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Efficacy and Tolerability of Preservative-Free Eye Drops Containing a Fixed Combination of Dorzolamide and Timolol in Glaucoma Patients

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Abstract

Purpose: To evaluate the efficacy and tolerability of preservative-free eye drops (dorzolamide/timolol) in routine management of preservative-sensitive glaucoma patients.
Methods: Data from 2,298 glaucoma patients requiring intraocular pressure (IOP) reduction and suffering from intolerance to benzalkonium chloride or active agents of previously used eye drops were valid for baseline and safety analysis in this prospective, open, noncomparative, multicenter, noninterventional study. Patients were treated with preservative-free dorzolamide/timolol eye drops for 12 weeks. Main efficacy endpoint was IOP reduction after 12 weeks of treatment. Two thousand forty-nine patients were considered for efficacy analysis. Tolerability was assessed by evaluating adverse drug reactions.
Results: Mean baseline IOP was 20.8 mmHg. Baseline IOP was reduced to 16.7 mmHg after 12 weeks of treatment corresponding to a mean absolute (percent) change of −4.1 mmHg (−17.3%). The proportion of patients with IOP ≤21 mmHg increased from 59.9% at baseline to 94.6% after 12 weeks. The most frequently reported ocular adverse drug reactions were burning eyes (2.4%) and hyperemia (0.9%). Local tolerability improved in 79.3% of patients compared to their previous glaucoma therapy.
Conclusions: This observational study confirms the IOP lowering effect of preservative-free eye drops containing the fixed combination of dorzolamide/timolol in a large patient's population. The drug was well tolerated and improved the local tolerability in the vast majority of patients.

Introduction

The benefit of preservatives in reducing microbiological contamination has to be weighed against their potential ocular side effects.[1] Preservatives can induce allergic reactions and even more frequently cytotoxic reactions.[2–7] Glaucoma medications containing preservatives often decrease precorneal tear film stability, lead to detergent effects on the protective lipid layer, are highly cytotoxic to human corneal endothelial cells, and commonly worsen pre-existing dry eye.[8–11] These side effects are dose dependent and increase with instillation frequency.[12] Recently, a German register revealed in a total of 20,506 glaucoma patients that the frequency of dry eye rose when >3 antiglaucoma drugs were used.[13] Due to the vicious circle of dry eye, eye drops containing benzalkonium chloride often compromise patients' compliance.[13] Long-term use of eye drops containing preservatives may be associated with failure of surgical treatment.[14–16] The most widely used preservative is benzalkonium chloride, which damages conjunctival and corneal cells, and inhibits the proliferation of trabecular cells *in vitro*.[17] Results of a European study that included 9,658 glaucoma patients in Italy, France, Belgium, and Portugal showed that preservative-free eye drops are significantly less associated with ocular symptoms and signs of irritation than preserved eye drops.[18]

Preservative-free eye drops answered an important medical need for preservative-sensitive patients to avoid corneal damage, eye irritation, and dry eye syndrome. Cosopt-S® (MSD SHARP & DOHME GmbH, Munich, Germany) are preservative-free eye drops that contain the carbonic anhydrase inhibitor dorzolamide (20 mg/mL) and the beta-adrenergic antagonist timolol maleate (5 mg/mL) in a fixed combination.

This study investigates the efficacy [intraocular pressure (IOP) lowering effect] and tolerability of preservative-free

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Cosopt-S® in 2,298 patients with different types of glaucoma requiring potent IOP reduction and being intolerant to the preservative benzalkonium chloride or active agents of previously used eye drops as judged by the corresponding investigator. Particular interest was paid to an effective IOP reduction by the use of preservative-free dorzolamide/timolol combination eye drops and the improvement of tolerability as compared to previous therapy.

Methods

Design

This was a prospective, open, noncomparative, multicenter, noninterventional study in 2,338 patients currently requiring topical glaucoma management and suffering from intolerance to their previous glaucoma treatment. Study sites were 470 ophthalmological practices in Germany. The enrolment lasted from October 2006 until April 2007 and was based on routinely scheduled attendance. The planned observation period was 12 weeks for each patient. IOP measurements were performed 3 times during the study period: at baseline, after 2–3 weeks, and after 12 weeks. Adverse drug reactions (ADRs) were assessed throughout the study period. Improvement of local tolerability as compared to previous treatment was assessed after 12 weeks from each investigator, based on evaluation of palpebral, conjunctival, and corneal signs.

Patients with open-angle glaucoma were switched from their previous antiglaucomatous therapy to preservative-free Cosopt-S® at baseline. If previously untreated, patients started their anti-glaucomatous therapy with Cosopt-S®. After patients' informed consent was obtained, all participants received a unit dose of the preservative-free dorzolamide/timolol eye drops (Cosopt-S®) twice daily according to prescription information. The study was performed according to good clinical practice (GCP) guidelines and followed the tenets of the Declaration of Helsinki. The study was approved by the competent authorities (Federal Institute for Drugs and Medical Devices; BfArM, Bonn, Germany, and National Association of Statutory Health Insurance Physicians, NASHIP, Berlin, Germany), according to the German drug law § 67 (6) for postmarketing surveillance studies.

Statistical analysis

Analysis of IOP was based on the eye with the higher IOP in case both eyes were affected. For analysis of IOP measurements only patients with data available for all 3 visits (baseline, week 2/3, and week 12) were considered.

Absolute and percent change of IOP between baseline and after 12 weeks was calculated by means of the formula: absolute change = value at week 12 − value at baseline; percent change = [(value at week 12 − value at baseline)/value at baseline] × 100%.

ADRs (causality rating by the investigator: yes, probable, possible, or not assessable) were coded according to MedDRA® (Version 10.0) and analyzed on preferred term level.

Subgroup analyses were performed with respect to previous antiglaucomatous therapy for change of IOP and improvement of local tolerability. Subgroups included only patients who received previous antiglaucomatous therapy and treatment with Cosopt-S® eye drops as monotherapy, that is, without any other concomitant antiglaucomatous treatment. In addition, only subgroups comprising at least 30 patients were considered for statistical analysis.

All statistical analysis was performed descriptively by means of the SAS® system, version 9.1 (SAS® Institute, Cary, NC).

Results

In total, data of 2,338 patients were documented. Data of 40 patients were not subject to statistical analysis because of the following reasons: use of Cosopt-S® before baseline (25 patients), missing documentation of the course of treatment (7 patients), or age <18 years (8 patients). Therefore, data of 2,298 patients with different forms of glaucoma and intolerance to benzalkonium chloride or other agents of previously used glaucoma medication (eg, allergic reaction, irritation, redness, or dry eye sensation) were subject to baseline and safety analysis.

Two hundred forty-nine patients were excluded from efficacy analysis because they did not provide IOP measurement data for all 3 visits (baseline, 2–3 weeks, and 12 weeks). Therefore, $N = 2{,}049$ patients were considered for efficacy evaluation (Fig. 1).

Baseline characteristics

More female (60.9%) than male patients were enrolled in this study. Mean patient age was 66.0 years. Open-angle glaucoma types were divided as following: primary open-angle glaucoma ($N = 795$, 34.6%), normal tension glaucoma ($N = 224$, 9.7%), pseudoexfoliation glaucoma ($N = 212$, 9.2%), and others ($N = 1{,}067$, 51.1%). In 92.3% of glaucoma patients, both eyes were affected; 2,047 patients (89.1%) were receiving antiglaucomatous therapy before enrolment.

The most frequently prescribed previous medications (>10% of patients) were timolol ($N = 576$, 25.1%) and the fixed combination dorzolamide/timolol containing preservatives ($N = 402$, 17.5%) followed by latanoprost ($N = 287$, 12.5%) and dorzolamide alone ($N = 254$, 11.1%).

Three hundred sixteen patients (13.8%) received further antiglaucomatous medications concomitantly to Cosopt-S®. Among these, the most commonly used preparations were latanoprost ($N = 132$, 5.7%) and travoprost ($N = 48$, 2.1%).

Previously treated patients were switched to preservative-free Cosopt-S® eye drops at baseline; 84.5% of patients reported local intolerance to previously used preparations. About 1,405 (61.1%) patients suffered from local intolerance to the preservative benzalkonium chloride contained in previously used glaucoma medications. Active ingredients of the previous antiglaucomatous agents were reported to be responsible for local intolerance in 288 (12.5%) of patients.

The most frequently reported intolerance symptoms were eye irritation ($N = 1{,}095$, 47.7%) and redness of the eye ($N = 1{,}052$, 45.8%). Other important reasons to switch to Cosopt-S® included insufficient IOP reduction ($N = 1{,}037$, 45.1%) and poor compliance ($N = 239$, 10.4%).

Mean treatment duration, that is, the interval between start of treatment with Cosopt-S® and the final examination (week 12) was 3.1 months (median: 3.1 months).

Efficacy

Mean IOP at baseline was 20.8 mmHg (median: 20.0 mmHg).

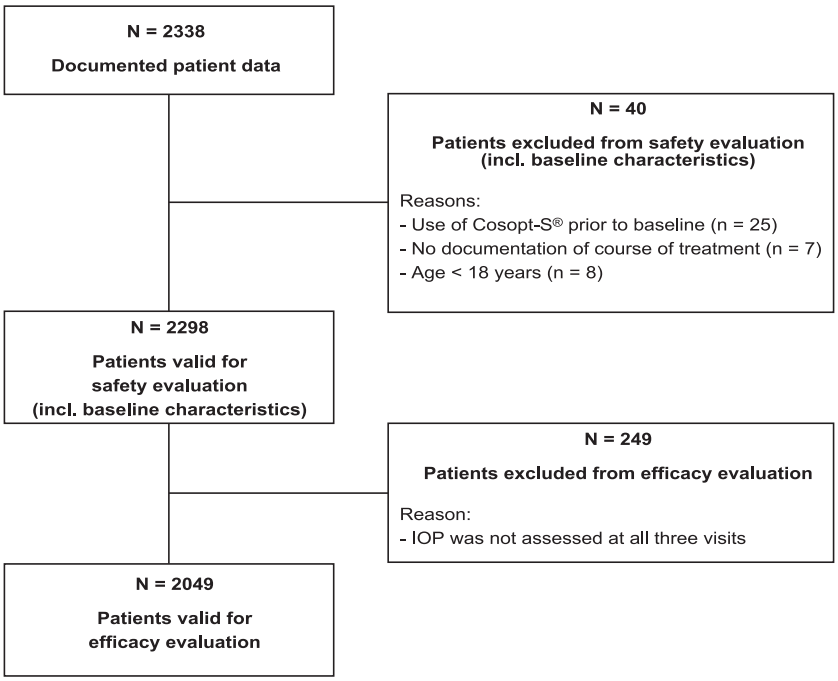

FIG. 1. Patients' eligibility for evaluation.

Mean baseline IOP was reduced to 17.1 mmHg after 2–3 weeks and 16.7 mmHg after 12 weeks of glaucoma treatment with Cosopt-S®. This corresponds to a mean absolute (percent) change of −4.1 mmHg (−17.3%) after 12 weeks. The proportion of patients with IOP ≤21 mmHg increased from 59.9% at baseline to 94.6% after 12 weeks.

The overall mean percent change in IOP for patients on Cosopt-S® monotherapy during treatment phase was −17.8%. For patients receiving Cosopt-S® as monotherapy, subgroup analysis for change of IOP was performed with respect to previous antiglaucomatous therapy. The highest mean percent change in IOP between baseline and after 12 weeks (eg, reduction < − 20%) was observed for preparations containing timolol (−22.6%), metipranolol (−22.6%), dorzolamide (−21.3%), and brinzolamide (−20.8%). The lowest mean percent change in IOP was detected in patients pretreated with dorzolamide/timolol containing preservatives. The highest IOP reduction was registered in patients without any previous antiglaucomatous therapy (−30.7%, Fig. 2).

However, IOP decrease was related on IOP levels at baseline: in fact, patients with high IOP at baseline, for example, patients without any previous antiglaucomatous therapy, showed a more pronounced IOP reduction than patients with lower baseline levels, for example, patients pretreated with dorzolamide/timolol containing preservatives (Table 1). These results are in accordance with the fact that the 25% of patients with the highest baseline IOP had a much stronger IOP reduction under Cosopt-S® monotherapy than the 25% of patients with the lowest baseline IOP (−31.1% vs. −4.7%, Fig. 3).

Tolerability

In total, 220 ADRs (causality rating by the investigator: yes, probable, possible or not assessable) occurred in 143 patients (overall incidence: 6.2%). One hundred seventy-six nonserious ocular ADRs occurred in 125 patients (5.4% of 2,298 patients), which are displayed in Table 2.

The most frequently reported terms were burning eyes in 56 patients (2.4%) and ocular hyperemia in 20 patients (0.9%). An increased risk for eye infections was not observed. Two serious ADRs occurred in one patient (0.04% of 2,298 patients): a 63-year-old woman with open-angle glaucoma reported anginal discomfort and shortness of breath. The treating ophthalmologist assessed both events as being probably related to study treatment. The local therapy with

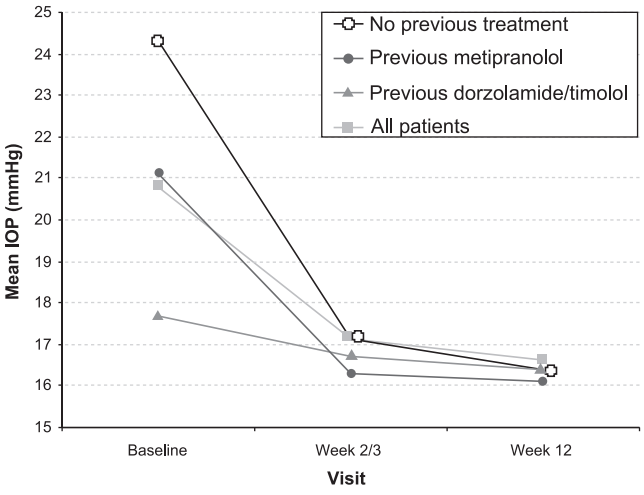

FIG. 2. IOP change under Cosopt-S® monotherapy in respect to previous glaucoma therapy. IOP, intraocular pressure.

Table 1. IOP (mmHg) and IOP Change Overall and by Type of Previous Treatment for Patients on Cosopt-S® Monotherapy During Treatment Phase

		Preservative-free dorzolamide/timolol combination			
Previous treatment[a]	*No. of patients*	*Baseline, mean ± SD*	*Week 12, mean ± SD*	*Change, mean ± SD*	*% Change, mean ± SD*
No previous treatment	230	24.3 ± 4.9	16.4 ± 3.2	−7.9 ± 5.0	−30.7 ± 14.8
Metipranolol	42	21.1 ± 3.6	16.1 ± 2.4	−5.0 ± 3.0	−22.6 ± 11.6
Timolol	335	21.7 ± 3.7	16.5 ± 2.6	−5.2 ± 3.4	−22.6 ± 12.9
Dorzolamide	103	21.1 ± 3.9	16.5 ± 4.1	−4.5 ± 2.9	−21.3 ± 12.4
Brinzolamide	64	20.4 ± 4.2	15.8 ± 2.8	−4.6 ± 3.7	−20.8 ± 16.0
Brimonidine	51	20.5 ± 4.0	16.2 ± 2.5	−4.3 ± 3.2	−19.4 ± 11.7
Bimatoprost	51	19.9 ± 4.4	16.3 ± 2.9	−3.6 ± 4.4	−15.4 ± 17.9
Travoprost	79	19.4 ± 3.8	16.0 ± 2.7	−3.3 ± 3.8	−15.4 ± 15.2
Latanoprost/timolol	43	19.7 ± 4.4	16.6 ± 3.0	−3.1 ± 3.7	−13.4 ± 17.1
Latanoprost	101	19.2 ± 4.0	16.5 ± 2.8	−2.7 ± 3.4	−12.4 ± 13.5
Brimonidine/timolol	51	19.8 ± 4.5	17.2 ± 2.8	−2.6 ± 3.7	−10.9 ± 18.3
Travoprost/timolol	27	19.6 ± 3.0	17.6 ± 2.5	−2.0 ± 2.3	−9.4 ± 10.3
Dorzolamide/timolol	248	17.7 ± 3.5	16.4 ± 3.2	−1.3 ± 2.5	−6.3 ± 13.9
Total[b]	1,749	20.8 ± 4.5	16.6 ± 3.0	−4.2 ± 4.1	−17.8 ± 16.2
Highest baseline IOP	435	26.7 ± 3.3	18.2 ± 3.6	−8.5 ± 4.4	−31.1 ± 13.3
Lowest baseline IOP	402	15.3 ± 1.8	14.5 ± 2.5	−0.8 ± 2.3	−4.7 ± 16.2

Entries are sorted by % change of IOP in descending order.

[a]Criteria for definition of subgroup populations: (i) previous treatment as monotherapy; (ii) Cosopt-S® monotherapy during treatment phase.

[b]Criteria for definition of total population: (i) no restriction in respect to previous antiglaucomatous treatment; (ii) Cosopt-S® monotherapy during treatment phase.

IOP, intraocular pressure; SD, standard deviation.

Cosopt-S® was discontinued, and the patient recovered from both events without sequelae.

Local tolerability as assessed by the investigators improved during the treatment with Cosopt-S® eye drops compared to the previous glaucoma therapy in 1,576 patients (79.3% of 1,987 patients with previous antiglaucomatous therapy and documented tolerability data). Subgroup analysis showed the strongest improvement of local tolerability (eg, >90% of affected subjects) in patients pretreated with bimatoprost (97.7%) and brimonidine (93.9%). Improvement rates for all other pretreatment subgroups ranged from 79.3% (travoprost/timolol) to 89.7% (metipranolol; Table 3).

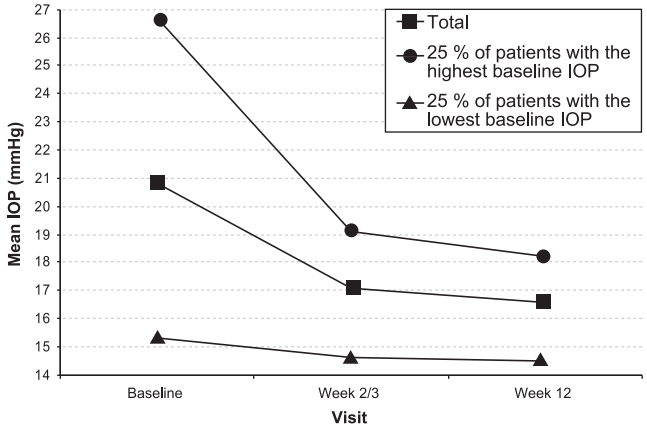

FIG. 3. IOP change under Cosopt-S® monotherapy in respect to baseline IOP.

Discussion

The objective of this study was to investigate whether a preservative-free dorzolamide/timolol combination is efficient in reducing IOP and has an improved side-effect profile for routine use in glaucoma patients.

During study treatment with Cosopt-S®, a marked and sustainable reduction of IOP could be achieved (mean percent change −17.3%), although IOP changes were dependent on previously used anti-glaucomatous medication.

Table 2. Patients with Nonserious Ocular Adverse Drug Reactions to Preservative-Free Dorzolamide/Timolol Eye Drops

Adverse drug reactions	*No. of patients with ADRs*	*% of 2,298 patients*
Burning eyes	56	2.4
Ocular hyperemia	20	0.9
Tearing eyes	13	0.6
Eyelid oedema	10	0.4
Allergic conjunctivitis	9	0.4
Eye irritation	6	0.3
Conjunctival hyperemia	6	0.3
Eyelid erythema	6	0.3
Eyelid irritation	6	0.3
Blepharitis	5	0.2
Itching eyes	5	0.2
Conjunctival irritation	4	0.2
Allergic blepharitis	4	0.2
Blurred vision	4	0.2
Eye pain	3	0.1

ADRs, adverse drug reactions.

Table 3. Improvement of Local Tolerability Under Monotherapy with Preservative-Free Dorzolamide/Timolol Overall and by Type of Previous Treatment

	Preservative-free dorzolamide/timolol combination		
Previous treatment[a]	*No. of documented patients*	*No. of patients improved*	*%*
Bimatoprost	44	43	97.7
Brimonidine	49	46	93.9
Metipranolol	39	35	89.7
Latanoprost	98	87	88.8
Latanoprost/timolol	44	39	88.6
Travoprost	73	64	87.7
Brimonidine/timolol	52	44	84.6
Dorzolamide/timolol	263	221	84.0
Brinzolamide	59	49	83.1
Dorzolamide	80	65	81.3
Timolol	282	227	80.5
Travoprost/timolol	29	23	79.3
Total[b]	1,438	1,216	84.6

Entries are sorted by % improvement in descending order; missing data were excluded from this analysis (valid data analysis).

[a]Criteria for definition of subgroup populations: (i) previous treatment as monotherapy for at least 30 patients; (ii) Cosopt-S® monotherapy during treatment phase.

[b]Criteria for definition of total population: (i) no restriction in respect to previous antiglaucomatous treatment; (ii) Cosopt-S® monotherapy during treatment phase.

At the same time, side effect rates were considerably low with the most reported side effects being burning eyes (2.4%) and hyperemia (0.9%). Local tolerability improved in the vast majority of patients (79.3%) when compared to previous glaucoma treatment. This observation is substantiated by the fact that after 12 weeks the treatment with Cosopt-S® was continued in 86.8% of the cases.

A large European study compared the prevalence of side effects between eye drops with or without preservatives in 9,658 glaucoma patients. Compared to preserved eye drops, preservative-free preparations were significantly less associated with ocular symptoms, for example, pain or discomfort during instillation (48% vs. 10%), foreign body sensation (42% vs. 15%), or stinging or burning (48% vs. 20%).[18]

In the present study, the most reported intolerance symptoms before Cosopt-S® were eye irritation (47.7%) and eye redness (45.8%). The incidence rates of ocular symptoms observed in this study with the preservative-free dorzolamide/timolol fixed dose combination were considerably lower (eg, burning eyes in 2.4% of patients as the most frequent reported ADR) than those found by Jaenen and colleagues.[18] Although different reporting procedures were applied in the 2 investigations, the present results indicate a good tolerability of the preservative-free dorzolamide/timolol preparation.

In this study, patients who switched from the preserved (Cosopt®) to the preservative-free dorzolamide/timolol combination (Cosopt-S®) had a mean IOP reduction of 6.3%. This may be the result of a better patient compliance based on an improved tolerability of the preservative-free solution.

The availability of preservative-free topical glaucoma medications has increased the treatment options for glaucoma patients intolerant to preservatives such as benzalkonium chloride. Preservative-free topical glaucoma preparations appear to be as efficacious as preparations with preservatives, whereas they induce less conjunctival inflammation and local side effects,[19–22] as also shown by the present data.

In conclusion, this study adds further evidence concerning the benefit of preservative-free eye drops in glaucoma treatment. Cosopt-S® offers an efficient and safe treatment alternative for glaucoma patients suffering from intolerance to the preservative benzalkonium chloride or active agents other than dorzolamide or timolol. The results of this study underline the good tolerability, the safety profile with low incidence of adverse events, and the pronounced IOP-lowering effect of Cosopt-S® eye drops in preservative-sensitive glaucoma patients.

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Author Disclosure Statement

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