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Fentanyl Disposition in Cerebrospinal Fluid and Plasma and Its Relationship to Ventilatory Depression in the Dog

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Although fentanyl is a short-acting narcotic analgesic, unexpected respiratory depression has been seen in the postanesthetic period several hours after the last dose. This study has defined the pharmacokinetic characteristics of fentanyl in cerebrospinal fluid (CSF) of the dog and determined their relationships to ventilatory depression. ^{3}H-fentanyl citrate (10 μg/kg) was injected intravenously in dogs anesthetized with enflurane–O_2. Arterial plasma and cisternal CSF were analyzed for concentration of unchanged ^{3}H-fentanyl [F] and for total radioactivity (^{3}H). Maximum [F] in CSF occurred 2–10 min after injection and declined at the same rate as [F] in plasma. Values of [F] in CSF averaged approximately 46 per cent of those in plasma, and reflected the binding of fentanyl to plasma proteins. There was a dose-dependent decrease in minute ventilation, and end-tidal CO_2 increased. The extent of ventilatory depression correlated closely with the log [F] in arterial plasma and in cisternal CSF (*i.e.*, Δ $P_{ET_{CO_2}}$ *vs.* log $[F]_{CSF}$, r = 0.97, $P < 0.01$). An early phase in the recovery of ventilation paralleled the initial, rapid elimination of fentanyl from CSF and plasma. Complete recovery was protracted, and the terminal elimination phases of fentanyl from both CSF and plasma were prolonged ($t_{1/2}$ = 171 ± 8 and 201 ± 25 min, respectively). It is concluded that fentanyl, a highly lipophilic drug, equilibrated rapidly between plasma and CSF, and that there was a close correlation between the concentrations of fentanyl in plasma and CSF and the intensity of respiratory depression. Recovery from the ventilatory effects of fentanyl paralleled the initially rapid elimination of the unchanged drug from CSF and plasma. However, low levels of ventilatory depression and of [F] persisted. Repeated injections of the narcotic analgesic led to the accumulation of fentanyl and increased ventilatory depression. (Key words: Analgesics, narcotic: fentanyl. Anesthetics, intravenous: fentanyl. Pharmacokinetics: distribution. Ventilation: depression.)

FENTANYL CITRATE, a narcotic analgesic, is 75 times more potent than morphine in man.[1] It is noted for its rapid onset and brief duration of action,[1–5] but there have been reports of prolonged or recurrent ventilatory depression in patients given fentanyl during general anesthesia.[6–10] Knowledge of the disposition of fentanyl in the anesthetized patient, along with information about its relationship to the duration of ventilatory depression, should increase our understanding of this anesthetic complication. The pharmacokinetics of fentanyl in plasma of dogs given single or multiple intravenous doses have been described.[11] In this study the concentration of fentanyl in plasma was correlated with its concentration in cerebrospinal fluid (CSF) and with the intensity of ventilatory depression.

Methods and Materials

Fifteen mongrel dogs, 10 to 20 kg, were anesthetized and prepared as previously described.[11] Briefly, general anesthesia was induced rapidly with enflurane, 5 per cent, immediately following the intravenous injection of succinylcholine and atropine. Anesthesia was maintained with enflurane, 2–3 per cent, in oxygen, using a Bain® circuit at a flow rate of 4 to 6 l/min to prevent rebreathing.[12] Animals receiving the lower dose of fentanyl (10 μg/kg) were allowed to breathe spontaneously following the introduction of an oral endotracheal tube; ventilation was controlled in those given the higher dose (100 μg/kg).

Cisternal fluid (CSF) was collected through a Hustead-Touhy needle inserted at the base of the skull. Sample sizes ranged from 0.5 ml for the early samples to 2 ml for the later samples. The volume of CSF removed over an eight-hour experiment totaled approximately 12 ml, with the maximum number of samples for any one dog being 16.‡ Blood was sampled from a femoral-artery cannula and was replaced by an equal volume of Plasmanate§ (5 per cent human plasma protein fraction) injected intravenously. Urinary output, pharyngeal temperature, blood pressure, and electrocardiogram were monitored.

The endotracheal tube with its cuff inflated was connected by a Rovenstine connector to a Vortex respirometer in series with a Bain circuit. End-tidal gas was sampled for carbon dioxide and enflurane by Beckman LB-2® infrared spectrometers. Arterial blood gas analysis was performed intermittently. Pa_{O_2} remained above 300 torr throughout the experimental period; metabolic acidosis did not develop.

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‡ Only the minimum volume of CSF sufficient for analysis was removed; earlier samples had higher concentrations of fentanyl than later samples.

§ Purchased from Cutter Laboratories, Inc., Berkeley, California.

^{3}H-fentanyl citrate (specific activity 105 nCi/μg),¶ uniformly labeled with tritium on the aniline ring, was injected intravenously in a dose of 10 or 100 μg/kg over a 30-sec period. In four animals, three doses of 10 μg/kg each were administered at 90-min intervals and end-tidal gas values sampled. Samples of plasma and CSF were collected at specified intervals over the next three to eight hours. The methods for analysis of unchanged ^{3}H-fentanyl citrate in plasma and CSF have been described.[11]

The choice of doses of fentanyl was based on the following considerations. 1) We have performed similar studies with morphine, 0.3 mg/kg, in the dog. For purposes of comparison, an equivalent dose of fentanyl would be 4 μg/kg, assuming a potency ratio of 75:1.[1] 2) The ventilatory depressant effects of single 4-μg/kg doses of fentanyl were too small and brief for purposes of this study. Moderate ventilatory depression was achieved with a 10-μg/kg dose. 3) The 100-μg/kg dose was chosen to represent the upper limits of "anesthetic" doses of fentanyl and was studied in order to determine the effects of dose on the pharmacokinetics of fentanyl in the dog. 4) The doses studied in dogs are large compared with those normally employed in man, but the dog has been shown to be less sensitive than man to the actions of narcotic analgesics.[13]

The kinetics of decline of fentanyl in CSF were described by a biphasic exponential time-function calculated by the method of residuals as previously described for plasma.[11] The 20-min sample was chosen as the first point on the curve to allow time for equilibration of fentanyl between CSF and plasma.** The number of CSF samples collected during the brief period of fentanyl uptake by CSF was insufficient for kinetic analysis of the uptake phase. Only those experiments extending six hours or longer were used for kinetic calculations; therefore, kinetic data are presented for only five of the 11 dogs from which CSF samples were obtained.†† Table 1 summarizes data collected from individual dogs.

"Fentanyl" hereafter refers to the unchanged tritium-labeled drug. "Total tritium radioactivity" refers to both unchanged fentanyl and its radioactive metabolites. Concentrations of fentanyl and its metabolites are stated in equivalents of fentanyl citrate. Values are presented 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 statistical significance.

TABLE 1. Experimental Protocols for Individual Dogs

	Duration of Data Collection (Min)		
	Ventilation	CSF	Plasma
Fentanyl, 10 μg/kg × 1			
Dog M1	300	—	—
Dog M2	515	—	—
Dog M3b	295	—	—
Dog M9	480	—	—
Dog 27	540	105	480
Dog M3	300	80	180
Dog M4	500	360	360
Dog M12	410	90	270
Dog M16	—	180	480
Fentanyl, 10 μg/kg × 3			
Dog M26	380	—	540
Dog M32	405	—	480
Dog M44	320	—	540
Dog M45	310	—	540
Fentanyl, 100 μg/kg × 1			
Dog M19	—	390	480
Dog M22	—	480	480
Dog M23	—	45	480
Dog M41	—	180	240
Dog M42	—	480	480
Dog M43	—	480	480

Results

Concentrations of fentanyl in plasma declined rapidly, while those in CSF rapidly increased (fig. 1). Maximum concentrations in CSF occurred between 2.5 and 10 min in all 11 dogs (fig. 2). Subsequently, concentrations in CSF declined in parallel with those in plasma. The concentration of fentanyl in CSF was approximately proportional to dose after 90 min, and the rate of elimination of fentanyl from CSF appeared to be independent of dose in the terminal elimination (β) phase. The half-time of the terminal elimination phase of fentanyl from CSF was 171 ± 8 min (table 2), compared with the half-time of 201 ± 25 min for fentanyl in plasma for *all dogs* (table 3). (The half-time of the terminal elimination phase of fentanyl from plasma in the nine dogs previously reported was 199 ± 17 min.[11]) ^{3}H-fentanyl accounted for only a small portion of the total tritium radioactivity in plasma and CSF (fig. 1). The identity of the ^{3}H-labeled metabolites is not known.

There was close correlation between CSF and

¶ Generously supplied by McNeil Laboratories, Inc., Fort Washington, Pa.

** The entry of fentanyl into CSF corresponded to the initial distribution phase of fentanyl elimination from plasma. The half-time of the π phase averaged 2.6 ± 0.4 min,[11] and therefore, equilibration of the drug between plasma and CSF would be more than 99 per cent complete within 20 min.

†† Technical difficulties in the maintenance of the position of the cisternal needle, especially in dogs breathing spontaneously, limited the duration of CSF sampling in some dogs. Also, the low concentrations of ^{3}H-fentanyl in later samples from most dogs receiving the 10 μg/kg dose were below the limit of sensitivity for the analytical procedure.

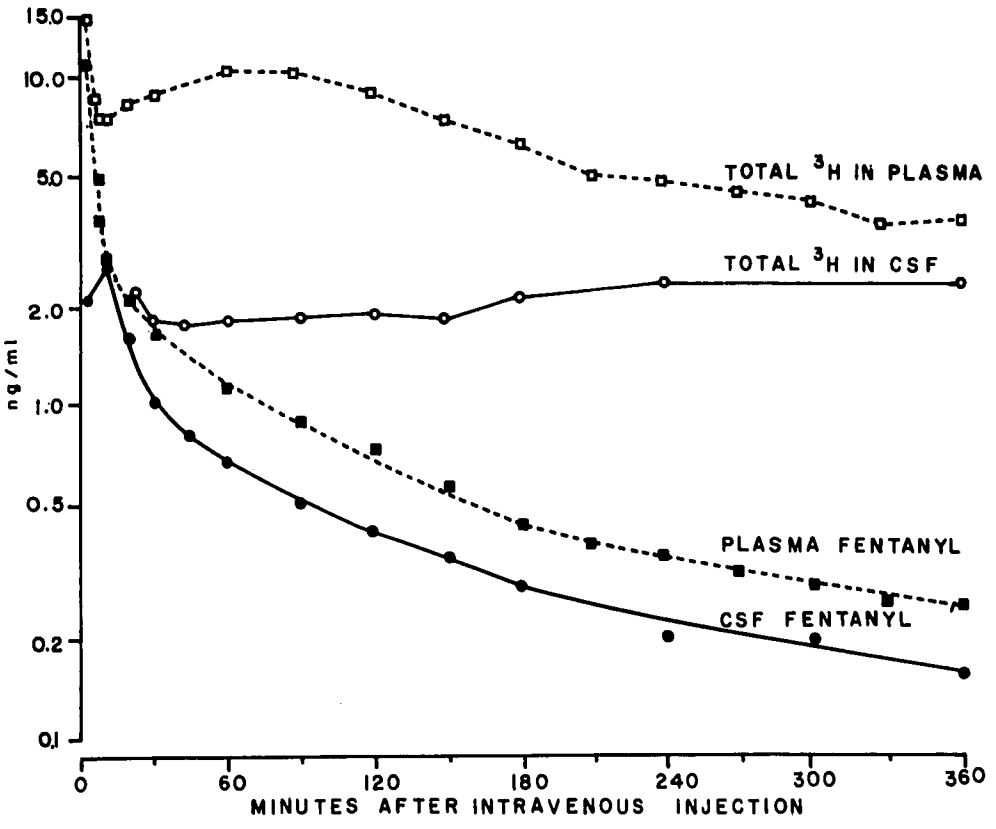

FIG. 1. CSF and plasma levels of total ^{3}H-radioactivity and of unchanged ^{3}H-fentanyl in one dog (M4) given an intravenous injection of 10 μg/kg. Each data point represents the mean of duplicate determinations. The curves for unchanged fentanyl were fitted to the data points by nonlinear least-squares analysis.

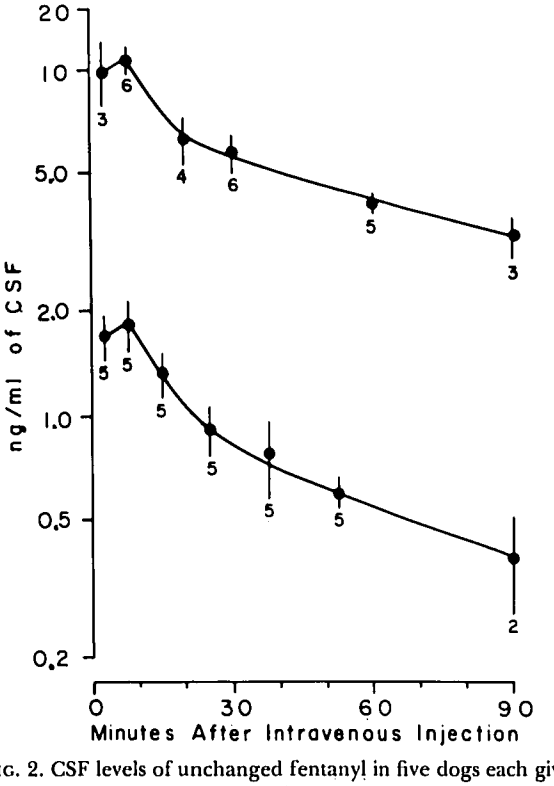

FIG. 2. CSF levels of unchanged fentanyl in five dogs each given an intravenous injection of 10 μg/kg (*lower curve*) and in six dogs each given 100 μg/kg (*upper curve*). Each point and vertical line represent the mean ± SEM for the number of dogs shown under the line. The range is shown where n = 2.

plasma levels of fentanyl in all dogs after the initial distribution (π) phase, and fentanyl concentrations in CSF averaged 46 per cent of those in plasma. This difference was accounted for by the binding of fentanyl to plasma proteins. The analytical procedure measured total unchanged fentanyl in biological samples, including both free and protein-bound drug. Approximately 57 per cent of the fentanyl added to dog plasma *in vitro* was bound to proteins in the *p*H (7.24–7.32) and concentration (0.1–100 ng/ml) ranges encountered in the plasma of intact animals breathing spontaneously.[11] Respiratory acidosis (Pa_{CO_2} 43–54 torr) resulted from ventilatory depression by fentanyl and enflurane.

Fentanyl, 10 μg/kg, administered intravenously over 30 sec produced an immediate onset of ventilatory depression, and apnea occurred within 1.5 min. There was rapid recovery of tidal volume, ventilatory frequency, and minute ventilation toward predrug levels in the first 30–45 min. End-tidal CO_2 declined rapidly in the first 60 min after an intravenous injection, but it remained slightly above control levels until 180 min after injection (fig. 3).‡‡ The recovery of minute ventilation and the return of end-tidal CO_2

‡‡ In six dogs anesthetized with enflurane–O_2 only and given no other drug, there was no significant change in the ventilatory variables over two-to-six-hour periods of observation. In another four

TABLE 2. Pharmacokinetic Characteristics of Fentanyl in Canine CSF Following Intravenous Injection*
$C_{CSF(t)} = A \exp^{-\alpha t} + B \exp^{-\beta t}$†

	A (ng/ml)	α (min^{-1})	$t_{1/2\alpha}$ (min)	B (ng/ml)	β (min^{-1})	$t_{1/2\beta}$ (min)	r^2‡
Fentanyl, 10 μg/kg							
Dog M4	1.4	.0280	24.8	.57	.00368	188	.981
Fentanyl, 100 μg/kg							
Dog M19	9.1	.0293	23.6	4.1	.00461	150	.998
Dog M22	3.3	.0387	17.9	5.4	.00408	170	.996
Dog M42	7.8	.0243	28.5	3.2	.00366	189	.998
Dog M43	8.1	.0375	18.5	4.7	.00434	160	.999
Mean (SEM)							
(n = 4)	7.1	.0324	22.1	4.4	.00417	167	
	(1.3)	(.0034)	(2.5)	(0.5)	(.00020)	(8)	

* Data are presented only for experiments in which CSF levels of fentanyl could be determined for six hours or longer. The initial rates of decline of fentanyl in CSF were similar in six other dogs studied for shorter periods.

† This biexponential equation describes the elimination of fentanyl from CSF after completion of the uptake phase. See Appendix.

‡ $r^2 = [\Sigma(\text{observed})^2 - \Sigma(\text{deviation})^2]/\Sigma(\text{observed})^2$.

TABLE 3. Pharmacokinetic Characteristics of Fentanyl in Canine Plasma Following Intravenous Injections*
$C_{p(t)} = P \exp^{-\pi t} + A \exp^{-\alpha t} + B \exp^{-\beta t}$†

	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‡
Fentanyl, 10 μg/kg										
Dog M4	15.9	.393	1.8	2.5	.0199	34.8	.57	.00232	298	.998
Fentanyl, 100 μg/kg										
Dog M19	58	.175	4.0	34	.0215	32.2	5.9	.00449	154	.999
Dog M22	56	.341	2.0	30	.0214	32.4	7.0	.00369	188	.999
Dog M42	69	.256	2.7	20	.0301	23.1	6.5	.00410	169	.994
Dog M43	47	.307	2.3	21	.0336	20.6	7.5	.00353	197	.995
Mean (SEM)										
(n = 4)	57	.270	2.7	26	.0267	27.1	6.7	.00395	177	
	(5)	(.036)	(.43)	(3.4)	(.0031)	(3.1)	(.35)	(.00022)	(9)	

* The corresponding plasma data are presented only for experiments in which CSF levels of fentanyl could be determined for six hours or longer. The rates of decline of fentanyl in plasma were similar in six other dogs studied for six hours or longer.[11]

† This triexponential equation describes the elimination of fentanyl from plasma. See Appendix.

‡ $r^2 = [\Sigma(\text{observed})^2 - \Sigma(\text{deviation})^2]/\Sigma(\text{observed})^2$.

toward control levels closely paralleled the decline in the log concentration of fentanyl in CSF and plasma. The increase in end-tidal CO_2 above control levels was a linear function of the log-concentration of fentanyl in plasma or CSF (fig. 4). It is estimated that for dogs maintained at a stable, light level of enflurane anesthesia, end-tidal CO_2 concentrations would return to control levels at a fentanyl concentration in plasma of 1.01 ± 0.07 ng/ml (n = 15, including all doses in all dogs; see below). The concentration *vs.* response lines for plasma and CSF were parallel.

When a dose of 10 μg/kg was repeated at 90-min intervals, the initial clearance of the drug from plasma was equally rapid after each dose, but accumulation was evident, in that both plasma concentrations and end-tidal CO_2 increased more after each successive dose (fig. 5). The period of apnea following each successive dose was more prolonged, and the return of minute ventilation toward control levels was slower. It should be noted that the 90-min dosage interval was chosen for experimental reasons and was much longer than the interval usually employed in clinical circumstances. Shorter dosage intervals should lead to greater cumulation of fentanyl and to more marked ventilatory depression.

The mean "threshold" concentration for all seven dogs after a single dose of fentanyl (0.87 ± 0.07 ng/ml) was the same as that for the first dose in the animals that subsequently received two additional doses (0.89 ± 0.13 ng/ml) (table 4). Comparisons of the mean "threshold" concentrations among the four dogs given three successive doses demonstrates a trend toward an increasing "threshold" concentration after

dogs anesthetized with enflurane–O_2 and a single dose of fentanyl, 10 μg/kg, ventilatory variables remained constant for a period of two to eight hours except for approximately the first 90 min, during which ventilatory depression by fentanyl was evident.

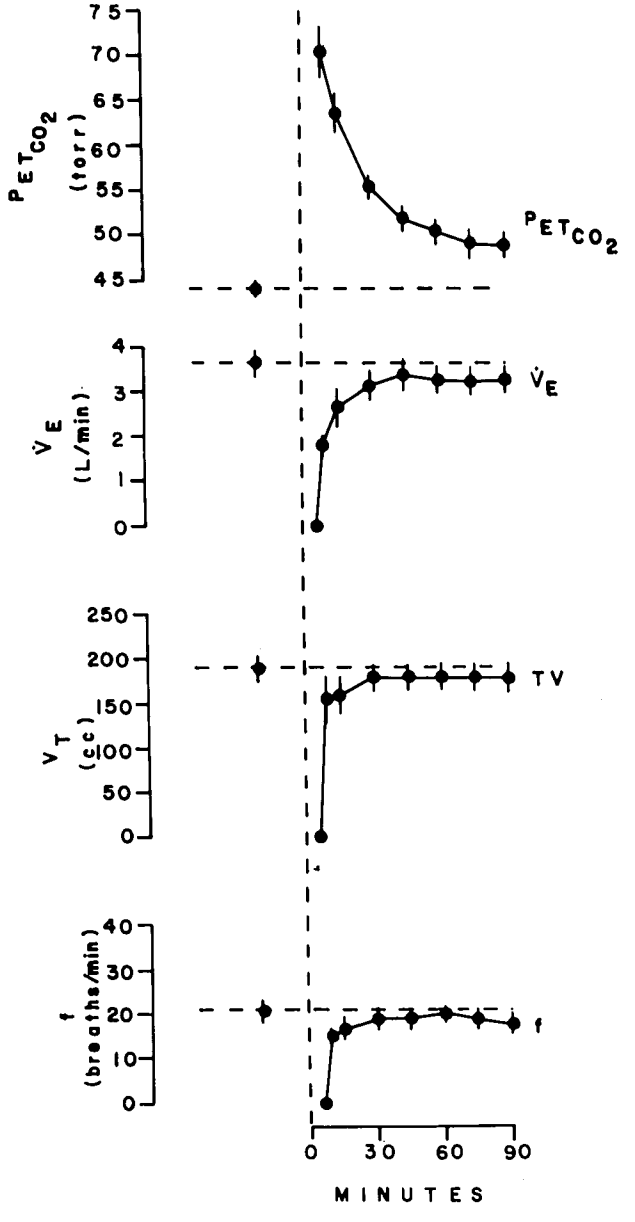

FIG. 3. Changes in respiratory rate (f), tidal volume (V_T), minute ventilation ($\dot{V}_E$), and end-tidal CO_2 ($P_{ET_{CO_2}}$) following an intravenous injection of ^{3}H-fentanyl (10 μg/kg) in 12 dogs. The control values represent the mean data for at least three consecutive 5-minute periods of stable ventilation preceding the injection of fentanyl. The ventilatory variables remained stable beyond 90 min in four dogs studied for an 180-min period following a single dose of fentanyl, 10 μg/kg. End-tidal enflurane concentrations were maintained within ±0.08 per cent throughout the experimental period.

successive doses; however, a stepwise trend was evident in only two of the four animals, and there was a statistically significant difference only between the first and third doses ($P < .05$). Additional studies are needed to determine whether the trend is real and whether it represents an example of the development of acute tolerance.

Discussion

The lipophilic nature of fentanyl assures its rapid penetration across biologic membranes, including the blood–brain barrier, thereby producing its characteristically rapid onset of action. The concentrations in cisternal CSF increased rapidly, and near-maximal concentrations were found in the earliest sample taken 2–3 min after intravenous injection. Respiratory depression was evident within the first minute. Twenty minutes after injection, the CSF concentration had equilibrated with that in plasma. Thereafter the concentrations in plasma and CSF declined in parallel.

Previous investigators have described the occurrence of marked respiratory depression or apnea within 2 min[2,4,6,10] and surgical analgesia within 6–8 min[14] after an intravenous injection of fentanyl. Hess *et al.*[15] demonstrated maximum brain concentrations of fentanyl in rabbits as early as 30 sec after intravenous injection, with maximal levels in CSF by 5 min. Schleimer *et al.*[16] found low levels, delayed peaks (10–40 min), lack of correlation with plasma concentrations, and great variation in lumbar CSF concentrations of fentanyl following its intravenous injection in man. Unlike the circulation of cerebro-ventricular fluid, that of spinal fluid is sluggish, and the exchange

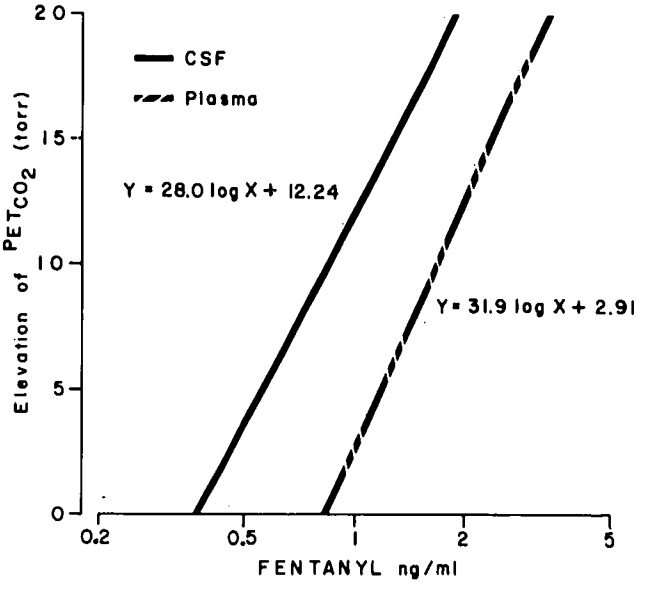

FIG. 4. Increase in end-tidal CO_2 above control values after an intravenous injection of ^{3}H-fentanyl, 10 μg/kg, expressed as a function of the log-concentrations of fentanyl in CSF and plasma. The values are from four dogs from which both CSF and plasma were collected during the period of depression of spontaneous ventilation. The mean r values were 0.97 for CSF and 0.95 for plasma.

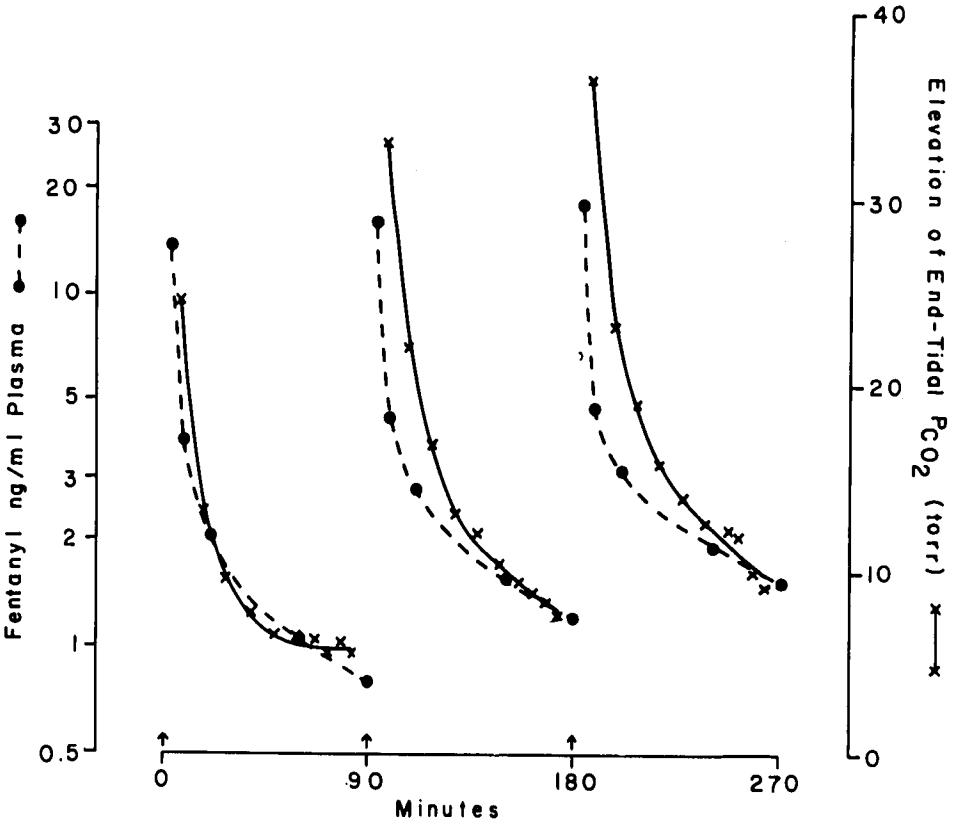

FIG. 5. Plasma concentrations of ^{3}H-fentanyl and increases in end-tidal CO_2 above control values in four dogs each given three successive doses (each dose was 10 μg/kg, iv) at 90-min intervals. Accumulation of fentanyl and ventilatory depression were evident as progressively higher values at the corresponding times after all doses. Each point represents the mean value for four animals. Injections of ^{3}H-fentanyl are indicated by the arrows.

of solutes with plasma more variable, especially in the lumbar area.[17] These facts and the possibility that the radioimmunoassay may not be absolutely specific for unchanged fentanyl may explain the differences between our observations and those by Schleimer *et al.* It is clear from our study that the disposition and kinetics of fentanyl metabolites in CSF and plasma are different from those of the unchanged drug.

The respiratory and analgesic effects of fentanyl are centrally mediated.[4,15,18–20] The antinociceptive activity of fentanyl correlates with its concentration in the brain,[15] which directly reflects those in CSF[19] and plasma. The plasma and CSF concentrations of fentanyl should therefore reflect the intensity of pharmacologic activity of fentanyl. We found that there is a linear relationship between respiratory depression as indicated by CO_2 accumulation in end-tidal gas and the log-concentration of fentanyl in plasma and CSF. The apparent "threshold" concentration of fentanyl for respiratory depression in the dog lightly anesthetized with enflurane is approximately 1 ng/ml plasma. Since end-tidal concentrations of enflurane were maintained constant, the extent of ventilatory depression due to enflurane should also have been constant. Nevertheless, the thresholds for ventilatory depression by fentanyl in awake and anesthetized subjects almost certainly differ due to interactions of fentanyl with the anesthetic drug.

The concentration of fentanyl in the CSF was approximately 46 per cent of that in plasma. This difference is largely explained by the binding of fentanyl to plasma proteins and a corresponding decrease in the concentration of free drug available for diffusion

TABLE 4. "Threshold" Concentrations of Fentanyl in Plasma for Ventilatory Depression in Dogs Anesthetized with Enflurane*

	Fentanyl (ng/ml)		
	Dose 1	Dose 2	Dose 3
Dog M3	0.92		
Dog M4	0.86		
Dog M12	0.76		
Dog M26	1.27	1.32	1.21
Dog M32	0.80	0.61	1.15
Dog M44	0.69	0.80	1.03
Dog M45	0.79	1.29	1.60
Mean (SEM)	0.87 (0.07) (n = 7)	1.00 (0.18) (n = 4)	1.25 (0.12) (n = 4)

* Threshold concentrations were determined as the intercept of the log concentrations–response line with the abscissa (*i.e.*, return of $P_{ET_{CO_2}}$ to control levels; see figure 4).

into CSF. CSF contains very little protein compared with plasma.[17]

The concentration of fentanyl in plasma was proportional to dose, a tenfold increment in dose producing approximately ten times greater concentrations in plasma.[11] In the case of CSF, the same increment in dose resulted in concentrations approximately six times higher at the early sampling times following injection; 90 min after injection, the concentration ratio was 8.7 for the 100 μg/kg dose *vs.* the 10 μg/kg dose. Differences in ventilation may have contributed to the less than proportional relationship between doses and CSF concentrations at the early sampling times following injection. Four of the five dogs receiving the low concentration were breathing spontaneously during the study and respiratory acidosis developed. Higher CSF levels of fentanyl may have resulted from increased cerebral blood flow associated with hypercarbia and also from lesser binding of fentanyl to plasma proteins with acidemia. In fact, the actual CSF concentrations of fentanyl were lower (0.58 ng/ml at 30 min) in the one dog in which ventilation was controlled than in the four other dogs given 10 μg/kg fentanyl during spontaneous ventilation (0.85 ng/ml at 30 min). Ventilation was controlled in all the dogs receiving the higher concentration in order to maintain normocarbia and avoid acidosis.

The prolonged terminal elimination phase ($t_{1/2\beta}$ = 3.3 hours) led to accumulation of fentanyl in plasma and to more intense and prolonged ventilatory depression after two or more intravenous doses. Cumulation was evident in our study, in which the drug effect was allowed to disappear almost completely before another dose was administered. In the usual clinical circumstances the dosing interval is much shorter so that the drug effects can be maintained. Shorter dosage intervals will lead to greater accumulation.[21,22]

These findings may also be used to explain the recurrent respiratory embarrassment reported for some patients hours after the last dose of fentanyl had been administered for anesthetic purposes.[6–10] The persistence of fentanyl in plasma and brain and the concomitant ventilatory depression may be masked at the end of operation when there is considerable stimulation of the patient associated with his transfer to the recovery room and other procedures. Noxious stimulation is antagonistic to the depressant effects of drugs such as fentanyl.[23] When the intensity of stimulation lessens, the depressant effects become more evident. Thus, fluctuation in postoperative ventilatory depression by fentanyl probably reflects its persistence in the body and a variable intensity of stimulation of the patient.[9]

In conclusion, the rapid onset and short duration of action of single doses of fentanyl are a result of its rapid entry into and elimination from the central nervous system. The intensity and duration of ventilatory depression are directly proportional to the concentrations of unchanged fentanyl in plasma and CSF. The slow elimination of fentanyl from the body allows accumulation of drug after two or more intravenous doses.

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Appendix

Following intravenous injection, the decline of fentanyl in plasma can be described by a triexponential equation[11]:

$$C_{p(t)} = P \exp^{-\pi t} + A \exp^{-\alpha t} + B \exp^{-\beta t}$$

where

$C_{p(t)}$ = the concentration of fentanyl in plasma at any time (t) after an intravenous injection,

P, A, B = the ordinal intercepts of the three single exponential lines comprising the concentration *vs.* time curve, which was computed by least-squares analysis of the data, and

π, α, β = the slopes of the individual lines and the first-order rate constants.[21,22]

By 20 min the uptake of fentanyl into CSF was essentially complete. If this initial uptake phase is ignored, the elimination of fentanyl form CSF may be fitted to the biexponential equation:

$$C_{CSF(t)} = A \exp^{-\alpha t} + B \exp^{-\beta t}$$

where

$C_{CSF(t)}$ = the concentration of fentanyl in CSF at any time (t) beyond 20 min after an intravenous injection.

A, B = the ordinal intercepts of the two single exponential lines comprising the concentration *vs.* time curve, which was computed by least-squares analysis of the data, and

α, β = the slopes of the individual lines and the first-order rate constants.