Ocular surface problems following topical medication

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Oberflächenprobleme nach lokaler Medikamentenapplikation

Zusammenfassung

Hintergrund: Oberflächenprobleme nach lokaler Medikamentenapplikation verursachen eine erhebliche okuläre Morbidität. Toxische und allergische Reaktionen sind die zweithäufigste Erkrankung des äußeren Auges. Die klinischen Begleitumstände, die zu diesen Reaktionen führen, sind wenig bekannt. Diese Studie untersucht die Faktoren, die gebräuchliche Lokalmedikationen zu potenten toxischen Substanzen werden lassen. **Patienten und Methode:** 168 Patienten, die von niedergelassenen Ophthalmologen zur weiteren Abklärung einer äußeren Augenerkrankung zugewiesen worden waren, wurden untersucht. Die klinischen Begleitumstände und Effekte der Lokalmedikation wurden mit einem modifizierten Protokoll nach Wilson (1983) erfasst und analysiert. **Resultate:** Mindestens 39 von 168 (24%) Patienten hatten Oberflächenprobleme, die im Zusammenhang mit der Lokaltherapie standen. Die folgenden Faktoren wurden für die Entwicklung klinischer Nebenwirkungen als relevant identifiziert: kompromittierte Augenoberfläche bei 17 Patienten (43%), Langzeittherapie bei 8 (21%), intensivierte Behandlung bei 8 (21%), neu aufgetretene akute Begleiterkrankung bei 4 (10%), und eine additive Medikamententoxizität (> 3 Therapeutika) bei 2 Patienten (5%). Die „toxische papilläre Keratokonjunktivitis" war die häufigste Oberflächenreaktion (n = 31; 80%) und trat bei 13 Patienten mit Epitheldefekten auf, bei 2 in Verbindung mit einer Keratinisierung der Konjunktiva und bei einem Patienten mit konjunktivaler Vernarbung und Fornixverkürzung. Die Aminoglykosidantibiotika wurden als häufigste Noxe identifiziert. **Schlussfolgerung:** Toxische Oberflächenreaktionen sind wesentlich häufiger als allergische Phänomene. Besonders häufig treten sie bei Augen mit kompromittierter Oberfläche auf sowie bei lange dauernder oder intensivierter Verabreichung.

Abstract

Background: Adverse effects following topical medication account for a significant ocular morbidity. Toxic and allergic reactions are second in frequency among all external eye diseases (after keratokonjunctivitis sicca). Knowledge on the clinical background that predisposes to such reactions is scarce. This study aims to identify the factors that render commonly used topical medications to powerful ocular irritants. **Patients and methods:** 168 consecutive tertiary referrals with external eye disease problems were studied. The adverse effects on the ocular surface were analysed using a modified Wilson's classification (1983). **Results:** At least 39 out of 168 (24%) patients had problems related to topical medication. Factors that predisposed to adverse reactions included a compromised ocular surface in 17 patients (43%), long-term drug exposure in 8 (21%), intensified treatment in 8 (21%), concomitant acute disorders in 4 (10%), and additive drug toxicity (> 3 medications) in 2 patients (5%). Toxic papillary keratokonjunctivitis was the most common adverse reaction (n = 31; 80%) and was associated in 13 patients with epithelial defects, in 2 with keratinisation of the ocular surface and in one with conjunctival scarring. Aminoglycoside antibiotics were the drugs that were most frequently involved in adverse ocular surface reactions. **Conclusion:** Toxic reactions are far more common than allergic ones. They are frequent in eyes with compromised surface, and after long-term or intensified therapy.

Key words

Adverse effects · medical therapy · ocular surface · cornea · conjunctiva

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Schlüsselwörter
Medikamentöse Therapie · Nebenwirkungen · Kornea · Konjunktiva

Introduction

Adverse effects following topical medication account for a significant ocular morbidity [1–7]. Toxic and allergic reactions are second in frequency among all external eye diseases (after keratokonjunctivitis sicca) [1]. Knowledge on the clinical background that predisposes to such reactions is scarce. This study aims to identify the factors that render commonly used topical medications to powerful ocular irritants.

Patients and Methods

168 consecutive tertiary referrals with external eye disease problems were prospectively studied over a period of 18 months. All patients underwent a thorough clinical evaluation using a standardised protocol. This included a meticulous examination of the entire ocular surface (lids, tear film, conjunctiva and cornea with epithelial surface), the assessment of staining patterns (rose bengal and/or fluorescein), the assessment of concomitant external eye diseases, the investigation of the clinical background (compromised ocular surface, long-term treatment, intensified treatment, concomitant acute disorders, additive drug toxicity) and drug history (aminoglycosides, contact lens disinfection, latanoprost, antivirals). After completing the form, the condition of the ocular surface was either classified as drug-related or non-related change. This distinction was based largely on the author's expertise in the assessment of external eye diseases. The condition was only classified as drug-related if there was strong evidence to support this mechanism. Doubtful cases were not included in this study. The adverse effects on the ocular surface were analysed using a modified Wilson's classification (Table **1**) and reference [2].

Results

At least 39 out of 168 (24%) patients had problems related to topical medication. Factors that disposed to adverse reactions are listed in Table **2**. They included a compromised ocular surface in 17 patients (43%), long-term drug exposure in 8 (21%), intensified treatment in 8 (21%), concomitant acute disorders in 4 (10%), and additive drug toxicity (> 3 medications) in 2 patients (5%). Toxic papillary keratokonjunctivitis was the most common adverse reaction (n = 31; 80%) and was associated in 13 patients with epithelial defects, in 2 with keratinisation of the ocular surface and in one with conjunctival scarring (Table **3**) (Fig. **1**). Aminoglycoside antibiotics were the drugs that were most frequently involved in adverse ocular surface reactions (Table **4**).

Discussion

Topical medication may be followed by a spectrum of adverse effects ranging from subclincal epithelial changes to chronic pro-

Table **1** Classification of topical adverse effects

1. Toxic papillary keratoconjunctivitis
2. Toxic keratoconjunctivitis with keratinization
3. Toxic keratoconjunctivitis with scarring
4. Toxic follicular keratoconjunctivitis
5. Allergic contact (dermato) conjunctivitis
6. Anaphylactoid conjunctivitis
7. Immune-mediated conjunctival scarring (pseudopemphigoid)
8. Anesthetic toxicity
9. Deposits

Table **2** Predisposing factors in the development of ocular surface problems following topical medication (analysis of 39 tertiary referrals)

Compromised ocular surface		n = 17 (43%)
Atopy/Severe Meibomitis/KCS	(8)	
Cicatricial pemphigoid/SJ-Syndrome	(7)	
Metaherpetic changes	(2)	
Long-term treatment/Exposure		n = 8 (21%)
CL-associated	(6)	
Antiglaucomatous drugs	(2)	
Intensified treatment		n = 8 (21%)
Aminoglycosides after corneal ulceration	(6)	
Preserved artificial tears	(2)	
Concomitant acute disorders		n = 4 (10%)
Adenovirus	(3)	
Bacterial conjunctivitis	(1)	
Additive drug toxicity (> 3 medications)		n = 2 (5%)

Table **3** Classification of 39 tertiary referrals with ocular surface changes following topical medication

Toxic papillary keratoconjunctivitis		n = 31 (80%)
With persistent epithelial defects	(13)	
With keratinization	(2)	
With conjunctival scarring	(1)	
Toxic follicular keratoconjunctivitis		n = 1 (2.5%)
Allergic contact (dermato) conjunctivitis		n = 3 (7.5%)
Immune-mediated conjunctival scarring (pseudopemphigoid)		n = 1 (2.5%)

Table **4** List of drugs involved in the development of ocular surface problems following topical medication (analysis of 39 tertiary referrals)

Aminoglycosides		n = 21 (54%)
Antiglaucomatous drugs		n = 7 (18%)
– Latanoprost	(4)	
– Dipivefrine	(1)	
Antiviral medications		n = 3 (7.5%)
Lubricants		n = 8 (21%)
Contact lens disinfection		n = 4 (10%)

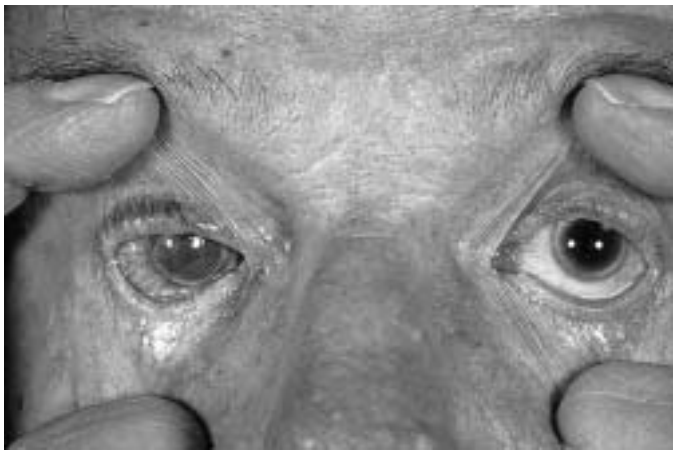

Fig. **1** Severe toxic keratoconjunctivitis with scarring in a 67-year-old patient. The diagnosis of herpes simplex keratitis was followed by many years of topical antiviral therapy (various combinations). Note the abnormal conjunctiva in the right eye, being inflamed and showing evidence of cicatrization.

Table **5** Therapeutic options for adverse effects following topical medication

Withdrawal of the drug that causes the reaction!
Preservative-free lubricants
Steroids in *allergic* reactions (preservative-free)
Epithelial defects: patching, soft contact lens
Symptomatic and antiinflammatory treatment (immunosupression) in immune-mediated conjunctival scarring

Table **6** Prevention of adverse effects following topical medication

Accurate diagnosis! (Lack of diagnosis leads to *overtreatment syndrome* when the adverse effects are misinterpreted as failure of therapy)
Knowledge of potential toxicities
Abandon the idea that most drug reactions are allergies and not toxicities (misconception that a change in therapy will solve the problem !)
Selection of the least toxic drug
Monotherapy when possible
Unpreserved formula
Contact lenses:
Disinfection using unpreserved peroxide systems or heat rather than chemical disinfection Disposable soft lenses (daily wear)

gressive conjunctival cicatrisation with corneal blindness. Although severe adverse effects have become infrequent, the ocular morbidity due to topical therapy is still considerable.

In this series of 168 external eye disease patients at least 23 % had drug related problems. Toxic reactions were far more common than allergic ones. They were particularly frequent in eyes with compromised surface, and after long-term or intensified therapy.

Options for treatment and prevention of problems following topical medication are summarised in Tables **5** and **6**.

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