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Retrospective analysis of common primary disease of drug-induced keratoconjunctivitis

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关于引起药物源性角结膜炎常见原发疾病的回顾性分析

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摘要

目的:分析药物源性角结膜炎最常见的原发疾病。

方法:对确诊为药物源性角结膜炎的18例患者的病历资料进行回顾性分析,观察药物源性角结膜炎的原发疾病、用药种类、药物使用频率、临床特征、治疗方法、上皮愈合时间和患者的非矫正视力(UCVA)。使用SPSS 18.0统计学软件进行分析,以$P<0.05$为差异有统计学意义。

结果:药物源性角结膜炎的常见原发疾病包括青光眼(6例)、单纯疱疹病毒性角膜炎(6例,其中2例为白内障术后)、带状疱疹病毒性角膜炎(1例)、角膜异物剔除后角膜炎(1例)和无明确病因角膜炎/角膜溃疡(4例)。患者的用药种类为3.3±1.5种,用药频率是9±3.9次/d。16例患者出现角膜病变,而仅有3例患者出现结膜病变(其中1例患者同时出现角膜和结膜病变)。患者的治疗方案包括停用原有药物,局部使用不含防腐剂的人工泪液或自体血清,以及低剂量类固醇眼药水。在治疗周期7±2.8d后,患者症状开始缓解。患者上皮愈合周期是21±8.8d。治疗前后患者的UCVA分别是0.15±0.13和0.43±0.27($P=0.003$)。

结论:病毒性角膜炎和青光眼是药物源性角结膜炎的最常见原发疾病。

关键词:角结膜炎; 药物毒性; 原发疾病; 青光眼;病毒性角膜炎

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Abstract

• AIM: To find out the most common primary diseases of drug-induced keratoconjunctivitis.

• METHODS: The clinical records of 18 patients with a confirmed diagnosis of drug-induced keratoconjunctivitis were retrospectively reviewed. Primary diseases, categories of induced-drugs, numbers of daily drops, characteristics of keratoconjunctivitis, treatment, epithelization period, and un-corrected visual acuity (UCVA) were studied. Data were analyzed by SPSS 18.0. $P<0.05$ were considered statistically significant.

• RESULTS: Primary diseases included glaucoma ($n=6$), herpes simplex keratitis ($n=6$; two patients were post-surgery of cataract), herpes zoster keratitis ($n=1$), keratitis after corneal foreign body taken ($n=1$) and keratitis/corneal ulcer with unknown etiology ($n=4$). Mean number of drugs was 3.3±1.5 and the frequency was 9±3.9 times a day. Keratopathy was found in 16 cases, while conjunctival changes were found only in 3 cases (One patient got corneal and conjunctival changes simultaneously). Withdrawing the drugs, preservative-free lubricants or autologous serum, and topical low dose steroid drops were used for treatment. After a mean period of 7±2.8d, symptoms began to relieve. The mean epithelization period was 21±8.8d. Mean pretreatment and post-treatment UCVA was 0.15±0.13 and 0.43±0.27, respectively ($P=0.003$).

• CONCLUSION: Viral keratitis and glaucoma are the most often events of drug-induced keratoconjunctivitis.

• KEYWORDS: keratoconjunctivitis; drug toxicity; primary disease; glaucoma; herpes simplex keratitis
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INTRODUCTION

With the development of medical research, more and more types of ocular topical drugs are available for ocular diseases treatment, which provide ophthalmologists more choices in clinical practice. But the toxicity is always accompanied with the efficacy, especially the toxicity caused by iatrogenic and factitious factors, which may cause extra physical suffering and economic burden to patients. Cornea and conjunctiva often are influenced by the side effects of the topical drugs[1], which is the main approach for the treatment of the anterior segment of the eye. The toxicity of eye drops

Table 1 The number, frequency and duration of eye drops used in the study $\bar{x}\pm s$

Primary disease	n	Number of drugs	Frequency of eye drops (times a day)	Duration of primary treatment (mo)
Viral keratitis	7	3.7±1.7	11.0±3.8	4.3±2.9
Glaucoma	6	2.8±1.2	6.3±3.3	32.0±14.5
Unclear etiology	4	4.0±1.8	10.8±3.8	2.8±2.2
Corneal foreign body	1	3.0±0.0	10.0±0.0	1.0±0.0

may occur in patients with acute or chronic ocular disease as a result of both the short-term and, more often, the long-term use of topical medications[2-3]. The clinical signs of both cornea and conjunctiva of drug-induced keratoconjunctivitis are usually nonspecific, such as punctuate keratopathy and follicular and papillary conjunctivitis, which can be normally seen in any other ocular surface disorders[4]. Persistent epithelial defect, stromal edema, even hypopyon also can be seen in the serious cases of drug-induced keratoconjunctivitis.

This study was undertaken to discuss what kind of ocular diseases and related drugs would easily induce keratoconjunctivitis and to remind ophthalmologists to pay more attention to avoiding the drug-induced keratoconjunctivitis happening during the treatment of these diseases.

SUBJECTS AND METHODS

This study analyzed the common primary diseases and risk factors of drug-induced keratoconjunctivitis retrospectively. The records of a total of 18 patients with confirmed diagnosis of drug-induced keratoconjunctivitis were reviewed. Patients were referred to and examined by the ophthalmologists in the Department of Ophthalmology, Peking University First Hospital in 2011 and 2012. This study was approved by the institutional review board of Peking University First Hospital. The principles of the Declaration of Helsinki were followed and informed consent was obtained from each study subject. The inclusion criteria includes: 1) history of long-term and frequent use of ocular topical drugs; 2) prolonged course of keratoconjunctivitis; 3) significant efficacy when treated as drug-induced keratopathy; 4) negative findings of pathologic examination[5]. All the responses were unilateral. The primary diseases, categories of induced-drugs, numbers of daily drops, characteristics of keratoconjunctivitis, treatment, epithelization period and un-corrected visual acuity (UCVA) of patients were analyzed. Data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS, Inc, Chicago, Illinois, USA) for Windows. $P<0.05$ were considered statistically significant.

RESULTS

Primary diseases of 18 patients in our study included glaucoma ($n=6$; four patients had the antiglaucoma surgery), herpes simplex keratitis (HSK; $n=6$; two patients were post-surgery of cataract), herpes zoster keratitis ($n=1$), keratitis after corneal foreign body taken ($n=1$) and keratitis/corneal ulcer with unknown etiology ($n=4$). All the patients (male: female=1:1) with the mean age of 65±9y had the medical history of long-term and combined therapy. Eye drops had been frequently used, including antimicrobial agents, antiglaucoma drugs, corticosteroids and mydriatic drugs. Mean number of drugs was 3.3±1.5 and mean frequency was 9±3.9 times a day. Keratopathy just like superficial punctuate keratitis ($n=8$), persistent corneal epithelial defect ($n=6$; Figure 1), pseudodendritic keratitis ($n=5$; Figure 2), corneal stromal infiltration ($n=2$) and hypopyon ($n=4$) was found in 16 cases. Eight patients showed more than two types of keratopathy. Only 3 patients showed conjunctival follicles of which 1 patient had keratopathy simultaneously.

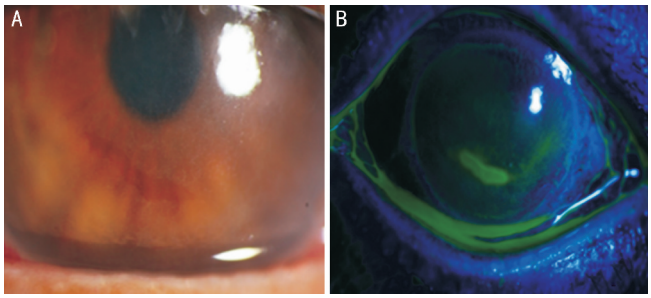

Figure 1 Persistent corneal epithelial defect A: Corneal epithelial defect with slit-lamp biomicroscop; B: Corneal epithelial defect with fluorescein sodium.

By analyzing the 7 patients of viral keratitis, we found that the mean number of drugs used before was 3.7±1.7, mean frequency was 11±3.8 times a day and mean duration of treatment as viral keratitis was 4.3±2.9mo. The same situation was also found in the glaucoma patients, the mean number of anti-glaucoma drugs used was 2.8±1.2, mean frequency was 6.3±3.3 times a day and duration was 32±14.5mo, significantly longer than any other disease in our study. In the 4 patients of keratitis/corneal ulcer with unknown etiology the mean number of drugs was 4±1.8, mean frequency was 10.8±3.8 times a day, and duration was 2.8±2.2mo (Table 1).

Withdrawing all the original drugs, preservative-free lubricants, autologous serum or cow serum were used for the treatment of keratoconjunctivitis. In severe cases, topical low dose steroid drops were added. After a mean period of 7±2.8d, symptoms of all the patients began to relieve. Mean epithelization period was 21±8.8d. Mean pretreatment and post-treatment UCVA was 0.15±0.13 and 0.43±0.27, respectively ($P=0.003$).

DISCUSSION

Drug-induced keratoconjunctivitis is a kerato-conjunctival disease caused by the application of systemic and topical drugs[5-6], which may manifest as conjunctival follicles, superficial punctuate keratitis, pseudodendritic keratitis,

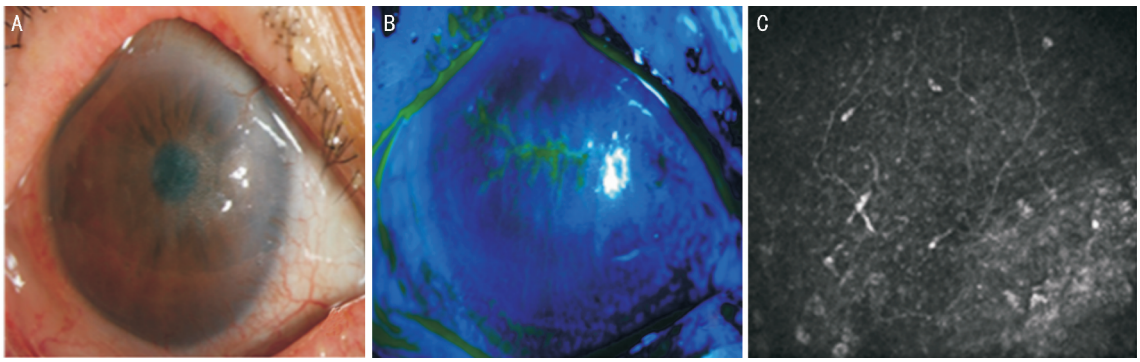

Figure 2 Pseudodendritic keratitis A: Pseudodendritic keratitis with slit-lamp biomicroscop; B: Pseudodendritic keratitis with fluorescein sodium; C: Pseudodendritic keratitis with confocal microscope.

corneal stromal infiltration and hypopyon. In this study, all of the cases were topical drug-induced keratoconjunctivitis. Drug-induced keratoconjunctivitis is mainly iatrogenic in nature, especially caused by abuse of topical drugs on the ocular surface. Wilson[2] found that 13% of the keratoconjunctivitis were iatrogenic or factitious, abuse of drugs and the direct damage of drug toxicity may contribute to it.

In this study, the 39% (7/18) of the patients diagnosed as drug-induced keratoconjunctivitis was viral keratitis, 33% (6/18) of the patients was glaucoma, and other 22% (4/18) patients was agnogenic keratitis/corneal ulcer. In another study conducted by Wilson[2] focusing on 134 patients diagnosed as drug-induced keratoconjuntivitis, 60% of the primary diseases of those patients were glaucoma, viral keratitis, corneal ulcer and dry eye disease, and the particular relevance was the number of medications used and the prolonged treatment period before diagnosis, which was consistent with our findings. Moreover, the sample size of our study is relatively small, which is the limitation inherent to this retrospective study.

Viral keratitis was one of the most common primary diseases of drug-induced keratoconjunctivitis with no doubt which was found in this study, not only the direct toxicity of the antiviral eye dropssuch as acyclovir but also the management of the treatment may contribute to it. *In vitro* and *vivo* studies, the toxicity was observed at the clinical concentrations of idoxuridine (0.1%), trifluridine (1.0%), and ethyldeoxyuridine (2.0%)[7-9], while punctuate keratitis and conjunctival follicles were commonly seen in patients who used antiviral agent. The direct damage of drugs played a part in the drug-induced keratoconjunctivitis. In addition to the toxicity of drug itself, the method of treatment also contributes to the occurrence of drug-induced keratoconjunctivitis. In China, there has not been any guidelines of the treatment of viral keratitis yet or an application standard of the numerous topical antiviral agents. Antiviral therapy, especially topical ganciclovir ophthalmic gel, is an effective way of the treatment for HSK. As reported, during the topical antiviral treatment by 5 times a day, the epithelium regeneration usually occurred in 2-5d, with complete resolution in 2wk[10-11]. Failure of epithelial healing after 2-3wk of antiviral therapy may demonstrate the epithelial toxicity. Looking back to the 7 cases of viral keratitis in this study, the high frequency and long term of therapy may contribute to the drug-induced keratoconjunctivitis, with the mean number of drugs of 3.7±1.7, mean frequency of 11±3.8 times a day, duration of 4.3±2.9mo. Antiviral toxicity may occur as soon as 10d after initiation of therapy, which is often the period when healing is occurring. The appearance of new fluorescein staining can give rise to considerable confusion. Ophthalmologists would easily mistake the onset of toxicity with the epithelial nonhealing for recrudescence of the infection, and then strengthen the topical antiviral therapy which increases the antiviral toxicity and epithelial damage. When there is doubt, cessation of topical antiviral therapy is often necessary.

In this study, 33% (6/18) of patients were glaucoma with or without anti-glaucoma surgery. Glaucoma had been another most common primary disease of drug-induced keratoconjunctivitis. First of all, long-term and combined therapy is the most important reason of drug-induced ocular surface impairment. Long-term use of anti-glaucoma eye drops such as brimonidine, tartrate and brinzolamide frequently can cause tear film and conjunctival involvement, sometimes result in sight-threatening ocular surface disorders. In these glaucoma patients, the mean number of anti-glaucoma drugs was 2.8±1.2, mean frequency was 6.3±3.3 times a day, duration was 32±14.5mo. Besides the fact of long duration and combined therapy of glaucoma, the safety of anti-glaucoma eye drops is noted, especially the preservatives in the eye drops, which plays an important role in the drug-induced keratoconjunctivitis in glaucoma patients. There have been many studies focused on the role of the preservatives in the anti-glaucoma eye drops on the ocular surface disease. In a recent study evaluating the toxicity of anti-glaucoma drugs using sreatified human cultivated corneal epithelial sheets, they found that a benzalkonium chloride (BAC) concentration of 0.001% or lower or non-BAC preservative sof Zia was suggested to be the least toxic to the ocular surface[12-13]. Another study also found that the cytotoxic effects of latanoprost, travoprost and bimatoprost were dependent on the BAC concentration in their formulations, and preservative-free tafluprost was the least toxic of the drugs tested in the study[14]. A prospective study of 4107 glaucoma patients found an increased incidence (>2 times) of discomfort such as burning-stinging, foreign body sensation, dry eye sensation and tearing in patients with preservative eye drops and the prevalence of signs and symptoms was dose dependent[15]. When replacing preservative eye drops used

before with preservative-free eye drops, the reduction in the signs was observed in patients. Moreover, the poor follow-up of patients with glaucoma could be another important reason of the occurrence of drug-induced ocular surface disease. In this study, some patients often adjusted the medication by themselves, even let relatives get the drugs for them, so their glaucoma doctors couldn't get the real condition and the intraocular pressure of the patients. Therefore, abiding the principle of treatment of glaucoma, educating patients the importance of regular follow-up, choosing the preservative-free eye drops as possible, adding drugs to protect cornea in specific patients can reduce the drug-induced keratoconjunctivitis in glaucoma patients.

Keratitis or corneal ulcer without confirmed etiology was another common primary disease of drug-induced keratoconjunctivitis, which was observed in this study. In clinical practice, the ophthalmologist often attempts to treat such keratitis or corneal ulcer with anti-bacterial, antiviral and antifungal eye drops together, with high dose, long term and more frequency in order to control the development of the disease as soon as possible. On the time of treating the disease, drug toxicity may happen during the therapy. We found that in 4 patients of keratitis/corneal ulcer with unknown etiology the mean number of drugs was 4±1.8, mean frequency was 10.8±3.8 times a day, duration was 2.8±2.2mo. We should consider the toxic keratopathy when the long-standing keratitis/corneal ulcer which was unresponsive to common antimicrobial treatment, and without any etiology findings[16]. In these situations, ophthalmologists can try to withdraw the previous administered drops and only maintain the preservative-free artificial tears with frequent follow-up.

The role of the preservatives in the drug-induced keratoconjunctivitis is often ignored in the clinical practice. All the eye drops used by the patients in this study contained preservatives, such as BAC and thimerosal which have been demonstrated corneal toxicity *in vitro* or *in vivo* researches by damaging the structure of corneal epithelial microvilli, inhibiting cell activity and delaying the corneal healing. *In vitro* study, it had been found that BAC can induce corneal epithelial cell growth arrest and death although at a concentration less than 0.01%, which was the most common level in ophthalmic topical solution[17]. Moreover, the preservatives also has been demonstrated to be related to allergic conjunctivitis and drug-associated pemphigoid[18].

Old-age is also a high riskfactor in the drug-induced keratoconjunctivitis. The mean age of patients in this study was 65±9y, 67% (12/18) of the patients were above 60y, in which age group people often have meibomian gland dysfunction (MGD). In Asia, over 60% of the population, particularly in the aged, are suffering from MGD which is responsible for dry eyes[19]. So the dilution effect of tears would decrease in these people, which may increase the ocular surface toxicity of preservatives.

It was interesting tofind that the incidence of keratopathy was higher than conjunctival changes, for there were 16 patients showed corneal damage comparing to that only 3 patients showed conjunctival follicles of which 1 patient had keratopathy simultaneously. The different structure of cornea and conjunctiva may contribute to the different incidences as the corneal epithelium has the tighter junction, smaller intercellular spaces and higher resistance to conjunctival epithelial which may cause the storage of eye drops and the accumulation of drug toxicity. In addition, conjunctiva has a rich supply of capillaries and lymphatics, drugs can be delivered into circulation system quickly which may reduce the drug's toxicity to conjunctiva[20].

Although viral keratitis and glaucoma are the most common diseases causing drug-induced keratoconjunctivitis, ophthalmologists should pay attention to the toxicity of eye drops used in any ocular disease, especially those need long term and combined therapy in the aged.

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