Pharmacokinetics and cardiopulmonary effects of fentanyl in isoflurane-anesthetized rhesus monkeys (*Macaca mulatta*)

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Objective—To determine pharmacokinetics and selected cardiopulmonary effects of fentanyl in isoflurane-anesthetized rhesus monkeys.

Animals—6 adult male rhesus monkeys.

Procedure—Fentanyl (8 mg/kg of body weight, IV) was administered to 6 monkeys anesthetized with isoflurane. End-tidal isoflurane concentration and esophageal temperature were kept constant, and ventilation was mechanically assisted. Heart rate, rhythm, aortic blood pressure, and blood pH, gas, and fentanyl concentrations were determined before and for 8 hours after administration of fentanyl. Pharmacokinetics of fentanyl were derived by use of noncompartmental methods based on statistical moment theory.

Results—Heart rate and mean arterial pressure decreased transiently following fentanyl administration. Maximal decreases were observed 5 to 15 minutes after administration. Arterial pH, $Paco_2$, and Pao_2 ranged from 7.46 ± 0.04 to 7.51 ± 0.05 units, 29.2 ± 3 to 34.6 ± 4.4 mm Hg, and 412.6 ± 105.3 to 482.9 ± 71.2 mm Hg, respectively. The clearance, volume of distribution area, volume of distribution steady state, mean residence time, area under the curve, elimination rate constant, and half-life were 32.5 ± 2.48 ml/kg/min, 9.04 ± 1.91 L/kg, 7.0 ± 1.2 L/kg, 218.5 ± 35.5 min, 0.247 ± 0.019 mg/ml/min, 0.004 ± 0.001/min, and 192.0 ± 33.5 min, respectively.

Conclusions and Clinical Relevance—Transient but potentially clinically important decreases in heart rate and mean arterial pressure were observed following fentanyl administration. Distribution and clearance data were similar to those reported for dogs and humans. (*Am J Vet Res* 2000;61:931–934)

In comparison to many commonly anesthetized animal species, clinical and laboratory experience suggests that monkeys are particularly sensitive to cardiovascular depressant actions of inhalation anesthetics.[1-3] In humans and dogs, **fentanyl (FEN)**, a synthetic opioid agonist that activates μ (principally), δ, and k receptors, is widely used as an adjunct to inhalation anesthetics to provide analgesia and decrease the incidence of inhalation agent-related cardiovascular complications.[4-8] This cardiovascular sparing effect is attributable to a reduction in the dose of inhalation anesthetic, which is positively correlated with increasing concentrations of plasma FEN in humans, dogs, cats,[a] and swine.[4-9]

To date, the effects of FEN in anesthetized monkeys have not been well characterized. In conscious monkeys, however, FEN causes a dose-dependent increase in the pain threshold, and, at lower doses, cardiovascular effects are minimal.[10] These favorable results encourage evaluation of the potential benefits of FEN as part of an improved anesthetic management plan for monkeys. Accordingly, the objective of the study reported here was to determine the pharmacokinetics of FEN in monkeys anesthetized with **isoflurane (ISO)**, a commonly used inhalation anesthetic. Selected cardiovascular and respiratory variables were also recorded in an effort to determine the effects of this opioid-inhalation agent combination.

Materials and Methods

Monkeys—Monkeys were maintained in accordance with standards established by the US Federal Animal Welfare Act, the American Association for Accreditation of Laboratory Care, and the Guide for Care and Use of Laboratory Animals. Six adult male rhesus monkeys (*Macaca mulatta*) that were (mean ± SD) 10.7 ± 3.0 years old and weighed 11.75 ± 1.88 kg were studied. Monkeys were judged to be healthy on the basis of results of complete physical examination performed under chemical restraint with ketamine[b] (10 mg/kg of body weight, IM) at least 7 days prior to the anesthetic trial. Blood for CBC and serum chemistry profile was collected at this time and evaluated for evidence of subclinical systemic disease or organ dysfunction. Food (but not water) was withheld for 12 hours prior to anesthetic exposure.

Study protocol—The experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee and the California Regional Primate Research Center of the University of California, Davis. On study days, monkeys were passively transferred into an induction chamber (30 cm wide × 55 cm long × 37.5 cm high) that was adapted to the front of the monkey's cage. Anesthesia was induced in the chamber with 5% ISO[c] in oxygen (6 L/min).

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Time from first anesthetic exposure to intubation was recorded. Following anesthetic induction and orotracheal intubation, monkeys were placed supine on a foam pad (4 cm thick) and maintained with a minimum end-tidal ISO concentration of 2.5% during instrumentation (approx 1 hour). The anesthetic was delivered by use of a standard small animal, semi-closed circle system, using an out-of-circle, agent-specific vaporizer. Inspired and expired respiratory gases[d] (oxygen and carbon dioxide) and ISO were continually sampled via a nylon catheter with the tip positioned near the distal end of the endotracheal tube. Isoflurane analysis was performed with an infrared analyzer[d] that was calibrated prior to each study and checked during and after each study with appropriate gas standards.[e]

A calibrated esophageal thermistor probe[d] was used to continuously measure body temperature. External heat was provided as necessary, using clothing (socks, hat), circulating water blankets, or infrared lamps to maintain body temperature at 37.5 ± 0.5 C. An ECG[d] (lead II) and pulse oximeter[d] (variable probe placement including cheek pouch and distal portion of the tail) were monitored continuously and recorded intermittently to assess heart rate and heart rhythm variations and oxygen saturation. A 20-gauge, 12.5-cm catheter[f] was surgically placed in the distal portion of the aorta via the femoral artery for measurement of systolic, diastolic, and mean arterial pressures and for collection of arterial blood samples. Pressure measurements were obtained by use of a calibrated pressure transducer[g] with the zero reference point at the level of the heart. A 20-gauge, 5-cm catheter[h] was placed percutaneously in the brachial vein for administration of lactated Ringer's solution at a rate of 7 ml/kg/h for 3 hours from the time of catheter placement and 5 ml/kg/h thereafter. Accurate administration was facilitated by use of a fluid administration pump.[i]

Prior to injection of FEN,[j] and for the remainder of the study, the end-tidal ISO concentration was reduced to 1.2% (0.8 times minimum alveolar concentration for rhesus monkeys),[1] and ventilation was controlled to maintain $Paco_2$ of 33 ± 5 mm Hg. Temperature, heart rate, respiration rate (total number and ventilator-controlled), systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, end-tidal ISO concentration, and oxygen saturation were recorded prior to (baseline, after 15 minutes at constant ISO dose) and 1, 2, 5, 15, 30, 60, 120, 180, 240, 300, 360, 420, and 480 minutes after FEN administration (8 µg/kg, IV, during a 1-minute period). An arterial blood sample was taken at each time point for determination of arterial pH, $Paco_2$, Pao_2,[k] PCV, and total protein and blood glucose[j] concentrations. All blood samples for blood gas and pH determinations were collected anaerobically in syringes that contained heparin and analyzed immediately. Blood gas and pH data were corrected to body temperature. Arterial blood samples were collected for determination of plasma FEN concentrations and subsequent pharmacokinetic analysis prior to and 0.625, 1, 1.25, 2, 5, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, and 480 minutes after completion of FEN administration. Blood (3 ml) was collected in heparinized tubes and briefly stored on ice, plasma was separated by centrifugation, and plasma samples were stored at –70 C until analysis.

Following the final set of measurements and administration of cefazolin[l] (20 mg/kg, IM), administration of anesthetic was discontinued, and monkeys were allowed to recover under constant observation until ambulatory. Times from discontinuation of ISO to extubation and ambulating (ability to sit up, hold cage bars, and reach for food when offered) were recorded.

Determination of fentanyl concentrations in plasma— Concentration of FEN in plasma samples was measured by use of a radioimmunoassay technique.[m] The assay is highly specific for FEN and has minimal cross-reactivity with FEN metabolites.[11] Sample determinations were performed in duplicate and each assay was repeated at least once; mean values are reported. Plasma calibrators were prepared in drug-free plasma with FEN added over a range of 0.1 to 80 ng/ml. Limit of quantitation for the assay was 0.1 ng/ml.

Pharmacokinetic analysis—Noncompartmental methods based on statistical moment theory were used to analyze the plasma concentration-time data obtained in each monkey.[12] An estimate of the overall elimination rate constant was obtained by linear regression of natural log plasma concen-

Table 1—Body temperature and respiratory and blood gas values for 6 rhesus monkeys anesthetized with isoflurane prior to and after IV administration of fentanyl (8 µg/kg of body weight)

	Variable					
Time (min)	Temp (C)	RR–T (breaths/min)	RR–VC (breaths/min)	pHa (units)	$Paco_2$ (mm Hg)	Pao_2 (mm Hg)
Baseline	37.3 ± 0.2	12.7 ± 7.2	8.8 ± 2.2	7.51 ± 0.04	31.9 ± 4.3	446.1 ± 107.1
1	37.2 ± 0.3	9.0 ± 2.2	8.7 ± 2.7	7.49 ± 0.04	30.0 ± 3.7	416.9 ± 94.5
2	37.2 ± 0.3	8.2 ± 2.6	8.2 ± 2.6*	7.50 ± 0.03	31.2 ± 3.7	415.9 ± 91.3
5	37.3 ± 0.3	8.0 ± 2.5	7.7 ± 2.0*	7.50 ± 0.04	31.6 ± 2.5	422.5 ± 110.3
15	37.2 ± 0.3	6.8 ± 1.7	6.3 ± 0.8*	7.48 ± 0.05	31.3 ± 4.3	412.6 ± 105.3
30	37.2 ± 0.3	6.3 ± 0.8	6.3 ± 0.8*	7.46 ± 0.04*	34.6 ± 4.4	433.2 ± 94.8
60	37.1 ± 0.3	7.5 ± 2.6	6.3 ± 0.8*	7.49 ± 0.03	32.5 ± 2.9	450.4 ± 104.7
120	37.2 ± 0.4	13.5 ± 3.6	7.0 ± 1.7*	7.48 ± 0.05	32.3 ± 5.4	456.9 ± 97.3
180	37.5 ± 0.2	18.0 ± 5.1*	7.7 ± 2.0	7.49 ± 0.04	29.6 ± 4.3	465.7 ± 56.7
240	37.4 ± 0.1	23.8 ± 4.8*	7.5 ± 1.6	7.51 ± 0.05	30.5 ± 2.2	456.9 ± 70.2
300	37.4 ± 0.2	23.3 ± 6.6*	6.8 ± 1.2*	7.49 ± 0.03	32.9 ± 2.5	482.9 ± 71.2
360	37.4 ± 0.3	26.6 ± 5.2*	7.0 ± 1.7*	7.49 ± 0.03	30.6 ± 2.3	474.2 ± 75.9
420	37.5 ± 0.3	28.3 ± 5.6*	6.7 ± 1.8*	7.50 ± 0.03	29.9 ± 2.7	468.5 ± 66.2
480	37.4 ± 0.4	29.7 ± 9.2*	6.7 ± 1.8*	7.53 ± 0.03	29.2 ± 3.0	472.4 ± 71.3

Data are expressed as mean ± SD.
*Significant ($P < 0.05$) difference from baseline value.
Temp = Body temperature. RR–T = Respiratory rate—total (spontaneous and ventilator-controlled breaths). RR–VC = Respiratory rate-ventilator controlled. pHa = Arterial pH.

Table 2—Hemodynamic and hematologic values for 6 monkeys anesthetized with isoflurane prior to and after IV administration of fentanyl

Time (min)	Variable						
	HR (bpm)	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	PCV (%)	TP (g/dl)	Glucose (mg/dl)
Baseline	123.0 ± 11.5	99.0 ± 17.1	60.8 ± 9.0	77.0 ± 11.9	38.5 ± 3.5	5.8 ± 1.0	71.8 ± 8.8
1	114.3 ± 8.7	71.0 ± 13.2*	42.8 ± 5.6*	55.2 ± 8.9 *	35.3 ± 5.2	4.9 ± 0.7	67.3 ± 11.5
2	108.0 ± 1.2*	62.5 ± 11.4*	36.3 ± 4.0*	47.8 ± 8.1*	35.8 ± 3.8	5.3 ± 0.8	70.3 ± 7.0
5	103.2 ± 11.5*	53.0 ± 9.5*	31.2 ± 2.5*	40.5 ± 8.6*	37.3 ± 3.7	5.4 ± 0.2	69.7 ± 5.2
15	102.7 ± 12*	50.0 ± 6.2*	28.7 ± 2.5*	40.5 ± 10.0*	33.2 ± 6.5*	4.7 ± 0.6*	60.5 ± 3.2
30	109.5 ± 14.4	68.7 ± 11.2*	43.2 ± 8.7*	51.3 ± 9.5*	33.0 ± 2.1*	4.7 ± 0.8*	68.3 ± 6.5
60	113.2 ± 13.3	83.8 ± 7.7	51.8 ± 5.7	62.8 ± 6.2	35.2 ± 1.7	5.0 ± 0.8*	70.7 ± 5.4
120	117.5 ± 11.3	102.0 ± 19.3	60.0 ± 11.6	75.0 ± 17.4	35.3 ± 1.8	5.2 ± 0.4	72.7 ± 4.5
180	125.5 ± 16.2	114.7 ± 21.8	64.3 ± 12.2	80.0 ± 16.2	33.8 ± 3.9	5.1 ± 0.9	73.7 ± 8.6
240	124.3 ± 15.2	113.8 ± 19.4	64.5 ± 12.6	79.3 ± 14.3	34.7 ± 3.7	4.7 ± 0.5*	75.2 ± 13.0
300	124.0 ± 17.4	113.8 ± 22.8	61.7 ± 10.6	78.2 ± 14.9	35.3 ± 1.9	5.2 ± 0.3	80.2 ± 18.9
360	124.0 ± 17.4	117.5 ± 14.1	60.7 ± 10.2	80.0 ± 12.3	34.2 ± 2.5	5.0 ± 0.5	64.3 ± 26.5
420	129.0 ± 18.9	115.2 ± 15.3	63.0 ± 5.7	77.5 ± 10.7	34.8 ± 2.7	5.1 ± 0.4	82.5 ± 20.8
480	128.5 ± 17.7	118.0 ± 15.4	63.8 ± 7.1	80.5 ± 12.3	34.8 ± 2.1	5.1 ± 0.3	86.8 ± 23.6

Data are expressed as mean ± SD.
*Significant ($P < 0.05$) difference from baseline value.
HR = Heart rate. bpm = Beats per minute. SAP = Systolic arterial pressure. DAP = Diastolic arterial pressure. MAP = Mean arterial pressure. TP = Total protein concentration.

trations versus time, commencing at 60 minutes after IV injection of drug. The decline in plasma concentration from 60 minutes was considered to represent the elimination phase of FEN disposition. Total areas under the zero- and first-moment curves were calculated and used to obtain systemic (body) clearance, apparent volumes of distribution, and mean residence time. Half-life was calculated from the overall elimination rate constant; elimination was shown graphically to be linear (first order).

Statistical analyses—Data were summarized as mean ± SD. A 2-way ANOVA was used to detect changes in cardiopulmonary variables over time. Monkeys served as blocks in the statistical analysis to reduce the variance in the repeated measure design. Because the focus was on changes relative to baseline measurements, the Dunette 2-sided multiple comparison was applied to perform mean separations over the time course. Significance for all statistical tests was set as $P < 0.05$.[n]

Results

Time from start of induction to endotracheal intubation was 17.2 ± 2.5 minutes. Intubation was easily performed in all monkeys with a 4.0- (1 monkey) or 4.5-mm (5 monkeys) endotracheal tube. Body temperature for the 6 monkeys ranged from 37.1 ± 0.3 C to 37.5 ± 0.3 C (**Table 1**). Mean end-tidal ISO concentration was consistently maintained at 1.2%. Heart rate and mean arterial pressure decreased transiently following FEN administration; heart rate decreased from 123 ± 11.5 to 102.7 ± 12 beats/min, and mean arterial pressure decreased from 77 ± 11.9 to 40.5 ± 10 mm Hg (**Table 2**). Maximal decreases were observed 5 to 15 minutes after FEN administration. Arterial pH, $Paco_2$, and Pao_2 ranged from 7.46 ± 0.04 to 7.51 ± 0.05 units, 29.2 ± 3 to 34.6 ± 4.4 mm Hg, and 412.6 ± 105.3 to 482.9 ± 71.2 mm Hg, respectively. Oxygen saturation was always > 97%. Respiratory rate, including spontaneous and ventilator-controlled breaths, ranged from 6.3 ± 0.8 to 29.7 ± 9.2 breaths/min.

Mean FEN plasma concentrations ranged from 35.42 ± 1.92 ng/ml at 0.375 minutes to 0.15 ± 0.01 ng/ml at 8 hours (**Fig 1**). Plasma concentration-time

Table 3—Pharmacokinetic values obtained from analysis of plasma concentration-time curves after IV administration of fentanyl in 6 monkeys anesthetized with isoflurane

Variable	Mean ± SD
Cl_B (ml/kg/min)	32.50 ± 2.48
Vd_{area} (L/kg)	9.04 ± 1.91
Vd_{ss} (L/kg)	7.0 ± 1.2
MRT (min)	218.5 ± 35.56
AUC (μg/ml/min)	0.247 ± 0.019
β (/min)	0.004 ± 0.001
$T_{1/2}$ (min)	192 ± 33.5

Cl_B = Clearance. Vd_{area} = Volume of distribution area. Vd_{ss} = Volume of distribution steady state. MRT = Mean residence time. AUC = Area under the curve. β = Elimination rate constant. $T_{1/2}$ = Half life.

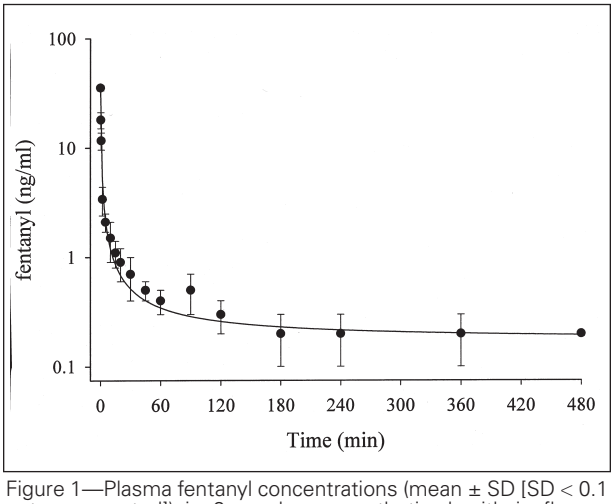

Figure 1—Plasma fentanyl concentrations (mean ± SD [SD < 0.1 not represented]) in 6 monkeys anesthetized with isoflurane after IV administration of fentanyl (8 mg/kg).

data were used to derive pharmacokinetic information (**Table 3**). Mean times to extubation and ambulation after discontinuation of ISO administration (8 hours at constant dose, approx 9 hours total time) were 5.0 ± 1.1 minutes and 15.7 ± 4.6 minutes, respectively.

Discussion

Anesthetic induction and endotracheal intubation was uncomplicated in the 6 monkeys reported here. Recovery after discontinuation of isoflurane administration was timely and without incident after a single dose of FEN administered IV and 8 hours of administration of a constant dose of ISO.

Changes in heart rate and blood pressure after FEN administration were transient and likely reflected direct effects of FEN (eg, opioid-mediated decrease in heart rate) and additive effects of FEN and ISO.[1,4,5,10] Concurrent use of FEN and ISO in other species results in a substantial reduction in the dose of inhalation agent required to maintain a consistent plane of anesthesia.[4-6,a] In the study reported here, ISO concentration was kept constant at 0.8 times rhesus minimum alveolar concentration (light plane of anesthesia), so the addition of FEN likely transiently increased anesthetic depth. Baseline heart rate and blood pressure recorded for the remainder of the study (after the transiently observed decreases) were similar to those reported during controlled ventilation at 1 minimum alveolar concentration in halothane- and isoflurane-anesthetized monkeys[1,2] and lower than those reported for awake chronically instrumented monkeys.[13,14]

Although significant changes were recorded, clinically relevant changes in ventilator-controlled breaths were minimal during the study. However, a progressive increase in spontaneous breathing was detected approximately 2 hours after FEN administration. The increase in respiratory rate coincided with a substantial decrease in plasma FEN concentrations (Fig 1) and likely reflected reversal of opioid-induced respiratory depression and a decrease in overall anesthetic dose.[1,10] Despite the variation in respiratory rate, Pa_{CO_2} did not vary significantly at any time point during the study and was similar to that reported in anesthetized monkeys breathing only oxygen and halothane (1 minimum alveolar concentration).[2] Arterial oxygen tensions also were similar to those reported in anesthetized monkeys during similar study conditions.[2]

For FEN, pharmacokinetic values derived from the plasma concentration time curve were similar to those reported for FEN in dogs[15,16] and humans.[17,18] Despite similarities in pharmacokinetic values, some authors suggest that humans and nonhuman primates are more sensitive to certain effects of opioids (eg, respiratory depression) than are dogs.[1,8,10,17] Because these effects cannot be explained on the basis of differences in distribution volumes or clearance for FEN, it is likely that they are the result of undefined pharmacodynamic differences between species. Results of the study reported here provide information necessary for subsequent investigations and clinical use of FEN in rhesus monkeys.

[a]Yackey M, Ilkiw JE, Pascoe PJ, et al. The effect of transdermally administered fentanyl on the minimum alveolar concentration of isoflurane in cats, in *Proceedings*. 6th Int Cong Vet Anesth, Thessaloniki, Greece, 1997.
[b]Vetamine, Mallinckrodt Veterinary Inc, Mundelein, Ill.
[c]Aerrane, Fort Dodge Laboratories, Fort Dodge, Iowa.
[d]AS/3 Datex anesthesia monitor, Datex Medical Instrumentation, Tewksbury, Mass.
[e]Matheson Gas Products, Newark, Calif.
[f]Central vessel catheterization kit, Arrow International Inc, Reading, Pa.
[g]Transpac IV, Abbott Critical Care Systems, North Chicago, Ill.
[h]Angiocath, Becton-Dickinson Vascular Access, Sandy, Utah.
[i]Flo-Gard 6200R, Baxter Health Corp, Round Lake, Ill.
[j]Sublimaze, Janssen Pharmaceutica, Titusville, NJ.
[k]Stat 5 Profile 5 Analyzer, Nova Biomedical, Waltham, Mass.
[l]Apothecon, Bristol-Meyer Squibb Co, Princeton, NJ.
[m]RDI Research Diagnostics Inc, Flanders, NJ.
[n]SAS STAT, SAS Institute Inc, Cary, NC.

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