CASE REPORT

Toxic epitheliopathy from a single application of preservative free oxybuprocaine (0.4%) in a patient with Sjogren's syndrome

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SUMMARY

Topical ocular anaesthetic agents are frequently used for ophthalmic diagnosis and surgery. While corneal complications following long-term use or misuse of local anaesthetic solutions have been described, toxic epitheliopathy after a single application of six drops of preservative free oxybuprocaine is rare. In order to increase the awareness of this ocular complication, we report such a case in a patient with Sjogren's syndrome who presented for elective cataract surgery. We outline the mechanisms proposed to explain the ocular toxic effects of oxybuprocaine and discuss the management principles in preventing this complication in the context of Sjogren's syndrome.

BACKGROUND

Topical ocular anaesthetic agents are frequently used for ophthalmic diagnosis and surgery.¹ While topical anaesthesia agents are generally safe, ocular complications can arise from both short-term and long-term abuse and misuse causing significant ocular morbidity.² Severe toxic epitheliopathy has been reported after the short-term frequent use of local anaesthetic solutions³; however, epitheliopathy after a single application of oxybuprocaine is rare. We report a case of toxic epitheliopathy after application of six drops of preservative free oxybuprocaine (0.4%) in a patient with Sjogren's syndrome during routine cataract surgery. In this setting, even low concentration local anaesthetic solutions can result in keratopathy involving conjunctiva, corneal epithelium, stroma, endothelium and the anterior chamber.^{2 4-7} We outline the mechanisms proposed to explain the ocular toxic effects of oxybuprocaine in this setting, and discuss the management principles in preventing this complication in the context of Sjogren's syndrome.

CASE PRESENTATION

A 69-year old female patient was admitted to a university teaching hospital for elective cataract surgery. She had a history of primary Sjogren's syndrome. There was no history of allergies. Medication included a non-steroidal anti-inflammatory agent and artificial tears and lubricants applied to both eyes daily. On arrival in the operating theatre, the patient was positioned at a 30°, and six drops of preservative free oxybuprocaine (0.4%) (0.5 mL unit dose) (Chauvin Pharmaceuticals, France) were administered into the eye for sensory anaesthesia (four drops on the cornea, and one each in the superior and inferior

conjunctival cul de sac). A peri-bulbar eye block was performed for surgical anaesthesia for the cataract extraction. A single inferotemporal injection using a transdermal approach was employed. The injection containing local anaesthetic 6–8 mL mixture containing 2% xylocaine and 0.5 marcaine in combination with 150 IU hyaluronidase was given at the junction of the lateral and medial two-thirds of the lateral orbital margin. Examination by the ophthalmologist prior to the cataract extraction identified a subepithelial peripheral ring infiltrate with conjunctival congestion over the superior and inferior nasal quadrants of the eye, attributed to the single application of the oxybuprocaine applied 10 min earlier. No further oxybuprocaine was applied.

TREATMENT

The patient was treated with topical dexamethasone (0.05%) without preservative, topical balanced salt solution eye drops and an eye patch. Over the course of the following week, the epithelial defect resolved, with resolution of the conjunctival congestion. No further treatment was required.

DISCUSSION

Sjogren's syndrome is a rare slowly progressive systemic autoimmune disease seen in 0.5–1.0% of population, characterised by xerostomia, keratoconjunctivitis sicca and B-lymphocytic hyperactivity.^{8 9} Ocular complications in patients with Sjogren's syndrome include corneal ulceration and scarring, bacterial keratitis, eyelid infections and blepharitis.¹⁰ To the best of our knowledge, this is the first case of toxic epitheliopathy in a patient with Sjogren's syndrome after the single application of topical preservative free oxybuprocaine (0.4%). This case emphasises that patients with Sjogren's syndrome are susceptible to ocular complications from low concentration local anaesthetic solutions.

Several possible mechanisms may explain the toxic effect of oxybuprocaine in this setting. Even a single application of topical local anaesthetic solution has been shown to cause punctate epithelial keratopathy.¹¹ Topical anaesthetic agents can interrupt the migration of epithelial cells, thereby delaying epithelial wound healing.¹¹⁻¹³ Factors like tear film instability, reflex tearing and a reduced blink rate combine to cause an increased rate of tear evaporation facilitating deterioration of the ocular surface.^{2 14} In the case described, the degree of corneal toxicity may have been exacerbated by corneal drying owing to the loss of corneal

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sensation resulting in diminished reflex tear production,^{14 15} which is a known complication of Sjogren's syndrome. Although only six drops of oxybuprocaine were applied in this case, persistent use of topical anaesthetic can result in the creation of epithelial defects.^{5 16} Epithelial defects allow greater access of the anaesthetic drug to the inner corneal layers, which can cause direct toxicity to the deeper tissues, thereby disrupting or delaying the healing process.^{5 16} Other topical anaesthetic agents such as tetracaine have also been shown to impair the oxidation of glucose and pyruvate by as much as 80%, thereby inhibiting oxygen uptake with accumulation of lactic acid.^{11 13} A second proposed mechanism in this case could be antibody mediated type 2 hypersensitivity reaction owing to the rapid development of epitheliopathy after application of the topical anaesthetic. The topical anaesthetic could have caused exposure of auto-antigens to the ocular surface, stimulating an antigen-antibody immunological response, which is postulated to be responsible for destruction of corneal epithelium, stromal cellular and tissue destruction, leading to corneal thinning or scarring as seen in infectious keratitis.^{2 5 14 16} Finally, while the oxybuprocaine solution used in this case was preservative free, preservatives such as benzalkonium chloride, chlorobutanol, benzoic acid, sodium benzoate and the hydroxybenzoates² found in other anaesthetic solution have been reported to be toxic to the corneal cells.^{5 16 17}

Proparacaine (proxymetacaine), tetracaine (amethocaine) and oxybuprocaine (benoxinate) are the three most commonly used topical anaesthetics.⁶ They have low cellular toxicity with no clinically significant difference in potency.⁶ Although minor corneal and conjunctival changes have been reported by their use, these reactions generally have very little clinical significance.¹⁸ Most serious deleterious effects of topical anaesthetics have been linked with chronic misuse, including their detrimental effect on the regeneration of damaged epithelium.¹⁸ Electron microscopic studies on rat and rabbit corneas have demonstrated that corneal changes can occur following normal usage of anaesthetics, even with a single application of topical anaesthetic.¹⁹ Brewitt *et al*²⁰ reported morphological changes in rabbit corneal epithelial cells after a single application of ointment formulations of proxymetacaine (0.5%) and oxybuprocaine (0.2%). Wilson *et al*²¹ showed a significant increase in epithelial cell sloughing for 6 hours after a single application of proxymetacaine (0.5%). Augsburg *et al*²² have shown that amethocaine (0.5%) can depress normal oxygen flux in rabbits by 20%, while the effect of oxybuprocaine (0.4%) was minimal. Carney *et al*¹⁸ described the effect of topical anaesthesia on corneal epithelial fragility in humans. They reported a significant change in the corneal damage threshold 20 min after the instillation of two drops of amethocaine hydrochloride (1.0%) with no significant changes observed with benoxinate hydrochloride (0.4%).¹⁸ These findings along with animal model studies suggest that even a single dose of topical anaesthetic in some instances has the potential to cause epithelial damage. This is supported by the case described here, highlighting the need for extra caution in preventing corneal damage while performing cataract surgery in patients with dry eye syndrome.

More than half of all patients undergoing cataract surgery have been found to have significant dry eye disease based on objective testing.²³ As a result, aggressive management of dry eye syndrome is recommended in patients undergoing cataract surgery.²³ Preoperative care includes use of anti-inflammatory agents such as topical corticosteroids, cyclosporine, punctal occlusion and management of lid diseases, as inflammation plays a critical role in the pathogenesis of dry eye syndrome.²⁴⁻²⁸ Intraoperative care should focus on the prevention of ocular surface damage from

anaesthetics and more importantly from desiccation.²³ Frequent irrigation with salt solution or viscoelastics can prevent or minimise the desiccating stress to the ocular surface.²⁹ The risk of ocular toxicity increases with the amount topical anaesthesia solution used; therefore, it is important to minimise the number of drops used. In addition, the use of povodone-iodine topical antiseptic solutions (eg, betadine solution) applied to the conjunctival sac may also increase corneal epithelial toxicity. Therefore, we recommend that these additional conjunctival applications be avoided in this setting. Postoperatively we advocate that medications, including non steroidal anti-inflammatory drugs, that have been reported to cause corneal melts in patients with Sjogren's syndrome, be stopped or tapered when no longer required.^{23 30}

A multidisciplinary approach including patient education is necessary to reduce risk of complications in patients with Sjogren's syndrome undergoing ophthalmology procedures. Patients are advised to discontinue any medication that may cause dryness of eyes.^{31 32} On the day of the operation the patients should be allowed to bring their topical medications and instructed to continue their usual eye care and medication regime. An ocular lubricant should routinely be used prior to surgery as a preventive measure. Attention needs to be paid to ambient humidity as levels of humidity in operating rooms and postoperative units may be very low, thereby increasing the risk of dry eye complications including corneal abrasions.^{31 32} Postoperative use of humidifiers is helpful in bedrooms and other rooms in which patients spend time.^{31 32} Regular eye examination and follow-up is necessary to minimise and manage complications. These approaches have the potential to reduce the perioperative risk and help in improving patient outcomes.

Learning points

- ▶ Topical anaesthetics should be used cautiously in patients with dry eyes where the integrity of ocular surface may be compromised.
- ▶ Patients with Sjogren's syndrome are susceptible to local anaesthetic solutions toxicity.
- ▶ To reduce the risk of ocular local anaesthetic toxicity, minimise the number of drops used and avoid povodone-iodine topical antiseptic solutions that can further increase corneal epithelial toxicity risk.
- ▶ Attention should be paid to environmental factors such as humidity levels in the operating and recovery rooms when patients with Sjogren's syndrome are undergoing ophthalmic procedures.
- ▶ Regular eye examination and follow-up is necessary to minimise and manage ocular complications in patients with Sjogren's syndrome.

Contributors LW was the principle anaesthetist involved in the case. LW and HA assisted with the literature review and the writing of the manuscript. NS was the principle ophthalmic surgeon responsible for managing the complication. She assisted with the writing of the manuscript.

Competing interests None.

Patient consent Obtained.

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