



# Topical Anesthetic Abuse Keratopathy and its Clinical Progression

## Topikal Anestetik Alışkanlığı Keratopatisi ve Klinik Progresyonu

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### Summary

To report a case series with topical anesthetic abuse and to define the clinical progression of the disease. Six eyes of three topical anesthetic abuser patients with various corneal abnormalities are reviewed. Signs of the disease are presented in order to document the natural progression of the disease. A report was filed to the General Directorate of Pharmaceuticals and Pharmacy, Ministry of Health, Ankara, Turkey describing the outcome of uncontrolled use of topical anesthetic. Topical anesthetic abuse can result in serious corneal complications such as corneal epithelium defect, ring keratitis, stromal infiltrate, hypopyon, superficial and deep corneal vascularization, corneal lysis, and at last spontaneous perforation. The General Directorate of Pharmaceuticals and Pharmacy issued that topical anesthetics can only be prescribed by an ophthalmologist up to four boxes a month, the prescription must be kept for one, year and criminal action will be taken against pharmacies disregarding these provisions. (Turk J Ophthalmol 2013; 43: 289-93)

**Key Words:** Topical anesthetic abuse, proparacaine, keratopathy

### Özet

Topikal anestetik alışkanlığı olan bir vaka serisini bildirmek ve hastalığın klinik progresyonunu tanımlamak. Anestetik kullanma alışkanlığı ve çeşitli kornea bozukluğu olan 3 hastanın 6 gözü gözden geçirildi. Hastalığın doğal gidişini belgelemek için hastalığın belirtileri sırayla anlatıldı. Sağlık Bakanlığı ilaç ve eczaneler genel direktörüne kontrolsüz topikal anestetik kullanma alışkanlığının sonuçlarını tanımlayan bir rapor gönderildi. Topikal anestetik alışkanlığı korneal epitel defekti, ring keratit, stromal infiltrat, hipopiyon, yüzeysel ve derin korneal vaskülarizasyon, korneal erime ve son olarak spontan perforasyon gibi çeşitli kornea komplikasyonlarıyla sonuçlanabilir. İlaç ve eczaneler genel direktörü topikal anestetik sadece bir oftalmolog tarafından ayda dört kutuya kadar reçete edilebileceğini, reçetenin bir yıl boyunca saklanması gerektiğini ve bu koşullara uymayan eczanelere karşı yasal düzenleme uygulanacağını yayınladı. (Turk J Ophthalmol 2013; 43: 289-93)

**Anahtar Kelimeler:** Topikal anestetik alışkanlığı, proparakain, keratopati

### Introduction

Topical anesthetics are routinely used for diagnosis and surgery in ophthalmology. Its professional use has never been linked to serious side effects. However, keratopathy associated with the toxicity of topical anesthetic abuse has been reported as a serious disorder where conjunctiva, corneal epithelium, stroma, endothelium, and anterior chamber may be involved.<sup>1-6,15</sup> Tetracaine, proparacaine, and oxybuprocaine have all been reported as abused topical anesthetic agents. We present a case

series of three patients who presented at various stages of topical anesthetic abuse from which we attempted to classify the stages for the natural progression of the disease retrospectively. All cases were males, had both eyes affected, and working as welders.

### Case 1

A 42-year-old patient was referred from the emergency department with decreased vision and pain in both eyes in December 2006. He was using proparacaine 0.5% (Alcaine;

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Alcon, Puurs, Belgium) drops to alleviate the pain for the last six months and increased the dosage to three bottles per day for the last twenty days.

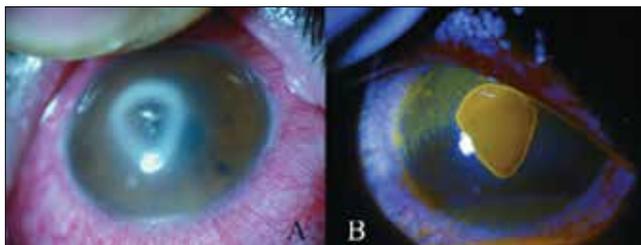
Visual acuity in the right eye was perception and projection, and in the left eye was hand motion. On biomicroscopic examination, both conjunctivae were injected. The right eye had complete absence of corneal epithelium, with white opaque and necrotic cornea, a 2.8mm hypopyon, iris and lens could not be visualized, and digitally normal tension. The left eye had a central 6mm corneal epithelial defect, white opaque corneal stroma, a 1.5mm hypopyon, normal iris, lens could not be observed, and digitally normal tension. Fundi could not be visualized.

Corneas were scraped for culture and smears but there was no growth. Topical rimexolone 1% q6h, cyclopentolate q8h, and ciprofloxacin 500mg q12 PO were prescribed with a bandage contact lens to the left eye.

During the third day of follow-up, left eye's epithelial defect decreased to 2mm and the height of the hypopyon was 1mm. While attempting to open the right eye's lids on the biomicroscope, the lytic cornea gave away 360° from its periphery, and the cornea completely detached and fell off resulting in a spontaneous corneal button perforation (Figure 1). The patient refused evisceration and was transferred to another hospital upon his request.



**Figure 1.** Spontaneous perforation of the right eye on third day of follow-up in Case #1



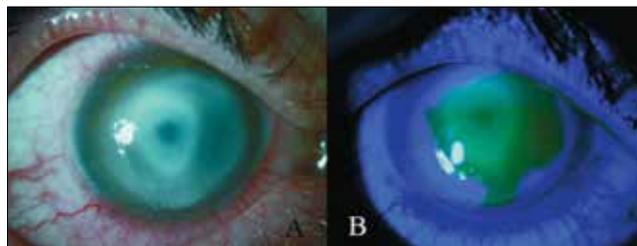
**Figure 2.** Ring-shaped stromal whitening that developed on day 5 of hospitalization (A) matched the shape and size of the corneal epithelial defect seen on the first day (B, fluorescein staining). (Right eye of Case # 2)

## Case 2

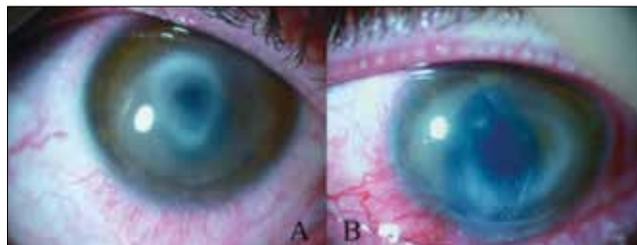
A 36-year-old patient was referred to our clinic with symptoms of mild itching for the last 2-3 months, and stinging and redness for the last five days.

Best-corrected visual acuity was 0.05 (Snellen decimal notation) in both eyes. On biomicroscopy, lids were edematous, conjunctivae were injected, both corneas had central epithelial defects with keratit striae. Anterior chamber, iris, and lens were within normal limits. Fundi were blurry and details could not be observed.

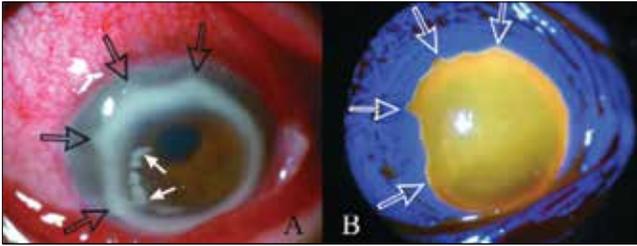
Proparacaine 0.5% (Alcaine; Alcon, Puurs, Belgium) use had been questioned but the patient denied using it. The patient was diagnosed as a probable adenoviral keratoconjunctivitis, was hospitalized, and prescribed topical autologous serum q6h, ofloxacin 0.3% q6h, and tape tarsoraphy. On day 5, both corneas developed ring-shaped stromal whitening, which was exactly matching the shape and size of the epithelial defect observed at the first examination (Figure 2), and hypopyon. Corneal cultures and smears were negative. On day 13, the patient's symptoms did not change and epithelial defect got worse. The patient had been referred to another university clinic. Five days after the referral of Case #2, Case #3 (see below) who was seen in the outpatient clinic had exactly the same symptoms and signs of Case #2 and was diagnosed as topical anesthetic abuse from the history. Thinking retrospectively, we had realized that Case #2 had been misdiagnosed. We had called Case #2 on day 54 and learned that the diagnosis made in the referred clinic was *Acanthamoeba* keratitis. When Case #2 was questioned again for topical anesthetic abuse, he admitted using it regularly. A second corneal white ring had developed peripheral to the first one concordant with the new borders of the widened epithelial defect (Figure 3) in both eyes. The left cornea had superficial



**Figure 3.** A new stromal whitening (A) corresponding to the new borders of the epithelial defect (B, fluorescein staining) is seen peripheral to the first one on day 56. (Right eye of Case #2)



**Figure 4.** On day 221, both corneas were clearer with deep neovascularization inferiorly and fixed vertically elongated pupilae (A, right eye; B, left eye; Case #2)



**Figure 5.** Corneal white-ring infiltrate matching the contour of the epithelial defect (A and B, compare the landmarks marked by empty black and white arrows. White fluffy keratic precipitates concentric with the corneal infiltrates (A, filled white arrows). (Right eye of Case #3)

neovascularization from 8:30 to 4:00 o'clock inferiorly reaching up to the outer corneal white ring.

Prednisolone 1mg/kg/day PO, diclofenac 75 mg/3ml IM q12h, ranitidine 50 mg/2ml IV q12h were prescribed, and bandage contact lenses were used. The corneal epithelial defects of the right and left eyes healed in 11 and 17 days, respectively. On day 112, both corneas developed inferior deep neovascularization up to where the outer corneal ring was. After 221 days of follow-up, epithelial defects did not recur, corneal white rings faded considerably, pupillae had a vertically dilated and fixed shape (Figure 4), best-corrected visual acuity on the right and left eyes increased to 0.3 and 0.4, respectively, oral prednisolone had been tapered to 8mg/day.

### Case 3

A 47-year-old patient with symptoms of redness, blurred vision, burning, and watering in both eyes who was on topical lodoxamide q12h, dexamethasone 0.1% q4h, and carboxymethylcellulose q4h had been referred to our clinic. His history revealed frequent use of proparacaine 0.5% (Alcaine; Alcon, Puurs, Belgium).

Best-corrected visual acuity was 0.3 and 0.05 (Snellen decimal notation) on the right and left eyes, respectively. On biomicroscopic examination, both eyes showed injected conjunctiva, corneal white ring infiltrates that matched the contours of corneal epithelial defects, white fluffy keratic precipitates, and normal appearing iris and lens (Figure 5). Fundi could not be evaluated.

Autologous serum q3h, ofloxacin 3% q6h, preservative-free dexamethasone q4h were started and tapered gradually for 20 days. Bandage contact lenses were tried for a day, but the patient was intolerant. On day 20, there still were epithelial defects and white corneal rings, and superficial corneal neovascularization had started inferiorly. All topical drops were stopped on day 20, and a new set of medications consisting of prednisolone 1 mg/kg/day PO, diclofenac 75 mg/3ml IM q12h, lansoprazol 30 mg PO, and bandage contact lenses were started. On day 26, the epithelial defects completely healed except for a small line of fluorescein uptake seen at the junction of the closing epithelial defect. The patient was discharged from the hospital with best-corrected visual acuity

of 0.16 and 0.2 on the right and left eyes, respectively. He came back on day 37 with recurring central epithelial defects about 3.0-3.5mm in diameter, counting fingers from 1 meter in both eyes, and denying any use of topical anesthetic. Same medications were started, and on day 54, the epithelial defects healed. The patient was discharged on day 64 with best-corrected visual acuity of 0.6 in both eyes, and prednisolone 8mg PO. At the last follow-up on day 210, best-corrected visual acuities on the right and left eyes were 0.5 and 0.6, respectively, and there was a slight white haze in the corneal stroma corresponding to the area of original epithelial defect and deep corneal neovascularization extending to the border of the corneal haze inferiorly.

### Discussion

We herein present three consecutive topical anesthetic abuse cases at various stages of the disease progression. The late diagnosis of the second case had given us the opportunity to view a significant part of the natural history of the disease. Combining this information with the first and third cases had enabled us to stage the progression of the disease process. To our knowledge, this is the first attempt to stage the natural history of topical anesthetic abuse given below:

**Stage I:** Punctate epithelial defects enlarging and forming a full central epithelial defect. Severe conjunctival injection is present at all stages. Eyelids and surrounding skin can be edematous and erythematous.

**Stage II:** Formation of a white opaque corneal infiltrate that forms a ring shape exactly matching the edge of the epithelial defect. Cornea central to the infiltrate is relatively transparent. If the epithelial defect and infiltrate is confined to the central cornea, inadequate treatment at this stage leads to widening of the epithelial defect up to corneal periphery with the formation of a second white opaque corneal infiltrate corresponding to the borders of the new epithelial defect. Cornea between the rings is hazy but not as opaque as the ring itself. White fluffy keratic precipitates and hypopyon can be seen at this stage.

**Stage III:** Superficial and then deep corneal neovascularization develops up to the peripheral edge of ring starting inferiorly and probably working its way up circumferentially.

**Stage IV:** Faster and continuous lysis of the cornea at the edge of the epithelial defect and the corneal infiltrate by lytic enzymes brought by neovascularization leads to a spontaneous corneal button perforation.

Topical anesthetic abuse is an infrequent encounter. Hence, most ophthalmologists do not see and treat one until they are well into practice. Although its signs as non-healing epithelial defect and ring shaped white corneal infiltrate have been suggested to be included in the differential diagnosis of herpetic, Gram-negative bacterial, fungal, mycobacterial, and Acanthamoeba keratitis, we believe that the appearance of the ring-shaped white corneal infiltrate does not look like any other ophthalmic disease and is typical for uncomplicated topical anesthetic abuse.<sup>1</sup> Nevertheless, all cases should be scraped for

microbiological examination, but most cases are proven to be non-infectious although sometimes a causative agent of infection can be determined.<sup>2</sup>

The mainstay of treatment is prevention of anesthetic use. This can be successfully done with pain management. Intramuscular opiate analgesia and sedation, oral diclofenac, topical diclofenac, oral indomethacin, or as in our last two cases, intramuscular diclofenac can be used.<sup>1,3-5</sup> Choosing delivery routes other than topical for pain management might be a better approach. Topical diclofenac inhibits corneal epithelial migration at high doses but not at clinical doses; moreover, it can induce expression of matrix metalloproteinases in corneal tissue.<sup>6,7</sup> Its preservative, benzalkonium chloride, induces cell growth arrest and death in conjunctival epithelium, as well as cytotoxicity to corneal epithelial cells. Moreover, bandage contact lenses frequently used in these cases may behave as a reservoir for topically used medications accentuating their side effects.<sup>8,9</sup>

The injury caused by topical anesthetic can be due to direct/indirect effects.<sup>10</sup> The mechanism of toxic effects of topical anesthetics on ocular tissues is still uncertain. Three possible mechanisms have been proposed. First, because even a single dose of topical anesthetics may cause mild punctate epithelial keratopathy, the toxic effects of topical anesthetics on ocular tissues were suggested to be direct. Evidence showed that anesthetics interrupted the migration of corneal epithelial cells and delayed epithelial wound healing.<sup>11</sup> Disruption of epithelial motility complexes like vinculin and actin filaments is the main cause of this delayed healing process.<sup>11</sup> As a result, overdosing of topical anesthetics might result in the presence and/or persistence of the epithelial defects. The epithelial defects then, allow the topical anesthetics greater access to the inner corneal layers and may be directly toxic to these deeper tissues, thereby disrupting the healing process.

A second proposed mechanism was that breakdown of the epithelial cells by anesthetics releases antigens that provoke an antigen-antibody immunologic response that may be associated with the stromal ring-like or disciform infiltration. This immune reaction has been postulated to be responsible for the primary destruction of the corneal epithelium, stromal cellular injuries, and tissue destruction, thus resulting in cornea thinning or scarring.<sup>10</sup>

Third, it was suggested that the preservatives in eye drops were also toxic to the corneal cells and contributed to the toxicity of topical anesthetics.<sup>10</sup> The toxicity of preservatives in eye drops and precipitation of intraepithelial proteins are other factors that may contribute to corneal damage.<sup>12</sup>

Besides corneal toxicities, topical ocular anesthetic agents can compromise tear function by decreasing aqueous tear secretion, disturbing tear film stability, and decreasing blinking rate.<sup>10</sup> Numerous studies have revealed that there are deleterious corneal effects associated with benzalkonium chloride (BAC) that include destabilization of the tear film, death of corneal and conjunctival epithelial cells, morphological changes in the corneal epithelial cells, and reduction of the corneal epithelial barrier function.<sup>13</sup>

Corneal anesthesia and toxicity may predispose individuals to infections. Superinfections with *Candida* species have been reported to occur during topical anesthetic abuse.<sup>2</sup> Furthermore, as in our Case # 2, the signs and symptoms related to topical anesthetic abuse can masquerade as *Acanthamoeba* keratitis because of similarities such as disproportionate pain, use of bandage contact lenses, and corneal ring infiltration.<sup>10</sup> In fact, the differential diagnosis for ring infiltrate is quite broad, and includes herpes simplex keratitis, gram-negative bacterial keratitis, fungal keratitis, and mycobacterial keratitis, but as we mentioned before, we believe that the appearance of ring-shaped white corneal infiltrate does not look like any other ophthalmic disease and is typical for uncomplicated topical anesthetic abuse.

Persistent epithelial defects can give an opportunity for superimposed infection which can interfere with diagnosis and increase the difficulty of treating toxic keratitis. Smears and cultures of *Acanthamoeba* and other pathogens should be obtained to rule out any possible superinfection. Delayed diagnosis of toxic anesthetic keratitis can result in corneal perforation and severe loss of vision.

Topical anesthetic agents are frequently applied in ophthalmic practice. Proparacaine 0.5% is the one most commonly used and was reported to reduce bacteria in the conjunctival flora when used before medical and surgical procedures.<sup>14</sup> This may be the reason why secondary bacterial infection is not encountered often in topical anesthetic abuse in our cases.

History taking, giving emphasis to patient's occupation, is crucial in arriving to the correct diagnosis. The ophthalmologist must also be familiar with the corneal signs of the disease. Otherwise, incorrect diagnosis, as in our Case #2, results in loss of valuable time. Topical anesthetic abusers mostly have psychiatric problems, so while managing the disease psychiatric consultation should also be kept in mind.

All three cases were put together in a report and sent to the General Directorate of Pharmaceuticals and Pharmacy, Ministry of Health, Ankara, Turkey. We learned that similar reports were also sent by other ophthalmologists nationwide. As a result, it was concluded that proparacaine ophthalmic solution should only be prescribed by ophthalmologists, the pharmacy selling the product should keep a copy of the stamped prescription for a period of one year, and that maximum four boxes per month in the form of prescription can be sold providing that the doctor is an ophthalmologist with documented submit. A letter regarding the subject was sent to the Turkish Pharmacists Association stating that criminal action will be taken against the pharmacies who sell the relevant drug disregarding these provisions.

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