Title: PHARMACOKINETICS OF FENTANYL FOR INFANTS AND ADULTS

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Introduction. Despite the frequent use of narcotics for analgesia and anesthesia in infants and children, these drugs have undergone minimal investigation in pediatric patients. Our clinical experience suggests that infants and children tolerate large doses of fentanyl without the prolonged respiratory depression seen in adults. To explore the possibility of age-related differences in either distribution or elimination, we determined the pharmacokinetics of fentanyl in infants and adults.

Methods. We obtained approval from the local committee on human research and informed consent to study seven infants (3-10 months) and five adults (18-41 years), all ASA I and II. Patients were scheduled for elective noncardiac surgery and received no premedication. Anesthesia was induced with thiopental (2-6 mg/kg), N_2O, and oxygen, followed by pancuronium (0.1 mg/kg). Ventilation was controlled to keep P_aCO_2 at 35-42 mmHg; nasopharyngeal temperature was maintained at 35-37°C. Fentanyl (30 ug/kg for infants, 20 ug/kg for adults) was then given as a constant 2-min iv infusion. Anesthesia was maintained with N_2O, morphine sulfate, and pancuronium. Blood samples were obtained from an arterial or central venous catheter at frequent intervals for 4 h after the start of the fentanyl infusion. Plasma was stored at -20°C until concentrations of fentanyl were determined using radioimmunoassay (sensitivity, 0.5 ng/ml; coefficient of variation, <5%). The concentration-time curve was fitted, using a least-squares, nonlinear regression, to a two-compartment pharmacokinetic model adjusted for the infusion. Using standard formulas, we determined: distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), volume of the central compartment (V_1), steady-state volume of distribution (Vd_{ss}), and total plasma clearance (Cl). Mean values for these variables were compared for the two groups using Student's *t* test for unpaired data; $P < 0.05$ was considered significant.

Results. Elimination half-life was shorter and clearance higher in infants than in adults (table). There were no significant differences for V_1, Vd_{ss}, or $t_{1/2\alpha}$. Three to 4 h after administration, plasma concentrations of fentanyl increased transiently in two infants and two adults.

Discussion. The combination of a similar Vd_{ss} and a higher clearance results in a shorter elimination half-life in infants. As a result, at 3 h, plasma levels of fentanyl were lower in infants despite administration of a larger dose. Since fentanyl is lipophilic, its Vd_{ss} will depend on body composition, particularly adiposity. Body fat represents about 25% of body weight in infants,[1] similar to the value for adults, which may account for the similarity of Vd_{ss} in infants and adults. Since Vdss is similar for these two groups, fentanyl levels after distribution are similar in infants and adults. We found that the clearance of fentanyl was higher in infants than in adults. This is not surprising since fentanyl is metabolized by "mixed-function" oxidase enzymes[2] (found primarily in the liver) which have greater activity in infants than in adults.[3] Also, the liver comprises 5% of the mass of an infant compared to 2% of the mass of the adult. The secondary increases we observed in infants are consistent with previous reports for adults,[4] and could explain the biphasic respiratory depression reported for fentanyl.[5] Since recovery from large doses of fentanyl depends on elimination, rather than distribution, the shorter elimination half-life in infants may account for less postoperative depression.

References.

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Table. Pharmacokinetic data for fentanyl (mean ± SD)

	Infants	Adults
n	7	5
$t_{1/2\alpha}$ (min)	1.1 ± 0.4	2.1 ± 1.6
$t_{1/2\beta}$ (min)	68.0 ± 19.9*	120.9 ± 39.7
V_1 (l/kg)	0.24 ± 0.11	0.24 ± 0.16
Vd_{ss} (l/kg)	2.30 ± 0.58	2.40 ± 0.63
Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	30.6 ± 5.3*	17.9 ± 2.8
Dose (ug/kg)	31.5 ± 1.5*	20.8 ± 1.5
Plasma conc. at 180 min (ng/ml)	1.84 ± 0.61	2.24 ± 0.66

*Different from adults, $P < 0.05$.