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GLAUCOMA

Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction

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Abstract
Background To compare the tolerability of commonly prescribed topical glaucoma medications by determining frequency and bother of side effects, patient satisfaction with their medication, and the chance of discontinuation of eye drops.
Methods The tolerability of topical glaucoma medication was studied in glaucoma patients from nine hospitals. The frequency and severity of side effects was investigated together with patient satisfaction with the medication and the probability to change medication due to reported side effects. To register side effects of topical glaucoma medication, patients were requested to fill in a questionnaire based on "the Comparison of Ophthalmic Medications for Tolerability" (COMTOL) questionnaire supplemented with items based on the most frequently observed and severe side effects.
Results The number of patients responding was 3,333 (87%). Most patients (79%) were satisfied with their eye medication. The median score for ocular side effects was 58 on a scale ranging from 0 to 320. The probability that medication would be changed by the ophthalmologist at the next visit due to reported side effects occurring since the patients' last or last but one visit to the ophthalmologist was 9%. The most frequently prescribed drugs were timolol, latanoprost, and the fixed combinations of dorzolamide/timolol (Cosopt®) and latanoprost/timolol (Xalcom®). Only small differences in tolerability were found between these drugs.
Conclusions The tolerability of timolol, latanoprost, and the fixed combinations of latanoprost/timolol (Xalcom®) and dorzolamide/timolol (Cosopt®) seem to be comparable. Patients are satisfied with their glaucoma medication and have a low chance of discontinuation of eye drops due to side effects.

Keywords Glaucoma · Glaucoma medication · Side effects

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Introduction

Side effects of glaucoma medication are frequently documented in case reports in a small series of patients without any comparison to other drugs. A comparison of tolerability between drugs can be made in a randomized controlled trial, but usually the comparison is made between only two drugs: a new glaucoma drug and one that has been available for a longer period of time. Such studies are generally performed in ideal circumstances with a selection of healthier patients and with standardized reporting of adverse events including systematic questioning of patients,

which may perhaps not reflect daily life. The scientific literature on adverse events of glaucoma medication is also limited because most often only one assessment method is used.

A useful method to study the side effects of glaucoma medication would be to combine clinical observations or measurements of side effects with more subjective measurements, such as assessing the patients' perspective with respect to side effects with a "patient reported outcome" (PRO) instrument. Additionally, directly comparing all commonly prescribed glaucoma medication in a large patient population may reflect a real life situation.

In the present study, the results of a patient questionnaire registering frequency and bother of side effects of different drugs and patient satisfaction with their medication were studied together with the probability of changing topical glaucoma therapy by ophthalmologists due to reported side effects, in the same study population of 3,841 glaucoma patients from nine Dutch hospitals.

Materials and methods

Sample and setting

The data from 3,841 patients who were recruited from nine centers (academic, teaching, and non-teaching hospitals) participating in the DUtch Research project on treatment outcome IN Glaucoma patients (DURING) study were used [1, 2]. The DURING study population consisted of glaucoma patients who already used or started to use glaucoma medication. Patients were enrolled between March 2001 and January 2004. The mean age±standard deviation of patients included was 69±12 years, ranging from 21 to 97 years, 1,920 (50%) were male. The majority of patients (85%) were diagnosed with open-angle glaucoma (69%), ocular hypertension (9%), or glaucoma suspect (7%).

Variables and measurements

The side effects of topical glaucoma medication were registered by asking patients to fill in a questionnaire based on "the Comparison of Ophthalmic Medications for Tolerability" (COMTOL) questionnaire [3]. The COMTOL questionnaire was designed and validated for comparing the tolerability of topical glaucoma medications. Since the COMTOL mainly focuses on side effects of pilocarpine and timolol, the questionnaire was modified for our present purpose. Several items were left out, such as items especially dealing with side effects of pilocarpine and items dealing with limitation in activities. Items dealing with compliance were also left out since it was not the purpose of the present study to thoroughly study compliance. Next, the questionnaire was supplemented with items listed in the Farmacotherapeutisch Kompas, a guide for medical therapy issued by the Dutch Health Care Insurance Board [4]. To ensure content validity, two glaucoma specialists studied these listed items independently of each other, after which the most frequently observed and/or severe side effects of all commonly used glaucoma medications were included in the final patient questionnaire. It was taken into account that patients should be able to notice the side effects themselves.

The ocular symptoms listed were burning, stinging, conjunctival hyperaemia, itching, ocular secretion, ocular pain, tearing, brow ache, dryness, foreign body sensation, eyelid redness, eyelid oedema, blurred vision, visual acuity loss, accommodation difficulties, and night vision problems. For each side effect, the frequency of the symptoms and the severity of bother for the patient were documented. The questions concerning the frequency of effects were graded from 'Did not experience', 'One day', 'Several days', 'About half of days', 'Almost every day' and 'Every day' in the preceding 14 days. The questions concerning the intensity of bother were graded from 'Not at all bothered', 'A little bothered', 'Quite bothered', 'Much bothered' and 'Extremely bothered'.

In addition, questions were asked concerning patient satisfaction with their medication. The patients were asked to indicate their level of satisfaction on a 7-point scale: 'Very unsatisfied', 'Unsatisfied', 'A little unsatisfied, 'Not unsatisfied nor satisfied', 'A little satisfied', 'Satisfied' and 'Very satisfied'.

Procedure

To identify as many patients as possible with recent changes in their glaucoma medication, consecutive patients, participating in the DURING study, were asked to fill out the questionnaire at least twice, each time after a visit to their ophthalmologist. They were asked to fill out at least two questionnaires to be able to find reported changes in response. Only the first questionnaire filled out was used in the final analysis to prevent double counting of the same patient. Changes in responses were not analyzed. After collecting all data, only patients who used their current glaucoma medication or combination of medications for the first time since their last or last but one visit to the ophthalmologist (e.g., new patients or patients switching or adding medication) were included in the study. This procedure was chosen to prevent loss to follow-up and to prevent bias originating from differences between patients using medications from a shorter or longer period of time. We wanted to include only subjects that recently started using a particular drug, since it is to be expected that

Table 1 The probability of discontinuing glaucoma medication due to side effects; the percentage of patients not (very) satisfied with their medication and the percentage of patients who obtained a score of 58 or more on the list of ocular symptoms

		Discontinued medication		Unsatisfied		Score of ocular symptoms	
		Total number of visits	(%)	Total number of patients	(%)	Total number of patients	(%)
	Total	1,630	9	960	21	960	58
♦	Timolol	119	8	71	18	71	58
♦	Timolol (gellans)	193	6	115	17	115	44
	Timolol (preservative-free)	24	13	18	17	18	39
	Betaxolol (Betoptic®)	44	9	30	27	30	60
	Betaxolol (Betoptic-S®)	36	17	28	25	28	57
♦	Other β-blockers	14	7	7	0	7	43
	Latanoprost	280	8	170	23	170	56
O	*Bimatoprost*	*45*	*13*	*28*	*29*	*28*	*75*
♦	Travoprost	30	3	12	8	12	25
	Brimonidine	22	23	14	36	14	50
	Dorzolamide	14	14	8	0	8	63
O	*Brinzolamide*	*22*	*23*	*12*	*33*	*12*	*67*
	Pilocarpine	13	8	4	0	4	75
	Other monotherapy (n<26)	7	29	4	25	4	50
	Dorzolamide/timolol (Cosopt®)	164	12	100	16	100	56
	Latanoprost/timolol (Xalcom®)	133	5	83	23	83	49
O	Pilocarpine/metipranolol; pilocarpine/timolol	16	13	12	25	12	67
	Latanoprost/timolol	37	3	18	22	18	83
	Latanoprost/Timoptol XE®	30	7	21	14	21	57
	Latanoprost/betaxolol (Betoptic®)	14	7	10	0	10	70
	Latanoprost/betaxolol (Betoptic-S®)	7	0	6	33	6	67
	Latanoprost/carteolol (Teoptic®)	14	14	7	14	7	57
	Latanoprost/levobunolol	9	11	3	0	3	67
O	Latanoprost/dorzolamide	18	22	9	56	9	89
	Latanoprost/brinzolamide	14	21	6	0	6	67
	Latanoprost/brimonidine	32	13	20	25	20	50
	Latanoprost/dorzolamide/timolol (Cosopt®)	73	5	45	13	45	62
O	Latanoprost/timolol/pilocarpine (Timpilo®)	6	17	3	33	3	67
	Other combinations of 2 medications (n<26)	153	8	73	19	73	66
	Other combinations of 3 or more medications	47	6	23	22	23	87
Chi^2-test		p=0.12		p=0.40		p=0.03	

Medications obtaining at least a median score or doing better on all three parameters are shown in **bold (♦)**. Medications obtaining a lower than median score on all three parameters are shown in *italic* (O).

patients who use a certain drug (e.g., timolol) for a longer period of time experience fewer side effects when compared to patients on newer drugs who have not used this drug for such a long period. In this latter group, patients and ophthalmologists are likely to stop the treatment when patients experience a lot of side effects from the beginning of their use. This difference between long-term and short-term users introduces a bias in the comparison of drugs.

The questionnaire was handed to the patients at their visit to the outpatient department. To provide the patients with ample time for answering all questions, they were asked to open the envelope with the questionnaire directly after arriving home, answer the questions, and return the questionnaire within 14 days. The questions asked referred to the period of 14 days preceding their last visit to the ophthalmologist at the outpatient clinic.

In addition, at each patient visit ophthalmologists indicated on a form if they had decided to stop glaucoma medication.

Analysis

The first questionnaires filled out by the patients were used for analysis. Since patients were considered as satisfied only when they had indicated to be “Satisfied” or “Very satisfied” with their eye drops, for the variable ‘patient satisfaction’ the percentage of patients who filled out “Satisfied” or “Very satisfied” was calculated.

The items concerning the frequency of side effects were scored on a scale from 0 to 5. On this scale, 0 represented 'Did not experience' and 5 represented 'Every day'. Likewise, the items concerning the severity of bother were scored on a scale from 0 ('Not at all bothered') to 4 ('Extremely bothered'). Both scores were multiplied to determine the final score per item on ocular side effects. Next, these final scores per type of side effect were summed over all types of side effects. This sum was used to assess the median value. The next step was to calculate per glaucoma drug the percentage of patients with a lower or higher score than this median value. For the variable 'stopping glaucoma medication due to side effects', the percentage of visits to the outpatient clinic during which the ophthalmologist decided to stop the use of a certain glaucoma medication was calculated. In this analysis, all the visits during which the ophthalmologist had filled out a form were included to a maximum of two visits per patient.

The Pearson Chi-square test was used to test for a statistically significant difference between the drugs. This test was conducted for every variable of tolerability: chance of stopping the drug, satisfaction, and reported side effects. In addition, standardized residuals were calculated if the *p*-value of the Pearson Chi-square was smaller than 0.05, to identify the drug(s) that had a more or less than expected value of this item for tolerability leading to a statistically significant difference between the drugs.

Results

The number of patients responding was 3,333/3,841 (87%). These patients returned at least one questionnaire. From these, only patients who used their glaucoma medication or combination of medications for the first time since their last or last but one visit to the ophthalmologist were included in the data analysis. The data analysis showed that 79% of patients were satisfied or very satisfied with their eye medication. The median score for ocular side effects was 58 on a scale from 0 to 320. The probability of changing medication due to side effects after a visit to the ophthalmologist was 9%.

The probability that the use of medication was discontinued by the ophthalmologist due to side effects after each visit to the outpatient clinic, the percentage of patients who were not satisfied with their eye drops and the percentage of patients who obtained a score of 58 or more on the list of ocular symptoms is shown in Table 1 for every drug (combination). Although in the table medications obtaining at least a median score or better are shown in bold, and medications obtaining a lower than median score on all three parameters are shown in italic, differences between medications for the variables "discontinued medication" (p=0.12) and "unsatisfied" (p=0.40) were not statistically significant. However, there was a statistically significant difference for the variable "score of ocular symptoms" (p=0.03). Further analysis revealed that for timolol gellans, the standardized residual was greater than 2, implying that fewer subjects on this medication had reported side effects. Also, for the group 'other combination of 3 or more medications' the standardized residual was lower than –2, implying that patients using these combinations reported more side effects.

The numbers per drug (combinations) were small, and most (combinations of) medications were reported in less than 50 questionnaires/visits to the ophthalmologist. Medications that were used by more than 50 patients were timolol, latanoprost, the fixed combination of dorzolamide and timolol (Cosopt®) and the fixed combination of latanoprost and timolol (Xalcom®). Even between these groups there were no large differences in side effects.

Discussion

In the present study, no statistically significant differences in tolerability between commonly prescribed topical glaucoma medications were observed as assessed by the chance of discontinuing the drug or patient satisfaction. There was a statistically significant difference for self-reported side effects. This was due to more reported side effects among the users of 'other combinations of three or more medications' and fewer reported side effects for the users of timolol gellans. This was a large study on side effects of commonly used (combinations of) medications in daily practice, using patient self-reported questionnaires and the discontinuation of drugs by the ophthalmologist as a consequence of side effects. Although a causal relationship between ocular complaints and discontinuing eye drop treatment cannot be proven, the ophthalmologists made the decision to continue or to stop drops on account of their observations of side effects. However, ophthalmologists may possibly have had more than one reason to decide to stop a certain medication. Therefore, it cannot be ruled out that other motivations, e.g., worsening of visual fields, could also have influenced their decision to discontinue a certain drop. Ocular complaints and symptoms were found to be the main cause for changing the medical regimen by the ophthalmologists.

Although differences in the amount and nature of side effects between the investigated glaucoma medications or combinations of glaucoma medications were found, these differences were small, even between the medications or combinations of medications that were used by at least 50 patients. These medications were timolol, latanoprost, the fixed combination of latanoprost and timolol (Xalcom®)

and the fixed combination of dorzolamide and timolol (Cosopt®). These results corroborate published review studies on glaucoma medication [5–13].

The present results also show that patients are satisfied or very satisfied with their eye drops. The probability of changing medication due to side effects was low.

However, patients with combinations of three or more medications had higher levels of ocular symptoms. Since the number of glaucoma operations in the Netherlands has almost halved after the introduction of new glaucoma medications, it may be that these patients rather accept more ocular symptoms than undergo glaucoma surgery [14].

The interpretation that certain complaints or symptoms leading to a discontinuation of a certain glaucoma medication are caused by the use of this medication needs to be carefully made. For example, preservatives in eye drops are potentially harmful to ocular tissues and may cause allergic reactions in certain individuals [15, 16]. A preservative-free drop might have been given to a patient who experienced side effects presumed to be caused by the preservative in the drops. In case the side effects did not wear off, the preservative probably was not the cause of these side effects. Consequently, the overall score for side effects may rise to a higher level. Additionally, selection bias could have occurred because frequently new medications are especially tried for patients who have experienced side effects for other drugs. Possibly these patients are more prone to side effects of eye drops or preservatives in drops.

As far as systemic side effects are concerned, many commonly presumed adverse effects of beta-adrenergic blocking agents observed via systemic or ocular administration are not supported by published randomized clinical trials [17]. In the present study, although fewer reported side effects were found for the users of timolol gellans, some patients may have stopped taking these drops because of the presumed systemic side effects. However, we could not prove a causal relationship since we did not refer patients for further physical examination.

Finally, several complaints or symptoms (like blurred vision) may have been caused by other ocular problems. Ocular side effects related to the use of systemic medications may also occur[18].

Side effects can possibly be severe [19]. Most side effects that were registered concerning glaucoma medications in the present study are reversible. Therefore, patients are often only temporarily bothered with significant side effects.

Although this was a fairly large study population, the medications and combinations of medications that were investigated were often used by only a small number of patients, making it difficult to show differences between drugs. Furthermore, a more detailed interpretation of the present results is hampered because rare side effects may have been missed. Therefore, discriminating between the different glaucoma medications on the ground of rare side effects is impossible. Additionally, side effects that occur after a longer follow-up period (e.g., iris pigmentation) were not found in the present study since we included only subjects who recently started using their medication.

Further study on side effects of topical glaucoma medication would be useful; by collecting more data in a larger study population using patient reporting lists differences between drugs may become more apparent, causality may be proven by studying observed changes in reporting after stopping a drug, a longer follow-up period could possibly reveal long-term and rare side effects, and a study of systemic side effects could be set up.

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