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### Original Article

## Clinical Evaluation over Intranasal Administration of Acepromazine and Diazepam in Pigeons (*Columba livia domestica*)

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ARTICLE INFO	ABSTRACT
<p><i>Article History:</i></p> <p>Received 22 March 2023            Revised 13 May 2023            Accepted 3 June 2023            Online 3 June 2023</p>	<p>Safe and effective sedation methods are as much momentous for small birds as for other animals not only for surgical procedures but also for safe handling and diagnostic and clinical procedures such as radiography, wound dressing, blood collection, and fracture repair procedures. This study intended to conduct a clinical evaluation of sedation efficacy in the intranasal administration of acepromazine in Pigeons. Thirty healthy adult domesticated Pigeons of both sexes, weighing <math>311.33 \pm 24.46</math> grams were used in this study. They were randomly segregated into three groups (<math>n = 10/\text{group}</math>). Acepromazine 0.5 mg/kg, Acepromazine 1 mg/kg, and diazepam 5 mg/kg were administered intranasally respectively in these three groups; using a micropipette. The onset time and duration of sedation time were measured and recorded. Also, heart rate and blood oxygen saturation before drug administration and after sedation time were measured and recorded. There was no statistically significant difference in heart rate and blood oxygen saturation between groups (<math>p &gt; 0.05</math>), but this study showed that intranasal drug administration could provide fast and reliable sedation in Pigeons, and also intranasal diazepam administration made the fast onset of sedation but acepromazine administration (at the dose of 1 mg/kg) can provide long and adequate sedation (<math>p &lt; 0.05</math>). So, for long-time diagnostic therapeutic procedures utilization of acepromazine is recommended.</p>
<p><i>Keywords:</i></p> <p>Acepromazine            Diazepam            Intranasal            Pigeon            Sedation</p>	

### Introduction

Retention of avian patients is routinely required for physical examination, diagnostic sample collection, diagnostic imaging, and other procedures. Stress induced by handling and manual restraint of birds remains a concern because a stress-induced response can result in serious noxious effects. A stressful event

(e.g., manual restraint) for birds can lead to immediate activation of the sympathetic nervous system, which results in changes to heart rate, respiratory rate, and body temperature.<sup>1</sup> Physiologic changes resulting from stress may also lead to changes in the leukogram of birds, which can confound the interpretation of the values.<sup>2</sup> To perform invasive procedures or potentially painful procedures, chemical restraint is necessary.<sup>3</sup>

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The procedure of sedation allows for ease of patient handling and can result in lower morbidity and mortality rates during restraint, especially in critically unhealthy patients.<sup>4</sup> Procedural sedation is becoming increasingly commonplace in avian medicine and can offer safety benefits over immobilization attained by the use of inhalation anesthetics (e.g., isoflurane) alone, which can cause severe dose-dependent hypotension in birds, among other complications.<sup>5</sup>

Sedation is usually achieved by the use of intramuscular (IM) or intravenous (IV) route administration, which needs technical expertise and can result in economic losses due to tissue injury.<sup>6</sup> The intranasal (IN) administration of sedatives offers extra benefits for birds, including improved client satisfaction and less influence on biochemical variables, in contrast to results with IM injection.<sup>7</sup> In birds with limited muscle mass, the IN route may lead to fewer adverse reactions than with IM injection of relatively large volumes. In patients with suspected or confirmed coagulopathies, the IN route avoids the risk of iatrogenic hemorrhage secondary to IM or IV administration of drugs.<sup>7</sup> The intranasal route is an acceptable alternative for the administration of sedatives in veterinary and human medicine.<sup>6</sup>

Acepromazine [acetylpromazine or 10-(3-dimethylaminopropyl) phenothiazin-2-yl methyl ketone] is a phenothiazine derivative that is rarely used in human medicine. However, it is widely used in veterinary medicine as a tranquilizer.<sup>8</sup> Acepromazine is a potent neuroleptic agent with relatively low toxicity. It induces mild to moderate tranquilization, muscle relaxation, and a decrease in spontaneous activity attributable principally to central dopaminergic antagonism. Acepromazine possesses antiemetic, anticonvulsant, antispasmodic, hypotensive and hypothermic properties.<sup>9</sup> Some studies showed the sedative and analgesic effects of acepromazine in duck.<sup>10</sup> The benzodiazepines, diazepam and midazolam have anxiolytic, anticonvulsant, amnesic, and sedative effects in birds.<sup>6</sup> Although benzodiazepines are used for premedication, they are commonly used for procedural sedation.<sup>11</sup> Diazepam mostly used to treat anxiety, panic attacks, insomnia, seizures, muscle spasms, restless legs syndrome, alcohol withdrawal, benzodiazepine withdrawal, opiate withdrawal syndrome and Meniere's disease. It may also be used before certain medical procedures to reduce tension and anxiety and in some surgical procedures to induce amnesia.<sup>10</sup>

The goals of the study reported here were: (1) to investigate whether the intranasal route is effective for the delivery of sedatives such as acepromazine and diazepam, and (2) to determine the appropriate dose of sedatives needed to produce moderate sedation for standing chemical restraint and deep sedation with sternal recumbency after intranasal administration of Acepromazine in pigeons.

## Materials and Methods

### Birds

Thirty healthy adults domesticated Pigeons (*Columba livia domestica*) of both sexes, weighing  $311.33 \pm 24.46$  grams were considered in this study. All birds were kept in a temperature-controlled environment (18–20 °C) with groups of ten birds per cage, with free access to water and a commercial diet. The birds were clinically healthy with a normal cloacal temperature, apparently active in motion, without any sign of gastrointestinal disorders and were adapting for at least 2 weeks before the study began.

A physical examination was performed before the beginning of the experiments. Evaluation of the results revealed no remarkable abnormalities, and all birds were considered to be healthy for the duration of the research. As a part of the physical examinations, the nares of each pigeon were examined before each experimental period to ensure they were patent and did not have gross abnormalities.

Food was withheld for 3 hours before start of the evaluations. The research protocol for this experiment was approved by the Amol University of Special Modern Technologies' ethics committee. (Ir.ausmt.rec.1401.02)

### Experiments

The pigeons were randomly divided into three groups of 10 to receive either Intranasal diazepam (5 mg/ml, Caspian Tamin, Pharmaceutical Co., Rasht, Iran), acepromazine (0.5 mg/kg, Alfasan, the Netherlands), and acepromazine (1 mg/kg, Alfasan, the Netherlands).

Each pigeon was physically restrained. Heart rate (HR) and peripheral capillary oxygen saturation (SpO<sub>2</sub>) were recorded in each case by a pulse oximeter (Edan, H100B, China) before start of administration. All drugs were administered over 20 seconds intranasally, using a micropipette (Dragon lab micropipette); while the head of the pigeons was extended an upright position to

prevent throw out the drugs from the nares. Immediately, after drug administration, each bird was placed in separate cages for observation. The onset time, the duration of sedation and the duration of dorsal recumbency time

Deep sedation was subjectively evaluated based on defined criteria and was recorded. Time from the intranasal administration of the drug to loss of consciousness was considered the time of the onset of the sedation; including the closure of the eyelids, drooping wings, loss of coordination, and ataxia. The time between loss and reappearance of consciousness was considered as the duration of sedation, characterized by a return to a normal standing posture, alertness, and voluntary movements. Time from laying in dorsal recumbency to returning to sternal recumbency was considered the duration of deep sedation.<sup>6</sup> The observer who had evaluated the sedation was blinded to the treatment. HR and SpO<sub>2</sub> were recorded after sedation.

### Statistical Analysis

Start time, duration of sedation period, and duration of deep sedation, as well as factors such as blood oxygen saturation and heart rate for the three studied groups (diazepam 5 mg/kg, acepromazine 0.5 and 1 mg/kg), expressed as mean and standard deviation. One-way ANOVA and Duncan's post hoc test were used to evaluate possible changes. Data analysis was done using SPSS version 26 statistical software (SPSS Inc., Chicago, IL, USA) and  $p < 0.05$  considered as significant.

**Table 1.** Sedative effects of intranasal administration of acepromazine and diazepam (mean  $\pm$  standard deviation) in domestic pigeons (*Columba livia domestica*) (In each group, n = 10).

Parameter	Group			p Value
	Diazepam (5 mg/kg)	Acepromazine (0.5 mg/kg)	Acepromazine(1 mg/kg)	
<b>Onset time (min)</b>	3.00 $\pm$ 0.70 <sup>a</sup>	6.40 $\pm$ 1.67 <sup>b</sup>	6.40 $\pm$ 1.51 <sup>b</sup>	0.002
<b>Duration of sedation (min)</b>	36.2 $\pm$ 2.68 <sup>a</sup>	17.40 $\pm$ 2.70 <sup>b</sup>	51.8 $\pm$ 2.48 <sup>c</sup>	0.001
<b>Deep sedation (min)</b>	13.75 $\pm$ 2.98	-	-	-

a-c: Different letters in each row indicate statistically significant differences ( $p < 0.05$ ). -: Indicating no observation of deep sedation in groups.

**Table 2.** Heart rate (HR) and peripheral capillary oxygen saturation (SpO<sub>2</sub>) before and after intranasal sedation of acepromazine and diazepam in domestic pigeons (*Columba livia domestica*) (In each group, n = 10).

Parameter	Time	Group			p Value
		Diazepam (5 mg/kg)	Acepromazine (0.5 mg/kg)	Acepromazine(1 mg/kg)	
<b>HR</b>	Before	344.20 $\pm$ 11.88	321.00 $\pm$ 29.48	344.60 $\pm$ 10.99	0.13
	After	343.20 $\pm$ 12.13	296.80 $\pm$ 50.49	341.60 $\pm$ 9.50	0.06
<b>SpO<sub>2</sub> (%)</b>	Before	94.20 $\pm$ 0.83	95.40 $\pm$ 1.51	94.80 $\pm$ 1.09	0.32
	After	93.60 $\pm$ 2.19	96.00 $\pm$ 1.22	94.40 $\pm$ 1.14	0.09

\*  $p < 0.05$  is statistically significant.

## Results

The weighted average and standard deviation of the studied pigeons were 311.33  $\pm$  24.46, and there were no significant differences between groups. The onset time and the duration of sedation significantly difference in the studied groups (Table 1). Onset time of sedation in the group receiving diazepam was the lowest, compared to acepromazine in different doses ( $p = 0.002$ ). Duration of sedation significantly different between all experimental groups ( $p = 0.001$ ). The Acepromazine group (1 mg/kg) had the longest duration of sedation (51.8  $\pm$  2.48 min), ( $p = 0.001$ ). The lowest duration of sedation was seen in the group of acepromazine (0.5 mg/kg), (17.4  $\pm$  2.7 min) (Table 1).

There was no significant difference between heart rate and peripheral capillary oxygen saturation before and after evaluation in all groups (Table 2).

## Discussion

Safe and effective sedation and anesthesia methods are as much important for birds, not only for surgical procedures but also for safe handling and diagnostic procedures, especially in the case of aggressive birds.<sup>10</sup>

Over the recent decades the interest in intranasal delivery as a non-invasive route for drugs is increased. Since the nasal mucosa offers numerous benefits as a target tissue for drug delivery, a wide variety of therapeutic compounds may be administered intranasally for topic, systemic and central nervous system action.<sup>12</sup> Intranasal administration of diazepam,

midazolam and xylazine in pigeons has been reported without any complications.<sup>13</sup> In the present study clinically, we found intranasal as a safe and effective method for drug administration. Furthermore, sedation has been achieved by the intranasal route in canaries (*Serinus canarius*), ring-necked parakeets (*Psittacula krameri*), pigeons (*Columba livia domestica*), Hispaniolan Amazon parrots (*Amazona ventralis*), budgerigars (*Melopsittacus undulatus*), and zebra finches (*Taeniopygia guttata*).<sup>11,14-16</sup> The intranasal administration is an effective way to systemically deliver drugs as an alternative to oral and intravascular routes. Actually, it seems to present fast and extended drug absorption.<sup>12</sup>

Acepromazine has anticholinergic, antihistamine, and antispasmodic effects and blocks alpha-adrenergic receptors that can be used for its neuroleptic feature in preanesthesia.<sup>17</sup> Acepromazine was reported as a vasodilator and could lower harmful effects of stress during physical restraint of animals.<sup>18</sup> Diazepam has potent muscle relaxant and anticonvulsant properties and has been used in a wide range of wild and domestic animals and birds.<sup>13</sup> Diazepam was administered at doses that have been studied in pigeons by Zamani Moghadam *et al.* (2009). In that study, diazepam was used at 5 mg/kg intranasally, 10 times more than the dose that was used in intramuscular (IM) injection. The dose of acepromazine for IM administration is 0.05–0.1 mg/kg.<sup>19</sup> Because of the low toxicity of acepromazine,<sup>20</sup> an attempt experimentally was made to determine the dose of acepromazine (by IN administration) that allowed sedation in pigeons, so we chose two doses (0.5 mg/kg and 1 mg/kg).

This evaluation is the first study on the intranasal administration of acepromazine for pigeons' sedation. The sedation observed in the present study has been sufficient to facilitate physical examination, venipuncture, beak and nail trimming, and diagnostic imaging in this species. Nikousefat *et al.* expressed that between the four groups of acepromazine, midazolam, atropine, and metoclopramide; acepromazine and midazolam are more sedatives than other groups.<sup>21</sup>

The onset of sedation effects after IN administration of drugs in pigeons was good, but handling and other stimulation were deliberately not performed after drug administration so that they would not interfere with induction of sedation. It has been proved that benzodiazepines are extremely short acting agents.<sup>22</sup> Vesal *et al.* (2006) proved that onset of sedation following intranasal administration of benzodiazepines, were

shorter than xylazine; whereas these conflicts with the results of Abbasi *et al.* (2014).<sup>10</sup> It must be mentioned that they tried the intramuscular administration injection route in duck.

Duration of sedation in the acepromazine 1 mg/kg group, was significantly more than diazepam; this result is in agreement with other studies.<sup>10</sup> As well as Hall *et al.* mentioned that acepromazine has a prolonged duration of effect.<sup>23</sup> Acepromazine 0.5 mg/kg made the lowest duration of sedation, we proposed that it is an insufficient acepromazine dose, for adequate sedation time in pigeons.

Other studies in pigeons and canaries, showed that dorsal recumbency was not a finding following xylazine administration, but it observed following diazepam and midazolam administration. Benzodiazepine's act on the benzodiazepine binding site of GABAA receptors. When bound it enhances the binding of GABA to the GABAA receptor which results in inhibitory effects on the central nervous system.<sup>13</sup>

Constant heart rate and peripheral capillary oxygen saturation before and after intervention may be a result of minimal side effects on cardiovascular and respiratory systems. Other studies also, didn't report changes in heart rate and respiratory rate of pigeons following intranasal that were administration of midazolam.<sup>24</sup>

Diazepam treatment produced rapid, deep but brief sedation in pigeons, compared with acepromazine which made a long-time sedation. It has been recommended that diazepam, be administered to birds when a short time sedation is needed; however, acepromazine intranasal administration (at the dose of 1 mg/kg), is strongly recommended for birds that require extended time of sedation.

All pigeons had a smooth recovery and did not show any signs of respiratory distress during sedation. Further studies are required to evaluate the effects of the combination of these drugs in more physiologic detail, especially on blood changes.

In conclusion, the results of the present study showed that intranasal administration can be an effective route for delivery of sedatives in pigeons. Intranasal acepromazine administration (at the dose of 1mg/kg) provided longer sedation compared to diazepam and can be helpful for pigeons requiring long-time sedation; as well, was an effective and safe option.

### Conflict of Interest

The authors declare no conflict of interest.

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