Pharmacokinetics of ketamine and its metabolite, norketamine, after intravenous administration of a bolus of ketamine to isoflurane-anesthetized dogs

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Objective—To determine the pharmacokinetics of ketamine and norketamine in isoflurane-anesthetized dogs.

Animals—6 dogs.

Procedure—The minimum alveolar concentration (MAC) of isoflurane was determined in each dog. Isoflurane concentration was then set at 0.75 times the individual's MAC, and ketamine (3 mg/kg) was administered IV. Blood samples were collected at various times following ketamine administration. Blood was immediately centrifuged, and the plasma separated and frozen until analyzed. Ketamine and norketamine concentrations were measured in the plasma samples by use of liquid chromatography–mass spectrometry. Ketamine concentration-time data were fitted to compartment models. Norketamine concentration-time data were examined by use of noncompartmental analysis.

Results—The MAC of isoflurane was 1.43 ± 0.18% (mean ± SD). A 2-compartment model best described the disposition of ketamine. The apparent volume of distribution of the central compartment, the apparent volume of distribution at steady state, and the clearance were 371.3 ± 162 mL/kg, 4,060.3 ± 2,405.7 mL/kg, and 58.2 ± 17.3 mL/min/kg, respectively. Norketamine rapidly appeared in plasma following ketamine administration and had a terminal half-life of 63.6 ± 23.9 minutes. A large variability in plasma concentrations, and therefore pharmacokinetic parameters, was observed among dogs for ketamine and norketamine.

Conclusions and Clinical Relevance—In isoflurane-anesthetized dogs, a high variability in the disposition of ketamine appears to exist among individuals. The disposition of ketamine may be difficult to predict in clinical patients. (*Am J Vet Res* 2005;66:2034–2038)

Rational design of dosing regimens requires knowledge of the pharmacokinetics of the drug to be administered. In addition, when multiple drugs are administered concomitantly, pharmacodynamic and pharmacokinetic interactions are possible. For example, agents like inhalant anesthetics are likely to alter the disposition of other drugs, attributable at least in part to their effects on systemic and hepatic hemodynamics.[1-4] Moreover, individual inhalant anesthetics may have different effects on blood flow; halothane depresses liver blood flow to a larger extent than isoflurane, whereas isoflurane causes less myocardial depression than enflurane or halothane.[5-8] Extrapolations of pharmacokinetic studies performed in unmedicated animals or animals receiving a different inhalant anesthetic may therefore be inappropriate to correctly predict the disposition of a drug in an animal anesthetized with a given inhalant agent.

Inhalant anesthetics are widely used in dogs. Among the agents in this class, isoflurane is the most popular in North America.[9] Inhalant anesthetics cause dose-dependent cardiorespiratory depression in many species, including dogs.[8,10-12] Balanced anesthesia is a technique that may limit inhalant anesthetic–induced cardiorespiratory depression by decreasing the requirements for these agents.[13,14] Balanced anesthesia relies on the concurrent administration of several drugs to reduce the dose of each drug and therefore the associated toxic effects.

Ketamine is a dissociative anesthetic commonly used to induce anesthesia in dogs.[15-20] Ketamine has been shown to reduce the requirements for inhalant anesthetics in dogs, horses, rats, and cats and is therefore a potentially useful agent for balanced anesthesia.[21-23,a] Ketamine is clinically used alone or in combination with other drugs to supplement inhalant anesthesia in dogs.[24,25]

Although the pharmacokinetics of ketamine have been reported[22,26-28] for unmedicated dogs and dogs anesthetized with halothane and enflurane, to our knowledge, no data are available for dogs anesthetized with isoflurane. The purpose of the study reported here was to determine the pharmacokinetics of ketamine given IV as a bolus (3 mg/kg) in isoflurane-anesthetized dogs.

Materials and Methods

Animals—Six healthy adult male castrated mongrel dogs (mean ± weight SD, 27.8 ± 2.6 kg) were used in the study. Food was withheld from dogs for 12 hours before experiments were initiated. An institutional animal care and use committee approved the study.

Anesthesia and instrumentation—Anesthesia was induced with isoflurane in oxygen by use of a facemask. The trachea was then intubated with a cuffed endotracheal tube, and anesthesia was maintained with isoflurane in oxygen via

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a circle circuit with a fresh gas flow of 20 mL/kg/min. Ventilation was spontaneous throughout the study. A catheter was passed through the lumen of the endotracheal tube so that its tip was positioned at the end of the tube. This catheter was connected to a Raman spectrometer[b] for continuous measurement of inspired and end-tidal oxygen, carbon dioxide, and isoflurane concentrations. The spectrometer was calibrated with room air and 3 calibration gases[c] of known concentrations (0.5%, 1.5%, and 2.5%) every 80 minutes, corresponding to its internal calibration interval. A 20-gauge, 4.7-cm catheter was inserted in a cephalic vein, and lactated Ringer's solution was administered at 3 mL/kg/h. A 20-gauge, 4.7-cm catheter was inserted in a dorsal pedal or median artery for blood sample collection. A Doppler crystal[d] and occluding cuff were placed over a median artery for systolic blood pressure determination. A pulse oximeter[e] probe was placed on the tongue for arterial hemoglobin oxygen saturation measurement. A thermistor,[f] calibrated prior to each experiment against a certified thermometer, was placed in the esophagus at the level of the midthorax and connected to a physiograph[g] for continuous temperature monitoring. External heat (warm water, forced-air blankets, or both) was supplied as needed to maintain body temperature between 38.5° and 39.5°C.

Minimum alveolar concentration determination— **Minimum alveolar concentration (MAC)** was determined in each dog in triplicate, according to methods reported in detail.[29] The mean value is reported.

Blood collection—Following MAC determination, the end-tidal isoflurane concentration was set at 0.75 times the individual's MAC, and 20 minutes was allowed for stabilization. Isoflurane concentration was subsequently adjusted (increased by steps of 10%) as needed to maintain immobility. A bolus (3 mg/kg) of ketamine[h] was administered IV over 5 seconds via the cephalic catheter. Arterial blood samples (1.5 mL) were collected immediately before and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 16, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, and 360 minutes after ketamine administration. The blood was transferred to a tube containing ethylenediaminetetraacetic acid and immediately centrifuged for 10 minutes; the plasma was collected and stored at –20°C until analysis for ketamine and norketamine concentrations.

Determination of plasma ketamine and norketamine concentrations—Standard solutions of ketamine[i] and norketamine[j] were prepared in **acetonitrile (ACN)**[k] at a concentration of 1 mg/mL. Working standard solutions were prepared by diluting the standard solution with ACN:acetic acid[l] (9:1, vol/vol) to concentrations ranging from 0.2 to 40 µg/mL. All standard solutions were stored in the dark at –15°C when not in use.

Ketamine and norketamine concentrations in canine plasma were measured by liquid chromatography–mass spectrometry after a simple protein precipitation cleanup procedure. Calibrators were prepared by adding appropriate volumes of the working standard solutions to drug-free control canine plasma. The range of concentrations used for serum calibrators was 0.04 to 14.0 µg/mL. Plasma samples and calibrators were processed for analysis by mixing 250-µL aliquots with 300 µL of ACN:acetic acid (9:1, vol/vol) and chilling at 4°C for 30 minutes, followed by centrifugation and harvesting of the deproteinated supernatant.

For quantitative measurements, high-performance liquid chromatography[m] and a triple quadrupole mass spectrometer[n] with electrospray interface were used. A 2.1 × 50-mm, 3-µm, column[o] and a linear gradient of ACN in water with a constant 0.05% trifluoroacetic acid[p] at a flow rate of 0.4 mL/min were used for chromatography. The ACN concentration was held at 2% for 0.2 minutes and ramped from 2% to 45% over 2.3 minutes and from 45% to 75% over 1.2 minutes. Prior to analysis, the deproteinated supernatant of all samples, controls, and calibrators was diluted up to 5-fold in the initial mobile phase. Injection volumes were 10 µL.

Multiple selected reaction-monitoring transitions of initial product ions for ketamine (**mass-to-charge ratio [m/z]**, 238→125, 220, 179, and 163) and norketamine (m/z, 224 →125, 207, 179, and 163) were used for detection and quantification. The total response for the major product ions of ketamine (m/z, 125 and 179) and norketamine (m/z, 207 and 179) was plotted, and peaks at the proper retention time were integrated by use of a software program.[q] The software program was used to generate calibration curves and quantitate these analytes in all samples.

Pharmacokinetic modeling and statistical analysis— Nonlinear least squares regression was performed on plasma ketamine concentrations following IV administration of a bolus with the use of a computer software program.[r] Data were weighted by the reciprocal of the plasma ketamine concentration squared. Data from each dog were fitted to 2- and 3-compartment models, and the appropriate model was selected by use of the Akaike information criterion.[30,31] Standard compartmental equations were used to estimate pharmacokinetic parameters for each dog.

Changes in plasma norketamine concentrations were evaluated by use of standard noncompartmental analysis. Linear trapezoidal areas were used in calculating the area under the plasma norketamine concentration versus time curve, and other pharmacokinetic parameters were determined with standard noncompartmental equations by use of a computer software program.[r] Significance was set at a value of $P < 0.05$. Data are presented as mean ± SD values.

Results

The mean MAC of isoflurane for dogs in our study was 1.43 ± 0.18% (range, 1.24% to 1.69%). To maintain immobility during the blood sample collection procedure, it was necessary to increase isoflurane concentration > 0.75% in all dogs. For all 6 dogs, time from ketamine administration to the first increase in isoflurane concentration ranged from 4 to 130 minutes and time to the second increase ranged from 12 to 295 minutes. Of the 6 dogs, 4 had a third increase in isoflurane concentration that ranged from 90 to 300 minutes after ketamine administration. One dog had a fourth increase in isoflurane concentration that occurred at 177 minutes after ketamine administration. Systolic blood pressure, hemoglobin oxygen saturation, and body temperature were 104 ± 11 mm Hg, 97 ± 2%, and 38.8 ± 0.3°C, respectively, in all dogs at all times.

A 2-compartment model best described the decline in ketamine plasma concentration following IV administration of a bolus (3 mg/kg; **Figure 1**). A high variability in the disposition of ketamine was observed among individuals (**Table 1**). The observed peak plasma concentration ranged from 3,184 to 13,607 ng/mL. The apparent volume of distribution at steady state was 4.06 ± 2.41 L/kg, the elimination half-life was 94.2 ± 36.7 minutes, and the total body clearance was 58.2 ± 17.3 mL/min/kg.

Norketamine concentration rapidly increased after IV administration of ketamine, to reach a maximum at 6.5 ± 4.8 minutes after. The maximal concentration reached was 810.7 ± 648.1 ng/mL and varied widely among individuals (**Table 2**). Norketamine concentra-

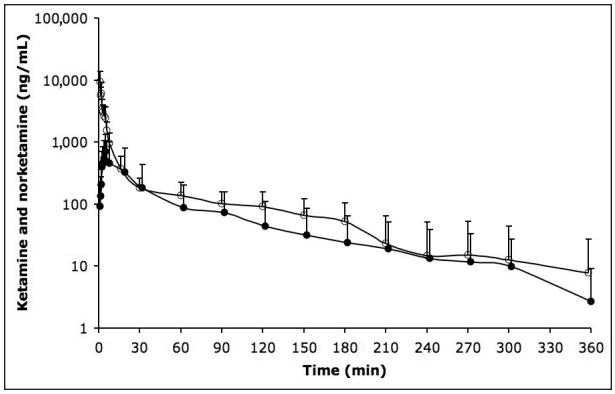

Figure 1—Mean ± SD changes in plasma ketamine (open circles) and norketamine (closed circles) concentrations in 6 dogs following IV administration of a bolus of ketamine (3 mg/kg) at time 0.

Table 1—Pharmacokinetic parameters of ketamine* determined from 6 dogs following IV administration of a bolus of ketamine (3 mg/kg).

Parameter	Mean ± SD	Range
A (ng/mL)	3,166.3 ± 1,600.0	1,606.4–5,566.9
B (ng/mL)	80.1 ± 40.1	21.2–120.1
α (/min)	0.37 ± 0.09	0.24–0.49
β (/min)	0.01 ± 0.00	0.01–0.01
$t_{1/2\alpha}$ (min)	2.0 ± 0.5	1.4–2.8
$t_{1/2\beta}$ (min)	94.2 ± 36.7	57.1–137.1
Vc (mL/kg)	371.3 ± 162.0	178.9–581.9
Vss (mL/kg)	4,060.3 ± 2,405.7	2,204.5–8,400.3
Cl (mL/min/kg)	58.2 ± 17.3	35.5–87.5
AUC (min·ng/mL)	55,426 ± 16,708	34,292–84,415
MRT (min)	72.0 ± 42.4	42.9–148.2

*Two-compartment model in which the concentration at time t is as follows: $C = Ae^{-\alpha t} + Be^{-\beta t}$.

$t_{1/2\alpha}$ = Distribution half-life. $t_{1/2\beta}$ = Elimination half-life. Vc = Apparent volume of the central compartment. Vss = Apparent volume of distribution at steady state. Cl = Total body clearance. AUC = Area under the plasma ketamine concentration-time curve. MRT = Mean residence time.

Table 2—Pharmacokinetic parameters of norketamine determined from 6 dogs following IV administration of a bolus of ketamine (3 mg/kg).

Parameter	Mean ± SD	Range
C_{max} (ng/mL)	810.7 ± 648.1	31–1,490
T_{max} (min)	6.5 ± 4.8	2.5–16.0
$t_{1/2(\lambda-z)}$ (min)	63.6 ± 23.9	31.3–87.3
AUC_{∞} (min·ng/mL)	23,935 ± 30,134	3,915–83,038
MRT (min)	80.3 ± 43.4	21–134

C_{max} = Maximal observed norketamine plasma concentration. T_{max} = Time after ketamine administration at which C_{max} was observed. $t_{1/2(\lambda-z)}$ = Terminal half-life. AUC_{∞} = Area under the plasma norketamine concentration-time curve, extrapolated to infinity.

See Table 1 for remainder of key.

tion declined rapidly, with an elimination half-life of 64 ± 24 minutes. The area under the plasma concentration-time curve was 23,753 ± 30,100 min·ng/mL, and the mean residence time was 80.3 ± 43.4 minutes.

Discussion

In our study, a 2-compartment model best described the disposition of ketamine in 6 dogs, following IV administration of a bolus. Previous studies[22,27,28,32-35] in dogs, cats, horses, and people use a similar model to describe the disposition of ketamine. In another study[29] in which we examined the effects of 6 plasma concentrations of ketamine on the MAC in the same dogs used in this study, we stated that data from 4 dogs best fitted a 2-compartment model, whereas data from the 2 remaining dogs best fitted a 3-compartment model. This discrepancy between the 2 studies is related to modeling strategy. The model in the study by Solano et al[29] was indeed optimized for the use of a target-controlled infusion system, for which it is particularly important to predict as accurately as possible the initial distribution phase. In the study reported here, the model was optimized to describe the overall disposition of ketamine and the weight of the initial concentrations was decreased in the analysis.

In previous studies,[22,26] ketamine was administered IV as a bolus of 10 mg/kg to enflurane-anesthetized dogs and as a bolus of approximately 3.3 mg/kg to halothane-anesthetized dogs. In both studies, the apparent volume of distribution at steady state was smaller and the clearance was lower than in the study reported here. Reasons for these findings are unclear. The higher clearance in the study reported here may be related to better preservation of blood flow (including liver and renal blood flows), allowing faster elimination of the drug. Several factors may have contributed to differences in blood flow among the 3 studies. At equipotent doses, halothane and enflurane produce more myocardial depression than isoflurane.[8] Halothane and enflurane also reduce hepatic blood flow to a greater extent than isoflurane, potentially limiting the delivery of ketamine to the liver and therefore its metabolism.[5] Moreover, equipotent doses of inhalant anesthetics were not used. Schwieger et al[22] reported an MAC of enflurane of 2.26% in their dogs and maintained an end-tidal enflurane concentration of 3% during their pharmacokinetic study, corresponding to 1.3 MAC. Henthorn et al[26] maintained halothane concentration at 2%; from their description, it is unclear whether this was the vaporizer setting, the inspired concentration, or the end-tidal concentration. Nevertheless, because the MAC of halothane is 0.86%,[36] dogs in that study likely received more than 1 MAC of halothane. We initially maintained end-tidal isoflurane concentration at 0.75 MAC after a lower dose of ketamine because ketamine has been reported to decrease MAC. That concentration was then altered as needed to maintain immobility. It is likely that the dogs in the studies of Schwieger et al[22] and Henthorn et al[26] were at a deeper plane of anesthesia than our dogs, resulting in more cardiovascular depression. Although blood pressure was measured in these studies, the results are not reported. The larger apparent volume of distribution at steady state may also be related to differences in blood flow; higher blood flow may indeed result in larger distribution of the drug. Interestingly, distribution and elimination half-lives in the study reported here were much closer to values reported[22,27,28] for awake dogs than for enflurane-anesthetized dogs.

Norketamine, or N-demethylketamine, is the first metabolite of ketamine and is further metabolized by oxidation.[37-39] Norketamine is of clinical importance because it has been reported[40] to have pharmacologic

effects similar to those of ketamine (ie, anesthesia and CNS excitation). In our study, plasma norketamine concentration rapidly increased after administration of ketamine. The decline in norketamine concentration was parallel to that of ketamine. Mean residence times were similar for both compounds. Norketamine had a short terminal half-life of slightly over an hour. Even though this metabolite may significantly contribute to the pharmacodynamic effects of ketamine, it appears to be rapidly eliminated and should not substantially prolong the effects of a single moderate dose of ketamine.

Plasma ketamine concentrations after IV administration of a bolus (3 mg/kg) were extremely variable among individuals, leading to a high level of variability in pharmacokinetic parameters, such as apparent volume of the central compartment, apparent volume of distribution at steady state, clearance, and elimination half-life. High variability among individuals was also observed in plasma norketamine concentrations and therefore in its pharmacokinetics. Different factors are known to affect pharmacokinetic variability. These include age, body weight, gender, disease, and genetics.[41] In our study, measures were taken to limit normal biological variability; all dogs were castrated males of similar age and weight. They were all healthy on the basis of physical examination findings and results of hematologic evaluation at the beginning of the study. However, differences in body composition, and particularly in the lean-to-fat ratio, cannot be excluded and, if present, may account for part of the differences in volume of distribution. More importantly, it has been suggested[42-44] that genetic factors may contribute significantly to the variation in metabolic clearance of drugs among subjects. Although no data are available on the influences of genetic variation on the disposition of ketamine in dogs, it is likely to have played a role. Variability in the disposition of ketamine may also be partly related to a variable effect of isoflurane among the dogs in our study. Although a similar MAC fraction (0.75 MAC) was used initially in all dogs, this concentration had to be changed at various times in each dog to maintain immobility. Even though this was expected (0.75 MAC was selected because ketamine has been reported to decrease MAC and this effect of ketamine should decrease over time), it possibly contributed to variable cardiovascular effects of isoflurane among dogs and therefore to some variability in the disposition of ketamine. On the other hand, the variable time at which isoflurane concentration needed to be adjusted may relate to the variable disposition of ketamine in these dogs. Additional variability related to isoflurane may be the result of differences in MAC among the dogs in our study. In our dogs, MAC ranged from 1.24% to 1.69%. Although cardiovascular depression resulting from inhaled anesthetic is clearly dose dependent and similar MAC multiples (or fractions) are considered equipotent when individual MAC values are used,[10,36] it is possible that absolute inhalant concentration plays a role. This may be supported by the lower variability observed in the study by Schwieger et al,[22] in which a 3% end-tidal enflurane concentration was maintained in all dogs, regardless of their individual MAC. Finally, although unlikely, it is possible that some of the variation observed in our study was related to analytic rather than biological factors. Precautions were taken to avoid this analytic variation, such as immediate processing of blood samples, batch analysis of all samples, and identical processing of all samples during analysis.

In conclusion, isoflurane may affect the disposition of ketamine differently from other inhalants, such as halothane or enflurane. In isoflurane-anesthetized dogs, ketamine administration resulted in rapid formation of norketamine, which was rapidly eliminated. A high variability in the disposition of ketamine was observed among dogs, making it difficult to predict the kinetics of this drug in clinical patients.

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d. Model 811-B, Parks Medical, Aloha, Ore.
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f. YSI 701 temperature probe, Yellow Springs Instruments, Yellow Springs, Ohio.
g. Gould Instrument Systems, Valley View, Ohio.
h. Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa.
i. Sigma Chemical Co, St Louis, Mo.
j. Cerilliant, Round Rock, Tex.
k. Burdick & Jackson, Muskegon, Mich.
l. Fisher Scientific, Pittsburgh, Pa.
m. 1100 Series, Agilent Technologies, Palo Alto, Calif.
n. Finnigan TSQ Quantum, Thermo Electron, San Jose, Calif.
o. Discovery HS C_{18}, Supelco, Bellefonte, Pa.
p Aldrich, St Louis, Mo.
q. LCQuan, Thermo Electron, San Jose, Calif.
r. WinNonlin, Pharsight, Cary, NC.

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