Pharmacokinetics of Fentanyl in Neonatal Humans and Lambs: Effects of Age


To determine whether the clearance of fentanyl in neonates varies with age, the authors determined the pharmacokinetics of fentanyl in 14 human neonates ages 1–71 days and 15 lambs ages 3–37 days. In humans, fentanyl, 54.1 ± 2.3 (mean ± SD) μg/kg, was administered as a 2-min iv infusion; in lambs, fentanyl, 50 μg/kg, was administered as an iv bolus. Ventilation was controlled to maintain end-tidal or arterial PaCO₂ normal, and potent inhaled anesthetics were not administered; in humans, additional anesthesia was provided with iv morphine. Arterial or venous samples were obtained for 12 h, and plasma concentrations of fentanyl were determined by radioimmunoassay. Plasma concentration versus time data were fitted to two- and three-compartment pharmacokinetic models, and clearance, volume of distribution at steady-state (Vdss), and elimination half-life were determined. Clearance increased with age in both humans and lambs. Two humans who had intraabdominal surgery had no clearance of fentanyl; plasma concentrations of fentanyl remained constant for approximately 10 h after an initial distribution phase. In lambs, but not in humans, Vdss increased with age; elimination half-life did not change with age in either humans or lambs. The authors conclude that at least two factors—postnatal age and the type of surgery—affect fentanyl clearance during the neonatal period. The effect of other factors, such as inhaled anesthetics, remains to be determined. (Key words: Analgesics; fentanyl. Anesthesia, pediatric. Pharmacokinetics: fentanyl.)

DESpite the importance of fentanyl as an anesthetic agent for neonates,¹,² little is known about the factors affecting its metabolism in these patients. Koehntop et al.,³ determining the pharmacokinetics of fentanyl in 14 neonates, noted that total plasma clearance of fentanyl was lowest in neonates having abdominal surgery; they attributed this to the effects of abdominal surgery on hepatic blood flow or hepatic function. We considered that other factors that alter hepatic blood flow or hepatic function such as postnatal age might influence the clearance of fentanyl in neonates; however, only two of the subjects studied by Koehntop et al. were older than 4 days of age, so those investigators were unable to examine the effects of age on fentanyl clearance. Because preliminary data from our laboratory suggested that the clearance of fentanyl in neonates increased with age, we determined the pharmacokinetics of fentanyl in neonates of varying postnatal ages. In addition, because these studies were performed in surgical patients in whom many other factors (e.g., surgical manipulation of abdominal contents⁴ or increased abdominal pressure⁵) might influence hepatic blood flow or hepatic function, we also determined the pharmacokinetics of fentanyl in lambs in whom no surgical procedure was performed.

Methods

HUMAN STUDY

After obtaining approval from our Committee on Human Research and informed consent from parents, we studied 11 neonates and three young infants, 1–71 days of age, having surgery. Subjects had no hepatic, renal, or cardiac diseases except as noted in table 1. Anesthesia was induced with thiopental, 4–6 mg/kg iv, followed by pancuronium, 0.1 mg/kg iv; nine patients received N₂O, 30–60%. After tracheal intubation, fentanyl, 54.1 ± 2.3 (mean ± SD) μg/kg, was administered as a 2-min iv infusion. Supplemental anesthesia, if necessary, consisted of morphine sulfate; potent inhaled anesthetics were not administered because of their effects on hepatic blood flow.⁶ No additional drugs, other than antibiotics, were administered during the study. Ventilation was controlled to maintain normal values for arterial (35–40 mmHg) or end-tidal (30–35 mmHg) PaCO₂ throughout the study. Patients were given lactated Ringer’s solution in 5% dextrose at 4 ml·kg⁻¹·h⁻¹; during abdominal surgery, additional lactated Ringer’s solution was administered at 10–20 ml·kg⁻¹·h⁻¹. Arterial (n = 9) or central venous (n = 5) plasma samples (0.5–1.0 ml, each) were obtained before and 2, 5, 8, 12, 18, 24, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, and 720 min after the start of the infusion.

LAMB STUDY

After obtaining approval from our Committee on Animal Research, we studied 15 mixed-breed lambs, 3–37 days of age. Before the study, catheters were inserted into the abdominal aorta and the inferior vena cava, via cutdown, using local anesthesia (1% lidocaine, 2–3 ml). Animals were preoxygenated, then given fentanyl, 50 μg/
kg, as an iv bolus. When ventilation slowed, pancuronium, 0.1 mg/kg iv, was administered and the trachea was intubated. Ventilation was controlled mechanically to maintain arterial $P_{CO_2}$ between 35 and 40 mmHg. Arterial plasma samples were obtained before and 7.5, 15, 22.5, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600, and 720 min after fentanyl administration.

**Determination of Fentanyl Concentration and Pharmacokinetic Analysis**

The concentration of fentanyl was determined with the use of a radioimmunoassay sensitive to 0.05 ng/ml with a coefficient of variation of 10% at a concentration of 0.1 ng/ml. Plasma concentration of fentanyl was plotted against time, and two- and three-compartment pharmacokinetic models (modified for the infusion in studies performed in humans) were fit to these data with the use of nonlinear least-squares regression analysis. Residuals were weighted by (plasma concentration)$^{-1.5}$. A three-compartment model was selected if it significantly improved data fitting. We used standard formulas to determine the following: elimination half-life ($t_{1/2\beta}$); volume of distribution at steady-state ($V_d$); and total plasma clearance (Cl). These values were plotted against the age of the subjects and analyzed by least-squares linear regression. A $P < 0.05$ was considered statistically significant.

**Results**

**Human Study**

Clearance increased with age (fig. 1, table 1); most of this increase occurred by 2 weeks of age. Approximately one-third of the variability in fentanyl clearance could be explained by age ($r^2 = 0.31$). Elimination half-life and $V_d$ did not change with age. For two subjects who had abdominal surgery, the decline in plasma concentration of fentanyl during the first 2 h was similar to that in the remaining subjects; however, during the remaining 10 h, plasma concentration of fentanyl changed minimally (fig. 2). For these subjects, data were not fit to two- or three-compartment models: Cl was estimated as 0.0 ml·kg$^{-1}$·min$^{-1}$, $t_{1/2\beta}$ was not estimated, and $V_d$ was calculated as dose of fentanyl divided by the plasma concentration of fentanyl at 12 h. For six subjects, a three-compartment pharmacokinetic model was selected; a two-compartment model was selected for the remaining six subjects.

**Lamb Study**

Clearance (fig. 3, table 2) and $V_d$ increased with age; most of this increase occurred by 2 weeks of age. More than half of the variability in fentanyl clearance could be explained by age ($r^2 = 0.56$). Elimination half-life did not change with age. A three-compartment model was se-
FIG. 2. Plasma concentration versus time data are shown for two neonates. The top panel shows data for a 1-day-old infant who had repair of an omphalocele and received fentanyl, 32.5 µg/kg, as a 2-min infusion. The bottom panel shows data for a 3-day-old infant who had repair of hydrocephalus and received fentanyl, 56.5 µg/kg, as a 2-min infusion. For both patients, after the initial distribution phase there is no further decrease in the plasma concentration during the remaining 10 h. These data suggest that no clearance occurred during this period.

Table 2. Demographic Data and Values for Clearance (Cl), Volume of Distribution at Steady-state (Vdss), and Elimination Half-life (t1/2b) for Lambs (Subjects Listed in Order of Increasing Age).

<table>
<thead>
<tr>
<th>Age (Days)</th>
<th>Cl (ml·kg⁻¹·min⁻¹)</th>
<th>Vdss (l/kg)</th>
<th>t1/2b (min)</th>
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<tbody>
<tr>
<td>3</td>
<td>25.9</td>
<td>9.1</td>
<td>286</td>
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<tr>
<td>4</td>
<td>36.1</td>
<td>12.4</td>
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<tr>
<td>6</td>
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<td>10.2</td>
<td>420</td>
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<td>17</td>
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</tbody>
</table>

Selected for only one lamb; a two-compartment model was selected for the remaining lambs.

Discussion

Although relatively little is known about the metabolism and elimination of fentanyl in humans and other species, fentanyl is probably metabolized nearly exclusively in the liver. This is supported by the findings that clearance of fentanyl decreases approximately 90% in dogs who have heptectomy,** that only a small fraction of fentanyl is eliminated unchanged in the urine,18 and that, in adults, the clearance of fentanyl is similar to hepatic blood flow.14 In addition, in mature cows15 (and possibly in humans), all fentanyl entering the liver during each circulation is eliminated. These observations suggest that the clearance of fentanyl in neonates is a function of two factors—blood flow to the liver and the ability of the liver to extract fentanyl.

The ability of the liver to extract fentanyl will be a function of the maturity of the enzymes responsible for its metabolism, the cytochrome P450 system.16 Activity of this enzyme system is low at birth and increases rapidly during the neonatal period, reaching adult values at several weeks of age.17 Although the activity of the specific isozyme of cytochrome P450 responsible for fentanyl metabolism has not been measured in neonates, we speculate that the 1-day-old neonate may be less able than the 1-month-old infant to metabolize all the fentanyl entering the hepatic circulation. Immaturity of hepatic metabolic enzyme activity may explain some of the age-related change in clearance that we observed in humans and lambs.

Blood flow to the liver is affected by many factors that may vary in neonates having surgery. First, the liver represents a larger proportion of body weight at birth than at subsequent ages.18 Consequently, liver blood flow should be greatest at birth; however, serial measurements of liver blood flow during the neonatal period are not available. Second, increased abdominal pressure, such as

might occur during closure of an abdominal wall defect in the neonate, significantly decreases flow through the portal vein, the source of 90% of hepatic blood. Finally, the ductus venosus, a vessel connecting the portal vein to the vena cava, remains patent for at least several days after birth. Recent studies suggest that even after its functional closure, the ductus venosus can reopen, diverting significant quantities of portal venous blood from the liver. The effects of other factors that might occur during surgery in the neonate (e.g., increased abdominal pressure or release of vasoactive substances) on the fraction of portal venous blood bypassing the liver are unknown.

One additional factor that may influence fentanyl clearance in neonates is the administration of potent inhaled anesthetics. Halothane and isoflurane decrease total liver blood flow, and halothane affects metabolic capacity of cytochrome P450; these findings are consistent with the observation that potent inhaled anesthetics decrease fentanyl clearance. We did not administer potent inhaled anesthetics to our patients. However, Koehntop et al. gave several patients halothane or isoflurane in varying concentrations for varying periods of time; this may explain the great variability of fentanyl clearance (3.4–58.7 ml·kg⁻¹·min⁻¹) they observed in patients who had non-abdominal surgery.

We and others observed that fentanyl clearance was low or absent in some neonates having abdominal surgery. In two subjects having abdominal surgery, the plasma concentration of fentanyl decreased during the first several hours at the same rate as in subjects having other types of surgery, then did not decrease further during the remainder of the sampling period. The initial decrease in plasma fentanyl concentration represents distribution to tissues; the lack of change in plasma concentration during the remainder of the sampling period suggests that there was no clearance. This would occur if liver function were significantly compromised, if there were no hepatic blood flow, or if the liver were immature and unable to metabolize fentanyl. Any of these might have occurred in our patients. Although we did not measure intraabdominal pressure in these subjects, Yaster et al. reported that intragastric pressure (the value these investigators used to estimate intraabdominal pressure) frequently exceeded 20 mmHg in neonates having abdominal surgery. Masey et al. found that increases in abdominal pressure of this magnitude are associated with significant decreases in blood flow to the intestines and presumably to the liver (these investigators did not measure blood flow through the ductus venosus and therefore were unable to determine hepatic blood flow). In addition, with a decrease in portal venous blood flow, the intestines might extract more oxygen, decreasing the oxygen content of portal venous blood. The combined effects of lower portal venous blood flow and a decreased oxygen content might significantly decrease delivery of oxygen to the liver, altering its ability to metabolize via oxidative pathways. This problem would be further exacerbated if patency of the ductus venosus resulted in large quantities of hepatic venous blood bypassing the liver. Fentanyl metabolism would be further compromised if the liver were immature. Thus, the absence of clearance in two neonates having abdominal surgery might result from one of several factors—decreased blood supply to the liver, decreased hepatic function as a result of hypoxia, or hepatic immaturity.

In summary, clearance of fentanyl increased during the neonatal period, and abdominal surgery was sometimes associated with low or absent clearance. Whether this age-related change in fentanyl clearance results from maturation of hepatic enzyme function or changes in blood flow through the ductus venosus remains to be determined. In addition, other factors such as potent inhaled anesthetics may influence fentanyl clearance in the neonate.

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References


