# ARCHIVES OF OPHTHALMOLOGY

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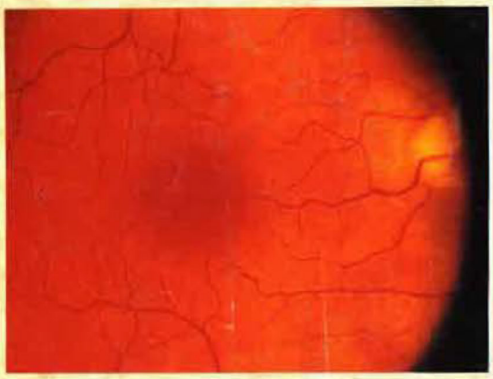



*Spontaneous resolution of a full-thickness macular hole. See page 130.*




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## CLINICAL SCIENCES




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# Acute and Chronic Conjunctivitis Due to Over-the-counter Ophthalmic Decongestants

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**Objective:** To describe patterns of conjunctivitis caused by ophthalmic decongestants.

**Design:** Case series.

**Setting:** Outpatient eye clinic.

**Patients:** We selected patients with conjunctival inflammation who were using nonprescription decongestant eyedrops, who had no other cause for conjunctivitis, and whose conditions improved after discontinuing the incriminated preparations.

**Main Outcome Measures:** Clinical characteristics of conjunctival inflammation and time to resolution of symptoms and signs after discontinuing the use of eyedrops.

**Results:** Seventy patients (137 eyes) were identified. Preparations containing the vasoconstrictors naphazoline, tetrahydrozoline, or phenylephrine were associated with 3 clinical patterns of conjunctivitis: conjunctival hyperemia (50 cases), follicular conjunctivitis (17 cases), and eczematoid blepharoconjunctivitis (3 cases). Decongestants were used daily for a median of 3 years (range, 8 hours to 20 years) prior to presentation. The median time to resolution of symptoms and signs was 4 weeks (range, 1-24 weeks), and patients remained asymptomatic for a median follow-up of 6 months (range, 0-12 years).

**Conclusion:** Nonprescription decongestant eyedrops can produce acute and chronic forms of conjunctivitis by pharmacological, toxic, and allergic mechanisms. Once recognized, conjunctival inflammation often takes several weeks to resolve.

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OVER-THE-COUNTER ophthalmic decongestants are commonly used to control ocular redness and discomfort.[1-11] The principal active ingredient in these eyedrops is an α-adrenergic, vasoconstrictive amine such as naphazoline, tetrahydrozoline, or phenylephrine; some preparations also contain an antihistamine for type 1 histamine-receptor blockade.

Adverse systemic reactions to topical vasoconstrictors are uncommon but include nervousness,[12] headache,[13-16] dizziness,[14] nausea,[14] hypotension,[17,18] hypertension,[13,14,16,19,20] and cardiac dysrhythmia.[14] The most frequent local side effect of ophthalmic vasoconstrictors is ocular stinging.[7,21,22] However, mydriasis,[5,7,23-25] blurred vision,[7,15] epithelial erosion,[21,26] punctal stenosis,[27,28] corneal epithelial pigment deposition,[29] iris pigment release,[22,23] iritis,[30] intraocular pressure change (ie, increase or decrease),[7,13,23,24,31,32] and acute angle closure[15,24,25] have also been described. Additionally, antihistamines may produce allergies and local irritations.[33,34]

Our experience indicates that decongestant eyedrops containing vasoconstrictors, with or without antihistamines, are causes of acute and chronic conjunctival inflammation.

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## RESULTS

Seventy patients with ophthalmic decongestant–related conjunctivitis were identified (50 from the external disease clinic and 20 from the general clinics) (**Table 1**). The mean age at presentation was 42.5±15.9 years (range, 18-82 years). The frequency of daily eyedrop application ranged from 1 to 12 times (mean, 3.7±2.2 times per day). The duration of medication use prior to presentation averaged

*See Patients and Methods on next page*

## PATIENTS AND METHODS

Adverse reactions to ophthalmic decongestants were sought in medical records coded with a primary diagnosis of conjunctivitis. These records were generated from patients examined during the past 12 years by 2 external disease specialists (K.R.W. and D.B.J.) at the Cullen Eye Institute, Houston, Tex, and from patients examined during the past 4 and 6 months at general ophthalmology clinics at Ben Taub General Hospital, Houston, and the Veterans Affairs Medical Center, Houston, respectively. Cases were excluded if other ocular surface disease was present, nondecongestant eyedrop use occurred within 2 weeks of presentation, or follow-up failed to demonstrate improvement of the conjunctival inflammation after discontinuing decongestant use. In some cases, conjunctival scrapings were obtained for cytologic examination and chlamydial infection testing (eg, Giemsa-stain examination, organism culture, or fluorescent antibody detection of the chlamydial antigen).

After resolution of decongestant-induced conjunctivitis by discontinuing use of their eyedrops, 4 patients agreed to be rechallenged for 2 weeks with new preparations of the presumed offending medications at the same frequency as used prior to presentation.

Nonparametric analyses included the Spearman rank correlation, the Wilcoxon rank sum test, and the Fisher 2-tailed exact test. Values are expressed as the mean(±1 SD).

3.5±4.5 years (range, 8 hours to 20 years). The ocular symptoms on presentation included eyelid swelling, epiphora, ocular awareness, irritation, itching, burning, pain, foreign-body sensation, or redness. Twelve brands of ophthalmic decongestants were implicated (**Table 2**).

Three clinical patterns of conjunctivitis were identified: (1) *conjunctival hyperemia* (**Figure 1**), which is defined as diffuse hyperemia and chemosis of the conjunctiva extending beyond the interpalpebral fissure, episcleral vascular dilation, and papillae of the upper and lower pretarsal conjunctiva; (2) *follicular conjunctivitis* (**Figure 2**), which is defined as bulbar or palpebral follicles with ocular symptoms, regardless of the degree of conjunctival inflammation; and (3) *blepharoconjunctivitis* (**Figure 3**), which is defined as subcutaneous edema and hyperemia of the eyelids, diffuse chemosis, and bulbar and pretarsal conjunctival hyperemia.

Eighteen patients (including all patients with follicular conjunctivitis) were tested for chlamydial infection; the results of all tests were negative. Ten patients (4 with conjunctival hyperemia and 6 with follicular conjunctivitis) underwent conjunctival scrapings, all of which demonstrated many lymphocytes, occasional polymorphonuclear leukocytes, and few or no eosinophils.

Conjunctival hyperemia was present in 50 cases (71%); follicular conjunctivitis, 17 cases (24%); and blepharoconjunctivitis, 3 cases (4%). Ophthalmic decongestants, individually and as a group, were most likely to cause conjunctival hyperemia ($P<.001$, data not shown). Naphcon-A (naphazoline hydrochloride, Alcon Laboratories, Fort Worth, Tex), an exception, was associated with follicular conjunctivitis ($P=.01$, data not shown).

All patients with conjunctival hyperemia or follicular conjunctivitis were first treated by discontinuing the topical medication. After initial improvement of their conditions, 24 (36%) of these 67 patients were then prescribed a corticosteroid drop at an initial frequency of 4 times daily; this frequency was tapered during a 1- to 10-week period. The corticosteroids used included 0.1% fluorometholone, 0.1% fluorometholone acetate, 0.125% or 1% prednisolone phosphate, and 1% prednisolone acetate. Patients with conjunctival hyperemia showed no difference in time to recovery whether they were treated with corticosteroids or not (Wilcoxon rank sum test, $z=-0.49$, $P=.63$, Table 1). In contrast, patients with follicular conjunctivitis showed faster improvement of their conditions with corticosteroid use (mean recovery time, 3.3±1.0 weeks vs 10.3±7.2 weeks; Wilcoxon rank sum test, $z=2.58$, $P=.01$). All patients with eczematoid blepharoconjunctivitis were treated with topical corticosteroids.

The time to resolution of signs and symptoms for all cases of conjunctivitis averaged 6.8±6.7 weeks (median, 4 weeks; range, 1-24 weeks). A positive correlation was found between the duration of decongestant eyedrop use prior to presentation and the time required for recovery (Spearman rank correlation, $r=0.346$, $P=.01$). No association was found between individual decongestant preparations or the frequency of daily eyedrop use and the time to recovery ($P=.62$).

Four patients in whom conjunctival hyperemia was diagnosed were rechallenged with new preparations of their vasoconstrictors. Three patients applied their decongestants (Visine [tetrahydrozoline hydrochloride], Pfizer Inc, New York, NY; Clear Eyes [naphazoline hydrochloride], Ross Laboratories, Columbus, Ohio; and Murine Plus [tetrahydrozoline hydrochloride], Ross Laboratories) in 1 or both eyes for 2 weeks and had a relapse of their signs and symptoms in the treated eye(s). The fourth patient was unavailable for follow-up.

## COMMENT

Nonprescription ophthalmic decongestants can cause acute and chronic conjunctivitis. Three clinical patterns are described that likely represent distinct pathophysiological mechanisms.

Conjunctival hyperemia, the most common form of decongestant-associated conjunctivitis, is probably a pharmacologically induced rebound phenomenon following vasoconstrictor discontinuation. The mechanism may be either vasoconstrictor-induced tissue ischemia[35] with release of a vasodilating substance or constrictor tachyphylaxis.[36] Nasal preparations containing α-adrenergic amines are well known to cause rebound vascular dilation in the nasal mucosa,[7,12,37-40] and such a reaction also occurs in the conjunctiva following epinephrine eyedrop use.[30,41] Although previous experience suggests that

**Table 1. Characteristics of Vasoconstrictor-Associated Conjunctivitis***

| Form of Conjunctivitis | Sex, No. of Cases (% of Total) M | F | Age, y | Frequency, Drops/d | Duration of Use, y | Time to Recovery, wk Without Corticosteroids | With Corticosteroids |
|---|---|---|---|---|---|---|---|
| Conjunctival hyperemia | 24 | 26 | 41.2±16.3 | 3.5±2.3 | 3.2±3.6 | 6.2±6.1 | 9.8±8.6 |
| | (89) | (60) | (38, 18-82) | (3, 1-12) | (3, 10 d-20 y) | (4, 2-24) | (5, 3-24) |
| Follicular conjunctivitis | 2 | 15 | 46.1±15.7 | 4.5±1.9 | 5.0±6.7 | 10.3±7.2† | 3.3±1.0† |
| | (7) | (35) | (43, 22-79) | (4, 2-9) | (2, 0.3-20) | (7, 3-20) | (3.5, 1-4) |
| Blepharoconjunctivitis | 1 | 2 | 44.3±2.1 | 3.7±1.5 | 0.2±0.2 | ... | 1.3±0.6 |
| | (4) | (5) | (45, 42-46) | (4, 2-5) | (0.2, 8 h-0.3 y) | | (1, 1-2) |
| All forms | 27 | 43 | 42.5±15.9 | 3.7±2.2 | 3.5±4.5 | 7.1±6.5 | 6.5±7.25 |
| | | | (41.5, 18-82) | (4, 1-12) | (3, 8 h-20 y) | (4, 2-24) | (4, 1-24) |

*Values are expressed as the mean ± 1 SD. The median and the range are given in parentheses unless otherwise indicated. Ellipses indicate data not applicable.
†Significantly different (P=.01).

**Table 2. Ophthalmic Decongestants Causing Conjunctivitis***

| Medication† (Manufacturer, Location) | Adrenergic Agonist, % | Antihistamine, % | Preservatives, % Benzalkonium Chloride | Edetic Acid |
|---|---|---|---|---|
| Albalon Liquifilm (Allergan Inc, Irvine, Calif) | Naphazoline, 0.050 | ... | 0.004 | 0.013 |
| Albalon-A Liquifilm (Allergan Inc) | Naphazoline, 0.050 | Antazoline, 0.50 | 0.004 | 0.013 |
| Clear Eyes (Ross Laboratories, Columbus, Ohio) | Naphazoline, 0.012 | ... | 0.010 | 0.100 |
| Collyrium Fresh-Eye Drops (Wyeth-Ayerst Laboratories, Philadelphia, Pa) | Tetrahydrozoline, 0.050 | ... | 0.010 | 0.100 |
| Murine Plus (Ross Laboratories) | Tetrahydrozoline, 0.050 | ... | 0.010 | 0.020 |
| Naphcon (Alcon Laboratories, Fort Worth, Tex) | Naphazoline, 0.012 | ... | 0.010 | 0.050 |
| Naphcon-A (Alcon Laboratories) | Naphazoline, 0.025 | Pheniramine, 0.30 | 0.010 | 0.010 |
| Naphcon Forte (Alcon Laboratories) | Naphazoline, 0.100 | ... | 0.010 | 0.050 |
| Prefrin Liquifilm (Allergan Inc) | Phenylephrine, 0.120 | ... | 0.005 | 0.015 |
| Vasocon-A (Iolab Corporation, Claremont, Calif) | Naphazoline, 0.050 | Antazoline, 0.05 | 0.010 | ... |
| Visine (Pfizer Inc, New York, NY) | Tetrahydrozoline, 0.050 | ... | 0.010 | 0.100 |
| Visine AC (Pfizer Inc) | Tetrahydrozoline, 0.050 | ... | 0.005 | 0.015 |

*Ellipses indicate data not applicable.
†Trademark names.

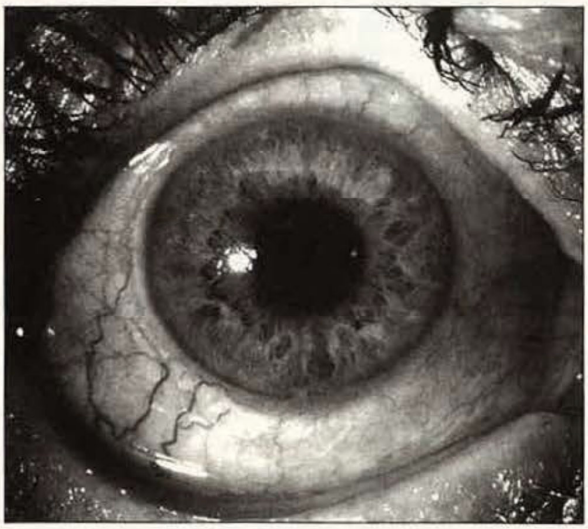

**Figure 1.** *Conjunctival hyperemia. A 43-year-old woman who used 0.05% tetrahydrozoline eyedrops, 3 times daily, for 12 years had bilateral, symmetric hyperemia of the upper and lower tarsal conjunctiva; marked, diffuse hyperemia of the bulbar conjunctiva; and dilated superficial episcleral vessels. One week after discontinuing use of the decongestant, her conjunctival and episcleral hyperemia were diminished. A 1-week tapering course of 0.125% prednisolone phosphate drops was used. In 3 weeks, she was asymptomatic and remained so during 7 months of follow-up.*

vasoconstrictors never[1,2,5,7,8,42-45] or rarely[43,46,47] incite conjunctival hyperemia, the 50 cases in this series clearly demonstrate that ophthalmic decongestants containing phenylephrine, naphazoline, or tetrahydrozoline can cause rebound dilation of conjunctival blood vessels.

Follicular conjunctivitis, which probably represents a toxic effect,[34,48] accounts for one fourth of the cases in this series. Follicles were most prominent in the lower palpebral conjunctiva and fornix but were also present on the bulbar and upper palpebral conjunctiva. These 17 cases are the first reports of bulbar follicles resulting from the use of decongestants. The factor(s) responsible may be any of a number of agents in the decongestant preparations: the vasoconstrictor,[30,34] an antihistamine (if present),[34] or 1 of the preservatives.[33,34,49-54]

Eczematoid blepharoconjunctivitis was the least common reaction in this series. Although benzalkonium chloride,[21,34] edetic acid,[34,55] and phenylephrine[21,22] can cause contact hypersensitivity, to our knowledge, our cases are the first reports of allergic blepharoconjunctivitis associated with preparations containing naphazoline and tetrahydrozoline.

The incidence of adverse reactions to ophthalmic decongestants is unknown. Even if the incidence is low, the

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