound Volume of Distribution ($l \cdot kg^{-1}$)	Unbound Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)
			50 $ng \cdot ml^{-1}$	500 $ng \cdot ml^{-1}$		
Patient with cirrhosis						
1	27	0.22	29.1	27.4	1.00	7.79
2	26	0.62	17.9	15.0	1.41	9.73
3	31	0.36	15.1	14.5	2.57	6.08
4	42	0.89	14.1	11.7	1.77	2.33
5	30	0.17	39.5	40.6	2.27	9.25
6	26	0.36	15.6	15.4	1.15	5.81
7	32	0.60	13.8	14.8	3.19	7.00
8	28	0.39	—	33.3	0.64	1.80
9	31	1.50	5.5	7.9	1.76	17.47
10	31	0.24	19.4	19.3	1.34	10.82
11	29	0.37	16.1	14.7	1.68	13.64
Mean ± SD	29 ± 5‡	0.52 ± 0.39	18.6 ± 9.4§	19.5 ± 10.0§	1.71 ± 0.74§	8.33 ± 4.61§
Control						
1	35	0.81	6.9	8.3	3.30	3.42
2	38	0.33	21.3	22.3	2.22	33.49
3	37	0.31	11.7	12.3	1.98	22.50
4	36	0.57	9.2	8.2	2.71	25.29
5	37	0.59	11.8	11.1	1.39	9.65
6	34	0.56	10.0	10.1	2.53	21.00
7	35	0.49	8.5	8.6	2.98	32.94
8	39	0.31	10.9	11.7	2.88	24.78
9	32	0.34	12.3	11.3	2.76	23.73
10	40	0.38	12.8	13.8	3.03	26.32
Mean ± SD	36 ± 2	0.47 ± 0.16	11.5 ± 3.9	11.8 ± 4.1	2.58 ± 0.57	26.31 ± 8.93

* Normal value: 30 $g \cdot l^{-1}$.
† Normal value: 0.50 $g \cdot l^{-1}$.
‡ $P < 0.05$.
§ $P < 0.01$ *versus* control.

value of Bovill *et al.*,[9] the extraction coefficient of alfentanil approaches 0.6, whereas a lower value of 0.3 is obtained in the controls from the present work and was found previously by Bower and Hull.[8] Therefore, afentanil can be classified among drugs with an intermediate hepatic extraction coefficient[8] and a decrease in hepatic plasma flow and in drug-metabolizing capacities probably both participate to the reduced clearance of alfentanil presently observed in patients with cirrhosis. Under the conditions of the present study, which was undertaken in anesthetized patients undergoing abdominal operations, the hepatic blood flow probably was diminished by both anesthesia and surgery. General anesthesia diminishes moderately the hepatic blood flow in comparison to abdominal surgery, which causes a profound decrease in the hepatic blood flow.[10] It remains difficult to extrapolate this effect of anesthesia and surgery obtained in patients with normal liver function to patients with cirrhosis. During the 10 h of blood sampling, the conditions were not identical from the start until the end of the study. The distribution phase was characterized during anesthesia and surgery, whereas the elimination phase occurred during the postoperative period. However, the conditions of the study were similar between the two groups of patients.

Alfentanil is bound extensively to plasma proteins,[1] and this factor may limit its hepatic uptake. In patients with cirrhosis, the decreased plasma binding capacities will minimize the influence of liver deficiency upon the kinetics of alfentanil elimination.[11] The decrease in the plasma clearance of the unbound fraction was greater than that in the total plasma clearance in patients with cirrhosis. A high free fraction of alfentanil should result in an increased volume of distribution of the drug.[12] However, no significant change was observed presently either in the volume of distribution of the central compartment or in the total apparent volume of distribution. In comparison, the decrease in the protein binding of alfentanil observed after extracorporeal circulation caused an increase in the volume of distribution and in the elimination half-life of alfentanil without affecting the plasma clearance.[12] The liver possibly may contribute to a large part of the volume of distribution of alfentanil in normal subjects, and then the reduced hepatic uptake of alfentanil in patients with cirrhosis will counterbalance the effect of the decreased binding on the volume of distribution.

Alfentanil is bound to α1-glycoprotein to a much larger extent than to albumin.[1] Therefore, the decrease in the albumin levels observed in cirrhotic patients

cannot explain by itself the decreased binding of alfentanil. The binding of drugs to plasma proteins is decreased or unchanged in patients with cirrhosis. The binding of acidic drugs frequently is diminished, owing to the decreased albumin plasma level, which reflects the decreased synthesis of hepatic proteins. In this respect, the decreased plasma protein binding of thiopental was correlated to hypoalbuminemia in patients with cirrhosis.[13] The binding of basic drugs such as lidocaine and propranolol, which occurs predominantly with α1-glycoprotein is altered unconstantly in patients with cirrhosis.[14] The plasma concentration of this acute phase reactant protein either may be diminished due to impaired hepatic synthesis or normal or even increased if an inflammatory process coexists in patients with cirrhosis, thus explaining conflicting results observed in these patients unless the concentration of α1-glycoprotein is not measured simultaneously. Presently the concentration of α1-glycoprotein was found to be normal in patients with cirrhosis, whereas the alfentanil-free fraction was higher in cirrhotic patients. These findings suggest that there was also a qualitative defect of the protein binding of alfentanil that was possibly due to a plasmatic factor[15] or to an alteration of this protein. The degree of sialylation of α1-glycoprotein was shown to be diminished in patients with cirrhosis,[16] and this change may lead to a protein with less binding sites.

Liver cirrhosis caused more profound pharmacokinetic alteration with alfentanil than with fentanyl. No changes in the elimination half-life nor in the plasma clearance of fentanyl were observed in patients with cirrhosis.[17] This difference may be explained by the much smaller total apparent volume of distribution of alfentanil, which is at least four times smaller than that of fentanyl.[2,9] The elimination of a drug with a large total apparent volume of distribution like fentanyl is influenced by the return of the drug from the deep tissue depots to the plasma, and the alterations caused by liver cirrhosis upon its kinetics are difficult to demonstrate.

Finally, we may conclude from the present study that alfentanil kinetics are altered markedly by cirrhosis, the two main alterations being a decreased plasma clearance and an increased unbound fraction. These changes were observed in patients with a moderate degree of hepatic insufficiency, and a more delayed elimination can be expected in patients with pronounced hepatic failure. The high free fraction of alfentanil encountered in patients with cirrhosis should enhance the initial effect of alfentanil, because entry into the brain is limited by its relatively low lipid solubility and extensive protein binding.[12] The delayed elimination kinetics of alfentanil in patients with cirrhosis will cause a prolonged effect only after the administration of a large single or cumulated dose. The decrease of the alfentanil plasma concentration below active threshold levels is dependent upon distribution process after a single small dose and upon the elimination half-life after large single dose, multiple small doses, or continuous infusion.[2]

References

1. Meuldermans WEG, Hurkmans RMA, Heykants JJP: Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. Arch Int Pharmacodyn Ther 257:4–19, 1982
2. Stanski DR, Hug CC: Alfentanil—a kinetically predictable narcotic analgesic. ANESTHESIOLOGY 57:435–438, 1982
3. Schuttler J, Stoeckel H: Alfentanil (R 39209): Ein neues kurzwirkindes opioid. Anaesthesist 31:10–14, 1982
4. Michiels M, Hendriks R, Heykants J: Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. J Pharm Pharmacol 35:86–93, 1983
5. Mancini G, Carbonara AO, Heremans JF: Immunochemical quantitation of antigens by single radial immunodiffusion. Immunochemistry 2:235–254, 1965
6. Benet LZ, Galeazzi R: Non-compartment estimation of the volume of distribution. J Pharm Sci 68:1071–1074, 1979
7. Wilkinson GR, Shand DG: Commantary: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377–390, 1975
8. Bower S, Hull CJ: Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 54:871–877, 1982
9. Bovill JG, Sevel PS, Blackburn CL, Heykants J: The pharmacokinetics of alfentanil (R 39209): A new opioid analgesic. ANESTHESIOLOGY 57:439–443, 1982
10. Gelman SI: Disturbances in hepatic blood flow during anesthesia and surgery. Arch Surg 111:881–883, 1976
11. Blaschke RK: Protein binding and kinetics of drugs in liver diseases. Clin Pharmacokinetic 2:32–44, 1977
12. Hug CC, De Lange S, Burm AGL: Alfentanil pharmacokinetics in patients before and after cardiopulmonary bypass (CPB). Anesth Analg 62:245–292, 1983
13. Pandele G, Chaux F, Salvadori C, Farinotti M, Duvaldestin P: Thiopental pharmacokinetics in patients with cirrhosis. ANESTHESIOLOGY 59:123–126, 1983
14. Piafsky KM: Disease-induced changes in the plasma binding of basic drugs. Clin Pharmacokinetics 5:246–262, 1980
15. Marshall JS, Williams S: Serum inhibitors of desialylated glycoprotein binding to hepatocyte membranes. Biochim Biophys Acta 543:41–52, 1978
16. Serbource-Goguel N, Corbic M, Erlinger S, Durand G, Agneray J, Feger J: Measurement of serum α1-acid glycoprotein and α1-antitrypsin desialylation in liver disease. Hepatology 3: 356–359, 1983
17. Haberer JP, Schoeffler E, Couderc E, Duvaldestin P: Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. Br J Anaesth 54:1267–1270, 1982