Sedative effects of midazolam and xylazine with or without ketamine and detomidine alone following intranasal administration in Ring-necked Parakeets

Nasser Vesal, DVM, MVetSc, and Mohammad H. Eskandari, DVM

Objective—To evaluate the effects of intranasal administration of midazolam and xylazine (with or without ketamine) and detomidine and their specific antagonists in parakeets.

Design—Prospective study.

Animals—17 healthy adult Ring-necked Parakeets (Psittacula krameri) of both sexes (mean weight, 128.83 ± 10.46 g [0.28 ± 0.02 lb]).

Procedure—The dose of each drug or ketamine-drug combination administered intranasally that resulted in adequate sedation (ie, unrestrained dorsal recumbency maintained for ≥ 5 minutes) was determined; the onset of action, duration of dorsal recumbency, and duration of sedation associated with these treatments were evaluated. The efficacy of the reversal agents flumazenil, yohimbine, and atipamezole was also evaluated.

Results—In parakeets, intranasal administration of midazolam (7.3 mg/kg [3.32 mg/lb]) or detomidine (12 mg/kg [5.45 mg/lb]) caused adequate sedation within 2.7 and 3.5 minutes, respectively. Combinations of midazolam (3.65 mg/kg [1.66 mg/lb]) and xylazine (10 mg/kg [4.55 mg/lb]) with ketamine (40 to 50 mg/kg [18.2 to 22.7 mg/lb]) also achieved adequate sedation. Compared with detomidine, duration of dorsal recumbency was significantly longer with midazolam. Intranasal administration of flumazenil (0.13 mg/kg [0.06 mg/lb]) significantly decreased midazolam-associated recumbency time. Compared with the xylazine-ketamine combination, duration of dorsal recumbency was longer after midazolam-ketamine administration. Intranasal administration of flumazenil, yohimbine, or atipamezole significantly decreased the duration of sedation induced by midazolam, xylazine, or detomidine, respectively.

Conclusions and Clinical Relevance—Intranasal administration of sedative drugs appears to be an acceptable method of drug delivery in Ring-necked Parakeets. Reversal agents are also effective when administered via this route. (J Am Vet Med Assoc 2006;228:383–388)

Most species of nondomesticated birds may react adversely to handling, which is required during medical procedures. Chemical restraint of captured birds is necessary to avoid stress, anxiety, and struggling that may reduce the chances of survival after a procedure.1,2 Excitement can increase the concentrations of catecholamines in the blood, which, in turn, sensitizes the myocardium to cardiac arrhythmias. Several sedative and anesthetic drugs and drug combinations have been used for the induction of sedation and anesthesia in birds.3,4 Because IV injection is difficult, the usual route of administration is via IM or SC injection. Intramuscular injection is generally accomplished in the pectoral muscles, which may involve the risk of accidentally puncturing large vessels or penetrating the coelomic cavity.1 Intravenous injection in the thigh muscles may increase the potential for nerve damage. Because birds have a renal portal system, excessive excretion through the kidneys may reduce drug bioavailability after injection of medication into the thigh muscles.1 Following IM injection, signs of considerable pain may develop, particularly with irritant agents. To avoid the pain and anxiety associated with IM injections, the intranasal route of drug administration has been evaluated for the induction of sedation or analgesia in pediatric human patients. In several studies in young children, intranasal administration of medications (ie, midazolam,5 sufentanil,10 diamorphine,11 and midazolam with ketamine12) has been shown to be efficacious and safe. Intranasal administration of anesthetic agents, alone or in combinations, has been reported13 in adult rabbits.

The objective of the study reported here was to evaluate the effects of intranasal administration of midazolam and xylazine, alone and in combination with ketamine, and detomidine in nondomesticated Ring-necked Parakeets. In addition to investigating whether these drugs would provide effective sedation via this route of administration, the effects of intranasal administration of their specific antagonists (flumazenil, yohimbine, and atipamezole) were also evaluated.

Materials and Methods

The protocol for this project was approved by the Institutional Animal Care and Use Committee of Shiraz University. Seventeen healthy adult nondomesticated Ring-necked Parakeets (Psittacula krameri) of both sexes were used in this study. Weights of these birds ranged from 104 to 146 g (0.23 to 0.32 lb; mean ± SD weight, 128.83 ± 10.46 g [0.28 ± 0.02 lb]). All birds were housed in groups of 3 to 4 in several cages in a temperature-controlled environment (18° to 20°C) and were allowed an acclimation period of at least 4 weeks prior to the beginning of the study. The birds had free access to water and were fed a variety of seeds, vegetables, and fruits ad libitum. Food was not withheld before the administration of medication.
**Experiment 1**—The objective of the first experiment was to determine the dose of midazolam, xylazine hydrochloride, and detomidine hydrochloride that resulted in adequate sedation. Different doses of each drug, ranging from 0.25 to 0.85 µL/g/naris (113.5 to 385.9 µL/lb/naris), were evaluated (ie, midazolam, 0.50 to 0.85 µL/g/naris [227.0 to 385.9 µL/lb/naris]; xylazine, 0.35 to 0.60 µL/g/naris [138.9 to 272.4 µL/lb/naris]; detomidine, 0.35 to 0.7 µL/g/naris [130.0 to 317.8 µL/lb/naris]). At least 3 birds were used to evaluate each drug administered at each drug volume. When only 1 drug was administered, each dose was administered into both nares. Parakeets were manually restrained in dorsal recumbency and equal volumes of drug administered slowly into each naris by use of a micropipette (Figure 1). To evaluate drug combinations, the sedative drug (midazolam or xylazine) was administered in the right naris first followed by administration of ketamine in the left naris. One minute after drug administration, the bird was placed in dorsal recumbency in a separate cage for observation. Placement of leads for ECG recordings was performed during dorsal recumbency; tracings were used to confirm absence of movement (Figure 2). Arbitrarily, adequate sedation was defined as the point at which the treated parakeets could be laid in dorsal recumbency for at least 5 minutes without restraint and movement.

**Experiment 2**—The objective of the second experiment was to evaluate the onset of action (time from drug administration to initial signs of sedation [ie, eyelid closure, sluggish movement, and drowsiness]), duration of sedation (time from the onset of sedation to full recovery [ie, holding head in normal, alert position; voluntary movement; perching; and feeding]), and quality of sedation induced by each drug or drug combination with the dose that was determined to be effective during experiment 1. Drugs and drug combinations were administered as described for experiment 1. Respiratory rate and toe pinch reflex were monitored and recorded during the period of sedation. The efficacy of flumazenil, yohimbine hydrochloride, and atipamezole to reverse the effects of midazolam, xylazine, and detomidine, respectively, was also evaluated. Saline (0.9% NaCl) solution or antagonist drugs in the same volume as that of the agonist agents were administered intranasally into both nares 10 minutes after administration of the sedative drugs. The response of the bird to painful stimuli (toe pinch reflex) was assessed during dorsal recumbency. Parakeets were randomly assigned to 1 of 4 treatment groups at weekly intervals in a crossover study design (6 birds/evaluation group within each treatment group; Appendix). Each bird was used on 3 to 4 occasions, and data were collected from 17 or 18 birds/treatment evaluation. Following the drug evaluations, a radiopaque medium (ioxitalamate meglumine) was instilled into both nares of 2 birds as described for drug administration; radiography was performed at 5, 10, and 15 minutes after administration of the contrast agent. In 2 birds, the same volume of midazolam was administered slowly into the oral cavity as described for intranasal drug administration.

**Statistical analysis**—Data collected regarding onset and duration of sedation, duration of dorsal recumbency, and respiratory rate were analyzed by use of a 1-way ANOVA followed by a Duncan test when appropriate. All results are expressed as mean ± SD, and differences were considered significant at a value of P < 0.05.

**Results**

**Experiment 1**—To determine the optimum dose of the sedative agents, we administered parakeets (via both nares) that resulted in dorsal recumbency without movement for at least 5 minutes, several doses (ranging from 0.25 to 0.85 µL/g/naris) were evaluated. Lower doses of the 3 sedative agents did not consistently result in unrestrained dorsal recumbency of at least 3 minutes' duration; higher doses increased only the duration but not the depth of sedation. Administration of 0.73 µL of midazolam/g into each naris (total dose, 7.3 mg/kg [3.32 mg/lb]) of the parakeets caused adequate sedation within 1 to 5 minutes (mean time from drug administration to signs of adequate sedation, 2.7 ± 1.2 minutes); birds did not move when placed in dorsal recumbency. The onset of action of xylazine (0.50 µL/g/naris) or detomidine (0.60 µL/g/naris) following administration into both nares was also rapid, and parakeets seemed heavily sedated and assumed sternal recumbency. After administration of detomidine, it was possible to place birds in dorsal recumbency; the duration of unrestrained dorsal recumbency was short. However, after administration of xylazine, it was not possible to place the birds in dorsal recumbency. Overall, the degree of sedation achieved after treatment with xylazine (at a dose of 20 mg/kg [9.1 mg/lb]) or detomidine (at a dose of 12 mg/kg [5.45 mg/lb]) was not sufficient to allow manipulation of the parakeets. Administration of a
higher dose of xylazine (0.60 µL/g/naris) did not induce dorsal recumbency, although the duration of action was more prolonged. Therefore, the lower dose was used in experiment 2. Combinations of midazolam (0.73 µL/g [3.65 mg/kg [1.66 mg/lb]] administered into 1 naris) or xylazine (0.50 µL/g [10 mg/kg [4.55 mg/lb]] administered into 1 naris) with ketamine (0.40 or 0.50 µL/g [40 to 50 mg/kg [18.2 to 22.7 mg/lb]] administered into the other naris) also resulted in adequate sedation.

From the ECG recordings, heart rate among the birds was 240 to 280 beats/min; no cardiac arrhythmias were detected in association with any of the treatments.

Experiment 2—For each treatment, onset of action and duration of sedation were evaluated (Table 1). In all treatment groups, onset of action was rapid; the time to onset of action was significantly (P ≤ 0.05) longer after administration of xylazine (7.9 ± 2.8 minutes), compared with that associated with administration of midazolam (2.7 ± 1.2 minutes) or detomidine (3.5 ± 1.2 minutes). Duration of dorsal recumbency after administration of midazolam (37.7 ± 24.4 minutes) was significantly longer than that achieved after administration of ketamine (11.0 ± 6.4 minutes). Intranasal administration of flumazenil significantly (P ≤ 0.05) decreased the duration of dorsal recumbency attained after administration of midazolam. Administration of saline solution after treatment with midazolam increased the duration of dorsal recumbency slightly, compared with the effect of midazolam alone, but this difference was not significant (P > 0.05).

Duration of sedation after administration of either α2-adrenoceptor agonists was longer (P ≤ 0.05) than that achieved after administration of the benzodiazepine. Of the 3 sedative agents, detomidine had the longest duration of effect (> 24 hours) and midazolam had the shortest (175.8 ± 14.2 minutes). Birds given detomidine typically lay on their sternum with minimum voluntary movement for a prolonged period; during the sedation period, they could be woken suddenly by external stimulation but relapsed into their previous sedated condition when left undisturbed. The birds were behaving normally by next morning. In the birds that were given either α2-adrenoceptor agonist, there was no clear cutoff point at which all signs of sedation had resolved; some residual sedation and a reduction in food consumption were evident until the day after drug administration. In contrast, birds recovering from sedation induced by administration of midazolam were more promptly alert and interested in eating. Intranasal administration of the antagonist flumazenil, yohimbine, or atipamezole significantly decreased the duration of sedation with midazolam, xylazine, or detomidine, respectively. The dose of flumazenil was 0.65 µL/g/naris (0.13 mg/kg [0.06 mg/lb]), the dose of yohimbine was 0.60 µL/g/naris (1.2 mg/kg), and that of atipamezole was 0.60 µL/g/naris (6 mg/kg [2.72 mg/lb]). No relapse into sedation was evident after the administration of the reversal agents.

Duration of dorsal recumbency after administration of the midazolam-ketamine combination treatment was significantly longer than that achieved via administration of the xylazine-ketamine combination treatment. Following administration of midazolam and ketamine, birds appeared to be heavily sedated and showed no resistance to manipulation. A combination of midazolam with a higher dose of ketamine (0.75 µL/g) resulted in deep analgesia in 2 parakeets. The birds did

<table>
<thead>
<tr>
<th>Drug or drug combination</th>
<th>Time to onset of action (min)</th>
<th>Duration of dorsal recumbency (min)</th>
<th>Duration of sedation (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam* alone</td>
<td>2.7 ± 1.2</td>
<td>57.7 ± 24.4</td>
<td>175.8 ± 14.2</td>
</tr>
<tr>
<td>Midazolam and saline (0.9% NaCl) solution†</td>
<td>6.6 ± 3.1†</td>
<td>62.0 ± 28.6†</td>
<td>ND</td>
</tr>
<tr>
<td>Midazolam and flumazenil†</td>
<td>NA</td>
<td>&gt; 240</td>
<td>&gt; 240</td>
</tr>
<tr>
<td>Xylazine* alone</td>
<td>7.9 ± 2.8*</td>
<td>NA</td>
<td>Approx 78†</td>
</tr>
<tr>
<td>Xylazine and saline solution†</td>
<td>NA</td>
<td>&gt; 240</td>
<td>&gt; 240</td>
</tr>
<tr>
<td>Xylazine and yohimbine†</td>
<td>NA</td>
<td>11.0 ± 6.4†</td>
<td>&gt; 1,440†</td>
</tr>
<tr>
<td>Detomidine* alone</td>
<td>3.5 ± 1.2</td>
<td>11.8 ± 4.8†</td>
<td>&gt; 1,440†</td>
</tr>
<tr>
<td>Detomidine and saline solution†</td>
<td>NA</td>
<td>ND</td>
<td>180.0 ± 9.5</td>
</tr>
<tr>
<td>Detomidine and atipamezole†</td>
<td>ND</td>
<td>70.7 ± 46.7‡</td>
<td>210.8 ± 17.5‡</td>
</tr>
<tr>
<td>Xylazine and ketamine†</td>
<td>7.7 ± 1.4‡</td>
<td>12.2 ± 14.1‡</td>
<td>251.3 ± 7.5</td>
</tr>
</tbody>
</table>

Six birds were used for each treatment group in a crossover design.

* Sedative agents were administered into both nares in each bird. † Saline solution or antagonist drugs in the same volume as that of the agonist agents were administered intranasally into both nares 10 minutes (flumazenil) or 20 minutes (yohimbine or atipamezole) after administration of the sedative drugs. ‡ In drug combinations, the sedative agent was administered into the right naris first, followed by administration of ketamine in the left naris. NA = Not applicable. ND = Not determined.

Value significantly (P ≤ 0.05) different from those obtained after administration of midazolam or detomidine alone or midazolam with ketamine. * Significantly (P ≤ 0.05) different from value obtained after administration of the sedative agent and saline solution. † Significantly (P ≤ 0.05) different from value obtained after administration of xylazine and ketamine. ‡ Significantly (P ≤ 0.05) different from value obtained after administration of midazolam.
Intranasal administration of midazolam has been successfully used to provide preanesthetic sedation in children, avoiding the discomfort associated with IV injection of the drug. Mild adverse effects such as transient burning sensation and lacrimation have been reported following intranasal administration of midazolam, which may be due to the low pH (approx 3.0 to 3.5) of the drug formulation.\textsuperscript{9,10} Olfactory activity was not affected in children that received midazolam intranasally.\textsuperscript{9} Intranasal administration of midazolam has been associated with decreased respiratory rate in rabbits but had no effects on hemoglobin saturation or venous blood gas variables; changes in arterial oxygen saturation following intranasal midazolam in children have not been reported.\textsuperscript{8,10} In cats, endotracheal administration of diazepam has been associated with deleterious effects on pulmonary tissues;\textsuperscript{17} however, in lambs, endotracheal administration of midazolam did not result in histologically detectable pathologic changes in the lungs.\textsuperscript{18} The vehicle used in the currently available formulations of diazepam (ie, propylene glycol) has been incriminated as the cause of the drug-associated pathologic changes in cats.

Although the precise site of drug absorption was not determined in the present study, the rapid onset of sedation after intranasal administration of midazolam suggested that the drug was absorbed through the mucosa of the nose, oral cavity, and pharynx. Oral administration of midazolam did not produce desirable sedation in parakeets. Radiographic evidence suggested that the drugs remain in the nasopharyngeal region. Although the viscosity of the contrast medium may not be exactly the same as that of the drugs used in our study, they were somewhat similar. Nasal mucosa offers the potential of a highly permeable port of entry for different drugs. It has been shown that several drugs are absorbed systemically via the nasal mucosa.\textsuperscript{4,11,13-15} Intranasal administration of epinephrine during experimentally induced cardiac arrest and cardiopulmonary resuscitation has been attempted in dogs.\textsuperscript{19} Intranasal drug administration has been used for the induction of sedation or analgesia in human pediatric patients.\textsuperscript{8,11} In humans, attainment of effective plasma concentrations occurs as early as 10 minutes after intranasal administration of midazolam.\textsuperscript{20} Mean time to onset of action and duration of sedation following intranasal administration of midazolam in rabbits were 3.0 minutes and 24.6 minutes, respectively.\textsuperscript{12} The bioavailability of midazolam administered intranasally (55% to 57%) is higher than that achieved via the oral or rectal routes; this difference is attributed to the absence of first-pass metabolism.\textsuperscript{4,10,20,22}

Among the birds of the present study, recovery from sedation induced via intranasal administration of midazolam was complete within approximately 2 to 3 hours, whereas full recovery from sedation induced via intranasal administration of xylazine or detomidine often took several hours and the birds usually appeared fluffed and sluggish for an extended time. In general, the birds given either α₂-adrenoceptor agonist remained immobile when left undisturbed before full recovery; some residual sedation and a reduction in food consumption were observed the day after drug.
administration. In contrast, birds recovering from midazolam sedation were more promptly active and interested in eating. Although there were no complications associated with prolonged recovery from sedation in the birds of the present study, it can be considered an undesirable feature. A relatively long recovery time precludes eating, which exacerbates development of hypothermia and hypoglycemia because of the birds’ high metabolic rate.12 After administration of α2-adrenoceptor agonists in birds, the degree of sedation may be insufficient to perform a procedure. In most species, α2-adrenoceptor agonists may cause bradycardia and partial atrioventricular heart block, respiratory depression, and often muscle tremors.7 In the present study, respiratory rate was lower in birds that received α2-adrenoceptor agonists (alone or in combination), compared with birds that received midazolam. In birds weighing 100 to 200 g (0.22 to 0.44 lb), the reference range for respiratory rate is 35 to 50 breaths/min.22

In the present study, a combination of midazolam and ketamine resulted in adequate sedation and analgesia in parakeets. Ketamine is a dissociative agent that induces a cataleptic state and has been administered alone and in combination with sedative drugs in birds. It is now rarely used as the sole anesthetic agent. Rapid onset of sedation and analgesia has been reported following intranasal administration of midazolam and ketamine in children12,22 and rabbits13; in another study14 in children, intranasal administration of ketamine alone resulted in higher systemic bioavailability (50%) than that attained after rectal administration of the drug (25%). Intranasal administration of the combination of midazolam and ketamine did not produce considerable cardiovascular and respiratory adverse effects in children,12,23 although significant decreases in respiratory rate and oxygen saturation may occur in rabbits.11 In the present study, respiratory rate in the birds was significantly higher after administration of the midazolam-ketamine combination, compared with that detected after administration of the xylazine-ketamine combination. In general, respiratory rate should never fall below half the normal resting value in anesthetized birds.2

Intranasal administration of saline solution after administration of midazolam resulted in a slight increase (albeit not significant) in the duration of dorso-recumbency, compared with that achieved after administration of midazolam alone, which may be attributed to a flushing effect and drug dispersion over a wider area. Although the surface area and volume of the nasal cavity were not investigated in our study, recommended optimum volume for intranasal administration in parakeets is approximately 0.02 to 0.03 mL/parakeet (administered bilaterally).

In parakeets that received sedative agents, reversal agents were effective when given intranasally. Full recovery from sedation occurred within 25 to 102 minutes after flumazenil administration in the birds that received midazolam. Flumazenil has been successfully used to reverse midazolam-induced sedation in pigeons15 and quails.13 It has been reported that intranasal administration of flumazenil in children results in systemic bioavailability similar to that obtained following IV administration, which may be sufficient to antagonize the effects of benzodiazepines when IV access is not readily available.25 When reversing the effects of a benzodiazepine administered in combination with ketamine, reversal must be timed appropriately to avoid allowing the bird to recover under the effects of ketamine alone because this can result in rough recovery. Intranasal administration of yohimbine or atipamezole resulted in rapid arousal in parakeets given xylazine and detomidine, respectively. Yohimbine is an effective reversal agent for anesthesia induced by administration of xylazine and ketamine in raptors and budgerigars.9,27 Tolazoline, another α2-adrenoceptor antagonist, has been used to successfully reverse anesthesia induced by administration of xylazine and ketamine in turkey vultures.28 The use of these reversal agents may make the use of xylazine in birds safer and more practical. Increased frequency of defecation by birds following xylazine or detomidine administration may be attributed to the diuretic effect of α2-adrenoceptor agonists.

Our data suggest that intranasal drug administration appears to be an acceptable noninvasive alternative method of drug delivery in parakeets. This method requires no special technical skills, and only transient restraint is needed to instill the drug into the nares. Intranasal drug administration has the potential to become a viable clinical option in avian medicine and may replace conventional IM or SC injections. Intranasal administration of midazolam, alone or in combination with ketamine, can be used effectively to provide adequate sedation and muscle relaxation for diagnostic procedures to be performed in birds. Because of prolonged recovery time and insufficient sedation, administration of α2-adrenoceptor agonist drugs alone is not recommended by the authors as a means of achieving sedation in parakeets. Additional studies are needed to determine whether these drugs (alone or in combination) are safe and effective for use in clinical practice.

References


Appendix

Treatment groups used in a crossover study to determine the sedative effects of xylazine and midazolam (with and without ketamine) and detomidine alone as well as the efficacy of appropriate reversals of xylazine-ketamine anesthesia in Ring-necked Parakeets.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Evaluation 1</th>
<th>Evaluation 2</th>
<th>Evaluation 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xylazine</td>
<td>Xylazine* alone</td>
<td>Xylazine* and saline (0.9% NaCl) solution†</td>
<td>Xylazine* and yohimbine†</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Midazolam* alone</td>
<td>Midazolam* and saline solution†</td>
<td>Midazolam* and flumazenil†</td>
</tr>
<tr>
<td>Detomidine</td>
<td>Detomidine* alone</td>
<td>Detomidine* and saline solution†</td>
<td>Detomidine* and atipamezole†</td>
</tr>
<tr>
<td>Drug combination†</td>
<td>Midazolam and ketamine</td>
<td>Xylazine and ketamine</td>
<td>NA</td>
</tr>
</tbody>
</table>

†Sedative agents were administered into both nares in each bird. †Saline solution or antagonist drugs in the same volume as that of the agonist agents were administered intranasally into both nares 10 minutes (flumazenil) or 20 minutes (yohimbine or atipamezole) after administration of the sedative drugs. In drug combinations, the sedative agent was administered into the right naris first, followed by administration of ketamine in the left naris.

NA = Not applicable.