Switching from Systemic to the Topical Carbonic Anhydrase Inhibitor Dorzolamide: Effect on the Quality of Life of Glaucoma Patients with Drug-Related Side Effects

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Abstract

Background: The frequent systemic side effects associated with the use of systemic carbonic anhydrase inhibitors have adversely affected the compliance to treatment in glaucoma patients, obviating their long-term use. The introduction of the topical CAI dorzolamide has further reduced their use. However, the tolerability of dorzolamide in patients who have been intolerant to systemic CAIs has not been evaluated prospectively.

Objectives: To study the tolerability and efficacy of dorzolamide (a topical CAI) in a selected group of glaucoma and ocular hypertensive patients who have been intolerant to systemic CAI.

Methods: A 3 month prospective study was conducted in 39 patients. Following recruitment, patients were evaluated on the day of switching from systemic CAI to dorzolamide and for five more visits. The SF-36 health assessment questionnaire was used to evaluate changes in well-being and quality of life, and the intraocular pressure was measured periodically.

Results: Within 4 weeks of switching from systemic CAI to dorzolamide, the mean health assessment scores improved significantly in seven of the eight categories of the SF-36, and remained generally unchanged for the rest of the study. No significant differences were noted between the mean IOP on day 0 and the following measurements throughout the 84 days of dorzolamide therapy.

Conclusion: In glaucoma patients who were intolerant to systemic CAI, topical CAI dorzolamide offers a similar efficacy and better tolerability.

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Though disliked by patients, the systemic carbonic anhydrase inhibitors were an integral part of the medical treatment of glaucoma for several decades. However, the long list of systemic side effects has obviated their use by many patients, leading to low compliance and resulting in the use of reduced and ineffective dose in some cases and discontinuation of the drug in others [1–3]. Some patients managed to continue these CAIs despite the adverse effects, at the cost of decreasing quality of life. Some CAIs were better tolerated than others by certain patients (acetazolamide versus metazolamide versus daranide), and switching to a long-acting medication (diamox sustets) was also better tolerated. The recent development of topical CAI was thus a welcome solution to an important but most unpleasant drug. Studies of treatment with topical CAI have shown effective pressure control in patients who shifted from oral to topical treatment [2,4,5]. With minimal side effects that were reported initially, the topical CAI dorzolamide seemed to be the perfect replacement for its systemic counterpart.

Intolerance to a systemic CAI leading to discontinuation of treatment has been reported to occur in approximately 25% of patients [2,5]. Although the rate of topical CAI-related side effects is considered to be low, the tolerability of the topical agent by those patients who discontinued the systemic drug due to adverse effects has not been specifically evaluated. We conducted a 3 month prospective study on the tolerance and efficacy of dorzolamide in ocular hypertensive and glaucoma patients who had been previously intolerant to acetazolamide or metazolamide.

Patients and Methods

Our study group consisted of 39 patients with open-angle glaucoma or ocular hypertension. They were recruited from the Glaucoma Clinic at the Ophthalmology Department of Hadassah University Hospital, Jerusalem between 1997 and 1998. Patients qualified for entry into the study if one of the following inclusion criteria was met: a) systemic CAI was discontinued in the past due to side effects, and the patient agreed to a re-challenge with the drug for at least 1 week prior to initiation of treatment with topical CAI; b) a systemic CAI was recently initiated and used for at least 1 week, and the patient complained of side effects and was reluctant to continue with systemic CAI; or c) patients who were on chronic treatment with systemic CAI despite continuous complaints of side effects and were reluctant to undergo surgery. Patients with visual acuity of 20/200 or less were excluded. Upon entry to the study, data on side effects attributed to systemic CAIs and their degree of severity were recorded.

Following recruitment, patients were evaluated on the day of switching from systemic CAI to dorzolamide (day 0), and on days 7, 14, 28, 56, and 84 of treatment with dorzolamide. Dorzolamide (Trusopt®) was supplied by Merck. On each of the follow-up visits the intraocular pressure was measured with a Goldmann applanation tonometer at approximately 9 a.m. and 11 a.m. The medication (systemic CAI on day 0, or dorzolamide on the following days) was taken following the 9 a.m. measurement. All other anti-glaucoma medications were continued unchanged throughout the study.

CAI = carbonic anhydrase inhibitor
IOP = intraocular pressure

The SF-36 health assessment questionnaire was used to evaluate and monitor patients' self-evaluation of well-being and quality of life during the study [6]. The SF-36 health questionnaire was filled out by the patients on day 0 (last day on systemic CAI), and on day 28 and day 84 of topical CAI therapy. Eight categories were addressed: a) limitations in physical activities because of health problems, b) limitations in usual role activities because of physical health problems, c) bodily pain, d) general health perceptions, e) vitality (energy and fatigue), f) limitations in social activities because of physical or emotional problems, g) limitations in usual role activities because of emotional problems, and h) general mental health (psychological distress and well-being). The responses for each category were summed and transformed based on a formula [7] to provide eight scores between 0 and 100.

Table 1. Side effects of treatment with acetazolamide in the 39 study patients (% of patients)

	Total	Mild	Moderate	Severe
Fatigue	100	12	55	33
Paresthesia	75	20	27.5	27.5
Depression	62.5	27.5	25	10
Epigastric discomfort	45	12.5	27.5	5
Nausea	42.5	15	22.5	5
Dizziness	40	22.5	15	2.5
Dyspnea	32.5	17.5	12.5	2.5
Dyspepsia	30	10	7.5	12.5
Diarrhea	20	2.5	7.5	10
Constipation	17.5	7.5	10	0
Intolerance to carbonated drinks	7.5	2.5	2.5	2.5

Table 2. Intraocular pressure in mmHg (mean SD) in 39 glaucoma patients switched from acetazolamide to dorzolamide

	Day 0	Day 7	Day 14	Day 28	Day 56	Day 84
9.00 a.m.	19.2 ± 3.9	18.8 ± 3.3	17.8 ± 3.2	18.0 ± 3.9	18.5 ± 4.1	18.0 ± 3.2
11.00 a.m.	16.7 ± 3.4	17.0 ± 3.4	17.1 ± 2.8	16.2 ± 3.5	16.5 ± 3.5	16.5 ± 3.3

Statistical methods

Paired *t*-test was used to analyze the IOP results (IOP differences between day 0 and each of the following visits), and the SF-36 questionnaire responses (by comparing the quantitative transformed scores at baselines and on days 28 and 84).

Results

Of the 39 patients in the study – 20 men and 19 women with a mean age of 65.5 ± 9.4 years – 22 had primary open-angle glaucoma and 17 had ocular hypertension. The mean number of topical glaucoma medications was 2 ± 0.8. Prior systemic CAI therapy included acetazolamide in 25 cases and metazolamide in 14. Fourteen patients took only partial dosage of acetazolamide or methazolamide due to limited drug tolerance.

The side effects associated with systemic CAI intake and their degree of severity experienced by the patients are listed in Table 1. All patients suffered from fatigue, which was severe in one-third of them. Other common side effects were numbness in the extremities (75%), depression (62.5%), dizziness (40%), epigastric discomfort (45%) and nausea (42.5%). Shortness of breath and other gastrointestinal symptoms such as diarrhea and constipation were less common. All side effects disappeared upon discontinuation of the systemic CAIs. Dorzolamide was well tolerated. Mild stinging (six patients), prolonged bitter taste (four patients) and occasionally blurred vision after instillation (two patients) were often mentioned by the patients but none chose to discontinue the topical medication on these grounds. None of the patients left the study due to intolerance of the topical agent.

The IOP throughout the study is depicted in Table 2. The data from day 0 reflect the pressures on the last day of systemic CAI therapy, prior to switching to dorzolamide. For the analysis, results from the right eye only were included for each patient except for those in whom only the left eye was involved. In general, no significant differences were noted between the mean IOP on day 0 and the following measurements throughout the 84 days of dorzolamide therapy (paired *t*-test between all visit days) This was true for both the trough (the 9.00 a.m. reading; 19.2 ± 3.9 mmHg on day 0 and 18.0 ± 3.2 mmHg on day 84) and the peak (11 a.m. reading) 16.7 ± 3.4 on day 0 and 16.5 ± 3.2 on day 84. However, in one patient pressure was uncontrolled, and within 2 months the treatment was discontinued and she underwent filtering surgery.

Table 3. Quality of life (measured by transformed SF-36 scores in 8 categories) in glaucoma patients switched from treatment with acetazolamide to dorzolamide.

	Day 0	28 days	84 days
Physical functioning scale	65.4 ± 4.0	74.2 ± 4.1	76.8 ± 4.2
Role-physical score	46.0 ± 6.7	81.4 ± 5.6	75.8 ± 6.0
Bodily pain score	64.7 ± 4.6	76.4 ± 4.2	78.9 ± 4.2
General health score	48.0 ± 3.8	53.9 ± 3.3	60.6 ± 3.7
Vitality score	36.6 ± 3.7	59.5 ± 3.5	60.0 ± 3.7
Social functioning score	59.9 ± 4.6	80.1 ± 4.3	84.3 ± 3.9
Role emotional score	57.0 ± 7.1	88.9 ± 4.5	82.8 ± 5.8
Mental health score	53.0 ± 3.7	72.5 ± 3.2	75.5 ± 2.8

Results are mean ± SE.
Score scale is 0–100 (100 being the highest subjective impression of performance)

The patients' general well-being was assessed with the SF-36 questionnaire [Table 3]. In each category the highest possible score (100) corresponds to a subjective impression of highest functional performance. Thus low scores reflect poorer health. Adverse affect of systemic CAI on the general well-being was reflected particularly in three categories: vitality (energy and fatigue), the role-physical (limitations in usual role activities because of physical health problems), and the general health perception category. In each of these three categories the initial scores were below 50. Categories related to emotional and mental health also scored low (57 and 53

Table 4. Change in transformed scores of SF-36 Questionnaire, between days 28, 84 and day 0

Category	Mean change between days 28 and 0	95% CI 95% CI	Significance	Mean change between days 84 and 0	95% CI, 95% CI	*P*
Physical functioning	10.5	17.8, 3.2	0.006	11.4	20.2, 2.6	0.012
Role limitations-physical	33.1	4 48.3, 17.8	0.000	26.6	43.9, 9.3	0.004
Bodily pain	12.1	21.2, 2.9	0.011	9.2	19.6, 1.1	0.080
General health	4.5	12.8, -3.8	0.282	9.3	18.6, 0.1	0.048
Vitality	23.1	30.9, 15.3	0.000	20.9	30.6, 11.2	0.000
Social functioning	17.7	29.0, 6.4	0.003	18.9	28.9, 8.9	0.001
Role limitations-emotional	33.3	48.6, 18.0	0.000	24.7	42.0, 7.4	0.007
Mental health	20.5	28.6, 12.4	0.000	18.2	28.2, 8.2	0.001

respectively). On day 28 of treatment with dorzolamide, scores in all eight categories improved and remained generally unchanged for the rest of the study. The 95% confidence intervals for the change between transformed scores of the SF-36 eight categories on days 28 and 84 relative to day 0 are shown in Table 4. All differences in scores between days 28 or 84 and day 0 were significant at $P < 0.05$ except for general health score on day 28 ($P = 0.282$) and bodily pain score on day 84, which approached statistical significance ($P = 0.08$). The most impressive improvement was noted in the role-physical, role emotional and vitality scores, while bodily pain and general health perception were the least affected.

Discussion

This study demonstrates that the well-being of glaucoma patients who had systemic CAI-related side effects improved significantly soon after switching therapy to dorzolamide, while maintaining IOP control.

The hazard of losing vision and becoming blind has been the major incentive for continuing treatment with systemic CAI in patients with glaucoma. However, many patients discontinued systemic CAI due to the deleterious effects of the drug on their quality of life, as experienced also by the patients in this study. Upon switching to dorzolamide, improvement was noted in both physical and emotional status. This positive effect on the patients' well-being is probably due to two main reasons: discontinuation of systemic CAI resulted in cessation of side effects, and led to a remarkable physical and emotional relief and improvement in quality of life. In addition, the daily requirement of oral medications is upsetting for many patients and has a detrimental effect on their perception of their medical status. It is the impression of many physicians that patients do not consider eye drops as "medications," even when taken on a regular basis. Thus switching to topical treatment may also lead to an improved self-perception of health.

Dorzolamide was well tolerated. The various side effects observed in this study have all been reported previously [2,4,8,9]. Stinging, a prolonged bitter taste, and occasionally blurred vision after instillation were mentioned by some of the patients but were of a mild degree, and none elected to discontinue the drops.

Several studies have compared the IOP control with topical versus systemic CAI. Centofanti et al. [4] demonstrated that dorzolamide 2% was as effective as acetazolamide when added to glaucoma patients on maximal therapy. Hutzelmann et al. [5], comparing the efficacy and tolerability of dorzolamide and acetazolamide as adjunctive therapy to timolol, showed good IOP control with both medications, though systemic CAI led to slightly better IOP control. In this context it should be noted that the numerous side effects of systemic CAI lead to poor compliance, thus most patients switching from systemic to topical CAI still achieve adequate IOP control.

The validity and reliability of SF-36 has been confirmed in various patient populations [10]. This questionnaire uses eight health scales to measure three aspects of health: functional status (physical and social functioning and role limitations attributed to physical or emotional problems), well-being (mental health, energy, fatigue and pain), and overall evaluation of health (general health perception). Patients with different diseases show distinctive response profiles on the SF-36 [11]. Normative data for adult populations have shown an association between SF-36 scores and gender, age, and social class [12]. Including such a questionnaire as part of the assessment of a therapeutic outcome is increasingly gaining popularity. It has been used for both chronic medical conditions and surgical procedures [13,14]. Studies in ophthalmology incorporating health questionnaires are relatively scarce, and most studies attempted to establish the association between reduced vision and limitation of daily function [15–19]. Studies conducted in glaucoma patients tried to correlate the scores with the patients' visual function and thus looked at contrast sensitivity [20], or Esterman binocular visual field performance [21] in addition to the visual acuity. The VF-14 and the National Eye Institute-Visual Functioning Questionnaire were found to be more appropriate for assessment of association between visual function and functional impairment in daily life [17,18,22].

Our study differs from these other studies of glaucoma patients in that we studied the effect of treatment change on patients' perception of their quality of life, and not the visual function. In addition, patients with severe visual dysfunction (visual acuity less than 20/200) were excluded. In this study, comparing a systemic to a topical medication, the SF-36 was preferred to another questionnaire, the Comparison of Ophthalmic Medications for Tolerability (COMTOL), as the latter was specifically designed for comparing topical ophthalmic medications [23–25].

There are several limitations of this study. The lack of a control group is a major drawback. A control group matched for age, gender, socioeconomic status and co-morbidity is warranted. By looking at the change of SF-36 scores with time we attempted to circumvent this issue by having each patient be his or her own control.

Due to the numerous side effects of systemic CAI, the efficacy of topical CAI, and the advent of new pressure-reducing agents, the use of systemic CAI will probably decrease and the indications for their use will be limited to those cases when drops cannot be properly instilled, cases that require acute reduction of IOP, or in rare cases of patients who prefer tablets over eye drops. For most other patients a topical CAI offers a similar efficacy and better tolerability.

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Capsule

Flaws in immune defenses

In response to innate inflammatory signals, Toll-like receptors and interleukin-1 (IL-1) receptors activate the NF-Bk and p38-MAP kinase pathways by recruiting the IL-1 receptor-associated kinase (IRAK) to their intracellular Toll-IL-1 receptor domains. IRAK-4 deficiency in mice leads to a profound immune deficiency and a range of bacterial and viral infections. Picard et al. describe three patients with inherited mutations in the *IRAK-4* gene that lead to impaired immunity of certain common species of pyogenic bacteria. However, unlike the situation in mice, human *IRAK-4* appears to be redundant in coping with other types of viral, bacterial and fungal infection.

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