PERSPECTIVE

Adverse effects of topical antiglaucomatous medications on the conjunctiva

David Broadway, Ian Grierson, Roger Hitchings

With selected patients glaucoma filtration surgery is highly successful. However, there is growing evidence that chronic topical medical therapy has a deleterious effect on surgical outcome. It has been suspected that topical drugs exert an adverse effect on the conjunctiva which results in altered postoperative wound healing. In this review the effect of previous topical antiglaucoma medication on the conjunctiva and the outcome of subsequent glaucoma filtration surgery are discussed.

The effect of previous topical therapy on the results of glaucoma filtration surgery

In a study aimed at identifying potential risk factors for failure of pressure control following glaucoma triple procedures (trabeculectomy, cataract extraction and intraocular lens implantation), the only significant adverse factor identified was cumulative years of preoperative topical therapy (number of medications x the treatment duration for each). The hazard ratio for this factor was 1.1 indicating that the risk of failure doubled after 8 years of cumulative therapy. The number of preoperative medications used was not isolated as a significant risk factor and the data were insufficient to identify any specific type of medication as the major risk factor.

In a similar study, previous treatment with multiple topical agents was reported to be associated with a lower trabeculectomy success rate in comparison with a group of patients undergoing primary trabeculectomy (Fig 1). The largest single influence on the outcome of trabeculectomy alone was the number of preoperative antiglaucoma medications used (hazard ratio=5). This effect persisted despite controlling for factors that may have been confounders for the effect of medication number, in particular the presenting intraocular pressure (IOP). Since it was probable that the higher the IOP, the greater the number of treatments used, a higher order interaction was suspected. The duration of topical treatment was also significant, but with a hazard ratio just below 1, a longer duration appeared to have a borderline protective effect. It was thus proposed that large numbers of medications used during a relatively short period may have a greater adverse effect than the same amount of treatment over a long period. Previous exposure to sympathomimetics was identified as a significant adverse factor and the patients whose trabeculectomies failed had used more adrenaline-based preparations than those whose trabeculectomies were successful (55% vs 26%). In contrast, previous exposure to timolol had no significant effect on the outcome of surgery. Previous exposure to pilocarpine was not identified as a significant adverse factor, but this may have been due to the fact that only 2% of the treated patients in this study had not received pilocarpine and its use was thus a very poor determinant of risk of failure.

Previous topical therapy has also been identified as an adverse factor for the outcome of trabeculectomy performed in children with congenital glaucoma. With failure defined as an IOP >21 mm Hg the adjusted risk ratio was 5-6, and when defined as the requirement of additional surgical or medical therapy it was 7-2. Analysis by multiple regression also showed that the effect of previous topical therapy was detrimental, reducing the quality of IOP control at 3, 6, and 12 months. The effects of treatment type, amount, or duration were not analysed.

Topical therapy with sympathomimetics has also been reported to increase the risk of failure secondary to the development of Tenon's capsule cysts with a relative risk of 1.9. Neither miotics nor β blockers had a significant effect on the development of cysts but the effect of duration or amount of topical treatment was not addressed in this study and it is possible that the effect of sympathomimetics reflected these factors rather than one of treatment type.

Table 1 Mechanism by which the conjunctiva can react to drugs

<table>
<thead>
<tr>
<th>Number</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clearing conjunctivitis (pseudopemphigoid)</td>
</tr>
<tr>
<td>2</td>
<td>Anaphylactoid (allergic) acute or chronic conjunctivitis (type I</td>
</tr>
<tr>
<td></td>
<td>hypersensitivity)</td>
</tr>
<tr>
<td>3</td>
<td>Allergic contact (degranation) conjunctivitis (type IV hypersensitivity)</td>
</tr>
<tr>
<td>4</td>
<td>Non-specific (papillary) irritative/toxic conjunctivitis</td>
</tr>
<tr>
<td></td>
<td>(non-immunological irritation to factors such as pH, tonicity,</td>
</tr>
<tr>
<td></td>
<td>contamination)</td>
</tr>
<tr>
<td>5</td>
<td>Specific (follicular) irritative/toxic conjunctivitis</td>
</tr>
<tr>
<td></td>
<td>(characterised by the formation of lymphoid follicles)</td>
</tr>
<tr>
<td>6</td>
<td>Cumulative/deposition/dyschromia (for example, adrenochrome</td>
</tr>
<tr>
<td></td>
<td>deposition with sympathomimetics)</td>
</tr>
<tr>
<td>7</td>
<td>Microbial imbalance and secondary conjunctivitis (delayed allergic</td>
</tr>
<tr>
<td></td>
<td>response, type IV hypersensitivity)</td>
</tr>
<tr>
<td>8</td>
<td>Non-specific irritation (in the absence of clinical signs)</td>
</tr>
<tr>
<td>9</td>
<td>Subclinical cellular and ultrastructural change</td>
</tr>
<tr>
<td>10</td>
<td>Total tolerance</td>
</tr>
</tbody>
</table>

Figure 1 Percentage of successfully functioning trabeculectomies: primary surgery group (---) compared with multiple treatment group (- - -). There were significantly more failures in the multiple treatment group by 3 months (p<0.005) (*), with additional failures by 18 months (p<0.001) (△). (From Laves et al with permission of the American Medical Association.)
In conclusion it appears that long term therapy with topical antiglaucoma medications has an adverse effect on the outcome of filtration surgery, both in terms of success and the occurrence of complications. The specific factors of importance remain unknown, but it would appear that cumulative duration of preoperative therapy and, in particular, use of sympathomimetics are risk factors of particular significance. Despite the comprehensive statistical analysis used in these studies their retrospective nature means that the results have to be regarded as tentative. Unfortunately no prospective study has yet been published.

Effect of topical antiglaucoma medications on the conjunctiva
The reasons for the higher failure rate of glaucoma filtering surgery associated with previous topical therapy are not clear and several factors may be involved. It is likely that topical preparations are able to affect all parts of the eye including the aqueous and the trabecular meshwork. Since postoperative subconjunctival fibrosis is the commonest cause of trabeculectomy failure, the effect of topical medications on the conjunctiva and subconjunctival tissues is of particular interest. Sympathomimetics, in particular, are frequently associated with local effects including subjective irritation, epithelial adrenochrome deposition, reactive hyperaemia, blepharoconjunctivitis, and corneal oedema, but there is growing evidence that other medications also affect the conjunctiva.

Theodore and Wilson have reviewed the adverse external ocular effects of a number of topical drugs, including antiglaucomatous medication. It is clear that the conjunctiva is able to react in a number of ways in response to topical therapy (Table 1). It is probable that the development of pseudopemphigoid (drug-induced ocular cicatrisation) lies at the severe end of a spectrum of reactions, the other end of which is total tolerance (Fig 2). On a clinical basis this concept is logical, for a full range of tolerance is seen in ophthalmic practice.

Table 2 Clinical features of pseudopemphigoid

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Canthal keratinisation (non-wetting appearance)</td>
</tr>
<tr>
<td>2</td>
<td>Shallowing of canthal recesses</td>
</tr>
<tr>
<td>3</td>
<td>Flattening/obliteration of conjunctival folds, plica, and caruncle</td>
</tr>
<tr>
<td>4</td>
<td>Non-specific chronic conjunctivitis and hyperaemia</td>
</tr>
<tr>
<td>5</td>
<td>Conjunctival thickening</td>
</tr>
<tr>
<td>6</td>
<td>Abnormal conjunctival vascularisation</td>
</tr>
<tr>
<td>7</td>
<td>White lines of subepithelial fibrosis</td>
</tr>
<tr>
<td>8</td>
<td>Inferior punctal occlusion</td>
</tr>
<tr>
<td>9</td>
<td>Symbiophora</td>
</tr>
<tr>
<td>10</td>
<td>Conjunctival ulceration</td>
</tr>
<tr>
<td>11</td>
<td>Precorneal tear film abnormalities and instability</td>
</tr>
<tr>
<td>12</td>
<td>Eyelash metaplasia, entropion, and trichiasis</td>
</tr>
<tr>
<td>13</td>
<td>Laggophthalmos and corneal exposure</td>
</tr>
<tr>
<td>14</td>
<td>Corneal opacification with vascularisation</td>
</tr>
<tr>
<td>15</td>
<td>Secondary infection</td>
</tr>
<tr>
<td>16</td>
<td>Total conjunctival cicatrisation and/or epidermalisation</td>
</tr>
<tr>
<td>17</td>
<td>Non-progressive and in unilateral cases occurs in a treated eye with no changes evident in the untreated fellow eye</td>
</tr>
<tr>
<td>18</td>
<td>Absence of systemic features of pemphigoid</td>
</tr>
</tbody>
</table>

Table 3 Histopathological, ultrastructural, and immunological features of pseudopemphigoid

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reduction in the number of goblet cells</td>
</tr>
<tr>
<td>2</td>
<td>Epithelial keratinisation</td>
</tr>
<tr>
<td>3</td>
<td>Squamous metaplasia</td>
</tr>
<tr>
<td>4</td>
<td>Loss of microvilli</td>
</tr>
<tr>
<td>5</td>
<td>Increased numbers of desmosomes</td>
</tr>
<tr>
<td>6</td>
<td>Bullous separation of the epithelium</td>
</tr>
<tr>
<td>7</td>
<td>Subepithelial fibrosis</td>
</tr>
<tr>
<td>8</td>
<td>Reduced intravascular space</td>
</tr>
<tr>
<td>9</td>
<td>Increase in the number of subepithelial lymphocytes and plasma cells</td>
</tr>
<tr>
<td>10</td>
<td>Basement membrane thickening</td>
</tr>
<tr>
<td>11</td>
<td>Basement membrane staining for immunoglobulin (in some cases)</td>
</tr>
</tbody>
</table>
SEVERE CLINICAL EFFECTS
The number of reported cases of pseudopemphigoid related to the use of topical medications is relatively small but various topical antiglaucoma medications have been implicated in its aetiology. These include adrenaline, pilocarpine, β blockers, echotothiate iodide, demecarium bromide, and various combinations of therapy. The clinical and pathological features are summarised in Tables 2 and 3 and illustrated in Figures 3–6. The underlying aetiology of drug-induced pseudopemphigoid remains unknown with inconsistent immunological findings. However, a number of possible mechanisms explaining the role of topical medications have been proposed (Table 4).

Allergic reactions associated with topical antiglaucoma medications have been described, the clinical and pathological features of which are listed in Table 5. In many cases the allergy is due to the preservative and administration of preservative-free drops is often curative.

Follicular conjunctivitis has also been reported, both in response to sympathomimetic (dipivefrin) and miotic therapy. Furthermore, Cvetkovic et al. reported the development of conjunctival follicles after long-term (>1 year) exposure to pilocarpine and reported that this was unrelated to the presence or absence of preservative. There is no evidence that β blockers induce a follicular response and this provides further evidence that preservatives are not directly involved.

SUBCLINICAL EFFECTS

Despite the many ways in which the conjunctiva can react to topical medications, the majority of patients are able to tolerate such therapy and clinically obvious conjunctival changes remain the exception rather than the rule. Clinical signs are not always striking, however, and subtle changes are easily missed without a rigorous examination. Wright, for example, reported the development of relatively subtle squamous metaplasia or epidermalisation as an adverse reaction to topical antiglaucomatous medication. The first detectable change in the cases he observed was a loss of epithelial wetting by the tear film with disturbance of the light reflex from the conjunctival surface. Increasing keratinisation created a whitish, slightly foamy appearance and in cases where this remained unnoticed a thick white mass of keratin eventually formed. Histological findings included loss of goblet cells, epithelial keratinisation, keratothylaine granule formation, subepithelial infiltration with lymphocytes and plasma cells, and, in some cases, an increase in the number of fibroblasts and degree of fibrosis. The clinical signs resolved after cessation of the therapy, but since the conjunctiva was not re-biopsied it is not known if the histological changes were completely reversed. A similar reaction has been reported after use of topical dipivefrin and metipranol. In view of the pharmacological similarities between metipranol and practolol, a systemically administered drug known to cause ocular cicatrization, the authors considered the β blocker to be the cause of the conjunctival reaction.

Wright has shown that inferior fornical shallowing due to subconjunctival fibrosis may be induced by sympathomimetic therapy. A recent study has further investigated this frequently subtle reaction to topical medication. A significant foreshortening of the inferior fornix was found with increasing age and, after taking this into account, after at least 3 years' exposure to topical antiglaucoma medications, irrespective of type. The fact that different classes of topically administered medications were associated with conjunctival shrinkage indicated that a common pathway may result in fibrosis.

SUBCLINICAL EFFECTS

In order to determine the effect of topical antiglaucoma medications on the cellular content on the conjunctiva, Sherwood et al. quantitatively analysed biopsies obtained
from patients with glaucoma undergoing filtration surgery. The patients were divided into two groups. Primary trabeculectomy patients underwent trabeculectomy within a few weeks of their glaucoma diagnosis, following treatment with pilocarpine for a mean duration of only 3 weeks. Multi-treatment patients underwent trabeculectomy after treatment with at least two different types of topical medication, for a minimum duration of 1 year (mean 7.7 years). In the epithelium, the multi-treatment conjunctiva showed a significant decrease in the number of goblet cells and increase in the number of cysts and non-epithelial cells such as lymphocytes or macrophages. A significant increase in the number of fibroblasts, macrophages, lymphocytes, and mast cells was found in both conjunctival substantia propria and Tenon’s capsule (Fig 7). The authors proposed that the increased number of fibroblasts and inflammatory cells in conjunctiva exposed to topical medications might enhance the risk of bleb failure after trabeculectomy. This study is of both interest and importance but did not identify whether any specific antiglaucoma medication was responsible.

In order to identify specific drugs responsible for such changes, Smith et al. investigated the effect of antiglaucoma medications on the conjunctiva of rabbits, divided into four groups. Timolol, pilocarpine, adrenaline, or a combination of all three drugs were placed in one eye, twice daily, for 7 months. The other eye received distilled water and acted as a control. Analysis of the number of inflammatory cells, fibroblasts, and goblet cells revealed no statistically significant difference in number of any cell type between the control and treatment groups. However, as the authors point out the small number of eyes in each treatment group and the high variability in cell counts between each eye limited the power of such an analysis. A number of other reasons to explain the difference between these results and those of Sherwood et al. were discussed. Firstly, the mean durations of topical therapy were significantly different, 7 months rather than 7.7 years. Secondly, the treatment groups were not comparable. Sherwood et al. did not specify the types of medication used, but each patient had used a combination of medications. In addition, pilocarpine was only administered twice daily to the rabbits, rather than the usual four times a day. Thirdly, tissue handling and cell counting techniques differed. More importantly, perhaps, is the fact that animal models are not always representative of humans. The rabbit eye is relatively large and prominent, such that loss of effective drug from the exposed eye and reduced drug exposure time may be factors of importance in comparison with humans.

Our own work showed that long term therapy with β blocker alone had little effect on the cellular profile of the conjunctiva, whereas pilocarpine increased the number of macrophages in the epithelium, and fibroblasts and mast cells in the substantia propria. Pilocarpine in combination with β blocker resulted in an increase in the number of Langerhans cells and macrophages in the epithelium, and fibroblasts and lymphocytes in the substantia propria. Triple therapy (pilocarpine in combination with β blocker and sympathomimetic) had the greatest effect in reducing goblet cells and increasing Langerhans cells, macrophages, and lymphocytes in the epithelium, and fibroblasts, macrophages, lymphocytes, and mast cells in the substantia propria. The reaction to topical treatment is not caused solely by type of medication and a number of factors appear to be important (Table 6).

No other morphometric studies on patients treated with only one type of medication have been performed, although a few studies have looked at the effect of either single or multiple topical medications on specific features of the conjunctival surface. Surface changes themselves may have little effect on bleb formation or failure following trabeculectomy, but they may be indicative of subepithelial changes of more importance.

A number of studies have reported that application of β blocker results in asymptomatic corneal anaesthesia and tear film changes, but other studies report that such changes, if present, are usually clinically insignificant.

Conjunctival surface changes secondary to long term β blocker application have, however, been identified by a number of workers. Changes have included epithelial oedema, a reduction in goblet and secretory epithelial cells, a pronounced increase in cells with rough endoplasmic reticulum, abnormalities of the Golgi apparatus, a loss of desmosomes and tight junctions, and a reduction in the number of microvilli.

Steuhl et al. proposed that intracellular changes such as vacuolisation and dilatation of the rough endoplasmic reticulum of surface epithelial cells may be attributable to the action of preservative (benzalkonium chloride). Since these changes were greatest with β blocker medications it was proposed that the cytotoxic action of the preservative was intensified by the simultaneous application of β blockers because of their destabilising effect on the tear film.

In contrast, Quaranta et al. reported no evidence of pathological alterations to the conjunctiva after long term (6–10 years) therapy with timolol, although only four patients were compared with four controls. A similar conclusion was reached by Hoffman who reported that timolol placed in rabbit eyes for 1 year or beagle eyes for 2 years had no histomorphological effect on the conjunctiva.

The effect of pilocarpine on the density of goblet cells has been investigated by Gerstenberger and Marquardt who also demonstrated a circadian rhythm in goblet cell number. Long term use of pilocarpine (up to 20 years) was found to be associated with an increase in goblet cell number and it was proposed that this increase occurred secondary to maximal parasympathomimetic stimulation of the goblet cells. An
In vitro evidence for an adverse effect of topical antiglaucoma medications

Caution must be exercised in comparing in vitro studies with the in vivo state. Clinically, the instillation of eye drops exposes the conjunctiva to medication for a short period, whereas in tissue culture there is continuous exposure. Furthermore, in vitro experimentation does not allow for natural replacement of damaged tissue during intervals between drug installation. Nevertheless, in order to determine whether cellular changes in the conjunctiva are a direct effect of antiglaucoma medications, tissue culture experimentation enables carefully controlled investigation.

Takahashi et al. studied the effect of antiglaucoma medications and their preservatives on cultured human conjunctival cells. Preservative (benzalkonium chloride) was found to be cytotoxic at concentrations above 0.005%. Pilocarpine (1%) and timolol (0.5%) alone were not cytotoxic. Adrenaline (1.25%) and bethanol (0.5%) alone showed some cytotoxicity after exposure of more than 1 hour, but the β blocker, bupranolol (0.25%) alone was found to be the most cytotoxic, showing a differential effect of the β blockers tested. The cells used in these experiments were conjunctival epithelial cells and the results are thus of only limited value in our understanding of the effect that topical medications have on subepithelial fibroblast proliferation, which is of more importance with respect to failure of filtration surgery.

Williams et al., therefore, investigated the effects of the preservative benzalkonium chloride and commercially available β blockers (with or without preservative) on cultures of human Tenon’s capsule fibroblasts. None of the tested drugs stimulated fibroblast proliferation and, instead, they were found to be irreversibly toxic to fibroblasts at clinically used concentrations. In addition, it was found that pure preparations of the β blockers prevented cell attachment at a higher concentration than did the commercially available, preservative-containing versions, and therefore benzalkonium chloride was implicated as a toxic component in terms of cellular attachment. With respect to acute effects on cell proliferation the preservative-free timolol preparation was significantly less toxic than the preservative-containing timolol. Again this finding implicated benzalkonium chloride, which was identified as the most toxic agent tested. However, similar findings to those with timolol were not found with the other β blockers (levobunolol or betaxolol).

From the study of delayed effects on cell proliferation, using the commercially available preparations, levobunolol was found to be the only drug that became less toxic after the cells were washed free of drug and recultured. Since the benzalkonium chloride concentration in the preservative-containing levobunolol preparation was 2.5-fold less than in the other β blockers, it was proposed that the cells exposed to levobunolol may have been more able to recuperate from the initial injury in comparison with those exposed to the other drugs with more preservative.

The results of this study do not support the hypothesis that antiglaucoma medications directly stimulate fibroblast growth, and thus favour the concept of topical therapy causing tissue irritation, associated low grade chronic inflammation, and indirect fibroblast stimulation. Alternatively, it is possible that the effect of other classes of drug alone (for example, sympathomimetics or miotics) or combination therapy differs from that of β blockers and/or preservative, for few studies have looked at the effect of β blockers alone on the cellular content of the conjunctiva.

The relationship between conjunctival changes and the outcome of trabeculectomy

The most important issue in relation to trabeculectomy is whether any conjunctival changes are directly related to the
Adverse effects of topical antiglaucomatous medications on the conjunctiva

595

surgical outcome. A pilot study using an animal model has provided evidence for an adverse effect of topical therapy on fistulised rabbit conjunctiva but an equivalent analysis in humans is not feasible. In this animal study conjunctival specimens were obtained 5 days following filtration surgery. In comparison with untreated conjunctiva, that pretreated with 4 months of pilocarpine, timolol, or artificial tears had significantly more myofibroblasts. Surprisingly, adrenaline treated conjunctiva showed a non-significant increase and the risk was significantly less than that in conjunctiva exposed to artificial tears. The fact that artificial tears elicited a response suggested that the benzalkonium chloride preservative, present in all the medications used, was responsible and it was suggested that the vasoconstrictive properties of adrenaline may have accounted for its low response. Unfortunately the significance of this study is limited by being a non-primate animal study, the small number of animals included in the study, and that the statistical analysis may have been biased by the fact that both eyes of each animal were analysed. However, in conclusion the authors suggested that prior medical treatment, especially with pilocarpine, may contribute to a lower success rate of filtration surgery by stimulating an exaggerated myofibroblastic response. The actual effect of these cellular changes on the eventual outcome of surgery was not determined although no correlation was established between any type of medication and bleb function or IOP before conjunctival biopsy. In order to determine the effect of medication on surgical outcome the blebs would have to be observed for a longer duration. Filtration surgery of this type in untreated rabbit eyes has been shown to fail predictably by 2 weeks and in the light of the study by Young et al it would thus be of interest to determine whether pilocarpine treated eyes fail earlier.

Conclusion

Long term therapy with topical medication induces a degree of conjunctival inflammation and also has an adverse effect on the outcome of filtration surgery. Whether conjunctival changes are the cause rather than merely an association with the poorer surgical results requires further clarification. Symptomatistics and, to a lesser extent, moieties appear to have a more pronounced adverse effect in comparison with β blockers, but preservatives and factors such as duration of therapy undoubtedly play a significant role. Further studies aimed at identification of specific causative factors would be useful.

In spite of our ignorance, there is growing evidence that long term therapy with multiple topical medications is detrimental to both conjunctiva and the success of filtration surgery. In terms of the management of patients with glaucoma such evidence lends support to the strategy of earlier surgical intervention.

DB is supported by the Frost Trust, London, UK.

DAVID BROADWAY
IAN GRIESON
ROGER HITCHINGS

Moorefields Eye Hospital,
City Road, London EC1V 2PD

27 Wright P. Squamous metaplasia or epidermalization of the conjunctiva as an adverse reaction to topical medication. Trans Ophthalmol Soc UK 1979; 99: 244-6.
Adverse effects of topical antiglaucomatous medications on the conjunctiva.

D Broadway, I Grierson and R Hitchings

Br J Ophthalmol 1993 77: 590-596
doi: 10.1136/bjo.77.9.590

Updated information and services can be found at:
http://bjo.bmj.com/content/77/9/590.citation

These include:

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/