Pharmacokinetics of detomidine following intravenous or oral-transmucosal administration and sedative effects of the oral-transmucosal treatment in dogs

Kristen M. Messenger DVM
Marie Hopfensperger DVM
Heather K. Knych DVM, PhD
Mark G. Papich DVM, MS

Received March 19, 2015.
Accepted June 5, 2015.

From the Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27607 (Messenger, Hopfensperger, Papich); and the K. L. Maddy Equine Analytical Laboratory, Department of Veterinary Molecular Biosciences, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616 (Knych). Dr. Hopfensperger’s present address is Department of Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824.

Address correspondence to Dr. Messenger (kmmessenger@ncsu.edu).

OBJECTIVE
To determine the pharmacokinetics of detomidine hydrochloride administered IV (as an injectable formulation) or by the oral-transmucosal (OTM) route (as a gel) and assess sedative effects of the OTM treatment in healthy dogs.

ANIMALS
12 healthy adult dogs.

PROCEDURES
In phase 1, detomidine was administered by IV (0.5 mg/m²) or OTM (1 mg/m²) routes to 6 dogs. After a 24-hour washout period, each dog received the alternate treatment. Blood samples were collected for quantification via liquid chromatography with mass spectrometry and pharmacokinetic analysis. In phase 2, 6 dogs received dexmedetomidine IV (0.125 mg/m²) or detomidine gel by OTM administration (0.5 mg/m²), and sedation was measured by a blinded observer using 2 standardized sedation scales while dogs underwent jugular catheter placement. After a 1-week washout period, each dog received the alternate treatment.

RESULTS
Median maximum concentration, time to maximum concentration, and bioavailability for detomidine gel following OTM administration were 7.03 ng/mL, 1.00 hour, and 34.52%, respectively; harmonic mean elimination half-life was 0.63 hours. All dogs were sedated and became laterally recumbent with phase 1 treatments. In phase 2, median global sedation score following OTM administration of detomidine gel was significantly lower (indicating a lesser degree of sedation) than that following IV dexmedetomidine treatment; however, total sedation score during jugular vein catheterization did not differ between treatments. The gel was subjectively easy to administer, and systemic absorption was sufficient for sedation.

CONCLUSIONS AND CLINICAL RELEVANCE
Detomidine gel administered by the OTM route provided sedation suitable for a short, minimally invasive procedure in healthy dogs. (Am J Vet Res 2016;77:413–420)

Oral-transmucosal drug administration is attractive to veterinarians and their clients for several reasons. The noninvasive drug delivery should not cause pain or distress to the patient. For a sedative, such as an α₂-adrenergic receptor agonist, this route of drug delivery is even more attractive for patients needing sedation that are difficult to inject or fearful when restrained. This method of administration requires minimal restraint or technical skill and was successfully used in a study comparing IM and OTM routes of dexmedetomidine delivery in cats. In addition, the first-pass hepatic effect of orally administered drugs is avoided with OTM administration, and the rich blood supply to the oral mucosa allows for therapeutic circulating concentrations to be reached.

The sedative effects of detomidine gel administered by the OTM route have been evaluated in horses.
that received the drug for restraint and sedation for procedures in the field.\textsuperscript{8} In dogs, parenterally administered dexmedetomidine is a typical protocol for sedation and restraint.\textsuperscript{1,2} Although previous studies\textsuperscript{9,10} have explored the premedicant effects of parenterally administered detomidine in dogs, this drug is not commonly used in small animal practice. Recently, a research group including authors of the present study evaluated the anxiolytic and sedative effects of the detomidine gel formulation in dogs, with OTM dosing at concentrations intended to facilitate handling of dogs while maintaining their ability to ambulate.\textsuperscript{4} To our knowledge, there are no studies assessing the efficacy of detomidine gel administered by the OTM route at higher doses to induce sedation and recumbency in dogs, such as would be required for minimally invasive procedures or diagnostic imaging. There is also limited information on the pharmacokinetics of detomidine in dogs,\textsuperscript{11} and information regarding the pharmacokinetics of detomidine gel following OTM administration in dogs is lacking. In horses, the pharmacokinetics and pharmacodynamics of detomidine gel following OTM (sublingual) administration have been described, with a reported elimination half-life between 0.86 and 1.5 hours, and F of approximately 22%\textsuperscript{7,12}; in addition, at a dose of 40 µg/kg, the gel treatment results in sedation adequate for minor procedures for 1 to 2 hours in horses.\textsuperscript{8}

The objectives of the study reported here were to determine the pharmacokinetics of detomidine administered IV and detomidine gel administered by the OTM route in dogs and to determine the sedative effects of the detomidine gel treatment. We hypothesized that the gel formulation would have good systemic F in dogs. We also hypothesized that the gel formulation of detomidine administered at 0.5 mg/m\textsuperscript{2} OTM would provide sedation equivalent to that achieved with dexmedetomidine at a dose of 0.125 mg/m\textsuperscript{2} administered IV.

**Materials and Methods**

**Animals**

Six healthy adult purpose-bred dogs were used in each phase of the study. Animals were considered to be healthy on the basis of physical examination and results of routine CBC and serum biochemical analysis. Dogs were acclimated to the study procedure room for \( \geq 24 \) hours prior to each study day. Food was withheld for 12 hours prior to beginning each study and was returned when dogs were fully recovered from sedation. Water was available ad libitum except during sedation. For the first phase of the study (phase 1: pharmacokinetic evaluation), 3 male and 3 female dogs (all sexually intact) were used. These dogs were of a mixed breed (hound and Golden Retriever cross), with mean ± SD weight and age of 23.85 ± 4.44 kg and 2.15 ± 0.55 years, respectively. In the second phase (phase 2: assessment of sedative effects), 2 adult Beagles and 4 hound-type dogs (5 females and 1 male; all sexually intact) were studied; mean ± SD weight of these dogs was 15.3 ± 4.1 kg, and median age was 1.5 years (range, 1.4 to 3.7 years). Both phases of the study were approved by the North Carolina State University Institutional Animal Care and Use Committee (protocol Nos. 10-138-O and 11-072-O).

**Treatments**

In phase 1, dogs received either detomidine hydrochloride\textsuperscript{9} (0.5 mg/m\textsuperscript{2}, IV, via an aseptically placed cephalic vein catheter) or detomidine hydrochloride gel\textsuperscript{10} (1 mg/m\textsuperscript{2}, applied to the buccal pouch for OTM administration) in a randomized crossover design. The mean ± SD dose and volume of detomidine gel were 35.3 ± 2.5 µg/kg and 0.11 ± 0.02 mL, respectively. The pH of the oral cavity was measured in all dogs prior to drug administration.\textsuperscript{8} After a 24-hour washout period (accounting for > 10 drug half-lives [on the basis of information available in equine studies\textsuperscript{7,11}]), the alternate treatment was administered. Baseline blood samples obtained on the second day of the crossover experiment ensured this was an adequate washout time. Patient monitoring during this phase included heart rate (evaluated with direct auscultation and pulse palpation) and indirect blood pressure measurement with an automated oscillometric blood pressure monitor\textsuperscript{6} with an appropriately sized cuff placed on a forelimb. Body position (standing, sitting, or sternal or lateral recumbency) was monitored and recorded for all dogs during this phase. One observer recorded the time at which each dog spontaneously assumed lateral recumbency and the time at which each dog spontaneously returned to a sitting or standing position. A digital timer attached to each dog's cage was used to record times for body position data.

In phase 2, dogs were assigned to receive either detomidine gel (0.5 mg/m\textsuperscript{2}, OTM) or dexmedetomidine hydrochloride\textsuperscript{9} (0.125 mg/m\textsuperscript{2}, IV) in a randomized crossover design, with the alternate treatment administered to each dog after a 1-week washout period. The sedative effects of treatments were assessed at predetermined time points. Random assignment in both study phases was accomplished by means of an online statistical computer program.\textsuperscript{13}

**Sample collection**

In phase 1, a catheter\textsuperscript{4} was aseptically placed in a lateral saphenous vein of each dog prior to drug administration to facilitate blood collection at multiple time points. Blood samples (3 to 4 mL) were obtained through this catheter at baseline (immediately prior to drug administration) and at 5, 10, 15, 30, and 45 minutes and 1, 1.5, 2, 4, 6, and 8 hours after IV detomidine injection. For the OTM treatment, samples were collected at baseline and at 10, 20, 30, 40, and 50 minutes and 1, 1.25, 1.5, 2, 4, 6, and 8 hours after application of detomidine gel. One additional sample (3 mL) was obtained from each of 2 dogs via direct jugular venipuncture at the 1.25-hour time point after OTM administration to compare plasma concentrations of
the drug from different sampling sites. Blood samples were immediately transferred to lithium heparin-containing vacuum tubes that were placed on ice and were centrifuged at 1,509 X g within 60 minutes after collection. Plasma was collected and stored at –80°C until analysis by liquid chromatography–tandem mass spectrometry.

**Sedation assessment**

In phase 2, the sedative effects of detomidine gel administered OTM were compared with that of injectable dexmedetomidine administered IV (used as a positive control treatment) in dogs undergoing jugular catheter placement. Depth of sedation was determined according to 2 independent scales. Assessment of sedative effects was performed by 1 trained observer who was blinded to the treatment group of dogs (MH).

Global sedation was subjectively scored on an ordinal scale of 1 to 7, using a modification of previously described sedation scales.13,14 (1 = very excitable, 2 = moderately excitable, 3 = slightly excitable, 4 = normal behavior, 5 = subtle signs of sedation, 6 = moderately sedated, and 7 = very sedated). Each dog was assessed observationally immediately prior to catheter placement (5 minutes after administration of dexmedetomidine IV or 45 minutes after administration of detomidine gel OTM), with the dog in lateral recumbency on the examination table.

Total sedation was assessed during the positioning for and process of jugular catheter placement. Jugular catheter placement was performed by 1 trained investigator who was blinded to the treatment group of dogs (KMM). Each dog was evaluated during each of 6 steps of the procedure, including placement on the procedure table, positioning in lateral recumbency, clipping of hair over a jugular vein with mechanical clippers, infusion of the catheterization site with 2% lidocaine (1.0 mL, delivered via SC infiltration), insertion of the catheter, and fixation with a suture and bandage. The dog’s degree of awareness (response) and physical tractability or intractability (resistance) during each step were separately rated on a subjective, 5-point ordinal scale (1 = excessive response or resistance, making it impossible to perform the procedure; 2 = strong response or very resistant, making it difficult to perform the procedure; 3 = subjectively normal response for a nonsedated dog, or somewhat resistant or tense; 4 = minimal response or minimal resistance [may orient to stimulus but otherwise unmoving]; and 5 = no response or no resistance to the task, making the procedure easy to perform). The total sedation score was reported as the sum of these 12 scores, yielding a possible range of total sedation scores from 12 (most responsive and resistant) to 60 (least responsive and resistant [most sedated]).

**Detomidine analysis**

Detomidine was quantified in canine plasma by liquid chromatography–tandem mass spectrometry with a method previously validated for equine plasma. A partial validation was performed with canine plasma used as a matrix. The response for detomidine was linear and indicated a correlation coefficient (R²) of ≥ 0.99. Interday and intraday precision and accuracy of the assay were determined by assaying detomidine quality control samples in replicates (n = 6). The intraday accuracy (% nominal concentration) was 102%, 90.0%, and 90.0% for 0.45, 1.5, and 45.0 ng/mL, respectively. Interday accuracy was 102%, 90.0%, and 90.0% for 0.45, 1.5, and 45.0 ng/mL, respectively. Intrayard precision (% relative SD) was 6.0%, 4.5% and 3.5% for 0.45, 1.5, and 45.0 ng/mL, respectively. Interday precision was 6.0%, 4.5%, and 3.5% for 0.5, 1.5 and 45.0 ng/mL, respectively. The assay was optimized to provide a limit of quantitation of 0.1 ng/mL and a limit of detection of 0.05 ng/mL.

**Pharmacokinetic analysis**

Plasma pharmacokinetics of detomidine following IV and OTM administration were analyzed with a commercial software program. Only data points (plasma concentrations) equal to or above the limit of quantitation for the assays were included in the analysis. A compartmental approach was used, and the model was chosen on the basis of visual inspection of observed versus predicted data, residuals plot, and Akaike information criteria. Data were weighted by the reciprocal of the predicted plasma concentration squared. The IV treatment data best fit a 1-compartment model, by the following equation:

\[
C(t) = \frac{(D/V)}{X} \exp\left(\frac{-K_{a}Xt}{1 + \frac{t}{\tau}}\right)
\]

where C is concentration, t is time, D is dose (in µg/kg), V is volume of distribution, and K is the elimination rate constant.

The OTM treatment data fit a 1-compartment model with a lag time according to the following equation:

\[
C(t) = K_{p} \times D / V / D + K_{10} / \exp(-K_{a}Xt - \exp(-\frac{t}{\tau}))
\]

where C is the plasma concentration; t is time; Kp is the non-IV absorption rate, assuming first-order absorption; K10 is the elimination rate constant; τlag is the lag time; Vd is the apparent volume of distribution (divided by F); and D is the dose. Secondary parameters determined from the model included the area under the plasma concentration-versus-time profile. The absorption and T1/2 were calculated with ln 2.0/Ka and ln 2.0/K10, respectively. Values for Cmax and time to maximum concentration were taken directly from the data. Bioavailability was calculated by means of the following formula:

\[
F(%) = \frac{AUC_{OTM} / AUC_{IV}}{(DOSE_{IV} / DOSE_{OTM})} \times 100
\]

where AUC is the area under the concentration-versus-time curve.

**Statistical analysis**

Data were tested for normality with a Shapiro-Wilk test and are presented as mean ± SD (for normal distribution).
bution) or median and range (nonnormal distribution), except for the pharmacokinetic parameter estimates, which are presented as median and range or harmonic mean ± pseudo-SD. Sedation scores were compared between groups by means of a Mann-Whitney test, as the data were considered categorical. All analyses were carried out with a commercially available statistical program. Values of $P \leq 0.05$ were considered significant.

**Results**

All dogs completed the assigned study phase. Oral cavity pH measured prior to drug administration ranged from 8.0 to 8.5. Following IV detomidine administration (0.5 mg/m$^2$) in phase 1, 2 of 6 dogs vomited, but no dogs vomited following OTM gel administration (1 mg/m$^2$). All dogs developed bradycardia (heart rate < 60 beats/min), which lasted up to 120 minutes in some dogs, after administration of detomidine IV and detomidine gel OTM. None of the dogs required intervention for bradycardia (ie, reversal of effects with atipamezole or anticholinergic administration). No other adverse effects were observed. All dogs became laterally recumbent following detomidine administration by either route in phase 1; after OTM detomidine gel administration at 1 mg/m$^2$, dogs became laterally recumbent within 38.7 ± 8.8 minutes. Recumbency lasted for 71.7 ± 21.1 minutes, which corresponded to detomidine plasma concentrations between 6.5 and 8.0 ng/mL.

During phase 2, no dogs vomited following IV dexmedetomidine administration (0.125 mg/m$^2$) or following OTM detomidine gel administration (0.5 mg/m$^2$). Similar to phase 1, all dogs in both groups developed bradycardia.

**Pharmacokinetics**

The plasma concentration-versus-time curves for detomidine following IV and OTM administration are summarized (Figure 1). The pharmacokinetic parameter estimates following IV and OTM detomidine administration are reported (Table 1). Plasma detomidine concentration in a jugular venous blood sample obtained from 1 dog 1.25 hours after OTM administration (1 mg/m$^2$ dose) was 67.46 ng/mL; the same dog had a plasma detomidine concentration of 8.00 ng/mL in a lateral saphenous venous blood sample obtained at the same time point. For the other dog that had the additional sample collected for this experiment, detomidine concentrations in samples obtained from the jugular and lateral saphenous veins were 51.00 ng/mL and 9.35 ng/mL, respectively.

**Sedation scores**

Global sedation scores following OTM detomidine gel administration or IV dexmedetomidine administration in phase 2 are shown (Figure 2). Total sedation scores following each treatment are summarized (Figure 3). Dogs had a significantly ($P < 0.002$) lower median global sedation score after OTM administration of detomidine gel than after IV administration of dexmedetomidine (5.0 vs 6.5, respectively), but there was no difference in median total sedation scores assessed during jugular catheter placement procedures (42.5 vs 49.5, respectively; $P = 0.13$). During this phase of the study, 1 dog with a total sedation score of 28 of 60 following detomidine gel treatment was resistant to restraint in lateral recumbency; and the jugular catheter could not be placed. After receiving dexmedetomidine IV, the same dog had a total sedation score of 49.

**Table 1**—Pharmacokinetic parameter estimates for detomidine following IV or OTM administration in 6 healthy adult mixed-breed dogs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IV</th>
<th>OTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC$ (h/µg/mL)</td>
<td>23.89 (17.92–36.61)</td>
<td>19.59 (9.95–26.93)</td>
</tr>
<tr>
<td>$K_{01}$ (1/h)</td>
<td>1.04 (0.93–1.79)</td>
<td>1.05 (0.86–1.41)</td>
</tr>
<tr>
<td>$K_{10}$ (1/h)</td>
<td>NA</td>
<td>1.19 (0.91–2.04)</td>
</tr>
<tr>
<td>$T_{lag}$ (h)</td>
<td>NA</td>
<td>0.23 (0.12–0.28)</td>
</tr>
<tr>
<td>$K_{101}$ (1/h)</td>
<td>0.55 ± 0.18</td>
<td>0.59 (0.34–0.77)</td>
</tr>
<tr>
<td>$K_{101/2}$ (h)</td>
<td>0.63 ± 0.12</td>
<td>NA</td>
</tr>
<tr>
<td>$C_{max}$ (µg/mL)</td>
<td>7.03 (5.44–13.61)</td>
<td>NA</td>
</tr>
<tr>
<td>$V_{ss}$ (L/kg)</td>
<td>0.60 (0.44–0.92)</td>
<td>NA</td>
</tr>
<tr>
<td>$T_{lag}$ (h)</td>
<td>1.00 (0.83–1.50)</td>
<td>NA</td>
</tr>
<tr>
<td>$F$ (%)</td>
<td>34.52 (26.34–55.19)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Dogs were randomly assigned to receive detomidine hydrochloride (0.5 mg/m$^2$; IV) or detomidine hydrochloride gel (1 mg/m$^2$, OTM) in 1 experiment; the same dogs received the alternate treatment after a 24-hour washout period. Results are shown as median (range) or harmonic mean ± pseudo-SD.

$AUC = \text{Area under the concentration-versus-time curve.}\ CI = \text{ Clearance.}\ K_{01} = \text{Absorption rate constant.}\ K_{10} = \text{Elimination rate constant.}\ K_{101/2} = \text{Absorption half-life.}\ K_{101/2} = \text{Elimination half-life.}\ NA = \text{Not applicable.}\ T_{lag} = \text{Lag time.}\ T_{max} = \text{Time to maximum concentration.}\ V_{ss} = \text{Volume of distribution at steady state.}$
of 60 and could be restrained for successful IV catheter placement. On a separate occasion (data not included in analysis), this same dog received detomidine gel OTM at a higher dose (1.0 mg/m²) and became adequately sedated for jugular vein catheterization.

**Discussion**

To the authors’ knowledge, this is the first study to report the plasma pharmacokinetics of detomidine following OTM administration of the gel formulation in dogs as well as the first comparison of the sedative effects between detomidine administered by this route and a standard sedation protocol (dexmedetomidine administered IV). Following OTM administration to dogs, detomidine gel had pharmacokinetic parameter estimates similar to those reported in horses, which include a low to moderate F (calculated median value of 34%) and C<sub>max</sub> as well as a short elimination half-life (<1 hour). The sedative effects of detomidine gel administered at a dose of 0.5 mg/m² OTM to dogs were comparable to the effects of dexmedetomidine at a dose of 0.125 mg/m² IV, indicating that OTM detomidine gel is a feasible option for short-term sedation for minimally invasive procedures in healthy dogs.

Systemic F of detomidine following OTM administration of the gel formulation was variable, ranging between 26.5% and 55.2%. A high degree of interindividual variation is often reported following OTM drug administration in dogs and other species. Explanations for the described variation in F may include any of the following scenarios: loss of the drug from the dog’s mouth after administration (eg, by drooling.
or ejection), variation in oral cavity pH, differences in oral mucosal blood flow, or loss from swallowing. An alkaline environment is preferred for the uptake of unionized detomidine, which is considered a lipophilic weak base and has a pKa of 7.2. The pH of saliva from these dogs did not vary much and was slightly alkaline (between 8.0 and 8.5) in all dogs, indicating that differences in pH were unlikely to contribute to the observed variation in F in horses, F of detomidine gel has been reported to be approximately 22%, but with a coefficient of variation of 24%. The authors of that study attributed the low F predominately to loss by swallowing and first-pass hepatic metabolism. In the present study, it is unlikely that loss by swallowing was a major factor, considering that the volume administered was very small (approx. 0.1 mL), and the gel was placed in the buccal pouch rather than under the tongue. However, although F was somewhat greater in our study than in horses, it was nevertheless only moderate at 34.5%. Despite the variation in F, all dogs had signs of sedation, such as lateral recumbency, after the treatment.

The plasma elimination half-life of detomidine after OTM administration of the gel was short (0.63 hours) and was similar to that after IV administration of the injectable formulation in this study (0.55 hours). These findings were consistent with the reported plasma half-lives of other α2-adrenergic receptor agonists used in veterinary medicine, supporting its use as a short-term sedative in dogs. However, a short limitation of the present study was a slightly higher limit of quantitation for detomidine (0.1 ng/mL vs. 0.05 ng/mL), such that samples were below the limit of quantitation 4 to 8 hours after administration, potentially resulting in underestimation of the elimination phase of the drug. The median Cmax occurred 1 hour after OTM administration, with corresponding plasma concentrations ranging between 5.4 and 13.6 ng/mL. The time of Cmax was also consistent with the subjective determination of peak sedation (period of lateral recumbency) in these dogs. This estimate appears to be similar in dogs and horses; a Cmax ranging from 4.16 to 160.5 ng/mL has been reported to occur between 36 minutes and approximately 1 hour after OTM administration in horses. These findings indicate that detomidine gel should be administered OTM at least 45 minutes prior to the desired procedure to achieve adequate sedative effects, which is consistent with the recommendation for the use of the same product in horses.

The large discrepancies in the plasma concentrations between our study and the referenced equine studies can be explained by differences in sampling sites; samples were obtained from a lateral saphenous vein in the present study because samples collected from a jugular vein following OTM drug administration have high plasma concentrations and use of such samples results in an inaccurate estimate of F. This finding was confirmed in the present study by obtaining additional samples from 2 dogs by direct jugular venipuncture 1.25 hours after OTM detomidine administration and comparing plasma detomidine concentrations with those in samples obtained from a lateral saphenous vein catheter. Plasma concentrations of the drug in jugular venous samples were 5.5 and 8.4 times those in corresponding samples obtained from a lateral saphenous vein in the same dogs.

Mean plasma detomidine concentrations from 0.67 to 2 hours following OTM administration were consistently between 6.5 and 8.0 ng/mL in the present study. The narrow range in concentrations during this time may be a result of delayed drug uptake from the site of administration, which could result from local effects on vessel tone. Detomidine, like other α2-adrenergic receptor agonists, causes intense vasoconstriction. This effect was detectable in dogs of our study as pallor of the mucous membranes on the ipsilateral side of drug administration, an effect that was reported in a prior study. Similar results in the concentration-versus-time profiles of detomidine following OTM administration of the gel preparation were also observed in horses. We believe that this phenomenon might result in a limit to the amount of drug that can be absorbed from the administration site, thereby offering a safety factor to prevent drug overdose. Additional investigation is needed to further understand these results. On the other hand, it is also a potential limitation for the degree of sedation that can be achieved in an animal following OTM administration.

The sedative effects of detomidine gel in dogs during the pharmacokinetic study subjectively appeared to correspond well with plasma drug concentrations between 6.5 and 8.0 ng/mL. Detomidine gel (at a dose of 1 mg/m2) resulted in slightly < 1.5 hours of lateral recumbency in these dogs, with no major adverse effects observed. In an earlier study, a peak sedation was found to occur at approximately 45 minutes after detomidine administration (0.35 mg/m2) OTM, with a duration of 0.5 hours to 1 hour in most (n = 4) dogs and up to 1.75 hours in 1 dog. The duration of sedation in horses is reported to be approximately 2 to 3 hours, and although somewhat longer than the duration of lateral recumbency observed in the present study, this still suggests similar pharmacodynamic behavior across species.

A previous study evaluated the anxiolytic and physiologic effects of detomidine gel in dogs. That study assessed sedation during routine handling and examination after detomidine gel was administered OTM at 0.35 mg/m2. In the present study, we wished to further investigate sedation when a potentially noxious stimulus was applied, and routine jugular vein catheterization was chosen for this purpose. The total sedation scoring system consisted of interactive measures to assess the dogs’ degree of response and resistance to the procedure. The median total sedation score for dogs following OTM detomidine gel treatment (0.5 mg/m2) was not significantly different from that following IV dexmedetomidine treatment (0.125 µg/kg/min). This suggests that the equine halogenated anesthetics, with some exceptions, are not necessary to achieve adequate sedation in horses in the absence of additional stressors. Future study is needed to determine the sedative effects of detomidine gel in combination with other sedatives.
mg/m²), suggesting that a similar degree of sedation was achieved with the 2 methods. However, the median observational global sedation score was significantly lower than that after the dexmedetomidine treatment, indicating that dogs (being monitored but not restrained or stimulated) subjectively appeared to be less sedated after receiving detomidine gel OTM. An explanation for this finding is that the dose of detomidine in the gel, when corrected for F was not equipotent to the dose of dexmedetomidine that was given IV. Dexmedetomidine is approximately 6 times as potent as detomidine. With an F of 54%, a dose of 2.2 mg/m² of detomidine gel OTM would be approximately equipotent to 0.125 mg/m² of dexmedetomidine IV; however, further studies should be performed to confirm this estimation. Despite the lower OTM dose of gel used in phase 2 of the present study (0.5 mg/m²), sedation was observed in 5 of 6 dogs, and they could readily be placed and maintained in lateral recumbency for the placement of a jugular vein catheter. There was also a greater degree of variation in total sedation scores of individual dogs following OTM detomidine gel treatment, which may have also contributed to the lack of a significant difference in sedation scores between treatments. The inconsistency in sedation can be accounted for by variation in F, which ranged from 26.5% to 55.2% at a dose of 1 mg/m² in the pharmacokinetic experiments in phase 1 of the study.

The present study had limitations that should be kept in mind when interpreting the results. First, the total sedation scoring system used in the present study was designed specifically to assess sedation to a theoretically noxious stimulus (jugular vein catheterization), which only occurred at 1 time point following drug administration. We elected to modify previous scoring systems to better suit the study design. This numerical scoring system evaluated each dog’s response and resistance to a variety of stimuli associated with jugular catheter placement. Similar types of scoring systems have been used in a variety of studies; however, this scoring system has not undergone full validation in dogs. In addition, the dogs in this study were healthy university-owned Beagles and crossbred hounds kept for research purposes and were accustomed to handling and restraint; thus, experience with client-owned dogs in the veterinary hospital setting may differ. A veterinarian should use his or her best judgment regarding the depth of sedation necessary for each patient, in particular one that may be aggressive, before performing a procedure that includes this sedation technique. At the authors’ institutions, a muzzle, additional sedation with other agents, or both are recommended for aggressive patients treated with detomidine gel OTM.

Although the lower dose used in phase 2 (0.5 mg/m²) provided adequate sedation for jugular vein catheterization in 5 of 6 dogs, the authors recommend higher doses (at least 1 to 2 mg/m²) for procedures, as sedation is more profound and reliable at these doses in our clinical experience. Currently at the authors’ institutions, doses up to 5.0 mg/m² have been administered to aggressive or extremely anxious dogs with no adverse effects observed. The dose of 1.0 mg/m² administered in phase 1 of the present study provided adequate sedation for jugular vein catheterization in the 1 dog that could not be adequately restrained at the 0.5 mg/m² dose. The α₂-adrenergic receptor agonists cause a dose-dependent sedation, although a ceiling effect does occur. This is supported by findings of increased duration of sedation, but not necessarily depth of sedation, reported with other α₂-adrenergic receptor agonists. In dogs, dose-dependent sedation appears to occur following OTM administration of detomidine gel, as evidenced by the findings following administration of the drug at 0.35 mg/m² in an earlier study by authors from our group, compared with the increased sedation observed after administration of the 0.5 mg/m² dose in the present study. Although not directly compared in the present study, the 1.0 mg/m² dose subjectively resulted in more profound sedation than the 0.5 mg/m² dose. Overall, the results of our study support the clinical use of detomidine gel in healthy dogs for sedation purposes because it was simple to administer the small volume needed (a mean of approx 0.1 mL for the 1 mg/m² dose in dogs of the phase 1 study population) into the buccal cavity of dogs.

Acknowledgments
Supported by the Clinical Pharmacology Laboratory at North Carolina State University. At the time of this study, Dr. Messenger was supported by a combined fellowship from the Morris Animal Foundation, Zoetis, and North Carolina State University.

The authors declare that there were no conflicts of interest.

Presented in abstract form at the American College of Veterinary Anesthesia and Analgesia Annual Meeting, San Antonio, Tex, September 2012.

The authors thank Dr. Malte Schwartz and Grady Spoonamore for technical assistance with the dogs during the study.

Footnotes
a. Dexdomitor [package insert], Zoetis, Florham Park, NJ.
b. Dormosedan [package insert], Zoetis, Florham Park, NJ.
c. Dormosedan Gel [package insert], Zoetis, Florham Park, NJ.
e. Dormosedan, Zoetis, Florham Park, NJ.
f. Dormosedan Gel, Orion Corp, Espoo, Finland; distributed by Zoetis, Florham Park, NJ.
g. pHydrion, MicroEssential Laboratory, Brooklyn, NY.
h. Cardell Veterinary Monitor, Sharn Veterinary Inc, Tampa, Fla.
i. Dexdomitor, Zoetis, Florham Park, NJ.
k. BD Intracath, Becton Dickinson, Franklin Lakes, NJ.
l. BD Vacutainer, Becton Dickinson, Franklin Lakes, NJ.
m. Phoenix WinNonlin, version 6.2, Pharma, Cary, NC.
n. SigmaPlot, version 12.5, Systat Software Inc, San Jose, Calif.

References


