Annex III

Comparative Evaluation of Topical Anesthetics Proparacaine and Tetracaine

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Local anesthetics produce reversible loss of sensation in a limited area of an animal's body without the loss of consciousness or alteration of central nervous system activity (Wright et al. 1985). Topical anesthetics reduce pain by blocking sodium channels in excitable neurons, thus inhibiting the action potential generated by membrane depolarization when large, transient increases in sodium permeability are produced in response to painful stimuli (Catterall and Mackie 2001). The two most commonly used topical ocular anesthetics are proparacaine and tetracaine (Wilson 1990; Bartfield et al. 1994). A comparative evaluation of the relevant properties of proparacaine and tetracaine with regards to their impacts on corneal wound healing and irritant hazard classification is detailed below in **Table 1**.

Table 1 Comparative Evaluation of Topical Anesthetics Proparacaine and Tetracaine

Characteristic	Proparacaine	Tetracaine	References
Onset of Action	Faster, based on clinical veterinary experience and observations	Slower, based on clinical veterinary experience and observations	Webb 2009
	0.25 minutes (0.5% solution), species not specified	5 minutes (0.5% solution), species not specified	Bryant 1969
	Approximately 30 seconds after instillation, based on an assessed blink reflex in a human clinical study	Approximately 30 seconds after instillation, based on an assessed blink reflex in a human clinical study	Bartfield et al. 1994
	Within 60 seconds in rabbits	NP	Schwartz et al. 1998
	6-20 seconds	Tetracaine may not produce complete anesthesia to pain even when dosed twice and onset time is 10-15 min.	CPSC Report B
Duration of Action	Shorter, based on clinical veterinary experience and observations	Longer, based on clinical veterinary experience and observations	Webb 2009
	15 minutes, species not specified	30-120 minutes, species not specified	Bryant 1969
	Approximately 60 minutes in rabbits using 40 µl of 0.5% solution	NP	Schwartz et al. 1998
	Approximately 15 minutes, based on human refractive surgery procedures	Approximately 15 minutes, based on human refractive surgery procedures	Nomura et al. 2001
	10 minutes in humans using 0.5% solution, as determined by return of corneal blink reflex evaluated every 2 min	9 minutes in humans using 0.5% solution, as determined by return of corneal blink reflex evaluated every 2 min	Bartfield et al. 1994

continued

Table 1 Comparative Evaluation of Topical Anesthetics Proparacaine and Tetracaine (continued)

Characteristic	Proparacaine	Tetracaine	References
Duration of Action (continued)	34 minutes in normal human corneas using one drop of 0.5% solution, as determined by Cochet-Bonnet measurements	NP	Weiss and Goren 1991
	5 minutes in cats (maximal anesthetic effect) using one drop of 0.5% solution, as determined by Cochet-Bonnet measurements	NP	Binder and Herring 2006
	15 minutes in dogs (maximal anesthetic effect) using one drop of 0.5% solution, as determined using a Cochet-Bonnet measurements; 25 minutes for 2-drop treatment	NP	Herring et al. 2005
	Approximately 10-20 minutes	NP	Proparacaine (OPHTHETIC®) FDA Final Labeling Requirements (2000)
Usage/Dosage Requirements	For procedures in which a topical ophthalmic anesthetic is indicated: (e.g., corneal anesthesia of short duration); Safety and effectiveness of proparacaine HCl ophthalmic solution in pediatric patients have been established; Use of proparacaine HCl is supported by evidence from adequate and well-controlled studies in adults and children over the age of twelve, and safety information in neonates and other pediatric patients Removal of foreign bodies and sutures, and for tonometry: 1 to 2 drops (in single instillations) in each eye before operating. Short corneal and conjunctival procedures: 1 drop in each eye every 5 to 10 minutes for 5 to 7 doses	CPSC Policy states "when animal testing is the only feasible method of determining if a substance is an eye irritant, the animals are treated with two applications of tetracaine ophthalmic anesthetic, 10-15 minutes apart, prior to instilling the product to the eye, in order to reduce the pain and suffering of the animals tested".	Proparacaine (OPHTHETIC®) FDA Final Labeling Requirements (2000) CPSC Policy 1984

continued

Table 1 Comparative Evaluation of Topical Anesthetics Proparacaine and Tetracaine (continued)

Characteristic	Proparacaine	Tetracaine	References
Pain of Instillation	Less painful using a validated visual-analog pain scale following 1 drop	More painful using a validated visual-analog pain scale following 1 drop	Bartfield et al. 1994
	Negligible	Significant - stinging and burning	Bartfield et al. 1994
	Occasional temporary stinging, burning and conjunctival redness	NP	Proparacaine FDA Final Labeling Requirements (2000)
Common Preservative	Benzalkonium chloride (0.01%)	Chlorobutanol (0.4%)	Proparacaine FDA Final Labeling Requirements (2000) Tetracaine Hydrochloride Ophthalmic solution (Akorn 2009)
SEM examination	No disruptive effects with single dose application of 0.5% solution to rabbit eyes	No disruptive effects with single dose application of 0.5% solution to rabbit eyes	Pfister and Burstein 1976
In Vitro Toxicity (as evaluated with primary cultures of rabbit corneal epithelial cells)	NP	Approximately 4X more toxic than proparacaine, as determined by mitochondrial reduction assay, lactate dehydrogenase leakage cytotoxicity test, and morphological changes	Grant and Acosta 1994
Penetration of sulphorhodamine B into corneas of mice (ratio provides a numerical index of toxicity to corneal epithelium)	No effect on ratio using 0.1 and 1% proparacaine	Rise in the ratio of three out of a maximum achievable rise of 30 with 0.5% preservative-free tetracaine	Maurice and Singh 1986
In Vivo Toxicity (as evaluated with cultured human keratocytes)	Exhibited toxic effects, as determined by phase-contrast microscopy, and tetrazolium salt colorimetric assay	Produced a larger decrease in cell viability than proparacaine. Exhibited toxic effects	Moreira et al. 1999
Delayed Healing of Experimental Corneal Lesions in Rats	0.5% proparacaine (11 times over 3h) caused a complete inhibition of healing in test rat eyes compared with lesions in control	0.5% tetracaine delayed healing compared to contralateral ocular lesions; Some healing noted	Marr 1957

continued

Table 1 Comparative Evaluation of Topical Anesthetics Proparacaine and Tetracaine (continued)

Characteristic	Proparacaine	Tetracaine	References
Effect on Corneal Wound Healing in Humans after PRK	NP	1% tetracaine given every 30 minutes for 24 hours did not adversely affect corneal wound healing	Verma et al. 1995
Effect on Reparative Regeneration of Corneal Epithelium	NP	0.5% tetracaine caused more delay of wound healing than 2% cocaine and 2% lidocaine	Bykov and Semenova 1972
Effect on Corneal Epithelial Permeability	NP	Not significantly increased following five instillations of one drop of solution	Ramselaar et al. 1988
Effect on Tear Dynamics in Rabbits	0.5% solution significantly reduced tear production in rabbit eyes	0.5% solution significantly reduced tear production; Reduction in lacrimal turnover dependent upon number of drops applied	Patton and Robinson 1975
Effect of anesthetic pretreatment on administration of 10% SLS in rabbits	No statistical differences between anesthetized and unanesthetized rabbit corneas with 0.5% after TSA; Some evidence that intensity of reaction was increased following anesthesia	NP	Heywood and James 1978
Effect of anesthetic pretreatment on Ocular response and recovery time	Effective in producing anesthesia; Tended to increase the severity of ocular reactions and the time of recovery	Dosing pattern (single application) not fully adequate; Two different instillations are required to produce anesthesia from tetracaine; No adverse effects were caused by the dose administered	Falahee et al. 1981
10% dishwashing detergent application in rabbits	Proparacaine pretreatment caused significant opacity, iritis, and redness and an irritant classification; Without - not an irritant.	NP	CPSC Report A
40% dishwashing or powdered detergent application in rabbits	Irritancy not affected by pre-treatment with proparacaine	NP	CPSC Report B
Study examining pre-treatment anesthetics on the application of Acetic Acid (5%), NaOH (1%), dishwashing detergent (10%), ETOH (70%)	"Some of the scores produced by [these] substances were altered by proparacaine pretreatment, but their classification as irritants under the FHSA remained the same".	Long onset of action (5-10 minutes) and effect inconsistent; Repeat application required; Preliminary data indicates it does not alter test scores in general	CPSC Report A (date unknown)

continued

Table 1. Comparative evaluation of topical anesthetics proparacaine and tetracaine (continued)

Characteristic	Proparacaine	Tetracaine	References
Collaborative study investigating the potential of anesthetics to alter the irritation response in rabbits (eight labs)	2 drops of 0.5% solution; No appreciable effect on the course or intensity of ocular responses from treatment with 20% or 100% shampoo, 80% ethyl alcohol, or 100% talc	2 drops of 0.5% solution, 2 applications; No appreciable effect on the course or intensity of ocular responses from treatment with 20% or 100% shampoo, 80% ethyl alcohol, or 100% talc	Arthur et al. 1986
Repeated Application	0.5% solution (every 4h for 6 days) delayed corneal wound closure in rabbits	NP	Peyman et al. 1994
	NP	0.05% solution delayed reepithelialization in patient after overuse	Lee and Stark 2008
	0.5% proparacaine and tetracaine caused toxic keratopathy- non-healing epithelial defect, marked stromal edema in patients	0.5% proparacaine and tetracaine caused toxic keratopathy- non-healing epithelial defect, marked stromal edema in patients	Rocha et al. 1995

Abbreviations: NP = Not provided; FDA = Food and Drug Administration; CPSC = Consumer Product Safety Commission; TSA = Test Substance Administration; FHSA = Federal Hazardous Substances Act; PRK = Photorefractive Keratotomy; SEM = Scanning Electron Microscopy

Proparacaine is a widely used ophthalmic topical anesthetic in both human and veterinary clinical practices (Webb 2009). Although a range of onset times have been reported, proparacaine typically provides fast and effective anesthesia within 30 seconds following administration of a single dose (Bryant 1969; Bartfield et al. 1994; CPSC Report B (date unknown). In contrast, tetracaine, a related ester topical anesthetic, reportedly exhibits a slower onset of action of approximately 5-10 minutes and does not produce complete anesthesia to pain even when dosed twice (Bryant 1969; CPSC Report B (date unknown); Webb 2009). For studies where both anesthetics were evaluated, tetracaine generally provided a longer duration of action than proparacaine (Bryant 1969; Nomura et al. 2001; Webb 2009). However, Bartfield et al. (1994) reported that 0.5% proparacaine conferred slightly longer anesthesia (i.e., 10 minutes) than tetracaine (i.e., 9 minutes) on human volunteers. Studies of proparacaine for which there was no corresponding tetracaine data reported maximal anesthesia for a duration range of 5-60 minutes in a variety of species (Weiss and Goren, 1991; Schwartz et al. 1998; Binder and Herring 2006; Herring et al. 2005; Proparacaine (Ophthetic®) Final Label 2000).

The specified usage/dosage requirements for proparacaine in humans for short corneal and conjunctival procedures are 1 drop of proparacaine to be instilled into the eye every 5 to 10 minutes for 5 to 7 doses (Proparacaine (Ophthetic®) Final Label 2000).

Clinical studies indicate that instillation of proparacaine eye drops is considerably less painful than instillation of tetracaine (CPSC Report A (date not provided); Falahee et al. 1981; Bartfield et al. 1994). Proparacaine contains the common preservative benzalkonium chloride (0.01%), as opposed to tetracaine, which contains chlorobutanol (0.4%) (Proparacaine (Ophthetic®) Final Label 2000; Tetracaine Hydrochloride Ophthalmic solution Akorn 2009).

Several studies have evaluated the *in vitro* and *in vivo* toxicity of topical application of proparacaine on the cornea, in addition to its impact on the ocular irritant response.

Pfister and Burstein (1976) reported that a single dose application of 0.5% proparacaine or tetracaine to rabbit eyes produced no disruptive effects when examined by scanning electron microscopy. Proparacaine exhibited lower *in vivo* toxic effects than tetracaine on cultured human keratocytes when using phase contrast microscopy (Moreira et al. 1999). Topical application of tetracaine, unlike proparacaine, was also associated with an increase in acute toxicity to the corneal epithelium in mice, as measured by the penetration of sulforhodamine (Maurice and Singh 1986). In addition, a study utilizing primary cultures of rabbit corneal epithelial cells showed that tetracaine was significantly more toxic than proparacaine, as determined by several *in vitro* assays and observed morphological changes (Grant and Acosta 1994).

Tetracaine has previously been reported not to significantly effect corneal wound healing or corneal epithelial permeability, using either limited or repeated applications (Ramselaar et al. 1988; Verma et al. 1995). However, Bykov and Semenova (1972) noted that 0.5% tetracaine delayed wound healing more than either 2% cocaine or 2% lidocaine. Comparative data on the effects of proparacaine on corneal wound healing are not available.

Heywood and James (1978) reported no statistical differences in the ocular response of anesthetized (0.5% proparacaine) and unanesthetized rabbit corneas following the administration of 10% sodium lauryl sulfate. An increase in the intensity of the reaction was noted for the anesthetized animals, however this was not sufficient to alter hazard classification. A collaborative study involving eight laboratories investigated the potential of anesthetics to alter the irritation response in rabbits (Arthur et al. 1986). It was reported that pre-treatment with two drops of 0.5% proparacaine had no appreciable effect on the course or intensity of ocular responses after administration with 20% or 100% shampoo, 80% ethyl alcohol or 100% talc. CPSC Report B (date not provided) also found that ocular irritancy after application of 40% dishwashing or powdered detergent in rabbits was not affected by pre-treatment with proparacaine. In contrast, proparacaine pretreatment caused significant opacity, iritis and redness resulting in an irritant classification following the application of 10% dishwashing detergent in rabbits, where unanesthetized animals produced no response (CPSC Report A date not provided).

In summary, these findings indicate that there are advantages to using either proparacaine or tetracaine as the preferred topical anesthetic for ocular irritation studies. Both of these drugs have a long history of safe and effective use for relieving pain for either human or veterinary clinical practice.

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