A DISSERTATION

FOR THE DEGREE OF MASTER

Effects of Alphaxalone, Medetomidine, and Xylazine on Electroretinography of Domestic Pigeons (*Columba livia*)

Alphaxalone, medetomidine 및 xylazine이 비둘기 (*Columba livia*)의 망막전위도에 미치는 영향

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ABSTRACT

This study was conducted to compare the effects of 3 different sedative agents on electroretinography (ERG) in domestic pigeons (*Columba livia*). Alphaxalone, medetomidine, and xylazine were used with one week washout period. Six pigeons were sedated and underwent the modified electroretinography protocol adapted from the standardized protocol for dogs. The scotopic mixed rod and cone response was recorded after 20 minutes of dark adaptation, and the photopic cone response and photopic flicker response were recorded after 10 minutes of light adaptation. One-way ANOVA was used to compare the a- and b-wave implicit time and amplitude. No significant differences in the scotopic mixed rod and cone response

were observed among all 3 sedatives used. Compared to alphaxalone, medetomidine significantly prolonged the a-wave implicit time and depressed the b-wave amplitude of photopic cone response ($P < 0.05$). Compared to alphaxalone, medetomidine also significantly prolonged the peak implicit time of photopic flicker response ($P < 0.05$). There were no significant differences on all photopic responses of xylazine when compared to both alphaxalone and medetomidine. In conclusion, medetomidine has a depressant effect on photopic electroretinography in pigeons at a dosage that produced light sedation. Alphaxalone could be a better option than medetomidine and, to a lesser extent, xylazine for ERG recording in pigeons.

Keywords: alphaxalone, electroretinography, medetomidine, pigeon, sedation, xylazine.

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List of Abbreviations

ANOVA	Analysis of variance
GABA	Gamma-aminobutyric acid
cd m^{-2}	candela per square meter (luminous intensity)
cd s m^{-2}	candela times second per square meter (time integrated luminance)
cm	centimeter
ERG	Electroretinography
Hz	Hertz
kg	kilogram
mg	milligram
ms	millisecond
OP	Oscillatory potential
µg	microgram
µV	microvolt

CONTENTS

INTRODUCTION

In veterinary medicine, electroretinography (ERG) has been widely implemented for ophthalmologic examination especially in small animals. It is considered a valuable and noninvasive method to evaluate retinal functions, ranging from investigating different types of retinal degeneration to routine examination before the cataract surgery, each of them with different sets of protocols (Drazek *et al*., 2014; Ekesten, 2013; Ekesten *et al*., 2013; Maggs, 2013; Narfstorm *et al*., 2002; Ofri, 2013; Oria *et al*., 2004). In exotic species including birds, such protocols have not been established (Kuhn *et al*., 2014). To date, all the reports on ERG performed in birds, emphasizing those being done in the clinical setting (Kuhn *et al*., 2014; Hendrix and Sims, 2004; Labelle *et al*., 2012; Seruca *et al*., 2012), have been highly variable.

Many anatomical structures in a bird's eye are fundamentally different from those in a mammal's eye. Many factors ranging from the shape of the globe, to the size of the eye relatives to the body weight, to the existence of pecten instead of retinal blood vessels, contribute to the differences in the clinical ophthalmology of birds compared to that of other domestic animals such as dogs (Kern and Colits, 2013; Holmberg, 2013; William, 2012). Since a standardized ERG protocol for birds has not been established, any information on the technical aspect of ERG recording in birds is highly valuable, especially information that is practical and relevant to its clinical application, such as the effect of anesthetic drugs on ERG results. The use of anesthesia during ERG recording in animals has been a general suggestion (Ekesten, 2013; Maggs, 2013; Narfstorm *et al*., 2002). Although ERG recording without chemical restraint has been reported in several free-living

raptors (Labelle *et al*., 2012), the use of chemical restraint agents helps minimize artifacts resulting from involuntary muscle activity and decreases the stress on birds (Kuhn *et al*., 2014).

Many studies investigating different components of ERG in birds have mentioned using anesthetic agents such as sevoflurane in bald eagle (*Haliaeetus leucocephalus*) (Kuhn *et al*., 2014); isoflurane in Hispaniolan Amazon parrots (*Amazona ventralis*), Scops owl (*Otus scops*), and little owl (*Athene noctua*) (Hendrix and Sims, 2004; Seruca *et* al., 2012); chloral hydrate in little owl (Porciatti *et* al., 1989); and a combination of ketamine, xylazine, and urethane in Japanese quail (*Coturnix coturnix japonica*) (Endo *et al*., 2008). However, these studies did not focus on the effect of anesthesia on the results of ERG recording; therefore, their findings are of little value in interpreting the ERG results under the effect of some anesthetic agent in clinical examination.

Studies investigating the effects of different anesthetic agents on ERG recording in dogs showed that different anesthetic agents exerted specific impacts on ERG recording (Jeong *et al*., 2009; Kommonen *et al*., 2007; Norman *et al*., 2008). Therefore, it had been suggested that the anesthesia used in a clinical setting should be consistent, so that the results obtained were comparable (Narfstorm *et al*., 2002). The purpose of this study was to compare the effects of 3 different sedative agents including alphaxalone, medetomidine, and xylazine on ERG recording in pigeons.

MATERIALS AND METHODS

1. Experimental animals

Six domestic pigeons (*Columba livia*) were used in this study. This study was done with an approval from the Seoul National University Institutional Animal Care and Use Committee (SNU-170210-1). Each of the birds received 3 sedative agents with one week washout period. The sedative agents used were alphaxalone（10 mg/kg; Alfaxan®, Jurox, Australia), medetomidine (0.2 mg/kg; Domitor®, Zoetis, Korea), and xylazine (10 mg/kg; Rompun®, Bayer, Korea), all being injected intramuscularly in the pectoral muscle before the dark-adaptation stage of ERG recording. After the injection, the pigeons were dark adapted for 20 minutes before ERG recording.

2. Electroretinography

The ERG was recorded using RETIport (Roland Consult Stasche & Finger GmbH, Brandenburg, Germany). Goldring electrode 0.25 (No:3325RC; Roland Consult Stasche & Finger GmbH) was used as the corneal electrode. As the ground and reference electrodes, platinum subdermal needle electrodes (Model F-E2, Astro-Med Inc, West Warwick, RI, USA) were used and they were placed on the apex of the occiput subcutaneously and at approximately 0.3-0.5 cm lateral to the lateral canthus of the eye, respectively (Fig 1). Before ERG recording, proparacaine hydrochloride 0.5% eye drop (Alcaine®, Alcon, Belgium) was applied to the cornea as topical anesthesia before placing the corneal electrode. ERG was recorded from the right eye only for all the pigeons.

Three ERG recordings adapted from the guidelines of ERG in dogs (Ekesten *et al.*, 2013) were performed: 1) scotopic mixed rod and cone response, 2) photopic cone response, and 3) photopic flicker response. A single mixed rod and cone response was obtained at a stimulus intensity of 3.0 cd s m^{-2}. For photopic cone function, 4 flashes at a frequency of 4.9 Hz presented at the same stimulus intensity were obtained, and for the flicker response, 8 flashes were presented at a frequency of 31.25 Hz. The scotopic mixed rod and cone response was recorded after 20 minutes of dark adaptation. The pigeons were then light adapted for 10 minutes by using a background light of 30 cd m^{-2}, and the photopic cone response followed by the flicker response were then recorded.

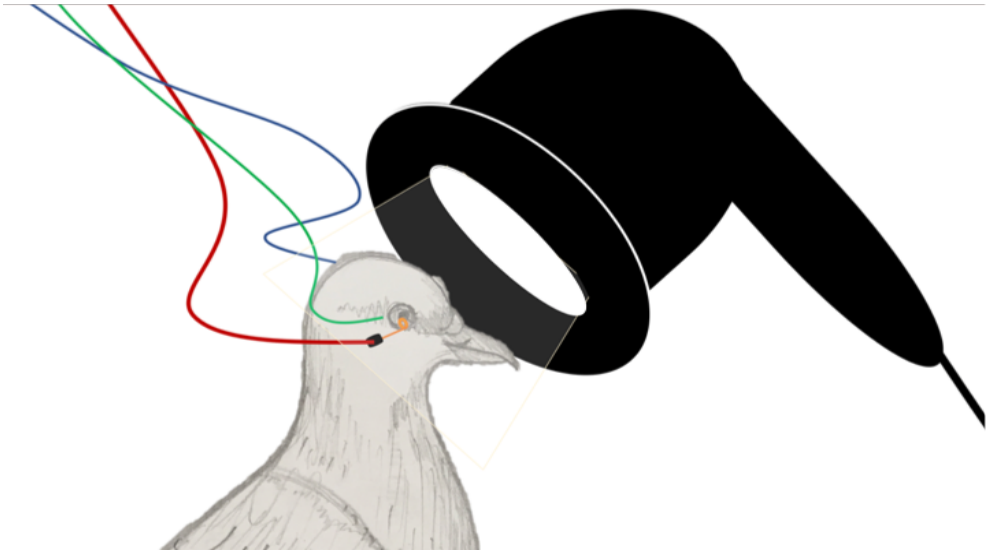

Fig 1. Pigeon underwent electroretinography with ground and reference electrodes placed subdermally on the apex of the occiput and the lateral canthus. The gold ring electrode was placed on the surface of the cornea.

3. Statistical analyses

For the scotopic mixed rod and cone and photopic cone responses, the data obtained were the a- and b-wave implicit time and amplitude. As for the photopic flicker response, the data being obtained were the peak implicit time and b-wave amplitude. One-way ANOVA was performed to compare the data among 3 sedatives by using SPSS Statistics 23 program (IBM Corp., Armonk, NY, USA). Post-hoc analysis was performed according to Bonferroni.

RESULTS

The ERG results of scotopic mixed rod and cone response under the influence of all the drugs used showed a distinct a-wave, which was a negative deflection followed by an ascending slope leading to the positive deflection of the b-wave (Fig 2 A - C). Between the a-wave and b-wave, the oscillatory potential (OP) superimposed at the ascending slope was observed during the scotopic response (Fig 2 A - C) but was absent during the photopic cone response (Fig 3 A - C). In the scotopic response result, a small positive deflection was sometimes observed before the negative a-wave, which was a stimulus artifact driven by the introduction of a brief white flash stimulus (Fig 2 A, C; Ekesten, 2013). In the photopic flicker response, a series of distinctive waves were observed, which showed that pigeon's retina was able to respond to the individual flashes presented at a frequency of 31.25 Hz (Fig 4 A - C). The b-wave amplitudes of the photopic cone and photopic flicker responses were, in general, lower than those of the b-wave amplitudes of the scotopic mixed rod and cone response for all 3 sedatives (Table 1 - 3).

For the scotopic mixed rod and cone response, no significant differences were observed in any of the ERG components for all of the drugs used. For the photopic cone response, significant differences were observed in the a-wave implicit time and b-wave amplitude between alphaxalone and medetomidine. Compared to alphaxalone, medetomidine significantly prolonged the a-wave implicit time by 3.28 ms (P = 0.011). The lower and upper 95% CI were 5.52 ms and 1.04 ms, respectively. Compared to alphaxalone, medetomidine depressed the b-wave amplitude by 55.55 μV (P = 0.015). The lower and upper 95% CI were 14.25 μV

and 96.86 μV, respectively. For the photopic flicker response, a significant difference was observed in the implicit time (P = 0.031), which also occurred between alphaxalone and medetomidine, and medetomidine significantly prolonged the implicit time by 4.91 ms. The lower and upper 95% CI were 9.27 ms and 0.56 ms, respectively. Compared to alphaxalone or medetomidine, xylazine showed no significant difference in any of the ERG recordings.

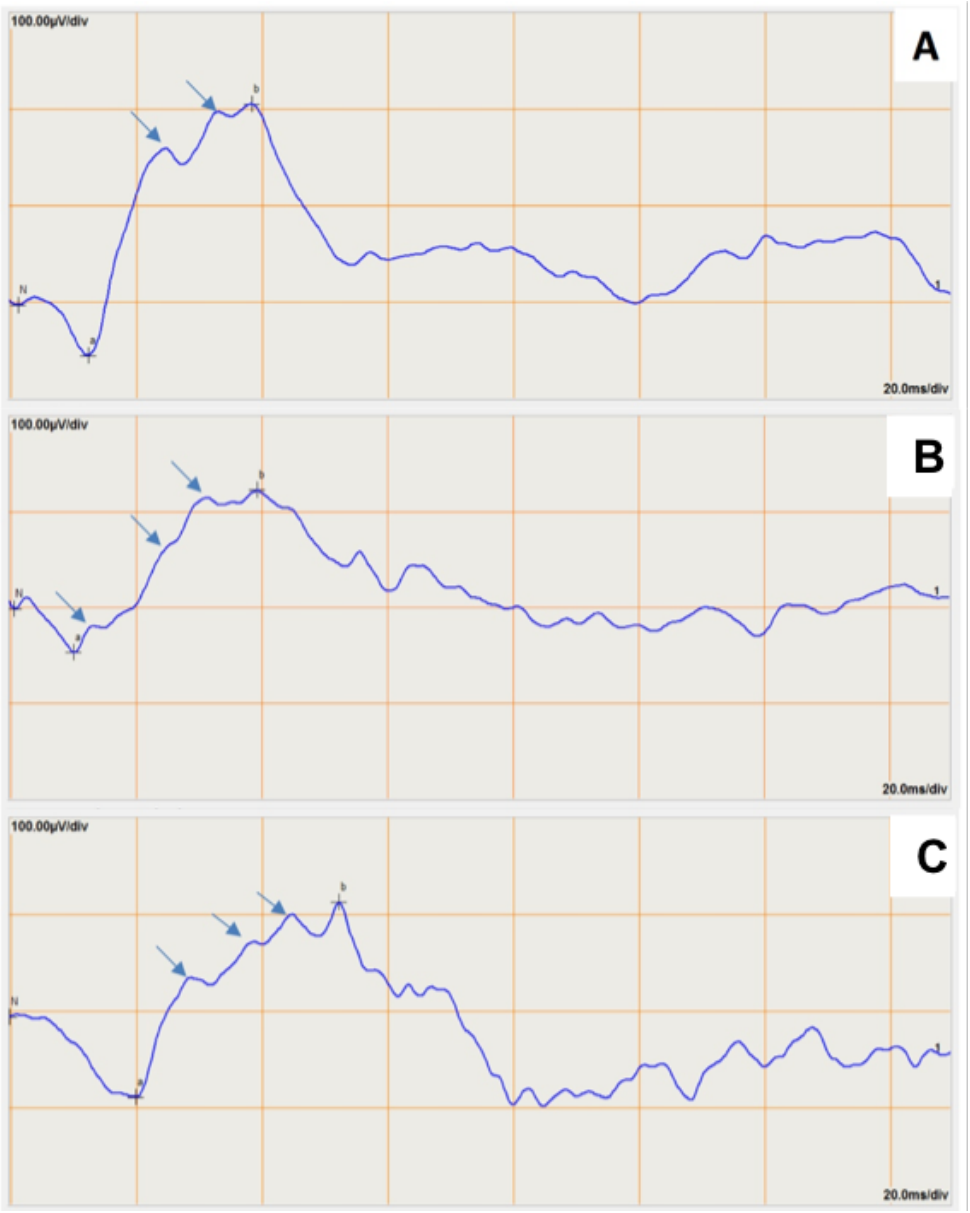

Fig. 2. Representative results of the scotopic mixed rod and cone response of pigeons sedated using 3 different sedatives: (A) alphaxalone, (B) medetomidine, and (C) xylazine. The oscillatory potential (OP) is visible between the a- and b-waves (arrows).

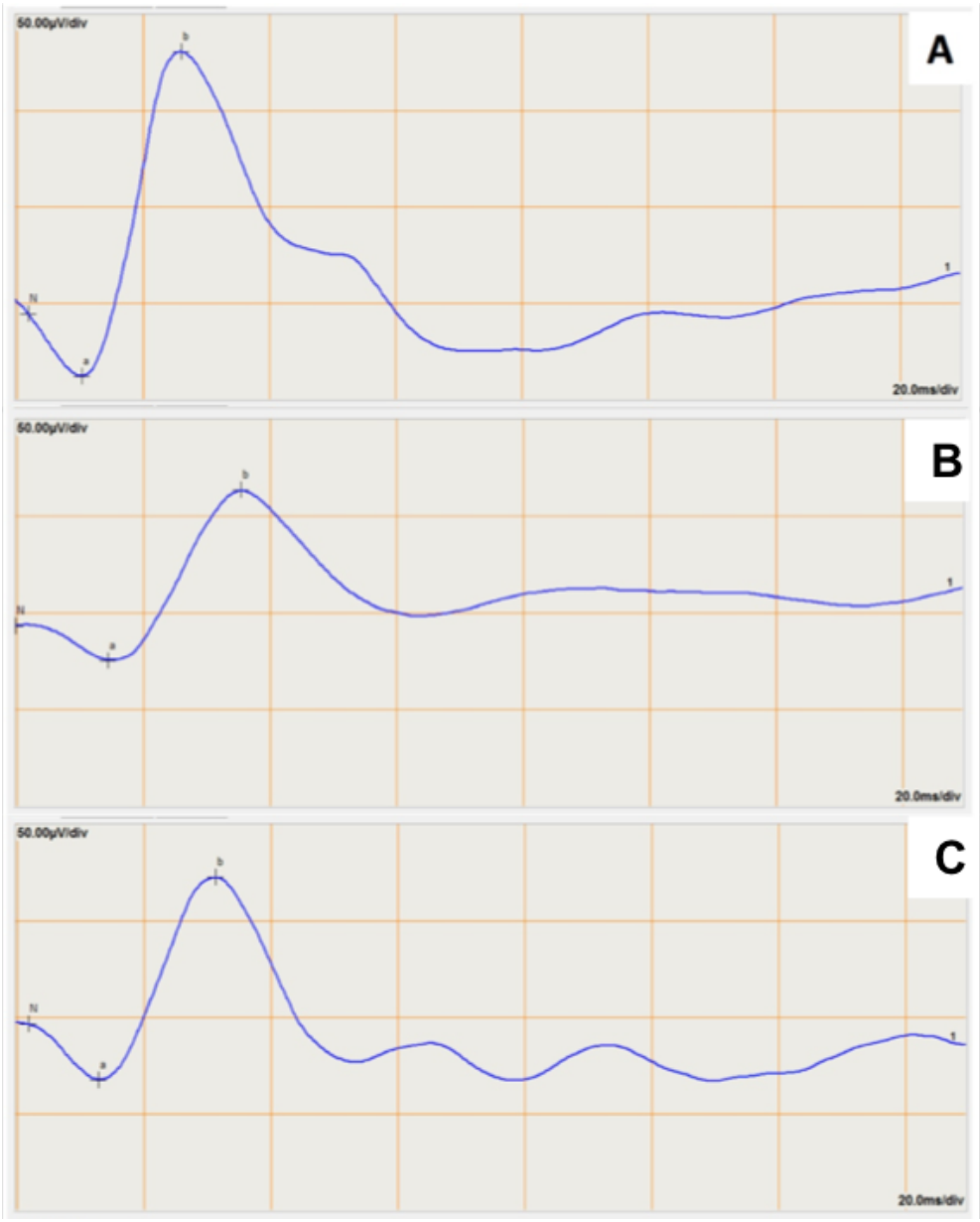

Fig. 3. Representative results of the photopic cone response of pigeons sedated using 3 different sedatives: (A) alphaxalone, (B) medetomidine, and (C) xylazine. Only the a- and b-waves are visible.

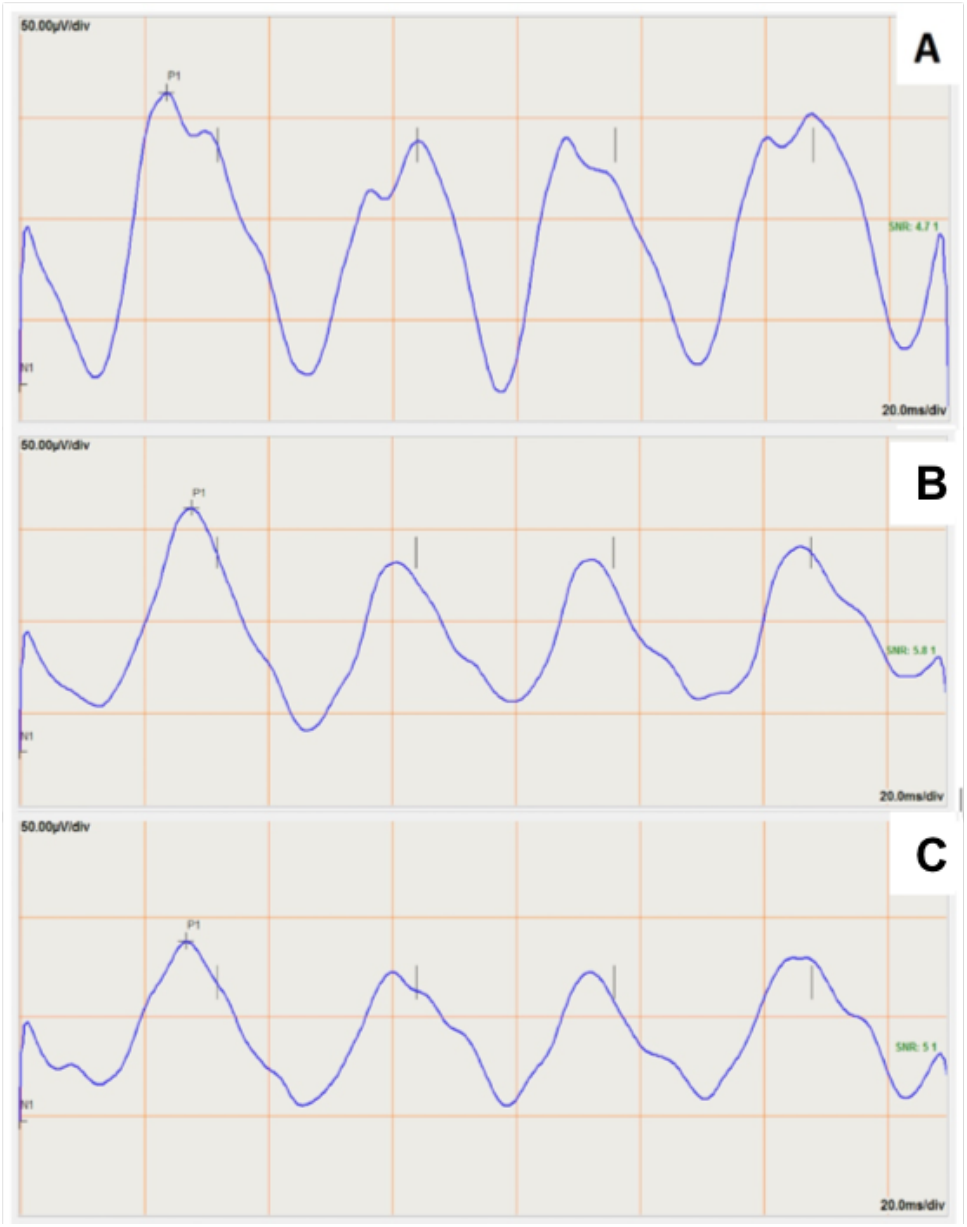

Fig. 4. Representative results of the photopic flicker response of pigeons sedated using 3 different sedatives: (A) alphaxalone, (B) medetomidine, and (C) xylazine. The stripes indicate the presentation of the light stimulations.

Table 1. Descriptive statistics of the scotopic mixed rod and cone electroretinography response in pigeons

	Scotopic mixed rod and cone response			
	Implicit time (ms)		Amplitude (μV)	
Drug	**a-wave**	**b-wave**	**a-wave**	**b-wave**
Alphaxalone	14.03 ± 1.58*	39.03± 11.04	56.51 ± 17.88	185.54 ± 82.53
Medetomidine	12.48 ± 2.18	41.51 ± 8.53	38.78 ± 17.41	161.34 ± 66.38
Xylazine	16.56 ± 2.57	39.66 ± 7.93	62.38 ± 18.00	161.38 ± 54.66

*Mean ± SD.

Table 2. Descriptive statistics of the photopic cone electroretinography response in pigeons

	Photopic cone response			
	Implicit time (ms)		Amplitude (μV)	
Drug	a-wave	b-wave	a-wave	b-wave
Alphaxalone	11.28 ± 2.31[a]*	28.86 ± 3.73[a]	29.26 ± 9.46[a]	156.81 ± 61.93[a]
Medetomidine	14.56 ± 2.28[b]	33.00 ± 2.23[a]	25.20 ± 11.07[a]	101.25 ± 44.99[b]
Xylazine	14.85 ± 2.44[a,b]	34.50 ± 5.91[a]	26.73 ± 6.61[a]	91.95 ± 25.02[a,b]

*Mean ± SD.

[a,b] Different superscript letters indicate significant differences in the same column ($P < 0.05$).

Table 3. Descriptive statistics of the photopic flicker electroretinography response in pigeons

Photopic flicker response		
Drug	**Implicit time (ms)**	**Amplitude (μV)**
Alphaxalone	23.40 ± 1.26[a]*	122.33 ± 46.33[a]
Medetomidine	28.31 ± 2.78[b]	89.81 ± 46.07[a]
Xylazine	28.81 ± 4.35[a,b]	73.65 ± 26.07[a]

*Mean ± SD.

[a,b] Different superscript letters indicate significant differences in the same column ($P < 0.05$).

DISCUSSION

In this study, oscillatory potentials (OPs) were observed only during the scotopic response for all 3 sedatives. This is an inhibitory circuit driven by amacrine cells whose appearance and numbers vary among individuals and species. It is highly dependent on retinal circulation and is reduced in the event of retinal ischemia; therefore, its use has been indicated in the diagnosis of some retinal diseases (Ekesten, 2013). Although special adaptation levels and filtering techniques are required to maximize OP recording, OPs are sometimes shown during general protocols used to record a- and b-waves, albeit only small and sometimes difficult to discern among the major components of ERG (Wachtmeister, 1998). Previous ERG studies on birds also observed OPs during scotopic ERG recordings in Hispaniolan Amazon parrots and several species of raptors (Hendrix and Sims, 2004; Labelle *et al*., 2012).

The amplitude gained during the photopic cone response is expectedly lower than those of the scotopic mixed rod and cone reponse (Ekesten *et al*., 2013) which might be caused by a different sensitivity between the rod and cone photoreceptors to the light. Rod is known to be very sensitive to light to the extent that it can detect individual quanta of light resulting on tremendous increase on signal gained during the phototransduction (Chen and Sampath, 2018), hence, the higher amplitude gained during the scotopic response where both rod and cone photoreceptors were active.

The scotopic response to a stimulus intensity of 3.0 cd s m^{-2} in this study were relatively low in amplitude when compared to those of a previous study on several species of raptors including Cooper's hawk (*Accipiter cooperi*), red-tailed hawk

(*Buteo jamaicensis*), American kestrel (*Falco sparverius*), turkey vulture (*Cathartes aura*), great horned owl (*Bubo virginianus*), barred owl (*Strix varia*), and eastern screech owl (*Megascops asio*) (Labelle *at al*., 2012). Aside from the different ERG machine, type of corneal electrode used, and absence of anesthesia in the raptor study, the species differences might contribute to the different results. Two other ERG studies conducted at the same institution on bald eagles and Hispaniolan Amazon parrots revealed that the amplitudes from the eagles were substantially higher than those from the parrots despite both studies using the same protocols and done under the same anesthetic agent (Kuhn *et al*., 2014; Hendrix and Sims, 2004).

The 3 drugs used in this study came from 2 different type of sedatives and anesthetics which act on 2 different receptors. Alphaxalone mainly acted through $GABA_A$ receptors while medetomidine and xylazine were both α_2-adrenoceptor agonists (Clarke *et al*., 2014a; Clarke *et al*., 2014b). The active enantiomers of medetomidine, i.e., dexmedetomidine, exhibits a more selective binding affinity to α_2:α_1 receptor at a ratio of 1620:1 than does xylazine, which has a selective binding affinity of only 160:1; hence, it has the more profound sedative effect (Murrel, 2016). The stronger character of medetomidine over xylazine might explain its suppressing effect when compared to alphaxalone, despite these drugs acting on different receptors. In contrast, xylazine, being a relatively weak drug, showed no significant differences compared to alphaxalone and medetomidine.

Another study on dogs also showed that medetomidine had a depressant effect on ERG recording (Norman *et al*., 2008). Medetomidine is known to significantly prolong the a- and b-waves implicit times and depressed the amplitude of both

waves on the scotopic response from 3.0 cd s m^{-2} light intensity. Compared to that previous study, some differences were observed in the depressant effect of medetomidine. First, the study on dogs was conducted on scotopic condition, but in the present study, the effect was observed in the photopic condition. Second, despite the difference in light adaptation, the overall effect of medetomidine on the ERG components in this study was minimum, with only the prolongation of the a-wave implicit time and depression of the b-wave amplitude. The rod versus cone ratio composition differences between the dog's and pigeon's retina might be the reason for this different observation, because dogs have a rod-rich retina and pigeons have a cone-rich retina (Miller, 2013; Samuelson, 2013; Nye, 1968). In the scotopic condition, the flash intensity of 3.0 cd s m^{-2} should stimulate both the rod and cone photoreceptor systems, but the main response would still be derived from the rod system. It has been said that the higher the number of photoreceptor cells being stimulated or activated, the higher the generated amplitude (Frishman, 2018) and because pigeon have a cone-rich retina with fewer rod cells, they might generate a much lower ERG response during the scotopic response relative to that shown by dogs, and hence, the amplitude differences across the 3 drugs were not significantly different.

Another possible explanation for the different results could be the sedation level in both studies. In the present study, medetomidine was administered via intramuscular injection, whereas in the previous study on dogs, it was administered intravenously; this difference in administration routes might have limited the bioavailability of medetomidine. Moreover, a previous study suggested that medetomidine may have a lower affinity to avian α_2-adrenoceptors than to

mammalian α_2-adrenoceptors that a much higher medetomidine dosage of 2 mg/kg will cause less sedation in pigeons than would a dosage of 80 μg/kg in dogs (Sandmeier, 2000).

The dosage of drugs used in this study was based on those recommended or commonly used by practitioners in pigeons (Marx, 2005), and these dosages mostly produced light sedation with the animals appearing calm but not fully immobilized. The sedation level produced by the 3 drugs were generally adequate to facilitate the ERG recording throughout the procedure. However, ERG recording in agile pigeons is difficult because they still struggle when restrained. One of the disadvantages of injected anesthetics is that their effects vary according to dosage and individual responses. Despite these disadvantages, injectable anesthetics have been used in birds when inhalation anesthetics are unavailable (Paul-Murphy and Fialkowski, 2001).

Considering that the pharmacokinetics among species of birds are highly varied, the data obtained from pigeons might not be directly transferable to other bird species, but these data may be better extrapolated than are data from mammalian species (Paul-Murphy and Fialkowski, 2001). Therefore, this study could provide better information on how these injectable anesthetics will affect ERG recording in avian species than would information obtained from mammalian species such as dogs. Furthermore, a bird's retina is different from the mammalian retina. Not only is the rod-to-cone ratio different, but the structures and types of their photoreceptors are also different, with birds having a double cone and possessing oil droplets in the distal ellipsoid region of the inner segment (Samuelson, 2013; Bowmaker *et al.*, 1997). Birds also have more varied visual pigments in the cone

photoreceptors, with pigeons having at least 4 types of visual pigments compared to the 2 types in dogs (Miller, 2013; Samuelson, 2013; Bowmaker *et al*., 1997). All of these differences could contribute to the differences in the ERG result.

Birds are highly dependent on their visual system, especially in conjunction with their flying behavior (William, 2012). Therefore, a bird's eye has a high temporal resolution, the ability to process temporally varying stimuli at a certain speed, which could be determined by flicker fusion frequency test. The frequency at which an individual could no longer resolve the stimuli of flickering light and therefore appears as a continuous light is called the critical flicker fusion frequency, and pigeons in particular are known to have the highest critical flicker fusion frequency reported for a vertebrate which is 143 Hz (Lisney *et al*., 2011). In this study, the photopic flicker presented at a flash intensity of 3.0 cd s m^{-2} and at a frequency of 31.25 Hz, which is a frequency that can still be resolved by pigeons. For this photopic flicker response, medetomidine was also prolonged the implicit time when compared to alphaxalone.

A limitation of this study is the lack of any attempt to induce mydriasis during ERG recordings. Generally, ERG recording should be performed in the mydriatic pupil to ensure an even distribution of light in the retina (Narfstorm *et al*., 2002). However, many recent studies of clinical ERG on some species of birds were performed without the use of mydriatic agents (Kuhn *et al*., 2014; Hendrix and Sims, 2004; Seruca *et al*., 2012). This is because the avian iris is insensitive to general mydriatic agents as its musculature consists of striated muscle fibers. It has been suggested that instead of parasympatholytics and sympathomimetics, nondepolarizing muscle relaxants such as d-tubocurarine solution should be used to

dilate a bird's pupil either through intracameral injection or through topical instillation (Endo *et al*., 2008; Gum *et al*., 2013). However, one study on pigeons showed that topical instillation of d-tubocurarine is not as effective as its intracameral injection in dilating the pigeon's pupil (Verschueren and Lumeij, 1991). Intracameral injection of a mydriatic agent for clinical examination is certainly not an option as it carries a risk of complications such as infection and cataract formation (Verschueren and Lumeij, 1991). Therefore, the use of mydriatic agents was omitted in this study. Further study is required to investigate the efficiency of topical mydriatic drugs in pigeons, e.g., rocuronium bromide that has recently been reported to dilate the pupil of orange-winged parrot (*Amazona amazonica*) (Dongo *et al*., 2017). ERG recording on a dilated pupil might produce a maximum amplitude and might be a better way to investigate retinal function in birds.

CONCLUSIONS

Compared to alphaxalone, medetomidine had a significantly different effect on ERG recording in pigeons. Under alphaxalone sedation, the amplitudes of b-waves were significantly higher than those under medetomidine sedation. Alphaxalone could be a better option than medetomidine and, to a lesser extent, xylazine for ERG recording in pigeons.

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국 문 초 록

Alphaxalone, medetomidine 및 xylazine이 비둘기 (*Columba livia*)의 망막전위도에 미치는 영향

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이 연구는 비둘기 (*Columba livia*)의 망막전위도에 대한 3 가지 진정제의 효과를 평가하기 위하여 수행하였다. Alphaxalone, medetomidine 및 xylazine을 사용하였고 각각의 약물사이에는 1 주일의 휴약기를 두었다. 여섯 마리의 비둘기를 진정하였고, 개를 위한 표준화된 protocol을 수정·적용하여 망막전위도 검사를 실시하였다. 20 분 간의 암순응 후에 scotopic mixed rod 와 cone response를 측정하였고, 10 분 간의 명순응 후에 photopic cone response 와 photopic flicker response를 측정하였다. 일원분산 분석을 사용하여 a 및 b 파의 implicit time 및 amplitude를 비교하였다. Scotopic mixed rod and cone response에서는 3 가지 진정제 간의 유의적

인 차이가 확인되지 않았다. Alphaxalone과 비교하여, medetomidine은 a 파의 implicit time을 현저하게 연장시켰고 photopic cone response의 b 파 amplitude를 감소시켰다 ($P < 0.05$). 또한, alphaxalone과 비교했을 때 medetomidine은 photopic flicker response의 최대 implicit time을 유의적으로 연장시켰다 ($P < 0.05$). Xylazine은 alphaxalone및 medetomidine과 비교했을 때, photopic cone response와 photopic flicker response에서는 유의적인 차이가 확인되지 않았다. 결론적으로 medetomidine은 가벼운 진정 효과를 나타내는 투여량에서 비둘기의 photopic cone response를 억제하는 것으로 나타났으므로, medetomidine과 xylazine에 비해 alphaxalone이 비둘기의 망막전위도 측정에 있어 보다 적절한 진정제로 사료된다.

주요어: alphaxalone, 망막전위도, medetomidine, 비둘기, 진정제, xylazine.

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