Analysis of Effectiveness and Cost of Cosopt, the Combination Solution of Dorzolamide Hydrochloride and Timolol Maleate .

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Special Studies

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Open-angle glaucoma is a chronic disease characterized by optic nerve damage and visual field loss, often with elevated intraocular pressure (IOP). Lowering the IOP is recognized to delay the progression of optic nerve damage and visual field loss. Currently, lowering the IOP is the only medical treatment for open angle glaucoma. The most common first-line therapy for glaucoma treatment is topical beta-blockers. The topical beta-blocker timolol maleate is the most widely prescribed treatment.[1] Studies report a mean percent reduction in IOP by 25 percent for timolol maleate.[2] Since glaucoma is a chronic progressive disease, the majority of patients eventually require additional medication to control IOP. During long term beta-blocker therapy , the IOP is not adequately controlled in 28 to 66 percent of patients.[3] Dorzolamide hydrochloride, a topical carbonic anhydrase inhibitor, is commonly prescribed as adjunctive therapy to timolol. Previous studies have shown that dorzolamide as monotherapy has a comparable IOP lowering activity as betaxolol, 21 to 23 percent reduction which is slightly less than timolol.[2] When used as an adjunctive therapy to timolol, dorzolamide has an IOP lowering activity comparable to two percent pilocarpine.[3] Dorzolamide demonstrated a 17 to 21 percent reduction in IOP when added to beta-blocker therapy.[3,4] Other agents that have been used as adjunctive therapy to timolol such as pilocarpine, epinephrine and oral carbonic anhydrase inhibitors have side effects that often result in discontinuation. The discontinuation due to side effects of dorzolamide is less than the other adjunctive therapies. A recent study showed that patients preferred timolol and dorzolamide therapy to timolol and pilocarpine therapy by a 10 to 1 ratio.[3]

Timolol and dorzolamide have been formulated as a fixed combination product of 0.5 percent timolol maleate and 2 percent dorzolamide hydrochloride (Cosopt, Merck & Co., Inc.). The recommended dosing regimen for Cosopt is twice daily. When compared to concomitant therapy, Cosopt therapy has fewer drop instillations. Studies show that patient compliance decreases with increased dose frequency. Patient compliance with twice-daily dosing is higher

than three or four times a day dosing. Studies also indicate that intervals between doses for three and four times daily regimens are not adequate 20 to 30 percent of the time. Mid-day doses are more likely to be missed than morning or evening doses.[5,6] Fixed combinations may improve patient compliance by reducing the number of medications (doses) and by simplifying the dosage regimen.

Previous studies have shown that Cosopt has a greater ability to lower IOP when compared to monotherapy of its components, timolol and dorzolamide. Cosopt showed a mean IOP reduction of 32.7 percent (-9mm Hg) compared to timolol 22.6 percent (-6.3mm Hg) and dorzolamide 19.8 percent (-5.4mm Hg).[5,7] Other research compared the combination to the components administered in their usual monotherapy doses, dorzolamide three times a day and timolol twice a day. This showed that the combination solution of dorzolamide and timolol, administered twice daily has equivalent efficacy to the concomitant administration of its components in their usual dosage.[6] A recent study finally compared the combination with the components administered twice daily. This also showed that the combination is equivalent in efficacy as dorzolamide and timolol administered twice daily.[1] However, no clinical study has researched patients on twice daily administration of dorzolamide and timolol that were switched to Cosopt. The purpose of this study is to determine if the fixed combination of dorzolamide-timolol (Cosopt) is equivalent in lowering IOP compared to the concomitant administration of its components 2% dorzolamide hydrochloride (Trusopt)and 5% timolol maleate (Timoptic) twice daily. This study will also determine if the fixed combination is more cost effective than the concomitant administration of dorzolamide and timolol.

Materials and Methods

A retrospective analysis of chronic open angle glaucoma patients in an ophthalmology practice was performed. Only patients on twice daily administration of dorzolamide

hydrochloride (Trusopt) and timolol maleate (Timoptic) that were switched to Cosopt were included. Patients on any other glaucoma medications were excluded. Over 1700 patient files were reviewed. Data on IOP for Timoptic and Trusopt treatment was recorded at three months (when available) and one day prior to switching to Cosopt. IOP was measured at one month and again at three months following initiation of the combination. The equivalency of Cosopt to the concomitant administration of its components was assessed by the analysis of variance (ANOVA) and F-test.

A cost comparison is based on pricing of trade and generic solutions of 10 and 15 ml bottles from national pharmacies. Timoptic is available in the generic form, timolol maleate. A generic equivalent of Trusopt and Cosopt is not currently available. Pricing was not analyzed for 5 ml bottles since this size is infrequently prescribed. A 5 ml bottle is typically used only during initial drug trials. The number of drops per bottle assumes a standard 20 drops per ml. The number of drops per bottle and drug price were used to calculate the cost per drop. The cost per day was calculated using twice a day dosing for both eyes. Cost per month was calculated for an average month of 30 days.

Results

A total of nine patients met the criteria of the study, patients on twice daily administration of dorzolamide and timolol that were switched to the dorzolamide-timolol combination. The change in IOP from the dorzolamide/timolol baseline ranged from +3mm Hg to -2mm Hg at one month (Table 1). The correlating percentage changes in IOP from baseline ranged from +17.65% to -11.11%. The mean IOP change at one month was +0.22mm Hg with standard deviation of 0.71mm Hg. The mean percent change in IOP was 1.49 ± 5.44. After three months, the change in IOP from the dorzolamide/timolol baseline ranged from +4mm Hg to -3mm Hg. The correlating percentage changes in IOP from baseline ranged from +28.57% to -12.50%. The

Patient	3 Months	1 Day	1 Month	3 Months	Change 1 Month	% Change	Change 3 Months	% Change
1	22	22	22	20	0	0	-2	-9.09
	22	24	25	21	1	4.17	-3	-12.5
2	22	17	20	18	3	17.65	1	5.88
	18	20	22	18	2	10	-2	-10
3		22	20	26	-2	-9.09	4	18.18
		18	16	20	-2	-11.11	2	11.11
4	20	20	20	21	0	0	1	5
	18	18	19	20	1	5.56	2	11.11
5	14	13	12	16	-1	-7.69	3	23.08
	14	14	13	16	-1	-7.14	2	14.29
6	12	13	16	15	3	23.08	2	15.38
	15	14	16	18	2	14.29	4	28.57
7	22	23	22	21	-1	-4.35	-2	-8.7
	24	24	25	24	1	4.17	0	0
8	18	20	19	19	-1	-5	-1	-5
	19	20	20	19	0	0	-1	-5
9	12	12	12	13	0	0	1	8.33
	14	13	12	13	-1	-7.69	0	0
Mean					0.22	1.49	0.61	5.04
Standard Deviation					0.71	5.44	1.41	6.43

Table 1. Intraocular pressure (mmHg) summary statistics.

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Column 1	18	327	18.17	16.97
Column 2	18	331	18.39	18.02
Column 3	18	338	18.78	11.59

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	3.44	2	1.72	0.111	0.895	3.179
Within Groups	791.89	51	15.53			
Total	795.33	53				

Table 2. Analysis of variance: ANOVA single factor test

	Variable 1	*Variable 2*
Mean	18.17	18.39
Variance	16.97	18.02
Observations	18	18
df	17	17
F	0.942	
P(F<=f) one-tail	0.548	
F Critical one-tail	0.44	

Table 3. F-test two-sample for variances comparing IOP at one day prior and one month after intiation of combination therapy.

	Variable 1	*Variable 2*
Mean	18.17	18.78
Variance	16.97	11.59
Observations	18	18
df	17	17
F	1.464	
P(F<=f) one-tail	0.22	
F Critical one-tail	2.272	

Table 4. F-test two-sample for variances comparing IOP at one day prior and three months after intiation of combination therapy.

	Walmart		Kmart	
	10 ml	15ml	10 ml	15 ml
Timoptic	44.78	61.78	NA	NA
timolol maleate	22.72	29.78	17.99	24.99
Trusopt	51.84		50.99	
Cosopt	84.54		83.97	

Table 5. Medication prices in dollars.

Walmart	Bottle Size	# Drops	# Days	Cost Per Bottle	Cost Per Drop	Cost Per Day	Cost Per Month
Timoptic	10	200	50	44.78	0.22	0.90	26.88
timolol maleate	10	200	50	22.72	0.11	0.46	13.68
Timoptic	15	300	75	61.78	0.21	0.82	24.72
timolol maleate	15	300	75	29.78	0.10	0.40	11.88
Trusopt	10	200	50	51.84	0.26	1.04	31.08
Cosopt	10	200	50	84.54	0.42	1.69	50.73
K-mart							
Timoptic							
timolol maleate	10	200	50	17.99	0.09	0.36	10.80
Timoptic							
timolol maleate	15	300	75	24.99	0.08	0.33	9.96
Trusopt	10	200	50	50.99	0.26	1.02	30.60
Cosopt	10	200	50	83.97	0.42	1.68	50.37

Table 6. Daily and monthly cost in dollarsof medications based on twice a day dosing.

	Cost per month			Cost per year		
	Walmart	K-mart	Average	Walmart	K-mart	Average
Timoptic (10 ml) & Trusopt	57.96	NA	57.96	695.52	NA	695.52
Timoptic (15 ml) & Trusopt	55.80	NA	55.80	669.60	NA	669.60
timolol maleate (10 ml) & Trusopt	44.76	41.40	43.08	537.12	496.80	516.96
timolol maleate (15 ml) & Trusopt	42.96	40.56	41.76	515.52	486.72	501.12
Cosopt	50.73	50.37	50.55	608.76	604.44	606.60

Table 7. Monthly and yearly cost in dollars of Cosopt and comcomitant therapy of its components.

mean IOP change after three months was +0.61mm Hg with standard deviation of 1.41mm Hg. The mean percent change in IOP was 5.04 ± 6.43. The ANOVA comparison of IOP at one day prior, one month and three months after switching to Cosopt is presented in Table 2. No significant difference in IOP was noted among concomitant therapy or therapy with Cosopt. The t-test comparison of IOP at one day prior and one month after switching to Cosopt is presented in Table 3. Table 4 shows the t-test comparison of IOP at one day prior and three months after switching to Cosopt. IOP after three months of Cosopt therapy is not significantly different that intraocular pressure with concomitant therapy.

The medication prices obtained from Walmart and K-mart are shown in Table 5. The cost per drop of medication, cost per day and cost per month are shown in Table 6. The cost per month and per year for Cosopt therapy and the concomitant therapy of its components, Timoptic and Trusopt are shown in Table 7.

Discussion

This study demonstrated that the administration of 2% dorzolamide hydrochloride and 5% timolol maleate in a fixed combination product slightly increased the IOP when compared to concomitant administration of its components twice daily. Switching from concomitant therapy to Cosopt showed an average increase in IOP by 0.61mm Hg or 5.04% after three months. The clinical increase in intraocular pressure was shown to not be significant by ANOVA and t-test analysis. The change in IOP was variable among the subjects, an increase of 4 mm Hg to a decrease of 3 mm Hg was recorded after three months of treatment. The variability could be attributed to a small sample size. Another possible factor is patient compliance. Because Cosopt is a fixed combination glaucoma medication, missing a dose can have more affect on regulating IOP than missing a dose of either one of its components.

The cost comparison analysis showed that the 10 ml bottle for both Timoptic and the generic equivalent, timolol maleate gives a higher price per drop than the 15 ml bottle. The overall cost of the trade drug Timoptic is almost twice the cost of the generic formulation. In a cost comparison of Cosopt and concomitant therapy of the trade medications Timoptic and Trusopt, Cosopt is lower in cost. Timoptic and Trusopt cost $5.25 or $7.41 more per month than Cosopt depending on the size of the bottle of Timoptic. On a yearly basis, Timoptic and Trusopt is $63 or $88.92 more than Cosopt, 10 and 15 ml bottle of Timoptic respectively. But when Cosopt is compared to Trusopt and the generic formulation of timolol, Cosopt is more expensive. Cosopt costs an average of $7.47 or $8.79 more than the concomitant therapy of Trusopt and timolol per month depending on bottle size of timolol. In a year, Cosopt is an average of $89.64 or $105.48 more. The most economical therapy one can prescribe is 15 ml bottles of generic timolol and Trusopt. When a patient has prescription insurance and pays a co-pay for medications, Cosopt provides dual therapy with only one co-pay instead of two with concomitant therapy. But for patients that must pay for their medications, concomitant therapy offers a significant savings. Due to the chronic nature of glaucoma, concomitant therapy can save a patient hundreds of dollars over years of therapy.

Overall, the current study shows than Cosopt slightly increased the IOP when compared to concomitant administration of its components twice daily. However this increase in IOP is not statistically significant. Also Cosopt is more expensive than concomitant administration of its components.

References

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Michigan College of Optometry
Research Awards

TO: Chair, Scholarship and Awards Committee

FROM: Julie Samo

SUBJECT: Senior Research Paper Submitted for MCO Award Consideration

DATE: March 28 (Deadline: April 1)

Title of the Senior Research Project/Paper:

Analysis of Effectiveness and Cost of Cosopt, the combination solution of Dorzolamide hydrochloride and Timolol maleate

Faculty Advisor(s):

Walter Betts

Objective of the Senior Research Paper:

To determine if the fixed combination of dorzolamide-timolol (Cosopt is equivalent in lowering IOP compared to the concomitant administration of its components 2% dorzolamide hydrochloride (Trusopt) and timolol maleate (Timoptic) twice daily. Another objective is to determine if the fixed combination is more cost effective than the concomitant administration of dorzolamide and timolol

The enclosed research paper should be considered for the award in the following category:

- [X] clinical optometric science
- [ ] administrative science
- [ ] primary care
- [ ] vision therapy
- [ ] original investigative work
- [ ] other _____