Title: PHARMACOKINETICS OF FENTANYL IN END-STAGE LIVER DISEASE

Authors: Y. G. Kang, M.D., M. Uram, M.D., Ph.D., G. K. Shiu, M.D., A. Bleyaert, M.D., D. J. Martin, M.D., E. Nemoto, Ph.D., T. Starzl, M.D.

Affiliation: Department of Anesthesiology/CCM, Presbyterian-University Hospital, University Health Center of Pittsburgh, Pittsburgh, Pennsylvania, 15213

Introduction. Fentanyl has become a major anesthetic agent for patients with unstable cardiovascular systems including patients undergoing liver transplantation. The rate of fentanyl biotransformation decreases in liver disease (1) and the elimination half-times of morphine and fentanyl are remarkably increased in anhepatic dogs (2). Extrahepatic biotransformation of fentanyl has been suggested in end-stage liver disease. However, it's pharmacokinetics remains unknown. The purpose of our study was to determine the pharmacokinetics of fentanyl in patients with end-stage liver disease.

Methods. This study was approved by the Review Board of Biomedical Research and informed consents were obtained. Seven consecutive patients undergoing homograft liver transplantation were included in the study (5 with primary biliary cirrhosis and 2 with sclerosing cholangitis). Anesthesia was induced with IV ketamine (2mg/kg) and maintained with isoflurane (0.25-1%). A single bolus of IV fentanyl (10ug/kg) was injected and arterial blood samples (3 ml each) were obtained at 1,3,5,10,15,30,60,90, and 120 minutes thereafter for determination of plasma fentanyl level. The plasma was separated immediately and kept frozen. Blood sampling was completed by the initial part of the operation to avoid the effects of blood volume changes on plasma fentanyl concentration. Plasma fentanyl levels were assayed by radio immunoassay (3) (commercial RAI kit from Damon Diagnostic). Pharmacokinetic coefficients and exponential equations were obtained by using residual analysis and weighed nonlinear least squares regression. Compartmental modelling was determined by the weighed sum of squared deviations and pharmacokinetic parameters were calculated.

Results. Pharmacokinetic parameters of each patient are shown in the table. The decline of plasma fentanyl was best described by a triexponential equation in all patients. The decline of plasma fentanyl was very rapid with the half-times of 1.2+0.8 min and 6.1+2.5 min in the first and second phase respectively. The elimination half-time of plasma fentanyl demonstrated widely ranging values and it was significantly prolonged in three patients (533, 1117, and 3850 min). The mean of volume of distribution was 3.9+1.5 l/kg. The volume of central compartment was small (149+91 ml/kg) and plasma fentanyl clearance varied (from 1 to 22.2 ml/kg/min). Although there was not any significant correlation between elimination half-time and the severity of the disease, it appears that patients with higher bilirubin level showed prolonged elimination of fentanyl.

Discussion. Although all patients suffered from end-stage liver disease, fentanyl pharmacokinetic parameters were not similar. Remarkably decreased biotransformation was observed in three patients and four patients demonstrated results similar to those of healthy volunteers(4). These four patients could have had better residual hepatic function or could have exhibited extrahepatic biotransformation of fentanyl. The observed of volume of distribution, which was similar to that of healthy volunteers, accompanied by a small central compartment volume may be attributable to the extensive systemic arteriovenous shunting seen with liver disease.

Our results demonstrate that the rate of fentanyl elimination varies significantly and the duration of fentanyl action cannot be predicted in patients with end-stage liver disease.

References.

1. Coral IM, Moore AR, and Strunin L: Plasma concentrations of fentanyl in normal surgical patients and those with severe renal and hepatic disease. Br J Anaesth 52:101, 1980.
2. Hug CC, Jr., Murphy MR, Sampson JF, et al: Biotransformation of morphine and fentanyl in anhepatic dogs. Anesthesiology No. 3, p A261, Sept 1981.
3. Michiels M, Hendriks R, and Heykants J: A sensitive radioimmunoassay for fentanyl. Europ J Clin Pharmacol 12, 153-158, 1977.
4. McClain DA, Hug CC, Jr: Intravenous fentanyl kinetics. Anesthesia and Analgesia Vol 58, No 5 Sept-Oct 1979.

PHARMACOKINETIC PARAMETERS OF FENTANYL

PATIENTS	$t_{\frac{1}{2}}$ II (min)	$t_{\frac{1}{2}}\alpha$ (min	$t_{\frac{1}{2}}\beta$ (min)	Vd (l/kg)	Vc (ml/kg)	Cl ($ml/kg/min^{-1}$)	Bilirubin mg%
1	0.57	6.84	192.5	3465	74.7	12.5	7.2
2	0.99	4.07	210	1790	144.5	5.9	4.0
3	2.79	2.91	169	4.241	66.0	17.4	1.1
4	1.44	8.06	196	3090	337.5	22.2	23.6
5	0.315	5.19	533	6380	83.0	8.3	58.5
6	1.3	1.86	1117	3379	176	2.1	18.9
7	0.76	8.01	3850	5479	143.0	1.0	54.0
Mean±SEM	1.16± 0.3	6.07± 0.93	895± 509	3974± 583	149± 34.4	9.9± 2.9	23.9± 8.9