Title: ALFENTANIL PHARMACOKINETICS IN PREMATURE INFANTS AND OLDER CHILDREN

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INTRODUCTION:

Alfentanil, a highly protein-bound synthetic opioid congener of fentanyl, has minimal cardiovascular effects. In healthy children undergoing routine surgery, alfentanil has a small volume of distribution (Vd) and short elimination half-life (t1/2β) (1). Because of increased medical and public concern regarding the adequacy of anesthetic techniques for premature infants, and the physiologic alterations (increased right-to-left shunting, hypoxemia, increased intraventricular pressure, intracranial hemorrhage) associated with stress and light anesthesia, opioid anesthesia is an evolving practice in pediatric patients. At present, however, many questions about the pharmacokinetics of opioids in premature infants have not been addressed. The purpose of this study was to evaluate the pharmacokinetic properties of alfentanil in premature infants and to compare these pharmacokinetic data to the pharmacokinetic profiles in older infants and children.

METHODS:

After our institutions' Human Rights Committee approval and the informed written consent of a parent were obtained, 15 patients were divided into 2 groups. Group I consisted of 6 premature infants, 1 to 3 days of age, 27-36 weeks gestation, undergoing stressful procedures (reintubation or chest tube insertion) or requiring sedation for medical management. Alfentanil 25 μg/kg was administered over 30 seconds into a peripheral vein. Arterial blood samples were obtained at 1, 3, 5, 10, 30, 120, 360, and 720 minutes postinjection. Group 2 consisted of 9 older children 9 months to 10 years of age (mean ± SD, 5.0 ± 2.8 yrs) who underwent various surgical procedures requiring invasive monitoring. 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, 2, 3, 5, 10, 12, 15, 20, 30, 45, 60, 90, 120, 180, and 240 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. It was verified that antibodies directed to alfentanil failed to bind fentanyl or sufentanil to any extent. Both parametric and nonparametric analyses were done to compare groups. Significance was considered for $P < 0.05$.

RESULTS:

The pharmacokinetic variables are listed in Table 1. Premature infants had significantly longer elimination half-life and slower clearance rate (Cl). Though the Vdss in premature infants was larger than in children, the difference did not reach statistical significance.

Table 1.

	t1/2β (min)	Vdss (l/kg)	Cl(ml/kg/min)
GROUP 1	540 ± 225*	0.60 ± 0.23	2.7 ± 2.1*
GROUP 2	55 ± 15	0.43 ± 0.10	6.0 ± 2.5

* $P < 0.05$ compared with Group II

DISCUSSION:

As did older children, premature infants displayed a wide variability in Vd and Cl of alfentanil. Compared with those in older children, premature infants have a markedly prolonged t1/2β and decreased Cl of alfentanil. Whether these changes in the pharmacokinetic profile are a function of age-related changes in hepatic blood flow, in mixed-function oxidase enzyme activity, or in protein binding has not been determined. Because of the longer elimination half-life and slower clearance rates, premature infants may require longer dosing intervals to maintain a desired plasma concentration.

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REFERENCES:

1. Meistelman C, Saint-Maurice C, Lepaul M, Levron J, Loose J, MacGee K: Anesthesiology 66:13-16, 1987