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Efficiency of Instillation Methods for Prostaglandin Medications

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ABSTRACT

Purpose: **The aim of this study was to determine the most efficient methods for instillation of prostaglandin analogs.**

Methods: **Drops were dispensed at room temperature from 2.5-mL bottles of bimatoprost, travoprost, and latanoprost. Two determinations of drop count were each made from bottles held vertically, at a 45-degree angle, and horizontally. The total volumes of medication dispensed from each bottle were measured.**

Results: **The mean number of drops dispensed was 111.0, 105.1, and 76.1 drops for bimatoprost bottles; 81.4, 101.1, and 85.3 drops for travoprost bottles; and 94.3, 88.4, and 67.1 drops for latanoprost bottles, held vertically, at 45 degrees, and horizontally, respectively. The mean volume of medication dispensed per 2.5-mL bottle was 3.17 mL for bimatoprost, 2.54 mL for travoprost, and 3.02 mL for latanoprost. The most efficient instillation methods provided 56 days of bilateral therapy per 2.5-mL bottle for bimatoprost, 51 days for travoprost, and 47 days for latanoprost, with corresponding yearly medication costs of $408 for bimatoprost, $449 for travoprost, and $475 for latanoprost. Yearly savings of $109 to $192 could be achieved by using the most efficient instillation methods, representing 5.6 months of medication saved for patients using bimatoprost, 3.0 months for patients using travoprost, and 4.9 months for patients using latanoprost.**

Conclusions: **Health care providers are urged to instruct glaucoma patients in the most efficient method of instillation. For bimatoprost and latanoprost, vertical instillation is recommended, with 45 degrees nearly as efficient, and for travoprost, instillation at 45 degrees is recommended.**

INTRODUCTION

Glaucoma is a progressive, irreversible ocular disease that affects the optic nerve, causing loss of visual field and contrast sensitivity. Therapeutic intervention with intraocular pressure (IOP)-lowering medication slows the progression of the disease and helps glaucoma patients to retain visual function.[1–4] Topically administered prostaglandin analogs, comprising bimatoprost, travoprost, and latanoprost, are the most effective and widely prescribed treatments for glaucoma and ocular hypertension.[5–7] They have the added advantage of once-daily administration, which helps to improve patients' adherence to their therapeutic regimen.[8–10]

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The cost-consciousness of managed care providers and of individuals who pay for most or all of their own prescriptions has prompted studies analyzing costs and cost-effectiveness of the prostaglandin analog class of IOP-lowering medications.[11–13] One area that has not yet been investigated is whether patients instill once-daily IOP-lowering drugs in the most efficient manner possible. Instillation of a smaller-size drop would be desirable because the volume of individual drops dispensed by most bottles of ophthalmic medications exceeds the maximum volume that the palpebral fissure can accommodate, which is approximately 30 μL.[14] Normal tear volume is estimated to be 7–10 μL,[15,16] giving a net volume available for instillation of 20–23 μL. Any medication in excess of 20–23 μL probably overflows immediately after administration. Because normal tear volume is restored within 2–3 min by reflex blinking, tearing, and drainage through the nasal-lacrimal duct, additional medication is probably lost as well.[14] By waiting 5 min in between administration of eye drop solutions, the effect of diluting the first medication is minimized.

Studies have shown that the bioavailability and efficacy of drops as small as 15 μL are equivalent to those of larger drops[14] Therefore, smaller drops would be preferable to minimize systemic exposure and spilled or wasted medication. Obviously, a smaller drop size would mean that more doses could be dispensed from each bottle of medication, providing cost savings to patients and managed care providers.

Drop sizes of ophthalmic solutions depend on properties of the solution itself, such as viscosity and surface tension, which probably vary little among medications with similar formulations. The dimensions and design of the dropper tip greatly influence drop size, as does the angle at which the bottle is held when the drops are dispensed.[14] The one variable affecting drop size that patients are able to control is the angle at which the bottle is held when the drops are instilled. In this study, we measured the number of drops dispensed from 2.5-mL bottles of the once-daily IOP-lowering drugs, bimatoprost, travoprost, and latanoprost, when the bottles were held vertically, at 45 degrees, and horizontally. The results show that patients can achieve significant savings in the cost of their IOP-lowering medication by choosing the most efficient angle for instillation.

METHODS

Procedures mimicking normal instillation were employed to determine the number of drops dispensed from 2.5-mL bottles of the once-daily IOP-lowering glaucoma medications, bimatoprost (Lumigan®; Allergan Inc., Irvine, CA), travoprost (Travatan®; Alcon Laboratories, Inc., Ft. Worth, TX), and latanoprost (Xalatan®; Pfizer Inc., New York, NY). Drops were dispensed slowly and evenly at room temperature into a graduated cylinder. Drops were counted from eight 2.5-mL bottles of each medication at each instillation angle (vertical, 45 degrees, and horizontal), and the total volume of medication dispensed from each bottle was recorded. Mean drop volume was calculated by dividing the mean measured volume of medication per bottle by the mean number of drops per bottle. In an additional analysis, drops were counted from the bottles held at 45 degrees, only 2 drops at a time, with the bottles placed back on the table between administration of 2 drops, to simulate daily dosing to both eyes.

The yearly cost of IOP-lowering medication was calculated for each instillation method. Once-daily bilateral treatment requires 730 drops per year. The number of bottles that would be required per year for once-daily bilateral treatment was first calculated by dividing 730 drops by the mean number of drops found per 2.5-mL bottle. Then, the calculated number of bottles per year (which was not rounded to an integer value) was multiplied by the published average wholesale price (AWP; Price Alert 2005, Medi-Span, Indianapolis, IN). The AWPs for 2.5-mL bottles were $62.10 for bimatoprost, $62.19 for travoprost, and $61.29 for latanoprost.

Statistical analyses employed unpaired Student t tests.

RESULTS

The mean number of drops dispensed from 2.5-mL bottles of prostaglandin analogs is presented in Figure 1. For bimatoprost, the greatest mean number of drops (111.0) was dispensed from bottles held vertically, with nearly as many drops (105.1) from bottles held at 45 degrees, and the least (76.1) from bottles held horizontally. A similar pattern was seen for latanoprost,

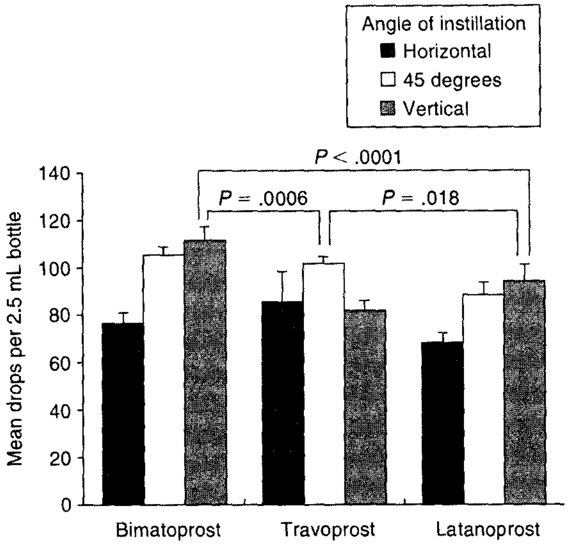

FIG. 1. Numbers of drops dispensed at room temperature from 2.5-mL bottles of prostaglandin analogs held at three different angles. Each bar represents the mean of 8 determinations, with standard deviations shown as error bars. P-values for comparisons between angles of instillation that yielded the greatest numbers of drops are shown in the figure. Other statistically significant comparisons were: bimatoprost, vertical versus 45 degrees ($P = 0.022$), vertical versus horizontal, and 45 degrees versus horizontal ($P < 0.0001$); travoprost, 45 degrees versus vertical ($P < 0.0001$), 45 degrees versus horizontal ($P = 0.0033$); latanoprost, vertical versus horizontal and 45 degrees versus horizontal ($P < 0.0001$).

with 94.3, 88.4, and 67.1 drops dispensed from bottles held vertically, at 45 degrees, and horizontally, respectively. For travoprost, the greatest number of drops was dispensed from bottles held at 45 degrees (101.1), with fewer drops dispensed from bottles held at horizontally (85.3) and vertically (81.4). The number of drops dispensed at the most efficient instillation angle would provide 56 days of once-daily bilateral therapy from a 2.5-mL bottle of bimatoprost, 51 days for travoprost, and 47 days for latanoprost (Table 1).

In the method where only 2 drops were dispensed from the bottles with table placement between administrations, the number of drops and recorded volume dispensed from the bimatoprost and travoprost bottles were similar to the previous results. However, for latanoprost bottles, fewer drops (83 vs. 88 drops) and less volume was captured into the graduated cylinder (2.6 vs. 3.0 mL). Visual observation of the tip of the latanoprost bottle during the procedure demonstrated liquid running down the outside the length of the tip after replacement of the bottle on the table.

Measurement of the total volume of medication that could be dispensed from 2.5-mL bottles showed that, on average, bottles of bimatoprost contained 3.17 mL, bottles of travoprost contained 2.54 mL, and bottles of latanoprost contained 3.02 mL (Fig. 2). The angle of instillation had no effect on the total volume of medication per bottle that could be dispensed. When drops were dispensed at the angles yielding the greatest number of drops, the calculated average drop volume was 28.7 μL for bimatoprost, 25.4 μL for travoprost, and 32.9 μL for latanoprost (Table 1).

The yearly costs of treatment with prostaglandin analogs are presented in Figure 3. For bimatoprost, the yearly costs were \$408, \$431, and \$596 for medication instilled vertically, at 45 degrees, and horizontally, respectively. For latanoprost, yearly costs were \$475, \$506, and \$667 for vertical, 45-degree, and horizontal instillation, respectively. For travoprost, yearly costs were \$449, \$532, and \$558 for 45-degree, horizontal, and vertical instillation, respectively. Vertical instead of horizontal instillation would save \$187 per year for patients using bimatoprost, and \$192 for patients using latanoprost (Table 1). Patients using travoprost would save \$108 per year by instilling at 45 degrees instead of vertically.

TABLE 1. DAYS OF THERAPY PER BOTTLE, DROP VOLUME, AND YEARLY COST WHEN THE MOST EFFICIENT INSTILLATION METHOD WAS USED

	Maximum days of therapy per bottle	*Drop volume*	*Lowest yearly cost*	*Most efficient instillation angle*	*Yearly savings*[a]
Bimatoprost	56	28.7 μL	\$408	vertical	\$187
Travoprost	51	25.4 μL	\$449	45 degrees	\$109
Latanoprost	47	32.9 μL	\$475	vertical	\$192

[a]Savings that would be achieved by using the most efficient instillation angle, as compared with the least efficient angle.

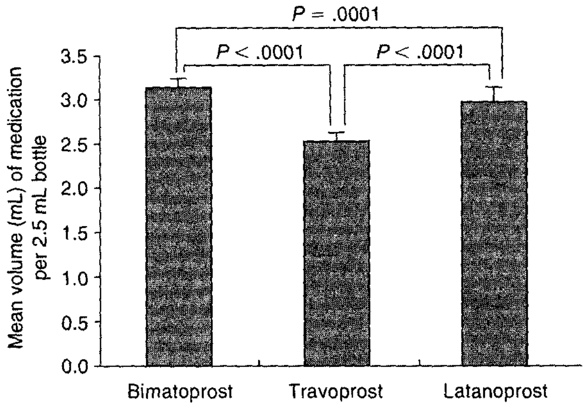

FIG. 2. Mean total volumes dispensed from 2.5-mL bottles of prostaglandin analogs. Each bar represents the mean of 24 determinations at all three instillation angles, with standard deviations shown as error bars.

DISCUSSION

Data presented in this study show that the angle at which prostaglandin analogs are dispensed greatly affects the numbers of drops that can be obtained from a 2.5-mL bottle. Vertical instillation was most efficient and instillation at 45 degrees was nearly as efficient for bimatoprost and latanoprost, yielding significantly more drops per bottle (31%–46%) than horizontal instillation of these 2 medications ($P < 0.0001$). By contrast, instillation at 45 degrees was most efficient for travoprost, yielding significantly more drops per bottle (19%–24%) than horizontal or vertical instillation ($P \leq 0.0033$). The mean number of drops dispensed by the most efficient instillation angle was significantly greater for bimatoprost than travoprost and latanoprost ($P = 0.0006$ and $P < 0.0001$, respectively), and was significantly greater for travoprost than latanoprost ($P = 0.018$). The mean numbers of drops dispensed at 45 degrees from 2.5-mL bottles of bimatoprost, travoprost, and latanoprost in this study, 105.1, 101.1, and 88.4 drops, respectively, correlated well with previously published findings, 103, 98, and 92 drops,[11] and 111.3, 102.9, and 97.6 drops, respectively.[12,17] The calculated volumes of drops dispensed at the most efficient angles of instillation, 28.7 μL for bimatoprost and 32.9 μL for latanoprost instilled vertically, and 25.4 μL for travoprost instilled at 45 degrees, exceed the volume of the palpebral fissure available for instillation, suggesting that fully efficacious volumes of medication are delivered by these instillation methods. Trying to account for any variations noted in actual patient administration, latanoprost may not last as long as bimatoprost or travoprost. This discrepancy may reflect the loss of latanoprost down the side of the dropper tip after each administration. This does not appear to be a problem with the bottle design of bimatoprost or travoprost.

Many aspects of eye drop formation and delivery may affect the size of the drop that falls from the bottle.[14] These include, changing from a vertical position to a horizontal position when administering the drop, the design of the outer surface of the dropper tip and the surface tension of the solution. As an example, a bottle with an annular recess at the tip may dispense a decreased drop size when tilted from 90 to 45 degrees.[14] However, tilting may also result in partially formed drop resulting in a variable drop size, depending upon the surface tension of the solution. A dropper tip with no annular recess and a lower surface tension may actually demonstrate an increase in drop size when the bottle is tilted from 90 to 45 degrees. Each bottle of the prostaglandin analogs studied was a different design. The bimatoprost bottle appeared to have a small rounded tip with no annular recess. The latanoprost bottle appears to have the largest inner and outer diameter tapered tip of all the prostaglandin analogs. Although modification of the latanoprost bottle years before allowed for

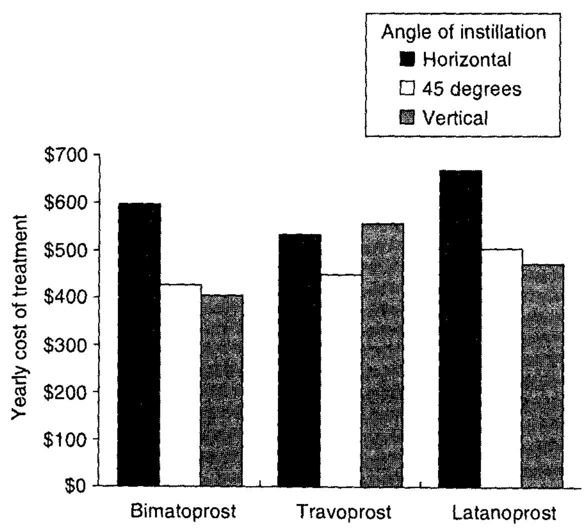

FIG. 3. Yearly costs for bilateral administration of prostaglandin analogs instilled at various angles. See Methods for calculations.

better control of drop administration, the drop itself appears to be larger with the newer bottle design.[12] Both bimatoprost and latanoprost produced more drops in the vertical, 45-degree, and horizontal positions, respectively, possibly reflecting the bottle tip design. The travoprost bottle has a conical design that appears to have a slight increase in internal diameter as it approaches the end of the tip. Travoprost produced the most drops in the 45-degree position. Although the tip does not appear to have an annular recess, perhaps the slight increase in the inner diameter at the end of the tip may affect the drop size as the bottle tilting proceeds from vertical to 45-degree positions. Other considerations previously mentioned, such as surface tension, may also be variables that may affect the drop size in various positions.[14]

The total volume of once-daily IOP-lowering medication dispensed from 2.5-mL bottles averaged 3.17 mL for bimatoprost (a 0.67-mL overfill), a volume significantly greater than that dispensed from bottles of travoprost, 2.54 mL (negligible overfill; $P < 0.0001$), and latanoprost, 3.02 mL (a 0.62-mL overfill; $P = 0.0001$). Previous studies reported medication volumes of 3.06, 2.92, and 2.98 mL,[11] and 3.3, 3.0, and 3.05 mL,[12] for 2.5-mL bottles of bimatoprost, travoprost, and latanoprost, respectively.

Of the 3 prostaglandin analogs, bimatoprost provided the greatest number of days of bilateral therapy per 2.5-mL bottle, 56 days, and the lowest cost per year, $408, when dispensed vertically. Vertical instillation of bimatoprost and latanoprost would save $187 and $192 per year, compared with horizontal instillation. Instillation of travoprost at a 45-degree angle would save $108 per year relative to instillation from a vertical angle. These savings are substantial: They represent the cost of 3.0 bottles and 5.6 months of bilateral therapy with bimatoprost, 1.8 bottles and 3.0 months of therapy with travoprost, and 3.1 bottles and 4.9 months of therapy with latanoprost.

CONCLUSIONS

Health care providers are urged to instruct glaucoma patients in the most efficient method of instillation for their prostaglandin analogs. For bimatoprost and latanoprost, the most efficient method is instillation with the bottle held vertically, with 45 degrees nearly as efficient. For travoprost, the most efficient method is instillation at 45 degrees.

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