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Pharmacokinetics of ^{3}H-Fentanyl in the Dog Anesthetized with Enflurane

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Fentanyl is often used as an anesthetic supplement for short procedures because it has a rapid onset and brief duration of action. However, persistence of ventilatory depression several hours following the last dose has been seen. The authors studied the pharmacokinetics of fentanyl in the dog to find an explanation for the occasionally prolonged duration of action. ^{3}H-fentanyl citrate, 10 or 100 μg/kg, was injected intravenously in dogs anesthetized with enflurane–O_2. Arterial plasma and urine were analyzed for unchanged ^{3}H-fentanyl and for total ^{3}H radioactivity. Kinetic indices were derived by nonlinear least-squares analysis of log concentration (ng/ml) *vs.* time relationships. Initially, the elimination of fentanyl from plasma was very rapid, and 98 per cent of the amount administered was removed from plasma in the first 5 min after an intravenous injection. However, the terminal elimination phase was prolonged ($t_{1/2}$ = 199 ± 17 min). The apparent volume of distribution was large (9.8 l/kg) and independent of dose. Repetitive doses produced an accumulation of fentanyl. ^{3}H-labelled metabolites of fentanyl were present in the earliest samples of plasma, and accounted for the major portion of the total ^{3}H radioactivity in both plasma and urine. Urine collected for six hours contained 36 per cent of the total ^{3}H radioactivity administered, but only 4 per cent of fentanyl administered was excreted as unchanged fentanyl. The authors conclude that most of a single dose of fentanyl is rapidly eliminated from plasma (and presumably brain) by biotransformation to inactive metabolites and by uptake of the active drug by body tissues. The high affinity of tissues for fentanyl limits the rate of its ultimate elimination from the body by biotransformation and leads to accumulation of the drug when administered in very large or repeated doses. Under these circumstances the slow release of drug from tissues results in persistent plasma levels of fentanyl and a prolonged duration of action. (Key words: Analgesics, narcotic: fentanyl. Pharmacokinetics.)

FENTANYL CITRATE is a potent narcotic analgesic notable for its rapid onset and brief duration of action. Fentanyl is often used as an anesthetic supplement, especially in procedures of brief duration. Because fentanyl administered as single intravenous doses has a short duration of action, such doses are sometimes repeated at regularly timed intervals in an effort to maintain its effects. However, unexpected respiratory depression several hours after the last dose has been reported.[1,2] This study defines the pharmacokinetics of fentanyl in dog plasma and offers an explanation for prolonged effects of an apparently short-acting drug.

Methods and Materials

Mongrel dogs, each weighing 10 to 20 kg, were each given an intravenous injection of succinylcholine chloride, 0.1–0.2 mg/kg,§ and atropine sulfate, 0.1–0.2 mg/kg, and anesthesia was immediately induced with enflurane, 3.5–5 per cent, in oxygen, administered via a mask and a Bain anesthesia circuit.[3] A cuffed oral endotracheal tube was introduced. ^{3}H-fentanyl citrate was injected intravenously.

Six dogs given 10 μg/kg fentanyl citrate were allowed to breathe spontaneously so that the ventilatory effects of fentanyl could be measured. Two dogs given 10 μg/kg and all of five dogs receiving 100 μg/kg (which produces prolonged apnea) were paralyzed with pancuronium, 0.25–0.5 mg/kg, and their ventilation was controlled with a respirator. Pa_{O_2} remained above 300 torr in every animal. Pa_{CO_2} and *p*H averaged 39 ± 1.1 torr and 7.38 ± 0.01, respectively, in artificially ventilated dogs, and varied in the ranges 43–54 torr and 7.24–7.32 in animals breathing spontaneously. Pharmacokinetic parameters did not differ between spontaneously breathing and mechanically ventilated animals. Anesthesia was maintained with 2–3 per cent enflurane in oxygen, flowing at 4–6 l/min to prevent rebreathing. End-tidal concentrations of enflurane varied less than 0.12 per cent in any single animal during the experimental period.

The dog's lungs were hyperinflated periodically to minimize atelectasis. A cannula was inserted in a foreleg vein and dextrose, 5 per cent, in lactated Ringer's solution was administered at a rate of 9–14 ml/kg/hr. Bilateral femoral-artery cannulas were

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§ The intravenous administration of succinylcholine allowed immediate positive-pressure ventilation with a high concentration of enflurane to produce a rapid induction of anesthesia. This sequence avoided the struggling and breath-holding that can delay the induction of anesthesia with an inhalational agent.

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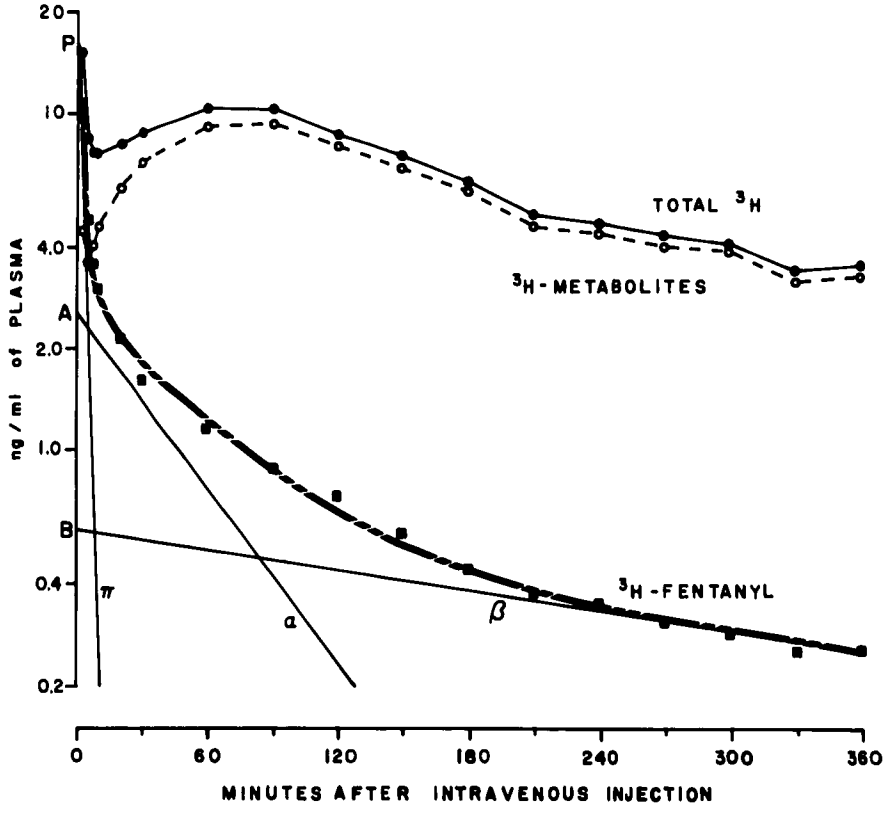

FIG. 1. Plasma levels of total ^{3}H-radioactivity, ^{3}H-metabolites, and unchanged ^{3}H-fentanyl in one dog (M4) given ^{3}H-fentanyl, 10 μg/kg, intravenously. Each data point represents the mean of duplicate determinations. The curve for unchanged fentanyl was fitted to the data points by nonlinear least-squares analysis and can be described by the triexponential equation: $C_{p(t)} = 15.9\exp^{-0.393t} + 2.5\exp^{-0.0199t} + 0.57\exp^{-0.00232t}$. The half-times for the π, α, and β phases are 1.8, 34.8, and 298 min, respectively. The intercepts (P, A and B) are indicated on the y-axis.

utilized for continuous blood-pressure recording and periodic sampling of blood. Transient (0.5–6 min) decreases in blood pressure were observed in some dogs immediately following the injection of fentanyl. The extent of systolic hypotension was variable (0–10 per cent) and unrelated to the dose of fentanyl. No consistent effect on heart rate was found. When blood was withdrawn it was immediately replaced with an equal volume of Plasmanate[¶] (5 per cent human plasma protein fraction), injected intra-

[¶] Cutter Laboratories, Inc., Berkeley, California.

TABLE 1. Pharmacokinetics of Fentanyl in Plasma after Intravenous Injection in Dogs
$C_{p(t)} = Pexp^{-\pi t} + Aexp^{-\alpha t} + Bexp^{-\beta t}$*

	Weight (kg)	P (ng/ml)	π (Min^{-1})	$t_{1/2\pi}$ (Min)	A (ng/ml)	α (Min^{-1})	$t_{1/2\alpha}$ (Min)	B (ng/ml)	β (Min^{-1})	$t_{1/2\beta}$ (Min)	r^2†
10 μg/kg											
Dog 27	16.8	7.4	.293	2.4	2.2	.0261	26.5	.45	.00346	201	.997
Dog M4	11.3	15.9	.393	1.8	2.5	.0199	34.8	.57	.00232	298	.998
Dog M15	16.5	5.5	.293	2.4	2.1	.0345	20.1	.92	.00513	135	.999
Dog M16	11.0	4.6	.382	1.8	2.7	.0300	23.1	.46	.00448	155	.996
Mean		8.4	.340	2.1	2.4	.0277	26.2	.60	.00385	197	
SEM		± 2.6	± .027	± .17	± .15	± .0031	± 3.2	± .11	± .00061	± 36	
100 μg/kg											
Dog M18	13.5	116	.342	2.0	15	.0240	28.9	6.3	.00298	233	.993
Dog M19	13.3	58	.175	4.0	34	.0215	32.2	5.9	.00449	154	.999
Dog M21	16.4	16	.134	5.2	22	.0169	40.9	5.0	.00280	248	1.000
Dog M22	10.8	56	.341	2.0	30	.0214	32.4	7.0	.00369	188	.999
Dog M23	12.5	116	.313	2.2	18	.0359	19.3	6.5	.00382	181	.998
Mean		72	.261	3.1	24	.0240	30.7	6.1	.00355	201	
SEM		± 19	± .044	± .64	± 3.6	± .0032	± 3.5	± .33	± .00031	± 17	

* This triexponential equation describes the elimination of fentanyl from plasma. See Appendix.
† $r^2 = [\Sigma(\text{observed})^2 - \Sigma(\text{deviation})^2]/\Sigma(\text{observed})^2$.

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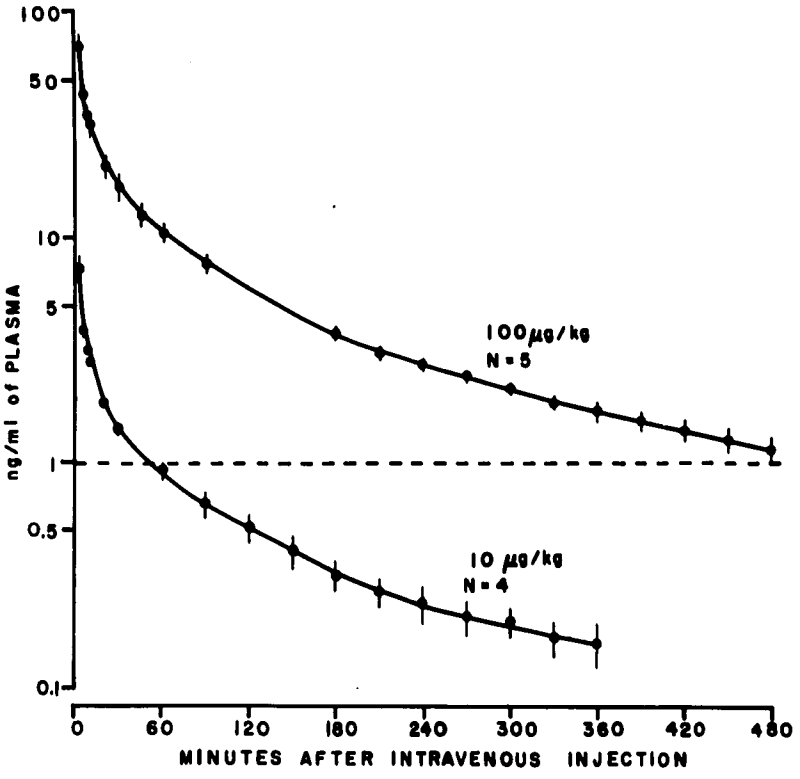

FIG. 2. Concentrations of unchanged fentanyl in plasma after different doses. Each data point represents the mean ± SEM for the number of animals indicated by "N." The lines were drawn by nonlinear least-squares analysis of the mean data points for each dose. Assuming that the pharmacologic effects of fentanyl correlate closely with its concentrations in plasma and that the threshold concentration for these effects is 1 ng/ml,[15] we have drawn the dashed horizontal line. The intersection of the plasma concentration–time curve with the dashed line indicates the duration of pharmacologic action for each dose (53 and 523 min, respectively, for the 10 and 100 µg/kg, doses).

venously. A volume of approximately 160 ml of blood was withdrawn during an eight-hour experiment. The pharyngeal temperature and the electrocardiogram were monitored. Urine was collected from a transurethral catheter.

Fentanyl citrate, uniformly labelled with tritium on the aniline ring (specific activity 105 nCi/µg),** was used for these experiments. ^{3}H-fentanyl citrate was injected intravenously over a 30-sec period in a single dose (10 or 100 µg/kg) or as three equal doses administered at 90-min intervals. Samples of blood and urine were collected at specified intervals over the next six to eight hours.

The lower dose of fentanyl was chosen so as to obtain moderate ventilatory depression, while the higher dose was chosen to represent the upper limits of anesthetic doses of fentanyl. Our doses are larger than those normally employed in man, but the dog has been shown to be less sensitive than man to the actions of narcotic analgesics.[4]

Values are expressed as means ± standard error of the mean unless designated otherwise. Student's t test was used for group comparisons, with $P < 0.05$ as the minimal limit of significance. "Fentanyl" hereafter refers to the citrate salt of the unchanged tritium-labelled drug. "Total radioactivity" refers to both unchanged fentanyl and its ^{3}H-labelled metabolites.

Results

Fentanyl accounted for a very small proportion of the total radioactivity in plasma following its intravenous injection (fig. 1). The decline of fentanyl in plasma could be described by a triexponential equation (table 1). Since the intercepts were proportional to the dose and the elimination constants for the three phases did not differ significantly for the two doses of fentanyl, we have combined the data for the two groups of animals; mean values (±standard error

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

Dose (µg/kg)	$C_{p(0)}$ (ng/ml)	V_d (l/kg)	V_c (l/kg)	$Cl_{(B)}$ (ml/Min)
10 (n = 4)	11.3 ± 2.6	10.2 ±0.96	1.00 ± 0.17	38.4 ± 5.1
100 (n = 5)	102 ± 17	9.42 ± 0.85	1.17 ± 0.30	32.6 ± 1.7

** Generously supplied by McNeil Laboratories, Fort Washington, Pennsylvania.

* Methods of calculating pharmacokinetic variables are given in the Appendix.

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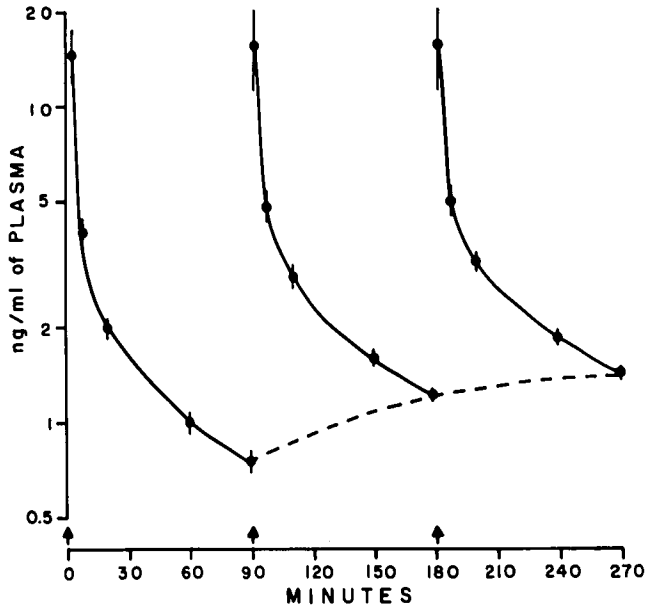

FIG. 3. Plasma concentrations of unchanged fentanyl following each of three successive doses (10 μg/kg) administered intravenously at 90-min intervals. Data points represent the means ± SEM for four dogs. The dotted line connects values for successive 90-min intervals and indicates accumulation of fentanyl with repeated doses.

of the mean, n = 9) are presented in the remainder of this report unless otherwise noted.

The initial decline of fentanyl in plasma was very rapid, with 98 ± 0.1 per cent of the dose cleared in the first 5 min. The average half-time of this initial (π) phase was 2.6 ± 0.4 min. The elimination from plasma was less rapid during the second (α) phase. By 30 min, 99 ± 0.7 per cent of the amount injected had disappeared from plasma. The terminal elimination (β) phase had an average half-time of 199 ± 17 min. Less than 0.3 per cent of the injected dose could be accounted for in plasma as fentanyl by 180 min. The terminal elimination phase was apparent only three to four hours following intravenous injection of the drug; therefore, kinetic indices are presented for only the nine animals studied for six or more hours following fentanyl administration.

The concentration of fentanyl in plasma was proportional to dose throughout the eight-hour period of study (fig. 2, table 1). The apparent volumes of distribution (V_d) of both doses were large and did not differ significantly for the 10 and 100 μg/kg doses. The apparent volume of the central compartment (V_c) and the total-body clearance ($Cl_{(B)}$) were likewise independent of dose (table 2).

Repeating the same dose of fentanyl (10 μg/kg, iv) at 90-min intervals produced accumulation of fentanyl in the body, as indicated by the progressively higher concentrations of fentanyl in plasma at corresponding times following the three injections (fig. 3). The second and third injections resulted in plasma concentrations 20 min after injection that were 44 and 60 per cent higher than that after the first injection. By 90 min, the concentrations were 61 and 90 per cent higher for the second and third injections, respectively, than for the first. It should be noted that the 90-min dosage interval was chosen for experimental purposes and is much longer than intervals usually used under clinical conditions. Shorter dosage intervals would produce greater accumulation.

Studies of plasma protein binding *in vitro* demonstrated that approximately 62 per cent of unchanged fentanyl was bound in plasma at *p*H 7.4. Binding was *p*H-dependent (fig. 4) and was the same for all concentrations of fentanyl between 0.1 and 100 ng/ml plasma *in vitro*.

^{3}H-labelled metabolites of fentanyl were evident in the first plasma sample at 2 min, and accounted for 29 ± 2.3 per cent of its total ^{3}H radioactivity (fig. 1). The concentration of metabolites peaked around 60 min (range 30–90 min), when they represented 84 ± 1.3 per cent of the total radioactivity in plasma. The decline of ^{3}H-labelled metabolites in plasma was slower than that of fentanyl. Six hours after the injection of fentanyl, the ^{3}H-labelled metabolites accounted for 94 ± 0.5 per cent of the plasma radioactivity.

Urine collected for six hours after intravenous injection of either 10 or 100 μg/kg contained 32 ± 3 per cent of the amount administered as ^{3}H-labelled

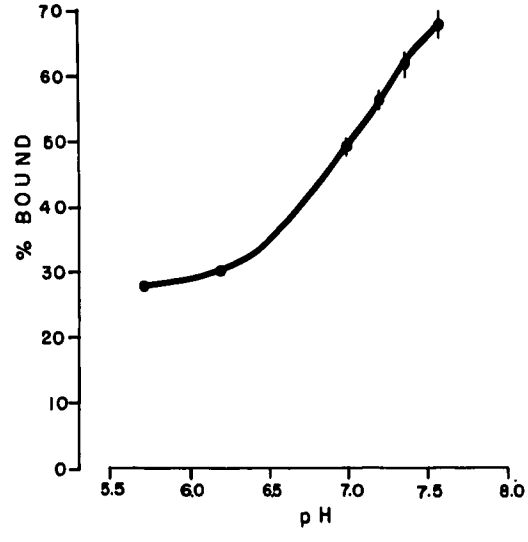

FIG. 4. The effects of *p*H on the binding of fentanyl to proteins in dog plasma *in vitro*. Data are means ± SEM for three determinations.

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metabolites. Only 4 ± 0.9 per cent of the amount administered was excreted as unchanged fentanyl.

Discussion

The pharmacokinetics of fentanyl in plasma would be expected to bear a close relationship to the time course of its production of analgesia and ventilatory depression. Lipophilic drugs such as fentanyl equilibrate rapidly across all biological membranes, including those of the blood–brain barrier.[5,6] Hence, changes in plasma concentrations of fentanyl should be reflected rapidly by proportional changes in concentrations in the central nervous system (CNS) and in the intensity of its effects. These concepts are supported by the experiments of Herz and Teschemacher[6] and those of von Cube *et al.*,[5] who related the lipophilic properties of narcotic analgesics to their analgesic potencies and to the time courses of their antinocioceptive actions in the rabbit.

The volumes of distribution are virtual volumes and do not correspond to anatomically defined compartments in the body. In fact, the total volume of distribution (V_d) = 9.8 ± 0.6 l/kg) exceeded the real volume of the dog (1 l/kg) by almost ten times. Such large virtual volumes indicate that fentanyl is highly concentrated in some or all tissues. Additional studies are needed to determine the extent and mechanism of accumulation in specific tissues and organs. Such studies would be useful to determine the upper limits of accumulation by various tissues (*i.e.*, saturation). The volumes of distribution were independent of dose, and therefore, there was no indication of saturation of tissue uptake mechanisms in the dose range (10–100 μg/kg) used in these experiments.

Until we determine the rates of uptake of fentanyl by specific tissues, it is not possible to assign individual tissues and organs to one particular compartment. However, because fentanyl's lipophilic nature allows it to cross biologic membranes rapidly, it is likely that the uptakes of fentanyl by various tissues are limited primarily by its rates of delivery to them, that is, by their blood flows. In this regard, fentanyl probably resembles thiopental and equilibrates most rapidly with tissues with the highest blood flows and less rapidly with tissues having lower blood flows.[7,8] It is likely that the three compartments generally correspond to those defined for other lipophilic drugs (*e.g.*, thiopental, halothane) as 1) vessel-rich tissues, 2) skeletal muscle, and 3) vessel-poor tissues.

The terminal elimination (β) phase has a long half-time (199 ± 17 min) and indicates a prolonged persistence of fentanyl in the body. The slow elimination of fentanyl could be the result of one or more factors.

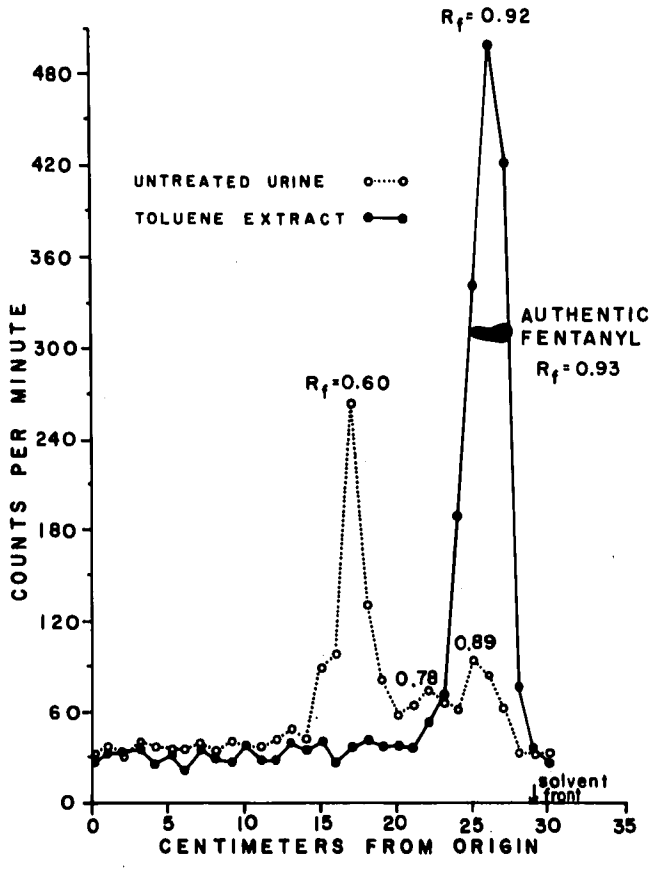

FIG. 5. Chromatographic demonstration of the specificity of the extraction procedure for unchanged ^{3}H-fentanyl. See Appendix for details. Authentic fentanyl was localized by spraying the chromatogram with iodoplatinate solution.[16]

There is only minimal excretion of the unchanged drug by the kidney.[9–12] Slow metabolism of the drug by the liver and possibly other tissues could contribute to persistence of the drug in the body. It is unlikely that the liver is inherently limited in its rate of biotransformation of fentanyl, since very large quantities of radioactive metabolites appeared in plasma soon after intravenous injection of the drug when large quantities of fentanyl were delivered in the blood flowing to the liver. Certainly the liver's capacity should not have been exceeded at later times when the blood levels of fentanyl were much lower.

A more plausible explanation for the persistence of fentanyl in the body is its extensive uptake by body tissues. A high affinity for body tissues will result in slow release of the drug from these tissues to the blood for transport to the liver for biotransformation to metabolites, which can be eliminated from the body. At the same time, the slow persistent release of fentanyl from tissues will serve to maintain a level of fentanyl in the circulating blood for a prolonged

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period.[8] The higher the tissue levels of fentanyl in this terminal equilibrium phase, the higher the concentrations of fentanyl that will persist in plasma and in the CNS. When these concentrations are above the threshold for pharmacologic activity, the effects of the drug will likewise be persistent. (Refer to "threshold" line in fig. 2.)

This phenomenon is well known for the ultrashort-acting barbiturates, such as thiopental. Fentanyl's elimination appears to be similar to that of thiopental. Higher tissue levels and persistence of drug effects result from repeated doses that are administered to maintain the effects of the drug, while at the same time they add progressively to the tissue and plasma levels (fig. 3).

To summarize, 1) the unchanged drug is rapidly eliminated from plasma by its uptake into tissues; 2) slow release of the drug from tissues results in the prolonged persistence of low levels for several hours after a single intravenous injection; 3) the drug appears to be metabolized efficiently, and the unidentified metabolites account for most of the radioactivity in plasma and urine after administration of ^{3}H-fentanyl; 4) only very small amounts of the unchanged drug are eliminated by the kidney.

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Appendix

For the analysis of unchanged fentanyl in plasma and urine, 0.5–4 ml volumes were used. The smallest reliable volume was used to conserve sample. Samples amounting to less than 4 ml were brought to a volume of 4 ml with distilled water. Nonradioactive fentanyl citrate, 100 μg in 1 ml water, was added as a carrier to decrease adsorption of the radioactive drug to glassware. The *p*H was adjusted to 9–10 with 2.5 N sodium hydroxide and the sample buffered with 1 M potassium phosphate, 3 ml. Following the addition of toluene, 10 ml, the samples were shaken for 20 min and centrifuged. Eight milliliters of the toluene layer containing the highly lipophilic fentanyl were transferred to a glass liquid-scintillation vial and 4 ml of concentrated fluor (9 g PPO and 600 mg dimethyl-POPOP†† per liter of toluene) were added. The samples were counted in a Beckman LS-230 liquid scintillation spectrometer. Concentrations of fentanyl citrate in biologic specimens were determined by comparing the radioactivities in the extracts of these specimens with radioactivities in extracts from solutions of known concentrations of ^{3}H-fentanyl citrate. Corrections were made for background cpm and sample size.

Recovery of known quantities (1 to 400 ng/ml) of ^{3}H-fentanyl added to plasma and urine averaged 96 ± 2.5 per cent (SD). Specificity of the extraction procedure for unchanged fentanyl was demonstrated by paper chromatography in the solvent system: n-propanol, n-butanol, 0.1 N ammonium hydroxide (2:1:1, v/v). Untreated urine from dog M19 produced three peaks of radioactivity corresponding to 61, 12, and 20 per cent of the total radioactivity in the untreated samples; the last area corresponded in R_f to authentic fentanyl. Paper chromatography of the toluene extract of similar samples of the same urine produced a single peak of radioactivity representing 98 per cent of the tritium in the toluene extract of the sample and corresponding in R_f to authentic fentanyl applied to the same chromatogram (fig. 5). Similar results were obtained by paper chromatography of untreated specimens and toluene extracts of the urine collected over eight hours for two other dogs (27 and M18).

Total tritium radioactivity (*i.e.* unchanged fentanyl and its metabolites) was determined in plasma and urine by counting untreated 0.1–0.5 ml samples in 12 ml of fluor (600 ml Beckman BBS-3 in 3,000 ml Mallinkrodt Dilufluor). Samples were corrected for quenching by the addition of ^{3}H-toluene as an internal standard. Standard solutions of ^{3}H-fentanyl were analyzed simultaneously and the quantity of total ^{3}H was expressed in terms of an equivalent concentration of ^{3}H-fentanyl citrate. The level of ^{3}H-metabolites was calculated as the difference between total ^{3}H and ^{3}H-fentanyl concentrations.

The extraction procedure measured total unchanged fentanyl, including both free and protein-bound drug. Protein binding of fentanyl in dog plasma was studied *in vitro*.[13] ^{3}H-fentanyl was added to fresh plasma from a single dog (for each experiment) and placed in a cellophane bag. The total volume in the bag was 3 ml, consisting of 90 per cent plasma and with a final fentanyl concentration of 0.1, 10, or 100 ng/ml. Equilibrium dialysis in 9 ml of Sorensen's buffer at various *p*H values (5.7–7.7) was accomplished over 18 hours at 37 C in a Dubnoff shaking incubator.

Pharmacokinetic Calculations

After intravenous injection, the decline of unchanged fentanyl concentrations in plasma was triphasic, and could be fitted to an exponential time function using the method of residuals as described by Gibaldi and Perrier[14] and modified for use as a computer program. The equation is as follows:

$$C_{P(t)} = Pexp^{-\pi t} + Aexp^{-\alpha t} + Bexp^{-\beta t}$$

where

$C_{P(t)}$ = the concentration of fentanyl in plasma at time t
P, A, B = the extrapolated zero intercepts computed from least-squares analysis of the data
π, α, β = the first-order rate constants

The apparent volume of distribution, V_d, the apparent volume of the central compartment, V_c, and the total-body clearance, $Cl_{(B)}$, were calculated by the following formulas[14]:

$$V_d = \frac{\text{dose}}{\text{area} \cdot \beta}$$

$$V_c = \frac{\text{dose}}{C_{P(0)}}$$

$$Cl_{(B)} = \frac{\text{dose}}{\text{area}}$$

where

Dose = total intravenous dose

$$\text{Area} = \frac{P}{\pi} + \frac{A}{\alpha} + \frac{B}{\beta}$$

$$C_{P(0)} = P + A + B$$

†† Fisher Scientific Co., Pittsburgh, Pennsylvania.

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