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# Daily Cost of Ophthalmic Solutions for Treating Glaucoma in Japan

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**Purpose:** We conducted a study of the daily cost of various ophthalmic solutions used in Japan for treating glaucoma: β-adrenergic blockers (11 products), epinephrine (3), cholinergics (3), prostaglandins (2), and carbonic anhydrase inhibitors (2).

**Methods:** The total number of drops in one bottle of each solution was counted drop by drop. The cost per drop was calculated by dividing the government-controlled standard prices by the total number of drops in one bottle. The daily cost of therapy was calculated by multiplying the cost per drop by the number of drops typically used per day.

**Results:** The average cost of each preparation was calculated based on the prices and the daily usage. The daily cost of the β-adrenergic blockers studied ranged widely, from $0.43 to $1.04.

**Conclusions:** These data may be useful in selecting ophthalmic products for glaucoma therapy in Japan. **Jpn J Ophthalmol 2001;45:99–102** 

**Key Words:** β-Adrenergic blocker, daily cost, glaucoma, ophthalmic solution, total number of drops per bottle.

## Introduction

Major considerations in choosing pharmacotherapy should be focused on the effect on the quality of life and also the cost of medical treatment.[1–5]

Topical ophthalmic solutions of β-adrenergic blockers, epinephrine, cholinergics, carbonic anhydrase inhibitors, and/or prostaglandins are generally administered in the treatment of open-angle glaucoma or ocular hypertension.[3,6] In deciding which of these preparations to use, the daily cost of the treatment can not be ignored because the treatment would extend over a long period. We therefore estimated the daily cost of these ophthalmic products for reference purposes. Estimation was made on the commercially available β-adrenergic blockers, epinephrine, cholinergics, carbonic anhydrase inhibitors, and prostaglandins adopted for use at the Hiroshima University Hospital.

## Materials and Methods

Eleven β-adrenergic blockers (Table 1) and 10 other preparations (Table 2) were examined. The β-adrenergic blockers were : Bentos® (1% befunolol hydrochloride), Betoptic® (0.5% betaxolol hydrochloride), Hypadil® (0.25% nipradiol), Mikelan® (1.0% and 2.0% carteolol hydrochloride), Timoptol® (0.25% and 0.5% timolol maleate), Rysmon®-TG (0.25% and 0.5% timolol maleate ophthalmic thermosetting-gel solution) and Timoptol®-XE (0.25% and 0.5% timolol maleate ophthalmic gel-forming solution). Included among the 10 other preparations were 3 epinephrine

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products, Epista® (1.25% epinephrine) and Pivalephirine® (0.04% and 0.1% dipivefrine hydrochloride); 3 cholinergics, Sanpilo® (1.0 and 2.0% pilocarpine hydrochloride) and Ubretid® (0.5% distigmine bromide); 2 carbonic anhydrase inhibitors, Trusopt® (0.5% and 1.0% dorzolamide hydrochloride); and 2 prostaglandins, Rescula® (0.12% isopropyl unoprostone) and Xalatan® (0.005% latanoprost). Each bottle was labeled as containing 5 mL per bottle except for the 2.5-mL bottles of Rysmon®-TG, Timoptol®-XE, and Xalatan®. The contents of each bottle were squeezed drop by drop into a graduated cylinder (Shibata Science Instruments, Tokyo; calibrated to be accurate within 0.5% [±0.05 mL/10 mL] at room temperature). The total number of drops per bottle was counted, and the fill volume (mL) of each bottle was measured.[6,7] The mean volume of one drop in each preparation was calculated by dividing the fill volume by the number of drops per bottle. The cost of one drop (cost/drop) was calculated by dividing the government-controlled standard price by the total number of drops per bottle[8]). The daily cost of each preparation was determined by multiplying the cost/drop by the number of drops indicated for use as described in the patient package insert.

## Results

### β-*Adrenergic Blockers*

Of the β-adrenergic blockers, the price of ophthalmic solutions ranged from $13.40 (the price in dollars was calculated using 107 yen to 1 U.S. dollar, May 2000) (1.0% Mikelan®) to $25.89 (0.25% Hypadil®). The total number of drops in 5 mL preparations ranged from 108.7 ± 0.9 (1.0% Mikelan®) to 168.7 ± 2.9 (0.5% Betoptic®), and in 2.5 mL preparations, from 46.0 ± 2.7 (0.5% Rysmon-TG®) to 78.7 ± 1.2 (0.5% Timoptol-XE®). The possible period of usage for one bottle was calculated by dividing the fill volume by the number of drops required per day. The longest period of usage was 42.2 days per bottle of 0.5% Betoptic® with the shortest period of usage being 27.2 days, seen with 1.0% Mikelan®. The cost/drop was calculated from the price per bottle and the total number of drops contained.

**Table 1.** Daily Cost of β-Blocker Ophthalmic Solutions Used for Glaucoma Therapy in Japan

| Active Ingredient | Trade Name | Strength (%) | Manufacturer | Price per Bottle* ($1 = ¥107) | Total Number of Drops per Bottle (± SD) | Measured Amount (mL) (± SD) | Duration of Usage per Bottle (days)† | Daily Dose‡ | Daily Cost ($1 = ¥107) |
|---|---|---|---|---|---|---|---|---|---|
| Befunolol hydrochloride | Bentos | 1.0 | Kaken Pharmaceutical | $15.11 | 135.0 ± 4.0 | 4.87 ± 0.04 | 33.8 | BID | $0.45 |
| Bextaxolol hydrochloride | Betoptic | 0.5 | Alcon Japan | $25.42 | 168.7 ± 2.9 | 4.97 ± 0.04 | 42.2 | BID | $0.60 |
| Nipradilol§ | Hypadil | 0.25 | Kowa Shinyaku | $25.89 | 139.3 ± 4.5 | 5.22 ± 0.04 | 34.8 | BID | $0.74 |
| Carteolol hydrochloride | Mikelan | 1.0 | Otsuka Pharmaceutical | $13.40 | 108.7 ± 0.9 | 4.93 ± 0.04 | 27.2 | BID | $0.49 |
| Carteolol hydrochloride | Mikelan | 2.0 | Otsuka Pharmaceutical | $19.86 | 109.7 ± 1.1 | 4.93 ± 0.04 | 27.4 | BID | $0.72 |
| Timolol maleate | Timoptol | 0.25 | Santen Pharmaceutical | $15.57 | 140.7 ± 0.9 | 5.07 ± 0.04 | 35.2 | BID | $0.44 |
| Timolol maleate | Timoptol | 0.5 | Santen Pharmaceutical | $23.76 | 150.0 ± 0.0 | 5.30 ± 0.00 | 37.5 | BID | $0.63 |
| Timolol maleate | Rysmon-TG | 0.25 | Wakamoto Pharmaceutical | $15.57 | 51.7 ± 2.5 | 2.50 ± 0.00 | 25.9 | OD | $0.60 |
| Timolol maleate | Rysmon-TG | 0.5 | Wakamoto Pharmaceutical | $23.93 | 46.0 ± 2.7 | 2.57 ± 0.06 | 23.0 | OD | $1.04 |
| Timolol maleate | Timoptol-XE | 0.25 | Santen Pharmaceutical | $15.57 | 73.0 ± 1.0 | 2.93 ± 0.06 | 36.5 | OD | $0.43 |
| Timolol maleate | Timoptol-XE | 0.5 | Santen Pharmaceutical | $23.93 | 78.7 ± 1.2 | 3.07 ± 0.06 | 39.4 | OD | $0.61 |

*Established by the Japanese government on April 2000, and converted to U.S. dollars on May 2000.
†Based on administration of one drop in each eye once daily.
‡BID: Twice per day; OD: Once a day.
§Also exhibits $\alpha$-$_1$ blocking; n = 3.

**Table 2.** Daily Cost of Other Ophthalmic Solutions Used for Glaucoma Therapy in Japan

| Active Ingredient | Trade Name | Strength (%) | Manufacturer | Price per bottle* ($1 = ¥107) | Total Number of Drops per Bottle (± SD) | Measured Amount (mL) (±SD) | Duration of Usage per Bottle† (Days) | Daily Dose‡ | Daily Cost ($1 =¥ 107) |
|---|---|---|---|---|---|---|---|---|---|
| Epinephrine | Epista | 1.25 | Takeda Pharmaceutical | $3.22 | 124.0 ± 2.0 | 5.53 ± 0.22 | 31.0 | BID | $0.10 |
| Dipivefrine hydrochloride | Pivalephrine | 0.04 | Santen Pharmaceutical | $10.53 | 132.7 ± 2.2 | 4.90 ± 0.04 | 33.2 | BID | $0.32 |
| Dipivefrine hydrochloride | Pivalephrine | 0.1 | Santen Pharmaceutical | $16.21 | 144.7 ± 2.4 | 5.03 ± 0.04 | 36.3 | BID | $0.45 |
| Isopropyl unoprostone | Rescula | 0.12 | Fujisawa Pharmaceutical | $24.73 | 145.7 ± 3.8 | 5.13 ± 0.09 | 36.5 | BID | $0.68 |
| Pilocarpine hydrochloride | Sanpilo | 1.0 | Santen Pharmaceutical | $1.42 | 119.3 ± 1.8 | 5.15 ± 0.02 | 14.9 | QID | $0.10 |
| Pilocarpine hydrochloride | Sanpilo | 2.0 | Santen Pharmaceutical | $1.74 | 121.3 ± 1.8 | 5.20 ± 0.07 | 15.1 | QID | $0.11 |
| Dorzolamide hydrochloride | Trusopt | 0.5 | Banyu Pharmaceutical | $10.75 | 149.3 ± 4.0 | 5.44 ± 0.31 | 23.9 | TID | $0.43 |
| Dorzolamide hydrochloride | Trusopt | 1.0 | Banyu Pharmaceutical | $16.51 | 150.0 ± 4.0 | 5.23 ± 0.02 | 25.0 | TID | $0.66 |
| Distigmine bromide | Ubretid | 0.5 | Torii Pharmaceutical | $9.11 | 108.0 ± 4.7 | 5.17 ± 0.24 | 27.0 | BID | $0.34 |
| Latanoprost | Xalatan | 0.005 | Pharmacia & Upjohn | $26.23 | 120.3 ± 3.1 | 3.02 ± 0.05 | 60.2 | OD | $0.44 |

*Established by the Japanese government on April 2000, and converted to U.S. dollars in May 2000.
†Based on administration of one drop in each eye daily of each product; n = 3.
‡BID: Twice per day; QID: four times per day; TID: three times per day; OD: Once a day.

The highest daily cost among the β-blockers was $1.04/day for 0.5% Rysmon-TG®; the lowest cost was $0.43/day was for Timoptol-XE ®(0.25%).

### *Other Preparations*

Of the 10 other preparations, the price of ophthalmic solutions examined ranged from $1.42 (the price in dollars was calculated using 107 yen to 1 U.S. dollar, May 2000) for Sanpilo® (1.0%) to $26.23 for Xalatan®.

The total number of drops ranged from 108.0}4.7 (0.5% Ubretid®) to 150.0}4.0 (1.0% Trusopt®). The highest daily cost was $0.68 per day for 0.12% Rescula®. The daily cost of Epista® and Sanpilo® (1.0%) were the lowest, at $0.10 per day (Table 2). The longest period of usage per bottle was 60.2 days for Xalatan®, and the shortest was 14.9 days for Sanpilo® (1.0%).

The daily cost of each preparation was obtained by multiplying the cost/drop by the number of drops for daily use indicated in the patient package insert. In the majority of products, the indicated usage was one drop for each eye in a range of 1 to 3 times per day. The exceptions were Sanpilo®(1.0% and 2.0%), which were administrated 4 times per day.

## Discussion

The present study investigated the daily cost of ophthalmic solutions used in treating glaucoma in Japan. While efficacy is important in establishing the cost-effectiveness ratio, the efficacy and safety of most of these ophthalmic products can be considered similar among β-adrenergic blockers.[1,9,10] We therefore focused mainly on the daily cost of these ophthalmic solutions for treating glaucoma. The daily cost of each preparation was simply calculated according to the price of one bottle, the total number of drops contained, cost/drop, and number of drops indicated per day.[11]

Among β-adrenergic blockers, there are 5 timolol preparations. Even among these preparations the daily costs varied from $0.43 to $1.04 as shown in Table 1. The daily costs of 1.0% befunolol hydrochloride, 0.25% timolol maleate, and 0.25% timolol maleate gel-forming solutions were cheaper than other β-adrenergic blockers. The duration of usage per bottle of the β-adrenergic blockers ranged from 23.0 to 42.2 days. Betoptic® (0.5%), which is administered twice a day, showed the longest period of use. This study suggests that substantial differences exist in daily cost and in duration of usage per bottle among β-adrenergic blockers. These data on the

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daily cost of β blockers should be taken into consideration in treating glaucoma.

Among the 10 other preparations, the daily costs ranged from $0.10 to $0.68. Cost-effectiveness is one of the important factors in selecting ophthalmic solutions for the treatment of glaucoma.[1] However, the number of drops to be administrated per day differs.[12–14] This should be taken into consideration, because it may influence preference as well as the quality of life.

Although the cholinergics, Sanplio® and Ubretid®, showed lower daily costs, they must be applied to each eye 4 times a day (Table 2). This may affect the patient's quality of life.

In the process of estimating the daily costs of the products, another issue should be noted that may affect the practical usage of the ophthalmic solutions. The duration of usage per bottle varied from the shortest period of about 15 days for Sanpilo®, to the longest of about 60 days for Xalatan®, which specifies once-a-day dosing. The Japanese government fixes a maximum duration of therapy for prescriptions.[5] In April 2000, the maximum duration for external use was set at 2 weeks except when a patient takes a long-term journey. Ordinarily, patients have to obtain a new bottle every 2 weeks. However, 15 days of estimated usage might be too short a period for some patients who receive only one bottle per visit because possible waste by patients is not taken into consideration in the estimate. Patients may use up the entire bottle in a shorter period than estimated. On the other hand, 60 or 42 days of usage would be too long for proper preservation. In the United States and the European Union, information in the package insert of Xalatan® indicates that once opened the container can be stored for 6 weeks. In Japan, the package insert of Xalatan® indicates that once opened the contents have to be used within 4 weeks. According to the Japanese package insert, a bottle of Xalatan® can be used for only 4 weeks; should the remainder be discarded? If so, the daily cost of Xalatan® will become $0.94 per day and, therefore, more expensive.

As mentioned above, consideration of the amount of ophthalmic solutions wasted by patients would also be important.[1] This includes medicine that drips down the side of the bottle while a patient is dispensing the medicine drop by drop, or is squirted out when only a single drop is required.

It should be noted that the present study does not include these factors that arise in actual usage.

Although we simply estimated the daily cost of treating glaucoma by factors such as the total number of drops, bottle fill volume, and the price, these data should be helpful in selecting topical ophthalmics from the point of view of daily cost.

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