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Dose-independent Pharmacokinetics of Fentanyl

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Fentanyl is used as an analgesic in small doses (1–2 $\mu g \cdot kg^{-1}$) and as an anesthetic in very large doses (>150 $\mu g \cdot kg^{-1}$). It has been demonstrated that the effects of fentanyl correlate with its concentrations in plasma. It is important, therefore, to know whether or not the pharmacokinetics of fentanyl vary with dose size in order to predict the plasma concentrations and effects produced by various dosage regiments. The authors studied the pharmacokinetics of fentanyl in dogs. ^{3}H-fentanyl (2.5–640 $\mu g \cdot kg^{-1}$) was injected intravenously in dogs anesthetized at a stable level with enflurane–O_2. Arterial plasma and urine were analyzed for unchanged ^{3}H-fentanyl. Kinetic indices were derived by nonlinear least-squares analysis of log concentration of fentanyl in plasma ($ng \cdot ml^{-1}$) *versus* time after a bolus injection. The terminal elimination half-time ($t_{1/2}\beta$ = 211 min), the apparent volume of distribution (9.5 $l \cdot kg^{-1}$), the volume of the central compartment (1.14 $l \cdot kg^{-1}$), and the clearance (37 $ml \cdot kg^{-1} \cdot min^{-1}$) of fentanyl were independent of dose over the 6.4–640 $\mu g \cdot kg^{-1}$ dose range. The distribution volume and distribution half-times were lower for the 2.5 $\mu g \cdot kg^{-1}$ than for some of the larger doses; this was attributed to differences in experimental conditions. The authors conclude that the pharmacokinetics of fentanyl are dose independent certainly over the 6.4–640 $\mu g \cdot kg^{-1}$ dose range. There is no evidence of saturation of biotransformation or tissue uptake mechanisms for doses in the range of 2.5 to 640 $\mu g \cdot kg^{-1}$. (Key Words: Analgesics, narcotic: fentanyl. Anesthetics, intravenous: fentanyl. Anesthetics, volatile: enflurane. Pharmacokinetics: fentanyl.)

FENTANYL IS USED CLINICALLY in a very wide range of doses. Low doses of 1–2 $\mu g \cdot kg^{-1}$ are used for analgesia and as anesthetic supplements, while doses of 50 to more than 150 $\mu g \cdot kg^{-1}$ have been used to produce general anesthesia.[1] It was demonstrated previously that the effects of fentanyl correlate with its concentrations in plasma.[2–4] It is important to know whether or not the kinetics of fentanyl distribution and elimination vary with dose size in order to predict the concentrations (and effects) resulting from different dosage regimens.

Fentanyl is eliminated primarily by metabolism in the liver. Saturation of biotransformation mechanisms has been demonstrated for other drugs.[5] Furthermore, the effects of increasing doses of some drugs may alter hemodynamics or other aspects of body physiology and thereby affect the rate of their own distribution and elimination.[6]

We determined the pharmacokinetics of fentanyl over a 256-fold dose range. Because it is difficult to justify the use of extremely large doses of fentanyl in volunteers or physically fit surgical patients, and since mongrel dogs have proven to be suitable animal models for normal humans in studies of the disposition of narcotic analgesics, including fentanyl, dogs were chosen for this study.[4,7,8]

Methods and Materials

Nineteen mongrel dogs, weighing 9–21 kg, were each given an intravenous injection of succinylcholine chloride (0.1–0.2 $mg \cdot kg^{-1}$) and atropine sulfate (0.1–0.2 $mg \cdot kg^{-1}$), and anesthesia was induced immediately with enflurane (3.5–5% in oxygen) administered via a mask and Bain anesthesia circuit. A cuffed oral endotracheal tube was introduced. The animals were paralyzed with pancuronium (0.25–0.5 $mg \cdot kg^{-1}$), and their ventilation was controlled with a Harvard respirator. The lungs were hyperinflated periodically to prevent atelectasis. Pa_{O_2} remained above 300 mmHg in every animal. Pa_{CO_2} and *p*H averaged 40 ± 1 mmHg and 7.36 ± 0.01, mean ± SE, respectively. Anesthesia was maintained with end-tidal enflurane concentrations of 2–2.5% with a mean of 2.4 ± 0.1 (SE)%.

A cannula was inserted in a foreleg vein, and 5% dextrose in lactated Ringer's solution was administered at a rate of 11 ± 1 $ml \cdot kg^{-1} \cdot h^{-1}$. A femoral artery cannula was utilized for continuous blood pressure recordings and periodic sampling of blood. When blood was withdrawn it was immediately replaced with an equal volume of 5% albumin. The electrocardiogram was monitored for cardiac rate and rhythm. The pharyngeal temperature averaged 37.0 ± 0.3° (SE) C. Urine was collected from a transurethral catheter.

Fentanyl citrate, uniformly labeled with tritium on the aniline ring (specific activity 105 $nCi \cdot \mu g^{-1}$),§ was used for these experiments. ^{3}H-fentanyl citrate was injected intravenously over a 30-s period in a single dose (calculated as the base) of either 2.5 (n = 4), 6.4 (n = 4), 64 (n = 7), or 640 (n = 4) $\mu g \cdot kg^{-1}$.¶ Samples of blood and urine were collected at specified intervals over the next 6–8 hours. Aliquots of plasma and urine were analyzed

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§ Generously supplied by Janssen Pharmaceutica, Beerse, Belgium.

¶ The data for the 6.4 $\mu g \cdot kg^{-1}$ dose and for five of the seven animals given the 64 $\mu g \cdot kg^{-1}$ dose have previously been reported but were reported as the citrate salt rather than fentanyl base. They were reported as 10 and 100 $\mu g \cdot kg^{-1}$ doses rather than 6.4 and 64, respectively, since 10 μg of the citrate salt of fentanyl is equivalent to 6.4 μg of the base.[2,7]

TABLE 1. Pharmacokinetics of Fentanyl in Plasma after Intravenous Injection in Dogs (Mean ± SE) $C_{p(t)} = P \exp^{-\pi t} + A \exp^{-\alpha t} + B \exp^{-\beta t}$*

Dose ($\mu g \cdot kg^{-1}$)	N	P ($ng \cdot ml^{-1}$)	π (min^{-1})	$t_{1/2}\pi$ (min)	A ($ng \cdot ml^{-1}$)	α (min^{-1})	$t_{1/2}\alpha$ (min)	B ($ng \cdot ml^{-1}$)	β (min^{-1})	$t_{1/2}\beta$ (min)
2.5	4	7.0 ± 0.8	0.561 ± 0.066†	1.3 ± 0.2†	0.76 ± 0.09	0.0693 ± 0.0172‡	12.0 ± 2.8‡	0.29 ± 0.05	0.00508 ± 0.00091	152 ± 29
6.4	4	5.2 ± 1.5	0.281 ± 0.040	2.6 ± 0.4	1.25 ± 0.15	0.0219 ± 0.0026	33.0 ± 3.9	0.33 ± 0.05	0.00351 ± 0.00062	222 ± 48
64	7	48.1 ± 9.8	0.275 ± 0.059	3.6 ± 0.9	13.9 ± 1.3	0.0246 ± 0.0033	31.9 ± 4.7	3.5 ± 0.3	0.00329 ± 0.00026	220 ± 20
640	4	375 ± 46	0.313 ± 0.035	2.3 ± 0.3	132 ± 16	0.0343 ± 0.0020	20.4 ± 1.1	49 ± 6	0.00380 ± 0.00025	184 ± 11

* This triexponential equation gives the concentration of fentanyl in plasma (C_p) at any time (t) as a function of the parameters which define the elimination curve using the method of residuals as described by Gibaldi and Perrier[11] and a standard nonlinear regression computer analysis.[12] The values for the terms of the equation are shown in the respective columns.
† $P < 0.05$ *vs.* other doses.
‡ $P < 0.05$ *vs.* 6.4 & 64 $\mu g \cdot kg^{-1}$ doses.

for unchanged fentanyl and its tritium-labeled metabolites by a solvent extraction procedure and scintillation counting as previously described.[7]

Each value is expressed as the mean ± standard error of the mean unless designated otherwise. One way analysis of variance with Bonferroni multiple comparison or Kruskal–Wallis one-way analysis of variance were used for group comparisons, with $P < 0.05$ as the minimal limit of significance. "Fentanyl," hereafter, refers to the base form of the unchanged tritium-labeled drug. "Total radioactivity" refers to both unchanged fentanyl and its ^{3}H-labeled metabolites, while the difference between total radioactivity and fentanyl concentrations was taken as an estimate of the concentration of metabolites in a sample.

Results

The decline of fentanyl in plasma for all four doses was best described by a triexponential equation (table 1, fig. 1) based upon nonlinear least-squares analysis of the log plasma concentration *versus* time.[7]** The concentration of fentanyl in plasma was proportional to dose throughout the period of study for the 6.4–640 $\mu g \cdot kg^{-1}$ doses but not for the 2.5 $\mu g \cdot kg^{-1}$ dose (tables 1 and 2). The half-time of the rapid distribution phase ($t_{1/2}\pi$) averaged 3.0 ± 0.5 min (n = 15) for the three larger doses and 1.3 ± 0.2 min for the 2.5 $\mu g \cdot kg^{-1}$ dose. The mean half-times for the slow distribution phase ($t_{1/2}\alpha$) varied between 12.0 and 33.0 min for the four groups of animals. The terminal elimination phase half-time ($t_{1/2}\beta$) averaged 211 ± 15 min for the three higher doses, was 152 ± 29 min for the lowest dose, but the difference was not statistically significant.

The apparent volume of distribution (V_d) and the apparent volume of the central compartment (V_c) were independent of dose over the 6.4–640 $\mu g \cdot kg^{-1}$ dose range and averaged 10.5 ± 0.5 and 1.14 ± 0.11 $l \cdot kg^{-1}$, respectively (table 2). The central and total distribution volumes for the 2.5 $\mu g \cdot kg^{-1}$ dose tended to be lower than those for the three larger doses (table 2). The clearance of fentanyl from the body (Cl) was not statistically different for the 2.5–640 $\mu g \cdot kg^{-1}$ dose range (35.5 ± 1.7 $ml \cdot kg^{-1} \cdot min^{-1}$, n = 19).

^{3}H-labeled metabolites of fentanyl were evident in the first plasma samples taken at 2 min after all four doses and accounted for 11 ± 3, 28 ± 3, 29 ± 4, and 24 ± 4% of the total ^{3}H-radioactivity in plasma at 2 min for the 2.5, 6.4, 64, and 640 $\mu g \cdot kg^{-1}$ doses, respectively (fig. 1). The concentrations of metabolites peaked between 30 and 90 min in all cases and the peak values averaged 81 ± 3, 86 ± 2, 80 ± 1, and 75 ± 4% of the total

** A triexponential equation provided a significantly (F-ratio test[9]) better description of the data than did a biexponential equation.

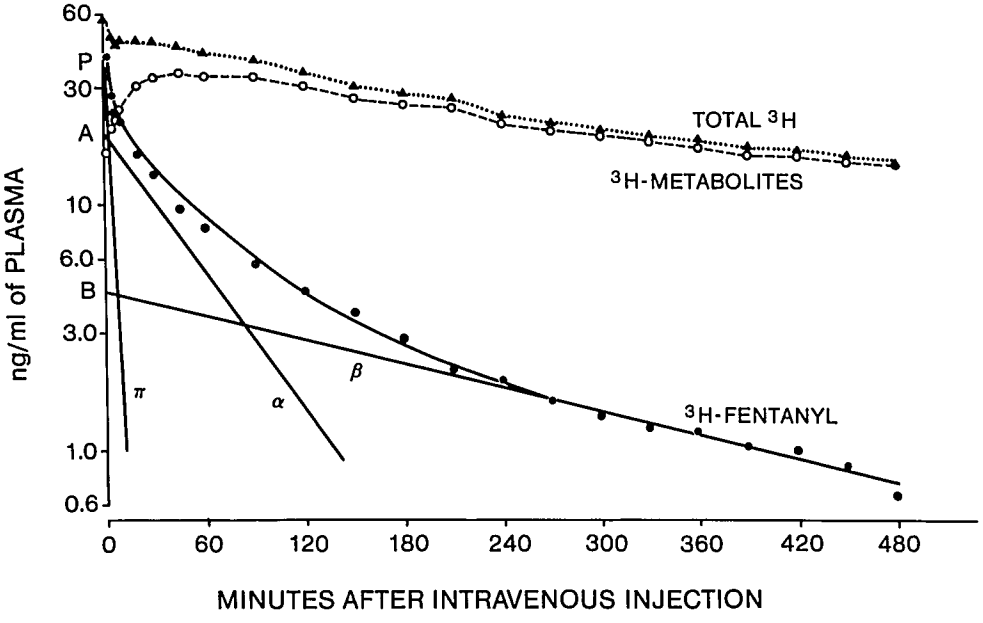

FIG. 1. Plasma levels of total ^{3}H-radioactivity, ^{3}H-metabolites, and unchanged ^{3}H-fentanyl in one dog (M22) given ^{3}H-fentanyl, 64 $\mu g \cdot kg^{-1}$, intravenously. Each data point represents the mean of duplicate determinations. The curve for unchanged fentanyl was fitted to the data points by the triexponential equation: $C_{P(t)} = 36 \exp^{-0.34t} + 19 \exp^{-0.021t} + 4.4 \exp^{-0.0037t}$. The half-times for the π, α, and β phases are 2.0, 32.4, and 188 min, respectively. The intercepts (P, A, and B) are indicated on the y-axis.

radioactivity in plasma for the lowest to the highest doses, respectively. The decline of ^{3}H-metabolites in plasma was slower than that of fentanyl. Six hours after injection of fentanyl, the ^{3}H-labeled metabolites accounted for 91 ± 1, 94 ± 1, 94 ± 1, and 93 ± 1% of the plasma radioactivity for the 2.5–640 $\mu g \cdot kg^{-1}$ doses, respectively.

By 6 h, 29 ± 4, 40 ± 5, 33 ± 6, and 30 ± 6% of the 2.5, 6.4, 64, and 640 $\mu g \cdot kg^{-1}$ doses, respectively, were recovered in the urine, primarily as metabolites. Only 4.3 ± 0.8% of the amount administered was excreted as unchanged fentanyl in the first 6 h after its intravenous injection, and the percentage of the dose recovered as unchanged drug did not differ for the four doses.

Discussion

The pharmacokinetics of fentanyl in plasma of dogs anesthetized at stable concentrations of enflurane were essentially independent of the dose of fentanyl over the 100-fold range of 6.4–640 $\mu g \cdot kg^{-1}$. The volume of distribution was large, 10.5 $l \cdot kg^{-1}$ and indicated that fentanyl was highly concentrated in some or all tissues. In fact, it has been demonstrated in the rat that fentanyl is accumulated rapidly and extensively in body tissues.[10] No evidence of saturation of tissue uptake mechanisms was evident up to the very large 640 $\mu g \cdot kg^{-1}$ dose. The smaller volumes of distribution found with the 2.5 $\mu g \cdot kg^{-1}$ dose indicate that somewhat more fentanyl would be available in plasma for clearance from the body. Since the clearance of fentanyl was not statistically different for any of the doses, the increased availability of fentanyl for biotransformation after the lowest dose was evident as a shorter terminal elimination half-life for the 2.5 $\mu g \cdot kg^{-1}$ dose compared with the higher doses ($t_{1/2}\beta$ = 152 *vs.* 211 min, respectively).

There was no evidence of saturation of biotransformation mechanisms even at the highest dose. The appearance of metabolites in plasma was rapid after all doses and the percentage of the injected fentanyl metabolized was not dose dependent. Minimal amounts of unchanged

TABLE 2. Kinetic Variables Calculated for Unchanged Fentanyl Concentrations in Plasma in Dogs (Mean ± SE)

Dose ($\mu g \cdot kg^{-1}$)	Estimated Plasma Concentration at Time Zero ($C_{P(0)} = A + B + C$) $C_{P(0)}$ ($ng \cdot ml^{-1}$)	Initial Volume of Distribution V_c = Dose/C_{P0} V_c ($l \cdot kg^{-1}$)	Volume of Distribution V_d area = $\frac{\text{Dose}}{\text{AUC} \cdot \beta}$ V_d area ($l \cdot kg^{-1}$)	Clearance Cl = Dose/Auc* Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)
2.5	8.0 ± 0.8	0.32 ± 0.0	6.5 ± 1.0†	30.5 ± 1.7
6.4	6.8 ± 1.5	1.05 ± 0.16	11.4 ± 1.1	38.6 ± 5.4
64	65.5 ± 9.8	1.17 ± 0.24	10.6 ± 0.7	36.2 ± 2.4
640	547 ± 33	1.16 ± 0.06	9.5 ± 0.7	36.0 ± 3.7

* AUC = $\frac{P}{\pi} + \frac{A}{\alpha} + \frac{B}{\beta}$ where the terms P, A, and B, and the exponents π, α, and β are taken from the triexponential equation shown in table 1.

† $P < 0.05$ *versus* 6.4 and 64 $\mu g/kg$ doses.

fentanyl were excreted through the kidneys and they, therefore, have little impact upon the elimination of fentanyl from plasma. Even so, there was no evidence of dose-dependent differences in excretion of either unchanged fentanyl or its metabolites.

The differences noted in the pharmacokinetics of fentanyl for the lowest dose compared with the higher doses is not explained readily and in fact may be more apparent than real. The differences are probably related to several problems encountered with the study of the lowest dose. First, the dose produced low concentrations of fentanyl in plasma that were at the limits of our analytic sensitivity, thereby reducing the reliability of estimates of fentanyl concentrations during the terminal elimination phase. Second, these dogs were studied at somewhat lighter levels of anesthesia. Although the enflurane concentrations were only slightly less (2.2% at the lowest dose compared with 2.4% in end-tidal gas for the higher doses), the *combined* anesthetic effects of enflurane and the lowest dose of fentanyl were probably much less than for any of the other three groups receiving substantially higher fentanyl doses. The smaller distribution volumes may reflect different hemodynamics (including altered regional blood flows) and presumably lighter levels of anesthesia. Heart rate changes were not consistent and were unrelated to dose. In general, heart rate tended to remain unchanged for the entire study or to decrease slowly and progressively 2–4 h after the fentanyl dose was given. Blood pressure, however, increased slightly (2–13%) following the 2.5 $\mu g \cdot kg^{-1}$ dose and did not change for the 6.4 $\mu g \cdot kg^{-1}$ dose. Blood pressure decreases for the 64 $\mu g \cdot kg^{-1}$ dose averaged about 9% and for the 640 $\mu g \cdot kg^{-1}$ dose about 13% and remained essentially unchanged throughout the remainder of the experiment.

Since the dog otherwise has served as a model for narcotics in humans, we hypothesize that the pharmacokinetics of fentanyl will be dose independent in the range of clinical doses used in humans.[4,7,8]

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