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Research article

SYSTEMIC EFFECTS RELATED TO THE USE OF 1% CYCLOPENTOLATE HYDROCHLORIDE EYE DROPS IN REFRACTOMETRY IN CATS

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In veterinary medicine, 1% Cyclopentolate hydrochloride (CP) has emerged as an intermediate-term cycloplegic and mydriatic agent. This study evaluated the pupillary dilation time and systemic effects related to the use of 1% CP eye drops in cats. Fifteen cats, aged 1 to 6 years and weighing 2.5 to 7 kg, were included in the study. After receiving written consent from the owners, each cat was administered two drops of 1% Cyclopentolate, 10 minutes apart, into both eyes. Data on pupil dilation, systemic symptoms, and behavioral changes were collected and analyzed using frequency and descriptive statistics. Pupillary dilation was observed 30 minutes after administering the second drop of 1% CP. The duration of pupillary dilation was 36 hours for 26.6% of the eyes, 48 hours for 53.4%, and 60 hours for 20%. Within the first hour after medication administration, seven cats exhibited episodes of salivation and vomiting, and four displayed behavioral changes, including aggressiveness and increased vocalization. Results suggest that 1% CP eye drops cause mydriasis for at least 36 hours and can lead to temporary adverse effects on the gastrointestinal and nervous systems.

Keywords: feline, cycloplegic, toxicity, mydriatic, cyclopentolate

INTRODUCTION

Mydriatic and cycloplegic drugs are routinely used in veterinary ophthalmology for various clinical reasons, including eye examination of the retina, retinal vessels, optic nerve, and peripheral areas of the lens, surgery, prevention of synechiae, and control of ocular pain in uveitis and corneal ulceration [1,2]. Among the mydriatic and cycloplegic agents available for animal use are: atropine, tropicamide, homatropine, and cyclopentolate [3].

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Cyclopentolate is a synthetic nonselective antimuscarinic drug with pharmacological properties similar to those of atropine. It blocks the responses of the iris sphincter muscle and the ciliary body muscle to cholinergic stimulation, inducing cycloplegia and pupillary dilation 30 minutes after application [4]. The typical duration of pharmacological pupillary dilation induced by CP is 24 hours for humans [5], 4 hours for rabbits [6], 14-72 hours for domestic dogs, and 56-66 hours for domestic cats [6,7].

The choice of a mydriatic or cycloplegic agent depends on understanding its pharmacodynamic characteristics and potential adverse effects. Tropicamide and atropine are the most commonly used agents in animals [8]. However, some protocols indicate using cyclopentolate hydrochloride (CP), such as in refraction exams [9,10].

The main risks associated with the use of mydriatic-cycloplegic drugs include increased intraocular pressure [8,11], reduction of tear production [12], corneal ulceration [8,13], and other systemic effects derived from absorption [14]. Topical 1% Cyclopentolate could be considered an effective and safe option for treatment and diagnosis in horses, dogs, and cats, as these parameters are not significantly altered with its use [6,7,15].

CP is absorbed through the corneal and conjunctival surfaces, nasolacrimal mucosa, and gastrointestinal tract [16]. CP eye drops can cause transient changes in the central nervous system of human patients, especially in children [17]. Major side effects, occurring in approximately 10% of human patients, include hallucinations, psychosis, hyperactivity, restlessness, ataxia, seizures, and tachycardia [17,18]. To our knowledge, no systemic effects due to CP use have been reported in animals, although local ocular changes have been noted.

As veterinary care for cats has increased considerably, it is important to understand the effects and potential risks of using these drugs in this species. Therefore, we aimed to evaluate pupillary dilation duration and the adverse effects associated with using 1% CP eye drops in felines.

MATERIALS AND METHODS

Ethical

This study adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. All procedures involving cats followed the Ethical Principles of Animal Experimentation established by the Brazilian College of Animal Experimentation (COBEA) and were approved by the Ethics Committee on Animal Use (CEUA protocol number 019003/17) of FCAV/UNESP. All cat owners who met the inclusion criteria were informed of the importance of the study. Those who agreed to have their animals participate provided a statement of informed consent.

Animals

Fifteen domestic cats (Felis catus) of both sexes, aged 8 to 72 months (mean ± standard deviation, 45.07 ± 21.35 months; approximately 4.3 years), and weighing 2.5 to 7 kg (4.5 ± 1.29 kg), were included in the study. The sampling was completely randomized. All animals included in this study were free of systemic illness and underwent ophthalmic examination, including a Schirmer's tear test (baseline reference interval) (Ophthalmos, SP, Brazil), slit lamp biomicroscopy (Kowa SL-15, Japan), measurement of intraocular pressure (mean 18.4 mmHg) (Tonopen-vet, Reichert, USA), indirect ophthalmoscopy (Eyetec, São Carlos, Brazil), and a fluorescein staining test (Ophthalmos, SP, Brazil). Cats without systemic diseases and without any ocular signs were included in this research. The cats included in this study were healthy patients who will be included in another refractometry study aiming to evaluate ametropias in cats.

Animal Procedures and Follow-Up

Each cat received one drop of 1% cyclopentolate hydrochloride (Ciclolato®, Latinofarma, Sao Paulo, Brazil) in both eyes. A second drop was administered 10 minutes after the first. The animals then underwent a refraction exam with an autorefractor/keratometer (Potec PRK-7000, Korea) 45 minutes after the first drop. The cats were observed for 3 days (72 hours), and pupillary dilation was measured by observation with slit lamp biomicroscopy. Procedures related to refractometry are part of another research study, and those materials and methods are not included here.

Statistical Analysis

Data on the duration of pupillary dilation and occurrence of systemic side effects were evaluated using descriptive statistics and are expressed as frequencies (%) and mean ± standard deviation. The Kolmogorov-Smirnov normality test was used to evaluate the normal distribution. Associations of systemic side effects with the sex and age of the cats were assessed using Fisher's exact test or the Wilcoxon signed-rank test, with values considered significant when $P < 0.05$. All calculations were performed using Minitab 18 software (Minitab, San Diego, CA, USA).

RESULTS

Dilated pupils were observed 30 minutes after the instillation of the second drop of 1% CP in each eye. The pupillary dilation lasted for 30 hours in 26.2% of the eyes, 48 hours in 53.4%, and 60 hours in 20%. The mean duration of pupillary dilation was 47.20 ± 8.44 hours.

Ten of fifteen cats (66.6%) presented with one or more systemic signs or symptoms indicative of an adverse reaction to using 1% CP eye drops (Table 1). Systemic signs began to appear 45 minutes (mean) after administering the second drop of 1% CP

and disappeared 60 hours later (average time). Of these, 46.5% of the cats (7 of 15) developed gastric disorders (salivation, vomiting, and nausea), and 26.6% (4 of 15) exhibited behavioral changes (aggressiveness and vocalization). Four of the ten cats (40%) that developed side effects from 1% CP eye drops showed both gastric disturbances and behavioral changes. None of the cat owners reported changes in the animal's appetite.

Table 1. Adverse effects and time of pupillary dilation in cats after topical instillation of cyclopentolate

Patient identification	Weight	Breed	Ages	Sex	Pupil dilation time duration (x)	Adverse effects
1	4.0kg	Mixed	5 years	Female	36 hours	Salivation, vomiting, and vocalization
2	4.0 kg	Mixed	6 years	Female	48 hours	x
3	5.6 kg	Persian	4 years	Male	36 hours	Salivation
4	6.3 kg	Persian	5 years	Male	36 hours	Salivation, vomiting, and vocalization
5	5.0 kg	Mixed	4 years	Male	48 hours	x
6	4.2 kg	Mixed	2 years	Female	48 hours	vocalization, vomiting, and aggressiveness
7	6.0 kg	Mixed	6 years	Male	48 hours	Salivation and vomiting
8	4.8kg	Mixed	4 years	Male	48 hours	Vomiting and salivation
9	7.0 kg	Mixed	4 years	Female	48 hours	Aggressiveness, vomiting, and salivation
10	4.0 kg	Mixed	2 years	Male	48 hours	x
11	2.5 kg	Mixed	8 months	Female	60 hours	Aggressiveness and vocalization
12	2.5 kg	Mixed	8 months	Female	60 hours	Salivation and vomiting
13	3.8 kg	Mixed	4 years	Female	36 hours	x
14	3.8 kg	Mixed	3 years	Female	60 hours	Aggressiveness
15	4.0 kg	Mixed	6 years	Female	48 hours	x

Fisher's exact test revealed no association between the cats' sex and the incidence of gastric disturbances (P = 0.608) or behavioral changes (P = 0.286). Additionally, no difference in age was observed between cats that experienced side effects from using 1% CP eye drops (median, 48 months; range, 8−72 months) and those that did not (median, 48 months; range, 24−72 months) (P = 0.439).

DISCUSSION

Cyclopentolate was used in this research to induce mydriasis and cycloplegia in feline patients requiring subsequent refraction examination. The choice of this agent was based on the relatively fewer adverse effects reported in this species, as noted by Kovalcuka et al. [6], who found only a decrease in Schirmer values with 1% CP in healthy cats, and Stadtbaumer et al. [8], who reported increased intraocular pressure without inducing glaucoma.

Digestive parameters were evaluated in horses using cyclopentolate, with results indicating no modifications in this system [19]. There are currently no reports of intoxication from using 1% CP drops in dogs and cats. Stadtbaumer et al. [8] used the same mydriatic agent without reporting adverse systemic effects in felines, although local effects, such as increased intraocular pressure, were noted. It should be mentioned that in the study by Stadtbaumer et al. [8], the cyclopentolate concentration was lower than in this study's protocol, and no repeated dosage was employed. Although intraocular pressure alteration was described, this variable was not evaluated in the present study, which may be considered a limiting factor.

Few scientific reports in human ophthalmology address adverse effects related to vagal excitation associated with cyclopentolate drops, which are more common in children [20] and newborns [18], although adults can also be affected by therapeutic doses [21]. Two conditions related to CP absorption cause adverse effects in children: [1] its easy systemic absorption and [2] better absorption by individuals with lower body surface area, such as newborns and patients with low weight or nutritional deficiency [22].

The body weight of the cats in this study ranged from 2.5 to 7.5 kg, considered ideal for an adult, but it may not have been sufficient to withstand repeated doses of the drug. The cats' weight and the number of drops administered during the refraction exam protocol likely contributed to the intoxication. Each animal received four drops (1.21 mg/animal), which were probably absorbed through the conjunctiva and nasolacrimal duct, which are highly vascularized [22], and thus reached the bloodstream. Additionally, some of the drug may have been ingested and absorbed in the gastrointestinal tract [17].

Once muscarinic antagonists enter the general circulation, they can induce cardiac changes, disturbances in the gastrointestinal tract [23], and effects on the central nervous system [18]. Clinical signs of central anticholinergic syndrome include mood changes, hallucinations, disorientation, and alterations in memory [24]. The gastric and

neurotoxic effects reported in this study are similar to those observed in adults and children intoxicated with cyclopentolate [20,25,26].

Felines are known to have a deficiency in eliminating drugs requiring phase II biotransformation reactions conjugated with glucuronic acid. However, cyclopentolate is metabolized through phase I reactions, specifically hydrolysis [27,28]. Therefore, the undesired effects observed in this study are not a consequence of drug metabolism or biotransformation failure.

Modifying the CP dose concentration, combining it with vasoconstrictors, or using a single drop might be alternative approaches to minimize systemic adverse effects and prolong pupillary dilation duration [6,28,29]. Alghamdi et al. [30] found that 0.5% CP drops produced the same cycloplegic effect as 1% CP in young adults. In newborns, using cyclopentolate at low concentrations in combination with phenylephrine produced the desired cycloplegia without side effects, even with repeated doses [31]. A single drop of 1% CP was effective in maintaining pupillary dilation and visual accommodation in children [32,33]. Reducing systemic absorption by modifying the 1% CP eye drop formulation, such as using mucoadhesive polymers proposed by Huupponen et al. [34], might be an alternative.

The lack of studies on animal intoxication with 1% CP led this research to use a previously established protocol for traditional refraction exams, with repeated doses to induce intoxication effects [9,17,35]. Although the drug effectively induced cycloplegia for refraction exams, the systemic effects observed suggest that repeated doses of 1% CP in felines should be contraindicated.

CONCLUSIONS

Using 1% CP eye drops in cats effectively induces mydriasis for refractive exams when needed. However, temporary adverse effects can occur if two doses are administered topically. Systemic toxicity is related to the anticholinergic effects on the central nervous, cardiovascular, and gastrointestinal systems primarily.

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Authors' contributions

CPBS Designed the experimental research, performed statistical and data analysis, carried out refractometry in cats. Participate in the coordination of the study and contributed to draft the manuscript. DYTP performed statistical and data analysis, drafted, edited and reviewed the final version of the manuscript. AAFBS Assisted and carried the cats exams of refractometry in cats and participate in all the experimental study. RMC Assisted in the experimental procedures and participated in the analysis

of the results. TGMA, MRF, MA and JLL participated in the experiment procedures, design and participated in the analysis of the results. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement of Informed Consent

The owner understood procedure and agrees that results related to investigation or treatment of their companion animals, could be published in Scientific Journal Acta Veterinaria-Beograd.

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SISTEMSKI EFEKTI UPOTREBE KAPI ZA OČI 1% CIKLOPENTOLAT HIDROHLORIDA U REFRAKTOMETRIJI KOD MAČAKA

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U veterinarskoj medicini, 1% ciklopentolat hidrohlorid (CP) se pojavio kao srednjeročni cikloplegični i midriatičan agens. Ova studija je procenila vreme proširenja zenice i sistemske efekte nakon upotrebe 1% CP kapi za oči kod mačaka. U studiju je uključeno 15 mačaka starosti od 1 do 6 godina i težine od 2,5 do 7 kg. Nakon dobijanja pismene saglasnosti vlasnika, svakoj mački su date dve kapi 1% ciklopentolata, u razmaku od 10 minuta, u oba oka. Podaci o proširenju zenice, sistemskim simptomima i promenama u ponašanju su prikupljeni i analizirani primenom deskriptivne statistike. Dilatacija zenice je primećena 30 minuta nakon primene druge kapi 1% CP. Trajanje proširenja zenice bilo je 36 sati za 26,6% tretiranih očiju, 48 sati za 53,4%, i 60 sati za 20%. U toku prvog sata nakon primene leka, sedam mačaka je pokazalo epizode pojačane salivacije i povraćanja, a četiri su pokazale promene u ponašanju, uključujući

agresivnost i povećanu vokalizaciju. Rezultati sugerišu da 1% CP kapi za oči izazivaju midrijazu u trajanju od najmanje 36 sati i mogu dovesti do privremenih štetnih efekata na gastrointestinalni trakt i nervni sistem.