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**STUDY OF THE HISTOPATHOLOGICAL EFFECT OF METAMIZOLE AS A  
PREMEDICATION IN PIGEONS**

**FARSHAD LOTFI<sup>1</sup>, GHOLAMREZA ABEDI<sup>1\*</sup>, AHMAD ASGHARI<sup>1</sup>, NARIMAN  
SHEYKHI<sup>1</sup>, SAEID HESARAKI<sup>2</sup>**

<sup>1</sup> Department of Clinical Science, Faculty of Specialized Veterinary Sciences, Science and  
Research Branch, Islamic Azad University, Tehran, Iran

<sup>2</sup> Department of Pathobiology, Faculty of Specialized Veterinary Sciences, Science and Research  
Branch, Islamic Azad University, Tehran, Iran

\*Corresponding Author: [grabedicha@gmail.com](mailto:grabedicha@gmail.com); Tel: +9809121024158

**ABSTRACT**

This study was conducted to compare the effects of metamizol , midazolam and ketamine as premedications in birds. Eighteen male pigeons with an approximate weight of 300 g were divided into three groups with six individuals per group. In the control group (group I), ketamine alone was injected. In group II, midazolam plus ketamine were used. In group III, metamizole plus ketamine was injected. The pathological changes in the three groups were evaluated after the drugs at different anesthetic levels were intramuscularly (IM) to the pigeons. A record was maintained of the clinical examinations, and pathological changes in each group. Finally, postmortem examinations were performed to assess tissue damages in the liver, kidney, spleen, brain, and pancreas tissues. The results of the necropsy examination of the three groups showed that the minimum rate of change was in the metamizole group and the maximum rate was in the control group. Regarding the tissues of the brain, pancreas and spleen, no significant pathological changes ( $p>0.05$ ) were observed in any of the three groups. In addition, the clinical findings showed that the maximum reflexes were in group III and no change in the anesthesia occurred in the control group. Metamizole plus ketamine is comparatively the premedication drug of choice in birds. No mortality was recorded in any of the groups.

**Keywords: Birds, Ketamine, Metamizole, Midazolam, Premedication**

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## INTRODUCTION

Methane sulfonic acid sodium monohydrate ( $C_{13}H_{16}N_3NaO_4S.H_2O$ ), metamizole or dipyrone, is used as an analgesic and antipyretic agent. The antipyretic and analgesic effects of metamizole are similar to those of other non-steroidal antiinflammatory drugs (NSAIDs), but the muscular relaxation that it induces differs significantly from that induced by the other NSAIDs [1]. Despite clinical usefulness, metamizole has several unwanted side-effects, the most common of which is the propensity to decrease the animal's external cooling; however, this effect is very small compared with that of other NSAIDs [2]. Metamizole has also been widely used by equine practitioners to treat equine colic and other conditions of gastrointestinal spasm in both small and large animals [3]. Birds have pneumatic bones, and use of inhalation anesthesia leads to dispersal of anesthetic gases in the environment and the hazards resulting from it, for surgeons and operating room personnel [4]. Also, anesthesia becomes light while in the ventricular area surgery for the purpose of discharge of the anesthetic gases. However, use of inhalation anesthesia requires a lot of equipments and tools. For this reason, an injected anesthetic drug can be used, provided that it has the maximum range of adaptation in the bird's body in terms of

anatomy and physiology. Because of this contradictory information, the aim of the present study was to evaluate the therapeutic credibility of metamizole in birds.

## MATERIALS AND METHODS

All pigeons used in the present research were kept according to the norms of the laboratory of animal experimentation in the Islamic Azad University Faculty of Specialized Veterinary Sciences, Tehran, Iran. This investigation was approved by the Committee of Ethics in Research with animals at Islamic Azad University. The study was designed to minimize the number of animals required for the experiments. A total of 18 pigeons were given antiparasetic drugs.

### Animals, housing, and diets

Eighteen pigeons were randomly divided into three groups with six individuals per group. Group I was control group, in which the birds were given an intramuscular (IM) injection of ketamine 40 mg/kg body weight. Each bird in group II was given an IM injection of midazolam 6 mg/kg body weight plus ketamine at 40 mg/kg body weight. In group III, 500 mg/kg metamizol plus ketamine 40 mg/kg body weight was given by IM injection. The findings are summarized in Tables 1-7. Water was provided to the birds. A record of clinical

examinations, signs, and symptoms of anesthesia and pathological findings was maintained regularly.

### Measurements and sample collection

After injection of the drugs in each group separately for 1 h, different reactions based on standard tables of the anesthesia's depth were studied ( data from the Text book of Veterinary Anesthesia). These reactions were included to study the following reflexes: cere reflex, feather plucking, pedal reflex, and surgical stimulation regarding the nervous system. We also recorded and blood pressure, dysrhythmia potential and heart rate concerning the cardiovascular system; and reflux potential, salivation, and vomiting probability regarding the digestive system. Regarding the musculoskeletal system, we assessed abdominal muscle tone, jaw tone, limb muscle tone, and the cloacal sphincter regarding. We also, evaluated the corneal reflex, palpebral reflex, and pupil size in connection with the operation of the eyes. Finally, we studied and measured cough, depth, intubation, mucous membrane color, pattern, and rate concerning the respiratory system, and we used a pin within the tibial bone marrow with the drill bit of a saw for orthopedic investigation. On the basis of the intensity of presence of the various reflexes, respectively, we assigned scores ranging from 0 (representing lack of

presence of a reaction) to +, ++, +++, and ++++ (indicating the intensity of reactions in at various times) ,and then assigned numeric values based on Kruskal-Wallis test. All of these qualitative cases were thus quantitat , cases and the results were studied. In all three of the groups, ketamine with the specified dose and the associated reactions were studied after injection of the drug and within 5 min following the first injection.

### Pathological findings and statistical analysis

The findings for mortality and postmortem pathological data were recorded during the experimental period. The collected data were analyzed statistically with one-way analysis of variance, including Kruskal-Wallis test, with SPSS, version 22, software. One day after medication in each group, postmortem evaluations were done. Five postmortem parameters were examined : liver, kidney, brain, pancreas, and spleen biopsies and staining.

## RESULTS AND DISCUSSION

### Results of necropsy findings

The birds were killed at the end of the experiments, and lesions in the liver, kidney, brain, pancreas, and spleen of the three groups were recorded.

### Liver

As shown in Table 1, the mean vascular degeneration value was 1.3 in the control

group. The corresponding mean values in groups II and III were 1 and 0.33, respectively. There was a significant difference ( $P<0.05$ ) in the mean values of vascular degeneration between the three groups [Table 2].

As shown in Table 1, the mean value for necrosis was 1.50 in the control birds. The corresponding mean values in group II and III were 1.17 and 0.33, respectively. There was a significant difference ( $P<0.05$ ) in the mean values for necrosis between the three groups [Table 2].

The mean values for inflammation in the metamizole and midazolam groups were 0.5 and 1.17, respectively. The mean value for inflammation in the control group was 1.5. There was a significant difference ( $P<0.05$ ) in the mean values of inflammation between the three groups [Table 2].

### Kidney

As shown in Table 3, the mean value for granular cast was 1.33 in the control group. The mean values in groups II and III were 0.67 and 0.33, respectively. There was a significant difference ( $p<0.05$ ) in the mean values for granular cast between the three groups [Table 4].

As shown in Table 3, the mean value for necrosis was 1.5 in the control birds. The mean values in groups II and III were 1 and 0.50, respectively. There was a significant difference ( $P<0.05$ ) in the mean values for necrosis between the three groups [Table 4].

The mean values for intermediate inflammation in the metamizole and midazolam groups were 0.50 and 1, respectively. The corresponding mean value was 1.67 in the control group. There was a significant difference ( $P<0.05$ ) in the mean values for intermediate inflammation between the three groups [Table 4].

### Brain, pancreas, and spleen

With regard to brain, pancreatic and splenic tissues, no significant pathological changes ( $P>0.05$ ) and no microscopic findings were observed in the three groups [Figures 1-3].

### Overall findings

The necropsy findings of liver and kidney tissues are illustrated in Figures 4-9. The findings in the three groups showed that, with regard to each of three factors, the minimum rate of changes was observed in the group III, and the maximum rate was seen in the control group.

Table 1: Various pathological parameters of liver in the three groups (n=18) values given as mean  $\pm$  SD

Group	Vascular degeneration	Necrosis	Inflammation
I (Control)	1.3 $\pm$ 0.516	1.5 $\pm$ 0.548	1.5 $\pm$ 0.548
II	1 $\pm$ 0.632	1.17 $\pm$ 0.753	1.17 $\pm$ 0.408
III	0.33 $\pm$ 0.516	0.33 $\pm$ 0.516	0.5 $\pm$ 0.548

Table 2: Result of necropsy findings of liver in the three groups

Index	Group	N	Mean Rank	Chi-Square	df	Sig.
Vascular Degeneration	I	6	12.67	6.989	2	0.03*
	II	6	10.33			
	III	6	5.5			
Necrosis	I	6	12.75	7.367	2	0.025*
	II	6	10.58			
	III	6	5.17			
Inflammation	I	6	12.75	7.529	2	0.023*
	II	6	10.25			
	III	6	5.5			

\* significant (P&lt;0.05)

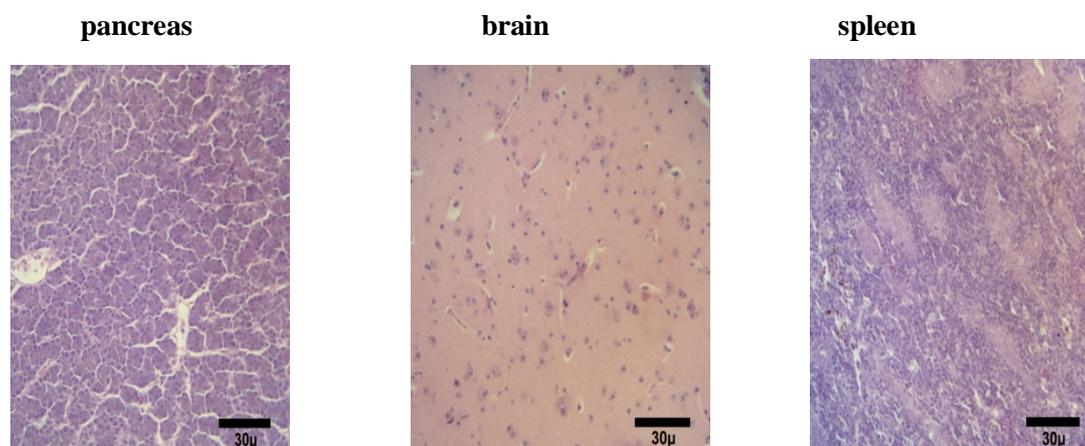
Table 3: Various pathological parameters of kidney in the three groups (n=18) values given as mean  $\pm$  SD

Group	Granular cast	Necrosis	Intermediate inflammation
I (control)	1.33 $\pm$ 0.516	1.5 $\pm$ 0.548	1.67 $\pm$ 0.516
II	0.67 $\pm$ 0.816	1 $\pm$ 0.632	1 $\pm$ 0.632
III	0.33 $\pm$ 0.516	0.50 $\pm$ 0.548	0.50 $\pm$ 0.548

Table 4: Result of necropsy findings of kidney in the three groups

Index	Group	N	Mean Rank	Chi-Square	df	Sig.
Granular cast	I	6	13.33	6.031	2	0.049*
	II	6	8.67			
	III	6	6.50			
Necrosis	I	6	13.00	6.375	2	0.041*
	II	6	9.50			
	III	6	6.00			
Intermediate inflammation	I	6	13.67	7.870	2	0.020*
	II	6	9.08			
	III	6	5.75			

\* significant (P&lt;0.05)



Figures 1-3: No pathological changes were observed in the three groups

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### Necropsy findings of liver in the three groups

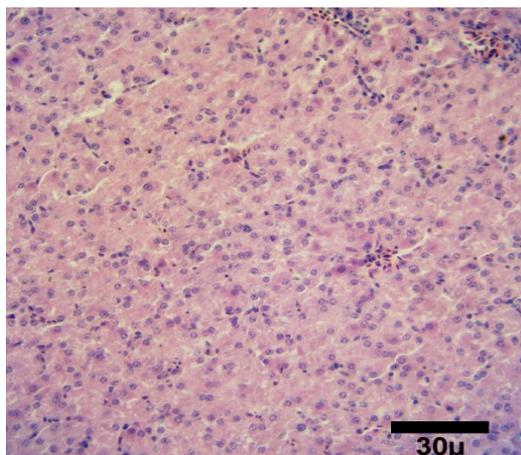


Figure 4 (Control group): Hepatic cells have bright nuclei and a natural cytoplasm. Inflammation or degeneration is not observed, and sinusoids have a natural visage. ( H&E 400 and degree line is equal to 30 microns)

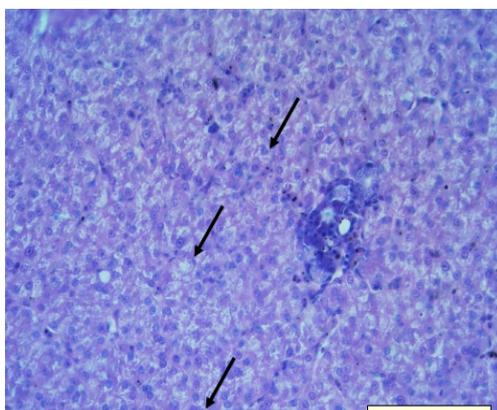
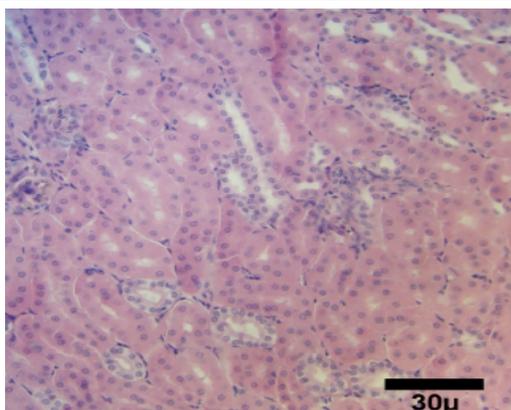


Figure 5 (Group II): Hepatic cells have not any necrosis. vacuolar degeneration (arrows) observed.

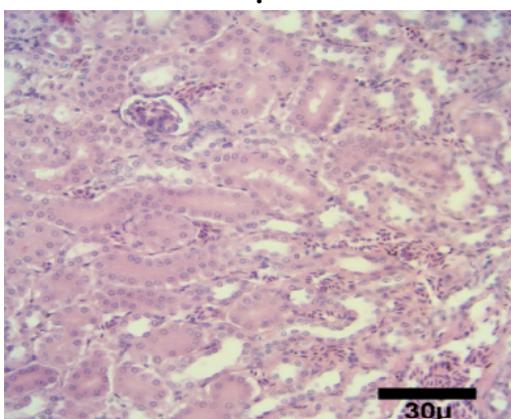


Figure 6 (Group III): Hepatic cells have no any necrosis. Vacuolar degeneration (arrows) is seen.

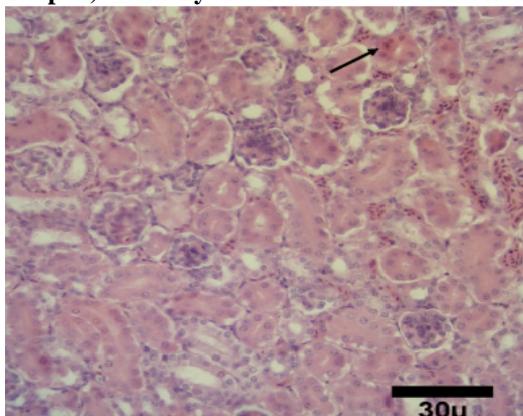
### Necropsy findings of kidney in the three groups



**Figure 7 (Control group):** Renal cells have bright nuclei and a natural cytoplasm. Inflammation or necrosis is not seen and tubules have a natural visage. (H&E 400 and degree line is equal to 30microns)



**Figure 8 (Group II):** Urinary tubule cells is observed in healthy form



**Figure 9 (Group III):** Renal cells have a mild necrosis.

### Clinical findings

During the experiments, differences observed in clinical analysis were recorded. Each bird of in control group received an IM injection of ketamine 40 mg/kg body weight. Each bird in group II received an IM injection of midazolam 6 mg/kg plus IM ketamine 40 mg/kg body

weight. Each bird in group III received an IM injection metamizole 500 mg/kg plus IM ketamine 40 mg/kg body weight.

The results of measurement of various clinical parameters in the three groups are given below.

The results for the midazolam group during four steps of anesthesia showed that there

was no significant difference ( $P>0.05$ ) in the Friedman values for heart rate, abdominal muscle tone, jaw tone, palpebral reflex, or rate of respiratory system. A significant difference ( $P<0.05$ ) was observed in the Friedman values for cere, feather plucking, pedal, dysrhythmia potential, limb muscle tone, cloacal sphincter, salivation, pupil size, and depth and pattern of respiratory system reflexes [Table 5].

The results for the metamizole group during four steps of anesthesia showed that

there was a significant difference ( $P<0.05$ ) in the Friedman values for all of reflexes in the central nervous, cardio vascular, gastrointestinal, musculoskeletal, ocular and respiratory systems [Table 6].

In the control group, no change occurred during four steps of anesthesia. Thus, a statistical test can not be used for comparison. The mean values of various clinical parameters in the three groups are given in Table 7.

Table 5: Result of clinical findings of group II ( n=18) values given as Friedman test

Clinical parameters	Mean Rank				Chi-Square	df	Sig.
	I	II	III	IV			
Cere reflex	3.92	2.67	2.00	1.42	15.245	3	0.002*
Feather plucking	3.00	3.00	2.42	1.58	10.034	3	0.018*
Pedal reflex	4.00	2.67	1.67	1.67	16.5	3	0.001*
Surgical stimulation	2.50	2.50	2.50	2.50	--	--	--
Dysrhythmia potential	2.92	2.92	2.92	1.25	15	3	0.002*
Heart rate	2.92	2.92	2.33	1.83	7.696	3	0.053
Abdominal muscle tone	2.58	2.58	2.58	2.25	3	3	0.392
Jaw tone	3.08	2.75	2.42	1.75	7	3	0.072
Limb muscle tone	4.00	2.00	2.00	2.00	18	3	0.001*
Cloacal sphincter	3.42	3.08	2.08	1.42	13	3	0.005*
Salivation	4.00	2.00	2.00	2.00	18	3	0.001*
Vomiting probability	2.5	2.5	2.5	2.5	--	--	--
Palpebral reflex	2.75	2.75	2.42	2.08	4.714	3	0.194
Pupil size	3.08	3.08	2.17	1.67	10.355	3	0.016*
Depth	4.00	2.58	2.08	1.33	16.059	3	0.001*
Mucous membrane color	2.5	2.5	2.5	2.5	--	--	--
Pattern	3.92	2.67	1.83	1.58	15.255	3	0.002*
Rate	3.08	2.75	2.08	2.08	6.231	3	0.101

\* significant ( $P<0.05$ )

Table 6: Result of clinical findings of group III ( n=18 ) values given as Friedman test

Clinical parameters	Mean Rank				Chi-Square	df	Sig.
	I	II	III	IV			
Cere reflex	4.00	2.67	2.00	1.33	16.154	3	0.001*
Feather plucking	4.00	2.33	1.83	1.83	16.286	3	0.001*
Pedal reflex	4.00	2.00	2.00	2.00	18	3	0.001*
Surgical stimulation	4.00	2.00	2.00	2.00	18	3	0.001*
Dysrhythmia potential	4.00	2.00	2.00	2.00	18	3	0.001*
Heart rate	4.00	2.67	1.67	1.67	16.5	3	0.001*
Abdominal muscle tone	4.00	2.00	2.00	2.00	18	3	0.001*
Jaw tone	4.00	2.17	1.92	1.92	16.84	3	0.001*
Limb muscle tone	4.00	2.50	1.92	1.58	15.76	3	0.001*
Cloacal sphincter	4.00	2.17	2.17	1.67	16.28	3	0.001*
Salivation	4.00	2.50	1.75	1.75	16.2	3	0.001*

Vomiting probability	1.00	3.33	3.33	2.33	16.5	3	0.002*
Palpebral reflex	3.83	2.92	1.83	1.42	15.42	3	0.001*
Pupil size	4.00	2.42	1.92	1.67	15.8	3	0.001*
Depth	4.00	2.42	1.92	1.67	16.8	3	0.001*
Mucous membrane color	2.92	2.92	2.58	1.58	9.23	3	0.019*
Pattern	3.00	3.00	2.42	1.58	10.034	3	0.018*
Rate	4.00	2.25	2.00	1.75	16.071	3	0.001*

\* significant (P&lt;0.05)

Table 7: clinical parameters of the three groups ( n=18) values given as mean  $\pm$  SD

Clinical parameters	I	II	III	IV
cere reflex	YES	2.33 $\pm$ 1.21	1.67 $\pm$ 0.816	1 $\pm$ 0
feather plucking	YES	YES	3.67 $\pm$ 0.516	3.17 $\pm$ 0.753
pedal reflex	YES	0.83 $\pm$ 0.753	NO	NO
surgical stimulation	YES	YES	YES	YES
dysrhythmia potential	YES	YES	YES	3.17 $\pm$ 0.408
heart rate	YES	YES	3.67 $\pm$ 0.516	3.33 $\pm$ 0.816
abdominal muscle tone	YES	YES	YES	3.83 $\pm$ 0.408
jaw tone	YES	3.83 $\pm$ 0.408	3.67 $\pm$ 0.516	3.33 $\pm$ 0.516
limb muscle tone	YES	NO	NO	NO
Cloacal sphincter	YES	3.83 $\pm$ 0.408	3.33 $\pm$ 0.516	3 $\pm$ 0
salivation	YES	NO	NO	NO
Vomiting probability	YES	NO	NO	NO
palpebral reflex	YES	YES	3.83 $\pm$ 0.408	3.67 $\pm$ 0.516
pupil size	YES	YES	3.50 $\pm$ 0.548	3.17 $\pm$ 0.753
depth	YES	2.67 $\pm$ 0.516	2.33 $\pm$ 0.516	1.83 $\pm$ 0.408
mucous membrane color	YES	YES	YES	YES
pattern	YES	2.67 $\pm$ 0.816	2 $\pm$ 0	1.83 $\pm$ 0.408
rate	3.5 $\pm$ 0.548	3.33 $\pm$ 0.516	3 $\pm$ 0	3 $\pm$ 0

## DISCUSSION

Gunkel., (2005) evaluated the current techniques used in avian anesthesia and stated that provision of anesthesia with a low risk of complications is, in part, associated with a working knowledge of avian cardiopulmonary physiology [5]. Therefore, a suitable premedication drug was needed in veterinary practice. Taking this into account, we designed to the present study of the effect of metamizole as a premedication to explore

the use of a non-hazardous drug to save bird's lives.

Postmortem findings of the birds given metamizole injections revealed mild hepatic and kidney lesions of focal necrosis and inflammation at the dose of 500 mg/kg body weight. No necrotic lesions were observed. Also, there were no pathological changes in brain, pancreatic, or splenic tissues. The results of this study are in accordance with those of Canory et al., (2003) and Tawina et al., (2011), who reported that metamizole led to increases

in liver and kidney weight at 450 mg/kg intravenously and that other NSAIDs significantly ( $P < 0.05$ ) increased the severity of lesions [6,7].

Levy et al., (2001) evaluated impairment of dipyrene metabolism in asymptomatic carriers of the hepatitis B virus, and reported that no significant differences were found between renal and non renal clearance for aminoantipyrine and the clearance of formation for acetylaminoantipyrine [8].

Sheena et al., (2012) studied the role of ATP-sensitive  $K^+$  channels in the induced by NSAIDs in nondiabetic rats and with streptozotocin-induced diabetes and reported that systemic NSAID are able to produce antinociception ( $P > 0.05$ ), in rats with streptozotocin-induced diabetes [1].

In our present study, there was mild damage to the liver. The results of this study are thus in accord with those of Canary et al., (2003) and Muhammad Shoaib et al., (2009), who reported that metamizole should not be used for treating hyperglycemia and exerts desirable pharmacological effects in poultry [6,9].

In our present study, the clinical findings in the birds injected with metamizole showed that there was significant reduction ( $P < 0.05$ ) in the Friedman values for central nervous system reflexes during four steps of anesthesia. The results of our study are

thus in accord with those of Richard et al., (1991), Sokolov et al., (2014), and Zhang et al., (2014), who reported that metamizole is widely used for acute treatment of migraine and inhibits neuronal death [10,11,12].

Naga et al., (2011) evaluated the antipyretic effect of dipyrene and found it is unrelated to inhibition of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesis in the hypothalamus [13]. They reported that the antipyretic effect of dipyrene was not mechanistically linked to the inhibition of hypothalamic PGE<sub>2</sub> synthesis.

Naga Kishore et al., (2012) evaluated the analgesic activity of metamizole and paracetamol alone in combination in mice for the degree of analgesia. Their study concluded that the combination of the metamizole and paracetamol has better analgesic activity than either drug alone [13].

Rezende et al., (2007) investigated the combined analgesic and spasmolytic effects of dipyrene, tramadol, and butylscopolamine in acute renal colic pain, and they reached the conclusion that dipyrene was significantly more effective than tramadol in reducing pain for the primary end point, pain intensity differences at 20, 30, and 50 min after drug administration ( $P < 0.05$ ) [3].

In a clinical trial, Sheena Derry et al., (2012) studied parecoxib versus dipyrene

for postoperative pain relief after hysterectomy and suggested that parecoxib 40mg twice daily provides postoperative pain relief equivalent to that of dipyrone 4 g daily during the first 48 h after hysterectomy [1].

Jedziniak et al., (2013) suggested use of a rapid method for the determination of metamizole residues in bovine muscle by liquid chromatography-tandem mass spectrometry, and they showed that validation of the method indicated a within-laboratory reproducibility in the range of 7-30% and recovery in the range of 45-95% [14].

Flor et al., (2013) investigated the effectiveness and safety of tramadol plus metamizole with or without an NSAIDs, for treating chronic neoplastic pain in dogs. They reported that tramadol plus metamizole combined with or without an NSAIDs was well tolerated and clinically effective in treating moderate to severe pain in dogs with cancer and improved their quality of life [15].

Gali et al., (2013) evaluated the effects of metamizole on bone healing of tibial fractures in rats, and reported that dipyrone maybe used safely for pain control in the treatment of fractures, without any interference with bone healing [4].

The results of our present clinical findings in the birds treated with metamizole

showed that there was a significant reduction ( $P<0.05$ ) in the Friedman values for abdominal and limb muscle tone during four steps of anesthesia. The results of the present study are in accord with those of Roelvink et al., (2011) Imagawa et al., (2011), and Patel et al., (2014), who reported that metamizole has no side effects in the management of pain after abdominal surgery and can provide adequate post-operative analgesia in animal models [16,17,18].

Japr in Oxford journal ., (2012) studied the monitoring of anesthesia depth in birds and reported that the corneal reflex in birds is the last reflex to disappear during anesthesia while respiration is maintained and is indicative of complete insensibility [19]. In our present study, showed that we observed a significant reduction ( $P<0.05$ ) in the ocular reflexes of birds during four steps of the anesthesia.

Sheena et al., (2012) evaluated the activity of flunixin meglumine and metamizole in a field study on 23 horses with colic, and reported that the time for colic symptomatic relief was shorter in horses treated with flunixin meglumine than with metamizole [1].

The clinical findings of the birds treated with metamizole showed that there was significant reduction ( $P<0.05$ ) in the Friedman values for gastrointestinal

reflexes during four steps of anesthesia. The results of the present study are in accord with those of Naga et al, (2011) and Vinagre et al., (2011), who reported that metamizole significantly reduced liquid gastric emptying and seemed to be a safe drug [13,20].

Churchill., (2000) studied the metabolic effects of benzodiazepines on the body, and reported that the benzodiazepines reduce the cerebral metabolic rate of oxygen consumption and produce respiratory system depression [21].

Canory ., (2003) found that chronic NSAID use increased the risk of CHF and has been shown to cause adverse effects on the respiratory system [6].

Poblete et al., (2003) investigated the metabolic effects of intravenous propacetamol, metamizole and external cooling in critically ill, febrile, sedated patients, and observed that metamizole produced only a small decrease in external cooling, from 38.9°C to 38.5°C in dogs [2].

In our present study, the metamizole group showed similar results and there was a significant reduction ( $P < 0.05$ ) in the cardiovascular and respiratory reflexes between the four steps of anesthesia.

## CONCLUSIONS

We conclude that metamizole plus ketamine is comparatively the choice drug in premedication of birds. No deaths were

recorded in any of the groups. On the basis of the necropsy findings, and biochemical and clinical analyses, we found that metamizole was a safe drug. Moreover, base ranking of metamizole shows that it is comparatively better in controlling pyrexia and inflammation in poultry and in veterinary practice. Metamizole has good pharmacological effects in veterinary medicine and maybe used instead of other premedication drugs in veterinary practice.

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## REFERENCES

- [1] Sheena, A., Drrry, C. Clinical drug investigation . 3<sup>th</sup> Edition, 2012, pp 24.
- [2] Poblete, B., Romand, A., Koning, P. Metabolic effect of i.v. propacetamol, metamizol or external cooling in erotically ill febrile sedated patients. Journal of veterinary anesthesia and analgesia, 2003, 10(3), 78 – 123.
- [3] Rezende, RM., Franca, DS., Menezes, GB., Bakhie, YS. Different mechanisms underlie the analgesic actions of paracetamol and dipyron in a rat model. British journal of pharmacology, 2007, 153(4), 760-768.
- [4] Gali, JC., Ventin, FC. Dipyron has no effects on bone healing of tibia

- fractures in rats. *Journal of veterinary anesthesia and analgesia*, 2013, 30(6), 82 – 97.
- [5] Gunkel, G. Evaluated the current techniques in avian anesthesia and assayed that provision of anesthesia with a low risk of complications is, in part, associated with a working knowledge of avian cardiopulmonary physiology. *Journal of Avian and exotic pet medicine*, 2005, 14(14), 263 – 276.
- [6] Canory, W. The European Agency for the Evaluation of medicine products. *veterinary medicines and inspection*, 2003, 2(10), 1 – 10.
- [7] Tawina, J., Zolinger, P. The pathologic effect of carprofen in a pigeon model. *Journal of Avian medicine and surgery*, 2011, 25(3), 173 – 184.
- [8] Levy, M., Safadi, R., Goranti, L. Impairment of the metabolic of dipyron in asymptomatic hepatitis – B. *Journal of veterinary anesthesia and analgesia*, 2001, 57(6), 5 – 46.
- [9] Muhammad , A., Owais, U., Mohammad, SH. Studies of dipyron toxicity in avian species. *JAPP*, 2009, 1(1), 1 – 6.
- [10] Richard, A., Hoppmann, M. Central nervous system side effect of NSAIDS. *Bulgarian journal of veterinary medicine*, 1991, 151(7), 309 – 313.
- [11] Sokolov, AY., sivachenko, I., Panteleev, SS. Effect of intravenous metamizol on ongoing and evoked activity of dura – sensitive thalamic neurons in rats. *Journal of veterinary anesthesia and analgesia*, 2014, p 32.
- [12] Zhang, Y., Wang, X. Dipyron inhibits neuron cell death. *Journal of pet medicine*, 2014, 69(4), 942-956.
- [13] Naga, R., Anjaneyulu, N., Canesh, MN. evaluated the analgesic activity of metamizole and paracetamol. *Journal of Advansced pharmaceutical Research*, 2012, 3(1), 1-4.
- [14] Jedziniak, P., Pietruk, K., Olejnik, M. Rapid method for the determination of metamizol residues in bovine muscle by LC – MS / MS. *Journal of veterinary anesthesia and analgesia*, 2013, p 82.
- [15] Flor, B., Yazbek, VB., Keila, K. Tramadol plus metamizol combined or not with NSAID<sub>s</sub> is clinically effective for moderate to sever chronic pain. *Journal of veterinary anesthesia*, 2013, 11(10), 21-23.
- [16] Roelvink, ME., Goossens, L. Analgesic and spasmolytic effect of dipyron. *Journal of veterinary anesthesia and analgesia*, 2011, pp 12.
- [17] Imagawa, VH., Fentoni, DT. The use of different doses of metamizol for

---

post – operative analgesia in dogs. Journal of veterinary anesthesia and analgesia,2011, 38(4), 85 – 93.

[18] Patel, CV., Koppikar, MG. Management of pain after abdominal surgery. J Clin,2014, 10(2), 351 – 353.

[19] Japr, A. monitoring of anesthesia depth in birds and reported that the corneal reflex in birds. The oxford

journal of poultry science,2012, 27(54), 5– 9.

[20] Vinagre, M.A. The effect of dipyrone on liquid gastric emptying. Journal of veterinary anesthesia and analgesia,2011, 4(2), 50 – 52.

[21] Churchill, L. Metabolic of Benzodiazepine in rats. Journal of veterinary medicine,2000, pp 51.