Quantitative and Cost Evaluation of Three Antiglaucoma Beta-Blocker Agents: Timoptic-XE® versus Two Generic Levobunolol Products

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Abstract

A randomized, single-masked trial was conducted to evaluate and compare the number of days of therapy and the cost per day of therapy of once-daily eyedrops Timoptic-XE (timolol maleate ophthalmic gel-forming solution) and two twice-daily generic levobunolol products (Schein and Bausch & Lomb). Twelve patients with glaucoma who were taking long-term medication (range, 3 to 17 years) were recruited and randomized to dispensing drops while holding the bottle at either 135° (halfway between vertical and horizontal) or 180° (vertical). In a given study period, a patient, holding the bottle at the assigned angle, dispensed the entire contents of the bottle, drop by drop, into a graduated cylinder. An observer recorded the number of drops, using a laboratory counter, and the volume and weight of the drops dispensed. Each patient dispensed the contents of exactly one bottle from each of the eight treatment groups (Timoptic-XE 2.5 mL and 5.0 mL; Bausch & Lomb levobunolol 5.0 mL, 10.0 mL, and 15.0 mL; and Schein levobunolol 5.0 mL, 10.0 mL, and 15.0 mL). The cost per day of therapy (once daily in both eyes for Timoptic-XE and twice daily in both eyes for levobunolol) was calculated from these data. The cost per day of therapy was significantly less for Timoptic-XE ($0.32 to $0.37) than for either the Schein product ($0.46 to $0.62) or the Bausch & Lomb product ($0.50 to $0.57), where the costs are the minimum and maximum cost for each treatment across packaging configurations and dispensing angle. Compared with the 2.5-mL and 5-mL bottles of Timoptic-XE, there were statistically greater costs for each brand and all packaging configurations of levobunolol tested ($P<0.001$ for all comparisons). Although the smaller bottle was less expensive, the difference in the cost per day of therapy between the 2.5-mL and 5-mL bottles of Timoptic-XE was not statistically significant. Generic products are not necessarily less expensive than branded alternatives. Factors that influence the daily cost of a topical ophthalmic medication include the size of the drop, the volume of medication in the bottle, and the frequency of administration.

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As a result of the increasing importance of health maintenance organizations, capitation, and pharmacy benefits managers, cost is becoming a significant factor in the selection of pharmacologic agents, especially when a choice can be made among multiple therapeutic options that have similar efficacy, tolerability, or both. Such is the case with ophthalmic beta-blockers.

Several studies have evaluated either the number of drops per bottle or the cost per day for ophthalmic beta-blockers. Schwartz et al[1] counted the number of drops in 10-mL bottles of Timoptic (timolol maleate, Merck & Co., Inc., West Point, PA) and in 10-mL bottles of levobunolol (Betagan, Allergan, Inc., Irvine, CA). They found that the Timoptic bottle contained a substantially greater number of drops ($P<0.001$). Ball and Schneider[2] measured the drop size of several topical beta-blocking agents. They found substantial variation in the drop size and variation in the number of drops per bottle. Their data were consistent with the data from the study by Schwartz et al in demonstrating the greater number of drops in a bottle of Timoptic than in a comparably sized bottle of Betagan. Meyer and Savitt[3] also reported a comparison between Betagan and Timoptic. The average length of use was 28.9 days for a 5-mL bottle of Betagan versus 36.6 days for a 5-mL bottle of Timoptic. This difference was statistically significant ($P = 0.009$).

Recently, new agents in the ophthalmic beta-blocking class have been developed. Timoptic-XE is a nonselective ophthalmic beta-blocker that combines the active drug timolol maleate with a gel-forming vehicle, allowing a once-daily application of the medi-

From Merck & Co., Inc., West Point, PA (D.H., M.S., B.H., and J.E.), and Tufts University School of Medicine, Boston, MA (A.W. and B.S.) Dr. Bernard Schwartz has applied for a patent on the effect of timolol on decreasing optic disc cupping and pallor and increasing nerve fiber layer thickness.

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cation. Several generic levobunolol products also have been introduced. Although the efficacy and tolerability of levobunolol, another nonselective beta-blocker, have been demonstrated to be comparable to those of timolol solution at equipotent concentrations and dosing regimens,[4-7] no published studies have compared the hypotensive efficacy of timolol in gel solution versus levobunolol.

Because these products' drop characteristics have not been evaluated, this study sought to assess their physical properties in a randomized manner, using glaucoma patients to dispense the drops. The physical properties measured were the number of drops and the volume of the medication in a bottle. The parameters calculated were drop size and cost per day of therapy.

··· METHODS ···

Experimental Design

Twelve patients with open-angle glaucoma who were being treated with long-term antiglaucoma medications were recruited and randomized to holding a bottle at either 135° (halfway between vertical and horizontal) or 180° (vertical) to the receiving container. Table 1 describes the patients' demographic characteristics.

In a given study period, a patient, holding a bottle at the assigned angle, dispensed the entire contents of the bottle, drop by drop, into a graduated cylinder. Patients were masked as to the contents of the bottles. They were seated at a table individually and were permitted to rest their arms on it in any manner that was comfortable. They were not allowed to rest the bottle on the rim of the graduated cylinder but could rest their hand during the procedure, as needed.

An observer, who also was masked as to the bottle contents, recorded the number of drops, and the volume and weight of the compound dispensed. Drops were counted manually, using a laboratory cell counter. Graduated cylinders were calibrated to 0.5 mL (0.2 mL, for 2.5-mL Timoptic-XE), and volumes were estimated between these subdivisions. Weights were measured on a top-loading semi-analytic balance with a readability of 0.01 g.

The study design used was a balanced, eight-period crossover with random selection for 135° and 180°. That is, each patient dispensed the contents of exactly one bottle from each of eight treatment groups (Timoptic-XE 2.5 mL and 5.0 mL; Bausch & Lomb levobunolol 5.0 mL, 10.0 mL, and 15.0 mL; and Schein levobunolol 5.0 mL, 10.0 mL, 15.0 mL). Before dispensing the test bottles, each patient dispensed the contents of one practice 5-mL bottle of levobunolol. Variability caused by interpatient differences in dispensing drops were minimized by the balanced eight-period crossover design.

The primary response variable was the number of drops per day, which permitted a calculation of the cost per day of therapy. Cost per day was calculated as:

$$\textit{Cost per Day} = \frac{\textit{Number of Drops per Day} * \text{Cost per Bottle (\$)}}{\text{Number of Drops per Bottle}}$$

The price of each bottle was assumed fixed at the average wholesale price (AWP) given in the January 1995 update of the *Red Book*.[8] Standard therapy for both eyes was assumed to be two drops per day for Timoptic-XE and four drops per day for generic levobunolol. With drops per day and cost per bottle fixed, cost per day is a function of number of drops per bottle. Thus, the experimental focus of this study was to determine the mean number of drops per bottle for each treatment. This information could then be used to compare the cost per day of therapy for each medication.

Statistical Methods

As noted, if the number of drops per day and the cost per bottle are fixed, then cost per day is a function of the number of drops per bottle. Because it is clear that the variability of the number of drops per bottle, the volume per bottle, and drop size (volume per number of drops) increases with the mean of each variable, all three were analyzed on a logarithmic scale (base e). Thus, the means reported are geometric means. A geometric mean is the mean of the sum of the natural logarithms of the variables. An antilog function is then performed to transform the results back to the original scale. To report the standard error of the mean (SEM), the following approximation was used:

Table 1. Patient Demographics

Age (yr)	
Mean	67
Range	42–85
Gender	
Male	7
Female	5
Duration of Glaucoma Therapy (yr)	
Mean	8
Range	3–17
Mean Number of Medications	3

$$SEM = \frac{Geometric\ Mean * \text{Standard Deviation on Log Scale}}{\text{Square Root of } n}$$

However, where confidence intervals are given, the intervals were calculated on the log scale and back transformed to the original scale (resulting in slightly asymmetric intervals). Significance testing and confidence intervals were calculated using the error estimate from a one-way analysis of variance model. For confidence intervals and tests that compared the two patient groups (the groups randomized to the two angles), the error term included an estimate of between-patient error. For tests within a patient group (eg, differences between products for angle = 135°), the random effect for between-patient variability canceled, and only the within-patient error term was used. All tests were two sided.

Because results for weight were very similar to those for volume, they are not reported in this paper.

··· RESULTS ···

Table 2 presents summary statistics for the number of drops per bottle and drop size for all eight products at both the 135° and 180° angles. The drop size for Timoptic-XE was smaller than

Table 2. Number of Drops per Bottle and Drop Size*

Product	Number of Drops per Bottle	Drop Size (μL)
Angle = 135° (n = 6)		
0.5% Timolol		
Timoptic-XE 2.5 mL	77.7 ± 2.2	38.6 ± 1.1
Timoptic-XE 5.0 mL	132.6 ± 3.6	44.6 ± 1.3
0.5% Levobunolol		
Bausch & Lomb 5.0 mL	110.3 ± 2.6	49.8 ± 1.2
Bausch & Lomb 10.0 mL	214.4 ± 5.8	48.4 ± 1.5
Bausch & Lomb 15.0 mL	295.0 ± 4.1	52.0 ± 0.5
Schein 5.0 mL	100.2 ± 6.7	57.0 ± 2.5
Schein 10.0 mL	178.3 ± 10.9	58.3 ± 3.5
Schein 15.0 mL	304.7 ± 8.8	50.3 ± 1.4
Angle = 180° (n = 6)		
0.5% Timolol		
Timoptic-XE 2.5 mL	87.1 ± 2.7	36.3 ± 1.0
Timoptic-XE 5.0 mL	146.8 ± 4.7	42.0 ± 1.3
0.5% Levobunolol		
Bausch & Lomb 5.0 mL	104.8 ± 4.7	52.9 ± 2.4
Bausch & Lomb 10.0 mL	203.1 ± 8.7	51.3 ± 2.1
Bausch & Lomb 15.0 mL	290.4 ± 12.7	52.9 ± 2.2
Schein 5.0 mL	119.7 ± 2.2	48.5 ± 1.1
Schein 10.0 mL	202.7 ± 8.1	51.6 ± 2.0
Schein 15.0 mL	297.0 ± 9.1	52.0 ± 1.6

*Numbers given are geometric means ± standard error of the mean

Table 3. Mean Cost per Day

Product	Drops per Day	Cost per Bottle ($)*	Mean Number of Drops per Bottle†	Mean Days of Therapy per Bottle	Mean Cost per Day ($)
Angle = 135° (n = 6)					
0.5% Timolol					
Timoptic-XE 2.5 mL	2	13.98	77.7	38.9	0.360
Timoptic-XE 5.0 mL	2	24.78	132.6	66.3	0.374
0.5% Levobunolol					
Bausch & Lomb 5.0 mL	4	13.75	110.3	27.6	0.498
Bausch & Lomb 10.0 mL	4	27.50	214.4	53.6	0.513
Bausch & Lomb 15.0 mL	4	41.25	295.0	73.8	0.559
Schein 5.0 mL	4	13.75	100.2	25.1	0.549
Schein 10.0 mL	4	27.50	178.3	44.6	0.617
Schein 15.0 mL	4	41.25	304.7	76.2	0.542
Angle = 180° (n = 6)					
0.5% Timolol					
Timoptic-XE 2.5 mL	2	13.98	87.1	43.6	0.321
Timoptic-XE 5.0 mL	2	24.78	146.8	73.4	0.338
0.5% Levobunolol					
Bausch & Lomb 5.0 mL	4	13.75	104.8	26.2	0.525
Bausch & Lomb 10.0 mL	4	27.50	203.1	50.8	0.542
Bausch & Lomb 15.0 mL	4	41.25	290.4	72.6	0.568
Schein 5.0 mL	4	13.75	119.7	29.9	0.459
Schein 10.0 mL	4	27.50	202.7	50.7	0.543
Schein 15.0 mL	4	41.25	297.0	74.3	0.556

*Average wholesale price from the *Red Book Update*, January 1995.[8]
†Geometric mean from Table 2.

Figure 1. 95% Confidence Intervals for Mean Cost per Day, 135° Angle

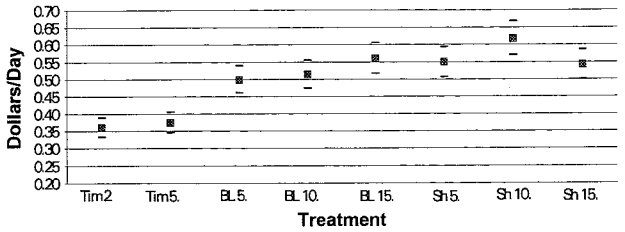
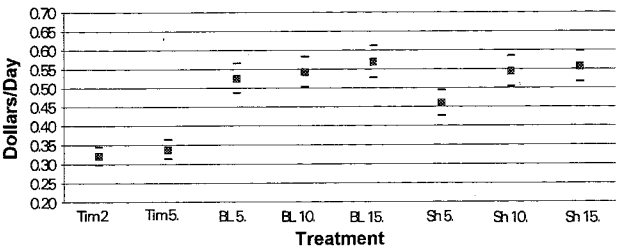


Figure 2. 95% Confidence Intervals for Mean Cost per Day, 180° Angle



Tim 2 5 and Tim 5 = Timoptic-XE 2 5 and 5 0 mL; BL 5, BL10, and BL 15 = Bausch & Lomb levobunolol 5.0, 10 0, and 15.0 mL; and Sh 5, Sh 10, and Sh 15 = Schein 5.0, 10 0, and 15 0 mL

that for levobunolol regardless of manufacturer or bottle size. Accordingly, for the 5.0-mL bottles, Timoptic-XE gives more drops per bottle than does levobunolol.

The mean cost for each product is summarized in Table 3; 95% confidence intervals for the mean cost per day of each product are shown in Figure 1 for the 135° angle and in Figure 2 for the 180° angle. The table and plots show that therapy with Timoptic-XE using either the 2.5-mL or 5.0-mL bottle costs less per day than does generic levobunolol therapy. Note that this result is based on a dose regimen of two drops per day of Timoptic-XE and four drops per day of levobunolol, using both eyes. When each levobunolol regimen was compared with Timoptic-XE 5.0 mL, the Timoptic-XE regimen was found to be less expensive, saving an average of 13.3% to 27.5% when the bottle was held at 135°, and an average of 12.9% to 25.9% when held at 180° (Table 4). These differences were statistically significant ($P<0.001$) for all comparisons between Timoptic-XE and levobunolol.

Table 4. Mean Cost per Day, Comparison with Timoptic-XE 5.0 mL

Product	Drops per Day	Mean Cost per Day ($)	95% CI for Mean Cost per Day ($)	% Increase in Cost per Day vs Timoptic-XE 5.0 mL	*P* Value for % Increase
Angle = 135° (n = 6)					
0.5% Timolol					
Timoptic-XE 2 5 mL	2	0.360	0.333, 0 389	-1.4	0 496
Timoptic-XE 5 0 mL	2	0 374	0.345, 0 404	0.0	—
0.5% Levobunolol					
Bausch & Lomb 5.0 mL	4	0.498	0.461, 0.539	13.3	<0.001
Bausch & Lomb 10 0 mL	4	0.513	0.474, 0.555	14 9	<0.001
Bausch & Lomb 15 0 mL	4	0.559	0.517, 0 605	20.4	<0 001
Schein 5.0 mL	4	0 549	0.507, 0 594	19.1	<0 001
Schein 10 0 mL	4	0 617	0 570, 0 667	27.5	<0.001
Schein 15.0 mL	4	0.542	0.500, 0.586	18 3	<0.001
Angle = 180° (n = 6)					
0 5% Timolol					
Timoptic-XE 2 5 mL	2	0 321	0 298, 0 346	-1.7	0 250
Timoptic-XE 5 0 mL	2	0 338	0.314, 0 364	0.0	—
0.5% Levobunolol					
Bausch & Lomb 5.0 mL	4	0.525	0.487, 0.565	20 6	<0.001
Bausch & Lomb 10 0 mL	4	0.542	0.503, 0.583	22.6	<0.001
Bausch & Lomb 15 0 mL	4	0.568	0 528, 0 612	25.9	<0.001
Schein 5.0 mL	4	0.459	0 427, 0 495	12.9	<0.001
Schein 10 0 mL	4	0.543	0.504, 0 584	22 8	<0.001
Schein 15.0 mL	4	0.556	0.516, 0.598	24.4	<0.001

CI = confidence interval

The preceding analysis shows that therapy with Timoptic-XE costs less per day than does levobunolol therapy, even though Timoptic-XE costs more than levobunolol per equivalent-sized bottle. A bottle of Timoptic-XE contains a greater number of drops per bottle for two reasons: (1) the Timoptic-XE drop size is smaller than the levobunolol drop size (Table 2); and (2) the percentage overfill for Timoptic-XE is greater than that for levobunolol (Table 5). Overfill is defined as the volume of drug in a bottle in excess of the volume stated on the label. Percentage overfill is thus defined as the overfill divided by the volume stated on the label.

Table 5. Volume and Percentage Overfill*

Product	Volume Dispensed (mL)	Overfill (%)
0.5% Timolol (n = 12)		
Timoptic-XE 2.5 mL	3.08 ± 0.03	23.3 ± 1.2
Timoptic-XE 5.0 mL	6.04 ± 0.07	20.7 ± 1.5
0.5% Levobunolol (n = 12)		
Bausch & Lomb 5.0 mL	5.52 ± 0.02	10.4 ± 0.4
Bausch & Lomb 10.0 mL	10.39 ± 0.05	3.9 ± 0.5
Bausch & Lomb 15.0 mL	15.35 ± 0.07	2.4 ± 0.4
Schein 5.0 mL	5.76 ± 0.08	15.2 ± 1.6
Schein 10.0 mL	10.42 ± 0.04	4.2 ± 0.4
Schein 15.0 mL	15.38 ± 0.05	2.5 ± 0.3

*Numbers given are geometric means ± standard error of the mean

Drop sizes for the 135° and 180° angles are compared in Table 6. Timoptic-XE drops were found to be slightly larger when the bottle was held at a 135° angle than when held at a 180° angle. However, this difference was not statistically significant. For Bausch & Lomb levobunolol, little variability between dispensing angles was found. Data for the Schein levobunolol product showed a statistically significant difference in drop size based on dispensing angle for the 5.0-mL and 10.0-mL bottles.

Several unsolicited patient observations were recorded during the study. Patients found the 180° angle the easiest of the two angles to use to dispense eyedrops. They also noted that it was more difficult to dispense the drops with the Timoptic-XE 2.5-mL bottle and all the Schein levobunolol bottles than with the Bausch & Lomb levobunolol bottles.

··· DISCUSSION ···

Previous studies identified the average drop size and number of drops per bottle for a branded levobunolol (Betagan).[1-3] The range of drop size in these studies was 46 to 61 uL, and the number of drops varied for each bottle size of Betagan tested (91 to 116 drops per 5-mL bottle, 220 to 228 drops per 10-mL bottle, and 342 drops per 15-mL bottle). The data from this study on drop size (48 to 58 uL) and on the number of drops per bottle (100 to 120 per 5-mL bottle, 178 to 214 per 10-mL bottle, and 290 to 304 per 15-mL bottle) for the generic levobunolol products are consistent with the results obtained in the studies of Betagan.

The importance of the results presented here become more apparent when the cost of therapy is extrapolated to an annual basis. Multiplying the daily cost of therapy by 365 days, the yearly costs for the 180-degree angle are as follows (*see next page*):

Table 6. Comparison of Drops Size for 135° and 180° Angles

Product	Drop Size (µL) Angle = 135° (n = 6)	Drop Size (µL) Angle = 180° (n = 6)	% Difference Angle 135°/ Angle 180°	95% CI for % Difference	*P* Value
0.5% Timolol					
Timoptic-XE 2.5 mL	38.6	36.3	6.3	(-3.9, 17.6)	0.229
Timoptic-XE 5.0 mL	44.6	42.0	6.3	(-3.9, 17.6)	0.228
0.5% Levobunolol					
Bausch & Lomb 5.0 mL	49.8	52.9	-5.7	(-14.8, 4.3)	0.245
Bausch & Lomb 10.0 mL	48.4	51.3	-5.7	(-14.7, 4.4)	0.248
Bausch & Lomb 15.0 mL	52.0	52.9	-1.8	(-11.3, 8.6)	0.712
Schein 5.0 mL	57.0	48.5	17.6	(6.3, 30.1)	0.003
Schein 10.0 mL	58.3	51.6	13.0	(2.1, 25.1)	0.019
Schein 15.0 mL	50.3	52.0	-3.3	(-12.6, 7.0)	0.509

CI = confidence interval

Timoptic-XE 2.5 mL	$117.17
Timoptic-XE 5 mL	$123.37
Bausch & Lomb 5 mL	$181.77
Bausch & Lomb 10 mL	$187.25
Bausch & Lomb 15 mL	$204.04
Schein 5 mL	$167.54
Schein 10 mL	$198.20
Schein 15 mL	$197.83

On the basis of this dispensing angle, savings for patients who use Timoptic-XE could range from $44.17 to $86.87 per year.

Many factors influence the daily cost of therapy for eyedrops. In a study of drop size, Brown et al[9] concluded that the design of eyedropper tips is important because it determines the size and flow rate of the bottle. Other factors that may influence drop size are the viscosity of the solution and the dispensing angle. The other significant factor that contributes to the daily cost of therapy is the actual volume of drug placed in a bottle. The amount of volumetric overfill varies between manufacturers.

Finally, the study illustrated two points. First, price comparisons cannot be made simply on the basis of the cost of a bottle of medication. Second, generic medications may not necessarily be less expensive than a branded alternative.

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