Ocular anesthesia is an important consideration in most diagnostic and therapeutic procedures. Anesthetic agents may be administered topically, intracameraly, or via local infiltration, retrobulbar injection, or intravenous administration. Local anesthetics (LA) reversibly block conduction of nerve impulses.

**Chemical structure and mechanism of action**

LA agents structurally consist of a hydrophobic aromatic ring (benzoic acid derivatives), a linkage site between the aromatic ring and an intermediate chain, and a hydrophilic amine. The hydrophobic portion is essential for activity, as it is the portion that enables diffusion through the lipid membrane of nerves -- increasing hydrophobicity increases access of the LA to its site of action and decreases its metabolism, thereby increasing potency and duration. Greater hydrophobicity is also associated with increased toxicity. The linkage site for the intermediate chain consists of an ester (unstable, rapidly metabolized) or an amide (stable, undergoes hepatic metabolism). Most topical LA contain an ester linkage, while injectable LA contain an amide linkage (Table 1). The hydrophilic amine portion may exist in an uncharged, poorly water-soluble form, or as the positively charge ammonium ion.

**Table 1. Structural classification of local anesthetics (adapted from Bartlett and Jaanus, 2008)**

<table>
<thead>
<tr>
<th>Ester linkage</th>
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<tbody>
<tr>
<td>Esters of benzoic acid – cocaine</td>
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<tr>
<td>Esters of meta-aminobenzoic acid – proparacaine</td>
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<tr>
<td>Esters of para-aminobenzoic acid – tetracaine, benoxinate, procaine, chloroprocaine</td>
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<tr>
<td>Amide linkage (amides of benzoic acid)</td>
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<tr>
<td>Lidocaine</td>
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<td>Mepivacaine</td>
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<td>Bupivacaine</td>
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<td>Etidocaine</td>
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The first step of LA activity involves diffusion across the nerve cell membrane, which is dependent upon the hydrophobicity of the aromatic ring and the ionization status of the terminal amine. Greater hydrophobicity and the existence of the amine portion in the unionized state favor membrane penetration. As LAs are weak bases, they easily ionized in acidic environments (i.e., inflamed tissue, which has a lower pH) and are unionized in basic environments (i.e., tears, which are neutral or alkaline). Following penetration, the amine ionizes to the ammonium cation, which is the active form that binds portions of the transmembrane voltage-gated Na⁺ channel. This binding inhibits movement of Na⁺ that is necessary for membrane depolarization, thus blocking impulse conduction.

The duration of action is determined by the time of contact between the LA and the receptor, which in turn varies with the chemical structure (as outlined above), the concentration, and the rate of removal by diffusion and circulation. Injectable LAs are heavily influenced by removal due to diffusion and/or circulation, providing justification for the addition of epinephrine, a potent vasoconstrictor. Vasoconstriction will decrease systemic absorption, and thus toxicity, also increasing the duration of action of LA, which is only pertinent with short-acting LA (i.e., lidocaine). Use of epinephrine may decrease circulation sufficiently to produce local tissue necrosis and delay wound healing, however. Regarding topical ocular anesthetics, a maximum effective
concentration exists for each agent, above which no further increase in activity is gained with increasing concentration, and the potential for local and/or systemic toxicity increases.

**Topical anesthetics**

The efficacy of topical anesthetics is largely dependent upon their chemical structure (as outlined above), and their concentration. Dose-response relationships identify a **maximum effective concentration** for each individual agent, which is the concentration above which further increases in concentration have no additional effect and also increase risk of local or systemic toxicity. The **optimum effective concentration** clinically may in fact be less than the maximum effective concentration, as it may be one that produces less irritation or local toxicity. The combined use of different topical anesthetics produces no additive effect, considering their identical mechanism of action.

Topical anesthetics are known to deleteriously affect the epithelial surface and to inhibit healing of existing wounds. Superficial punctate keratitis may occur following single instillation, either in association with a local allergic reaction or due to tear film instability, decreased tearing, and decreased blinking. More severe reactions may also occur after a single instillation, consisting of diffuse necrotizing epithelial keratitis with corneal edema and pain. If such a reaction occurs, an alternate topical anesthetic should be used on subsequent visits. Long-term administration will result in inhibition of cellular migration and mitosis and alterations in cellular metabolism, which may lead to ineffective or prolonged healing of wounds and may propagate infection. For these reasons, topical anesthetics should never be administered therapeutically.2-5

Systemic side effects of topical anesthetics rarely occur, but may involve the central nervous system, the cardiovascular system, or the respiratory system. CNS involvement may produce nervousness, tremors, convulsions, CNS depression, or loss of consciousness. Hypertension, tachycardia, or arrhythmias may occur, followed by subsequent hypotension and decreased perfusion. These side effects are more likely to occur if 1) too large of a dose was administered; 2) the drug was unusually rapidly absorbed across the conjunctiva (i.e., patient with conjunctival hyperemia); 3) drug detoxification is unusually slow; or 4) drug elimination is unusually slow. Metabolism of amide forms by the liver or ester forms by plasma esterases is frequently rapid and enables supportive care to be effective in management of such patients.

Contraindications to the use of topical anesthetics include a known hypersensitivity, liver disease, patients on anticholinesterases (esterases are necessary for metabolism of ester-containing topical LA), perforating ocular injury (damage to the endothelium, particularly with the preservative benzalkonium chloride), and when collecting ocular surface cultures (proparacaine, particularly without preservative in single-dose containers, causes less inhibition of microorganism growth).6,7

**Proparacaine 0.5%**

Proparacaine (proxymetacaine outside of the US) is commercially available both with and without sodium fluorescein 0.25%. The onset, intensity, and duration of action are similar to that of tetracaine 0.5% and benoxinate 0.4%. Discomfort on administration is less than that of tetracaine, and the occurrence of allergic reactions is also less. Unopened bottles may be stored at room temperature, however they should be refrigerated when opened, and discarded if discoloration develops. The efficacy of 0.5% proparacaine stored at room temperature or refrigerated was compared by performing Cochet-Bonnet aesthesiometry once weekly on clinically normal dogs.8 Throughout the study period, animals receiving proparacaine from the bottle stored at room temperature had higher mean corneal sensitivity (indicative of decreased efficacy of proparacaine), with the difference becoming significant at the week three measurement, suggesting that proparacaine is efficacious when stored at room temperature for no more than two weeks.

**Tetracaine 0.5% or 1%**

Tetracaine 0.5% produces topical anesthetic effects to the cornea and conjunctiva within 10-20 seconds and lasts 10 to 20 minutes in people, while the duration achieved with tetracaine 1% can be as long as 1 hour. It does not appear to provide effective scleral anesthesia however. Topical ocular side effects include ultrastructural epithelial cell membrane damage, loss of microvilli, and desquamation of superficial epithelial cells, as well as a moderate stinging or burning sensation following application. Topical allergies have also been reported with repeated use. It is potentially lethal in people at doses of 1.5 mg/kg of body weight (i.e., 10 ml of 1% solution to a 70 kg person). Tetracaine also produced greater inhibition of bacterial growth in samples obtained for corneal culture than did proparacaine.
**Benoxinate 0.4%**

Benoxinate (oxybuprocaine) 0.4% is only available in combination with vital dyes, either sodium fluorescein 0.25% or disodium fluorexon 0.35% (a high-molecular-weight fluorescein that does not stain hydrogel contact lenses, allowing contacts to be worn sooner following administration). It has a similar onset, intensity, and duration of action to that of tetracaine 0.5% and proparacaine 0.5%. In normal dogs, complete corneal anesthesia was achieved within 1 minute, with an average duration of maximal effect of 31 minutes.11 No significant difference was present between the oxybuprocaine or tetracaine in normal dogs.11 In normal European shorthair cats, oxybuprocaine 0.4% led to complete corneal anesthesia for 5 minutes, with mean duration of maximal effect of 21 minutes.10

**Injectable anesthetics**

As with topical LA, the duration of anesthetic effect is determined by the duration of binding between the drug and the target, which in turn is determined by the chemical structure of the drug, the concentration, the dose, and the rate of removal by diffusion and circulation. Epinephrine may be added at a concentration of 1:50,000 to 1:200,000, however risks to be aware of include local tissue necrosis and delayed wound healing due to intense vasoconstriction. Increasing the local pH by the addition of sodium bicarbonate increases the membrane-penetrating ability of LAs, potentially shortening onset time. The potential for systemic side effects associated with LAs emphasizes the need to ensure that total body doses are considered during administration of regional anesthesia.

Injection of LAs regionally may achieve eyelid akinesia (auriculopalpebral nerve block), analgesia (regional injection, frontal nerve block), or globe analgesia and akinesia (retrobulbar nerve block). Lidocaine and bupivicaine are most commonly used in veterinary ophthalmology, with a combination of the two containing the added advantage of rapid onset (lidocaine) with long duration of action (bupivicaine).

In dogs undergoing enucleation, most for painful ocular disease, pre-operative retrobulbar administration of bupivicaine (versus saline control) via an inferior temporal approach resulted in significantly fewer patients requiring administration of hydromorphine as post-operative rescue analgesia (2 of 11 dogs receiving bupivicaine, versus 9 of 11 dogs receiving saline control).11 Retrobulbar injection of bupivicaine via the ITP approach was no more effective than intra-operative splash block at managing pain or eliminating the need for rescue analgesia in dogs undergoing enucleation.12

A study evaluating the analgesic effect of systemic lidocaine infusion (1 mg/kg bolus followed by 0.025 mg/kg/min infusion) in dogs undergoing intraocular surgery found a comparable effect to that of intraoperative morphine, both of which resulted in fewer dogs requiring post-operative ‘rescue’ analgesia than did a saline control.13 Lidocaine serum levels were consistently below toxic levels and no dogs experienced adverse systemic side effects, however additional studies are necessary.

**Intracameral injection**

Intracameral anesthetic injection, generally utilizing lidocaine 1%, is employed primarily during cataract surgery to provide adjunctive pain control. Evaluations in humans have indicated that use of preservative-free lidocaine does not have toxic effects on the endothelium (versus potential toxicity associated with preservative-free 0.5% bupivicaine).14,15

**References**