Title: ALFENTANIL PHARMACOKINETICS IN CHILDREN WITH CHOLESTATIC LIVER FAILURE

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INTRODUCTION:

Growth, physiologic maturation and disease can greatly influence the pharmacokinetic profile of intravenous anesthetic agents. Alfentanil is a short-acting, highly protein-bound opioid, undergoes N dealkylation, and is eliminated almost exclusively by the liver. Only 1% of the drug appears unchanged in the urine. In adult surgical patients with hepatic disease, the pharmacokinetics of alfentanil are markedly different from pharmacokinetics in control patients (1). The effects of liver failure on alfentanil in children, however, have not been reported. In healthy children undergoing routine surgery, alfentanil has a small volume of distribution (Vd), short elimination half-life (t1/2β), stable cardiovascular properties and wide margin of safety (2). These attributes make alfentanil a potentially useful anesthetic in pediatric patients with hepatic disease. This study was designed to compare the pharmacokinetics of alfentanil in children with and without liver disease.

METHODS:

After our institution's Human Rights Committee approval and the informed written consent of a parent were obtained, 19 patients were divided into 2 groups. Group 1 (N=10) was patients with cholestatic liver disease (mean age ± SD, 5.4 ± 4.5 yrs) scheduled to undergo orthotopic liver transplantation. Group 2 (N=9) was patients (mean age ± SD, 5.0 ± 2.8 yrs) who required invasive monitoring for surgical procedures and had no evidence of hepatic disease. In all patients anesthesia was induced with nitrous oxide, oxygen and halothane. After an intravenous catheter had been inserted the halothane was discontinued and fentanyl or sufentanil along with pancuronium were administered to maintain anesthesia. After the trachea had been intubated and an arterial catheter inserted, alfentanil 25-100 μg/kg was administered over 30 seconds into a peripheral vein. Arterial blood samples were obtained at 1, 3, 5, 7.5, 10, 12, 15, 20, 30, 45, 60, 90, 120, and 180 minutes postinjection. Plasma was immediately separated and stored at -60°C. Alfentanil concentrations were determined with a specific radioimmunoassay. All samples were measured in duplicate. This assay accurately detects 0.1 ng/ml of alfentanil with interassay and intraassay coefficients of variation of 4 and 3, respectively. The pharmacokinetics were evaluated by model-dependent methods. The area under the concentration curve (AUC), t1/2β, steady-state volume of distribution (Vdss), and clearance (Cl) were calculated using standard formulas. Groups were compared with both parametric and nonparametric analyses. Significance was considered for $P < 0.05$. It was verified that antibodies to alfentanil failed to bind to fentanyl and sufentanil to any extent.

RESULTS:

Vd, t1/2β, or clearance (Cl) were all similar in the 2 groups.

	t1/2β min	Vdss (l/kg)	Cl(ml/kg/min)
Group 1	50 ± 15	0.48 ± 0.16	7.0 ± 3.4
Group 2	55 ± 15	0.43 ± 0.18	6.0 ± 2.5

DISCUSSION:

Hepatic disease appears not to affect the disposition and elimination of alfentanil in children. These findings contrast markedly with studies in adults where cirrhosis decreased the plasma clearance and prolonged the terminal elimination half-life. Whether these differences in the pharmacokinetic profile between adults and children with end-stage liver disease are a function of age or of differences in the underlying pathophysiology of adult and childhood disease states is unclear. It appears that in children with cholestatic liver disease, alfentanil may be a useful drug and that the dosage of alfentanil does not need to be altered.

This study was supported in part by Janssen Pharmaceutica.

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