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

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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 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.

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 strug-
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 $\mu$L/g/naris (113.5 to 385.9 $\mu$L/lb/naris), were evaluated (ie, midazolam, 0.50 to 0.85 $\mu$L/g/naris [227.0 to 385.9 $\mu$L/lb/naris]; xylazine, 0.35 to 0.60 $\mu$L/g/naris [158.9 to 272.4 $\mu$L/g/naris]; and detomidine, 0.35 to 0.7 $\mu$L/g/naris [159.9 to 317.8 $\mu$L/g/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 maximum 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 (flumazenil) or 20 minutes (yohimbine or atipamezole) 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 administered to 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 $\mu$L/g/naris) were evaluated. Lower doses of the 3 sedative agents did not consistently result in unrestrained dorsal recumbency of at least 5 minutes’ duration, and higher doses increased only the duration but not the depth of sedation. Administration of 0.73 $\mu$L 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 $\mu$L/g/naris) or detomidine (0.60 $\mu$L/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...
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 detomidine (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 decreased the duration of dorsal recumbency attained after administration of midazolam, although the duration of sedation after treatment with midazolam was 240 to 280 beats/min; no cardiac arrhythmias were detected in association with any of the treatments.

**Table 1**—Mean ± SD time to onset of action, duration of unrestrained dorsal recumbency, and duration of sedation after intranasal administration of xylazine or midazolam (with or without ketamine) or detomidine alone as well as the duration of sedation after administration of the appropriate reversal agents to Ring-necked Parakeets.

<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>66.0 ± 22.1</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Midazolam and flumazenil†</td>
<td>8.6 ± 3.1</td>
<td>62.0 ± 28.6</td>
<td></td>
</tr>
<tr>
<td>Xylazine* alone</td>
<td>7.9 ± 2.8</td>
<td>NA</td>
<td>&gt; 240</td>
</tr>
<tr>
<td>Xylazine and saline solution†</td>
<td>NA</td>
<td>&gt; 240</td>
<td></td>
</tr>
<tr>
<td>Xylazine and yohimbine†</td>
<td>NA</td>
<td>Approx 78</td>
<td></td>
</tr>
<tr>
<td>Detomidine* alone</td>
<td>3.5 ± 1.2</td>
<td>11.0 ± 6.4</td>
<td>&gt; 1440</td>
</tr>
<tr>
<td>Detomidine and saline solution†</td>
<td>11.8 ± 4.8</td>
<td>&gt; 1440</td>
<td></td>
</tr>
<tr>
<td>Detomidine and atipamezole†</td>
<td>ND</td>
<td>180.0 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Midazolam and ketamine†</td>
<td>2.2 ± 0.4</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.
not respond to handling or painful stimuli (ie, toe pinch reflex). Toe pinch reflex response was present in all birds in other treatment groups. Intranasal administration of flumazenil following treatment with midazolam and ketamine resulted in obvious excitement (tremors and wing flapping) and self-injury in 2 birds. These birds were wrapped in a towel for their protection. The excitatory phase lasted for approximately 5 minutes.

Respiratory rate in the birds treated with midazolam alone (46.0 ± 6.3 breaths/min) was significantly higher than that determined in birds treated with xylazine or detomidine alone (26.3 ± 4.6 breaths/min and 23.5 ± 2.2 breaths/min, respectively; \( P > 0.05 \)). Birds had higher respiratory rate after administration of midazolam and ketamine (54.7 ± 14.1 breaths/min), compared with that detected after administration of xylazine and ketamine (31.7 ± 9.9 breaths/min).

Parakeets tolerated the intranasal administration of drugs with no signs of resistance. There were no differences among treatments groups with regard to drug acceptability. Increased appetite was observed in birds that received midazolam alone following termination of sedation. Muscle tremors and movement in response to noise were frequently observed in parakeets that received xylazine or detomidine alone. Increased frequency of defecation was noted subsequent to \( \alpha_2 \)-adrenoceptor agonist administration.

Whole-body radiographic evaluation was performed in 2 birds after contrast medium was instilled into both nares. Contrast medium was detected in the area of nasal cavity in both birds at 3, 10, and 15 minutes after administration. No contrast medium was detected in the crop, stomach, trachea, or lungs in either bird at any of the time points. No adverse reactions or complications were encountered after intranasal drug administration to parakeets in the present study. Administration of the same dose of midazolam into the oral cavity did not result in notable sedation in 2 parakeets.

Discussion

Results of the study reported here indicate that intranasal administration of sedative agents could provide fast and reliable sedation in parakeets. Reversal agents were also effective when given by this route. In our study, intranasal drug delivery was well tolerated by the birds and no complications were detected. However, with the exception of respiratory rate, physiologic variables were not monitored during the present study; nevertheless, all parakeets had a smooth recovery from sedation and had no signs of respiratory distress during any sedation period.

Our data suggest that intranasal administration of midazolam can provide adequate sedation for diagnostic and minor therapeutic procedures in parakeets. Midazolam has the advantage of water solubility and shorter duration of action, compared with diazepam. In birds, midazolam is slightly more potent than diazepam and has minimal cardiopulmonary effects. Intramuscular injection of midazolam has not been associated with major alterations in cardiopulmonary function in Canada geese, pigeons, and quails. 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. Olfactory activity was not affected in children that received midazolam intranasally. 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.

In cats, endotracheal administration of diazepam has been associated with deleterious effects on pulmonary tissues; however, in lambs, endotracheal administration of midazolam did not result in histologically detectable pathologic changes in the lungs. 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 systematically via the nasal mucosa. Intranasal administration of epinephrine during experimentally induced cardiac arrest and cardiopulmonary resuscitation has been attempted in dogs. Intranasal drug administration has been used for the induction of sedation or analgesia in human pediatric patients. In humans, attainment of effective plasma concentrations occurs as early as 10 minutes after intranasal administration of midazolam. 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. 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.

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 \( \alpha_2 \)-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.
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 period precludes eating, which exacerbates development of hypothermia and hypoglycemia because of the birds’ high metabolic rate. 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. 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.

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 children and rabbits; in another study 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, although significant decreases in respiratory rate and oxygen saturation may occur in rabbits. 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.

Intranasal administration of saline solution after administration of midazolam resulted in a slight increase (albeit not significant) in the duration of dorsal 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/naris (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 pigeons and quails. 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. 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. Tolazoline, another α2-adrenoceptor antagonist, has been used to successfully reverse anesthesia induced by administration of xylazine and ketamine in turkey vultures. The use of these reversal agents may make the use of xylazine in birds safer and more practical. Increased frequency of defection 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 reversing agents following intranasal administration 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>

Six birds were used for each evaluation 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.