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ORIGINAL RESEARCH

Patient perspectives when switching from Cosopt® (dorzolamide-timolol) to Azarga™ (brinzolamide-timolol) for glaucoma requiring multiple drug therapy

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Background: This study aimed to determine the impact of switching patients requiring multiple drug treatment from the dorzolamide-timolol fixed combination to the brinzolamide-timolol fixed combination and potential effects on tolerability and compliance.

Methods: Patients were switched from dorzolamide-timolol to brinzolamide-timolol and questioned within a period of 4–26 weeks. Questions were asked to confirm if a specific side effect had been experienced, and then a numerical comparison between the two types of eye drop was made.

Results: Thirty-one consecutive patients (12 males and 19 females aged 41–89 years) successfully completed the questionnaire. Comparison of the severity and chronicity of the side effects of the two types of fixed-combination eye drops showed that brinzolamide-timolol caused significantly less stinging for a shorter amount of time than dorzolamide-timolol; it also produced less eye redness for a significantly shorter amount of time. Brinzolamide-timolol produced more blurring, although the length of time this was present was similar to that for dorzolamide-timolol. No differences between the two eye drops were found for taste, overall impression, and likelihood of compliance.

Conclusion: Our study confirms the findings of other researchers pertaining to the side effect profile of brinzolamide-timolol after switching from dorzolamide-timolol, which is a reduction in stinging but an increase in blurred vision. The advantage of one eye drop over the other then becomes patient-specific, depending on which side effect they find most tolerable. We suggest that both eye drops are acceptable choices in treating patients with glaucoma, and are interchangeable if compliance becomes an issue because of a specific side effect of one eye drop or the other.

Keywords: Azarga™, Cosopt®, brinzolamide, dorzolamide, timolol, side effects

Introduction

Reduction of elevated intraocular pressure is the only established modifiable risk factor shown to reduce the risk of glaucoma-associated optic neuropathy.[1,2] Topical beta-adrenergic antagonists and carbonic anhydrase inhibitors are well accepted medical treatments for reducing production of aqueous humor.[3,4] Newer prostaglandin analogs reduce intraocular pressure by promoting uveoscleral aqueous outflow.[4–6] However, the Ocular Hypertension Treatment Study showed that almost 40% of patients will require a combination of two or more medications to achieve a 20% reduction in intraocular pressure.[1]

Complex drug regimens requiring the use of numerous bottles can reduce the therapeutic effect, and use of multiple bottles has also been shown to be a barrier to compliance.[7–9] Coadministration of drops may introduce a washout effect if

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not adequately spaced in time.[10] Similarly, eye drop tolerability will affect compliance and treatment outcomes.[7]

Multiple-drop therapies have been formulated to address some of these compliance issues. Azarga™ (Alcon Laboratories Inc, Fort Worth, TX) is a fixed combination of brinzolamide 1% + timolol 0.5%, and is effective in reducing intraocular pressure.[11] In comparison, a fixed combination of brinzolamide 1% + timolol 0.5% is noninferior to a fixed combination of dorzolamide 2% + timolol 0.5% and achieved lower mean intraocular pressures at nine of 12 study visits.[12] Tolerability comparisons of these two fixed-combination eye drops seem to show a reduction in eye irritation using the brinzolamide formulation, but an increase in blurred vision.[12–15]

In this study, we directly switched patients requiring multiple-drug treatments from a fixed combination of dorzolamide-timolol to brinzolamide-timolol and investigated the impact of this change on tolerability and compliance.

Materials and methods

This study was performed at the Glaucoma Unit in the Royal Hallamshire Hospital, Sheffield, UK. Patients were switched from a fixed preparation of dorzolamide-timolol to brinzolamide-timolol. Following the switch, patients were contacted by telephone and a number of questions were asked over a period of 4–26 weeks after changing eye drops. One independent questioner read a preformed questionnaire to patients over the telephone (Figure 1). Telephone consultations were initiated by confirming the patient details and that correct antiglaucoma treatment was concurrent. A primary yes/no question was asked to confirm if a specific side effect had been experienced. If a side effect was noted for either drug, a comparison of the two types of eye drop was made by asking patients to assign a numerical value (1 to 9) comparing the new (brinzolamide-timolol) and old (dorzolamide-timolol) drops. Thirty-one consecutive patients whose medication had been altered were contacted and questionnaires were successfully completed.

Stinging
Since you have been using your new drop, Azarga™, have you experienced any stinging following installation of the drop (yes/no)? Did you have any stinging with your previous drop (yes/no)?
*Rate your new drop for stinging compared with your previous drop (1 much less; 5 the same; and 9 much more).
*Rate how long the stinging lasts compared with your previous drop (1 much less; 5 the same; and 9 much more).
Blurring
In the last few weeks since you have been using your new drop, have you experienced any blurring of your vision following installation of the drop (yes/no)? Did you have any blurring of your vision with your previous drop (yes/no)?
*Rate your new drop for temporary blurring of vision compared with your previous drop (1 much less; 5 the same; and 9 much more).
*Rate how long the blurriness lasts compared with your previous drop (1 much less; 5 the same; and 9 much more).
Redness
Have you experienced any redness of your eye following installation of your new drop (yes/no)? Did you have any redness with your previous drop (yes/no)?
*Rate your new drop for making your eye red. 1 being much less red than with the previous drop, 5 being the same and 9 being much more redness than before (1 much less; 5 the same; and 9 much more).
*Rate how long the redness lasts (1 much less; 5 the same; and 9 much more).
Taste
Since you have been using your new drop have you experienced any abnormal taste following installation of the drop (yes/no)? Did you have any abnormal taste following the instillation of your previous drop (yes/no)?
*Rate your new drop for the taste it produces (1 much less; 5 the same; and 9 much worse).
Overall impression
Please rate your overall impression of your new drop compared with your old drop (1 you prefer it; 5 no difference; 9 you preferred your old drop).
Compliance
Please rate how changing to your new drops will affect your treatment regime (1 I am less likely to use it than previous drop; 5 meaning the change in drops has made no difference to how I use them; 9 meaning I am more likely to use it than my previous drops).

Figure 1 Telephone questionnaire read to patients who had switched from a fixed combination of dorzolamide-timolol to brinzolamide-timolol.
Note: Questions marked with an asterisk were used if a specific side effect was recorded for either the new or old drops.

Results

Thirty-one consecutive patients (12 males and 19 females aged 41–89 years) successfully completed the questionnaire. The data were analyzed for significant differences from the assumed mean of 5 using the *t*-test if the sample set was >20. When the sample set was <20 the Wilcoxon signed-rank test was performed. A test for proportions was used to compare the numbers of patients experiencing a specific side effect.

The population varied in the percentages experiencing side effects, as shown in Table 1. Comparison of the percentages of side effects indicated less stinging but more blurring for brinzolamide-timolol compared with dorzolamide-timolol eye drops (Table 1). There were no differences in the proportions of patients who experienced altered taste or redness following instillation of the eye drops.

Table 1 Percentage of patients experiencing a side effect from fixed-combination brinzolamide-timolol or dorzolamide-timolol eye drops

Side effect	Patients experiencing side effects (%)		Test for proportions (*P* value)
	Brinzolamide-timolol	Dorzolamide-timolol	
Stinging	42	68	<0.05
Blurring	55	39	<0.05
Redness	26	29	NS
Taste	35	48	NS

Abbreviation: NS, not statistically significant.

A comparison of the severity and chronicity of the side effects of the two types of fixed-combination eye drops is shown in Table 2. The fixed combination of brinzolamide-timolol produced significantly less stinging and for a shorter amount of time than the dorzolamide-timolol eye drops; it also produced less eye redness and for a significantly shorter amount of time. However, the fixed combination of brinzolamide-timolol produced more blurring, although the length of time this was present was similar to that with dorzolamide-timolol. No differences between the two eye drops were found for taste, overall impression, and likelihood of compliance.

Discussion

Previous studies have shown the fixed-combination brinzolamide-timolol eye drop to be significantly more effective than its individual components and noninferior to fixed-combination dorzolamide-timolol eye drops in lowering intraocular pressure.[11,12] We suggest that although this crossover study was unidirectional and of limited size, it does demonstrate a different side effect profile for the two types of fixed-combination eye drops.

Stinging was significantly less and lasted for a shorter period of time with the brinzolamide-timolol eye drops, which is consistent with previous findings.[12–15] Apart from any intrinsic differences in the two molecules which may alter the stinging profile of the two drugs, the pH of the eye drops containing brinzolamide is relatively more neutral than that of dorzolamide (pH 7.5 and pH 5.6, respectively). Furthermore, eye drops containing dorzolamide use sodium citrate as a buffer whereas none is present in the eye drops containing brinzolamide. All these differences seem to cause the brinzolamide-timolol eye drop to sting less.

Table 2 Comparison of side effects between dorzolamide-timolol and brinzolamide-timolol eye drops

Side effect	n	Average	*P* value	Result
Stinging				
Severity	23	3.3	<0.05	Less stinging
Chronicity	23	3.5	<0.05	Shorter stinging
Blurring				
Severity	18	5.9	<0.05	More blurring
Chronicity	18	5.3	NS	
Redness				
Severity	15	4.1	<0.1	Mildly less redness
Chronicity	15	3.9	<0.05	Shorter redness
Taste				
Severity	12	4.4	NS	
Impression	31	4.9	NS	
Compliance	31	5.1	NS	

Notes: Average score from the evaluation ranking 1–9. Results column shows the outcome of changing from dorzolamide-timolol to brinzolamide-timolol eye drops.
Abbreviation: NS, not statistically significant.

Redness can be a problematic side effect of any antiglaucoma medication, and accordingly reduces compliance, but may also be a surrogate of general irritation and stinging. We found that fixed-combination eye drops containing brinzolamide or dorzolamide show a slight reduction in severity of redness, but of significantly shorter duration. Given that this represents another reduction in side effects, it should have the effect of increasing tolerability.[7,9]

Blurring of vision is a known side effect of brinzolamide,[11] but studies have shown conflicting results when compared with dorzolamide. Stewart et al did not find any difference between the two drops.[17] However, Silver found a higher incidence of visual blurring for brinzolamide than with dorzolamide, as did Manni et al and Mundorf et al.[12,13,16] This increase in blurring of vision with the eye drop containing brinzolamide was also observed in our study, but does not seem to last any longer than the blurring caused by the eye drop containing dorzolamide. The increase in visual blurring is probably due to the viscosity of the eye drop, with the brinzolamide-timolol combination eye drop being much thicker than the dorzolamide-timolol eye drop. Indeed, seven of the 31 patients we interviewed stated that they found the brinzolamide-timolol eye drop difficult to apply due to its thickness. Also, one patient switched back to the dorzolamide preparation because of this application problem, even though she preferred the side effect profile of the brinzolamide eye drop.

Unfortunately absolute levels of blurring and the finite time for which the blurring persisted were not assessed in this study. Thus, no assumptions can be made regarding how blurring affects general daily activities using either type of eye drop. It could be that blurring persists long term and causes a significant reduction in ability to perform daily tasks, or it could be very transient and cause few problems. An answer to this question would help to make a more meaningful comparison of the side effect profiles of the two combination preparations.

Carbonic anhydrase inhibitors are known to cause dysgeusia. Initial studies by Silver showed a higher incidence of altered taste sensation with brinzolamide than with dorzolamide,[16] although subsequent studies, including our study, showed no difference.[12,17,18]

There was no statistically significant difference between the overall comparison and likelihood of compliance with the fixed-combination brinzolamide-timolol and dorzolamide-timolol eye drops in this study. Previous studies have found a patient preference for the drop containing brinzolamide over the one containing dorzolamide.[13,15] However, this and

other studies show a reduction in stinging and redness at the cost of increased blurred vision. It is possible that the exchange of one side effect for another leaves the eye drops being equivalent overall. Interestingly, Jampel et al found that patients would pay more for an eye drop with reduced blurring but would not pay more for a reduction in any other side effect.[19] This observation would suggest a preference for the dorzolamide combination overall, but this does not appear to be the case in this study.

Conclusion

Our study confirms the finding of other researchers pertaining to the side effect profiles of fixed combinations of brinzolamide-timolol and dorzolamide-timolol, ie, a reduction in stinging and redness but an increase in blurred vision. The advantage of one eye drop over the other then becomes patient-specific, depending on which side effect they find more tolerable. We suggest that both types of eye drop are acceptable and interchangeable choices for treating patients with glaucoma, but compliance may be an issue as a result of the specific side effects of one drop or the other.

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