JOPAT Vol 22(1), 1078- 1085 Jan. – June, 2023 Edition

https://dx.doi.org/10.4314/jopat.v22i1.5

Objective assessment of the variation in number of doses of generic timolol eye drops along with their cost effectiveness.

Isaac Johnson Ajeh[3, *], Galadima Isa Hayatu[1] and Kazeem Toyosi Olatunji[2]

[1]Department of Medicinal Chemistry and Quality Control (MCQC), NIPRD, Abuja

[2]Department of Microbiology and Biotechnology (MB &BT), NIPRD, Abuja

[3]Department of Pharmaceutical Technology and Raw Materials Development (PT &RMD), NIPRD, Abuja.

ABSTRACT

First, this study aims to ascertain if truly the generic timolol eye drops circulating in Abuja and it environ are interchangeable. Secondly, we explore their cost effectiveness in naira based on the dispensing position. Using official guidelines, we assessed seven generic timolol ophthalmic preparations for organoleptic, pH, viscosity, sterility, and assay test. After this, they were tested in the vertical (90 º) and horizontal (30 º) positions for filled volume in a bottle, the total number of drops per bottle, drops per mL; and eventually the total number of bottles needed per year, cost per year and their cost effectiveness per mmHg were extrapolated. All brands were colorless and devoid of particulate contamination. Assay, pH, and viscosity values were within the compendia specification (BP and USP) for eye drops. The sterility assay showed no evidence of bacterial or fungi growth. All brands had actual filled volume less than or equal to the stated label claim. Their drops per 5 mL bottle range from 141-169 and 122-139 when dispensed in vertical and horizontal positions respectively; while for brands with 10 mL label volume, they range from 305-321 and 299-309 drops per bottle for vertical and horizontal dispensing respectively. Brand T1 (which is the most expensive) would need two bottles less in a year if the medication were to be dispensed vertically, amounting to N 3,200.00 ($ 7.04) reduction in treatment cost and a 45 % improvement in cost-effectiveness per intraocular pressure (IOP) reduction per year. In conclusion, the dispensing technique played a significant role in the number of drops per bottle, this would however impact on the treatment cost of glaucoma patient placed on timolol eye drop.

Keywords: Timolol eye drop, quality assessment, cost-effectiveness,

*Corresponding author: ajeh.johnson@niprd.gov.ng, johnsonisaac11@yahoo.com, +234 803 9185 040

INTRODUCTION

Glaucoma is one of the many chronic, progressive eye problems that could damage the optic nerve and result in the loss of sight function [1]. It is believed to be the second major cause of preventable irreversible blindness in persons aged 40 and above and has been associated with several risk factors such as family history, gene mutations, race, diabetes, and hypertension [1]. The sub-Saharan Africa region is known for its high incidence and prevalence of glaucoma probably due to limited resources and very few available ophthalmologists [2].

Usually, glaucoma increases the formation of aqueous humor; hence its treatment lies in lowering increased intraocular pressure (IOP) using a topical β-adrenergic antagonist, a topical prostaglandin analog, or through the surgical procedure.

Timolol (a non-selective β-adrenergic blocker) acts on the ciliary epithelium to reduce aqueous humor production and eventually lower IOP [3]. It is a drug of choice for persons who may respond insufficiently to topical prostaglandins, and the efficacy of other drugs for glaucoma has been generally compared with it. It has been documented that 70 % of glaucoma and ocular hypertensive patients would respond to timolol. Other studies have proven that timolol could decrease aqueous humor production by about 48 % in the normal human eye [1]. Local hypersensitivity reaction, ocular irritation, blurred vision, and dry eyes are common adverse effects associated with timolol [1]. A good proportion of topical timolol if administered could drain through the nasolacrimal duct and absorb systemically causing cardiac and respiratory adverse effects such as bradycardia, bronchospasm, cough, hypotension, and syncope [2]. In the human aqueous humor, the mean concentration of timolol after 2 h of administration has been reported to be 538±304 ng/mL and 210±175 ng/mL for 0.5 % and 0.1 % respectively [1].

The position of administering an eye drop has been noted as the major cause of variations among generics with respect to the drop size and number of doses per bottle [4]. Proper administration of eye drop requires coordinated control of eye movement with hand movement and adroitness linking visual acuity with a steady hand and accurate kinesthesis [4]. Not surprisingly, it is documented that glaucoma patient would use about 1.4-1.8 drops when trying to administer a single eye drop [5]. It has been proven that the drop volume in an eye drop could vary from 25-70 µL [6]; and given that the normal tear film volume is about 7 µL and only capable of containing 30 µL without overflow, it then means a substantial portion of an eye drop is wasted [6]. Interestingly, a cross-sectional study revealed that a fourth of ophthalmic patients has reported problems associated with early eye drop bottle exhaustion [7]. How long an eye drop would last and the influence of cost of a generic could affect patient adherence to the prescribed regimen. While the minimum volume of eye drops a patient should expect is on the label, it does not always translate to the number of applications, and may result to possibility of inconsistencies in the number of drops of medicine available in a bottle [7]. In comparing the cost effectiveness of fixed combination antiglaucoma eye drops, the medications were dispensed horizontally and the mean actual volume, number of drops, volume per drops and cost per year were shown to vary significantly across brands [8]. It is with this view in mind that we conduct this study. First, we carried out an expository discourse on the quality of seven brands of ophthalmic timolol (0.5 %) marketed within the Federal Capital Territory of Nigeria, and then evaluate the possibility of objectively measuring the number of eyes drops in each bottle based on the position of administration, after which we performed a cost-effective analysis by determining the cost to be incurred by a patient per mmHg of IOP reduction.

MATERIALS AND METHODS

Materials

All brands were sourced from major pharmaceutical retail outlets within the Federal Capital Territory of Nigeria and represented available generic timolol (0.5 %) eye drops. We ensured that all medications purchased from a given manufacturer are of the same lot. They were stored at temperature not more than 30 ºC before the analysis.

Toluene and sulfuric acid were product of Sigma Aldrich, Germany; while sodium bicarbonate and anhydrous sodium carbonate were manufactured by BDH Chemicals, China. Thioglycolate agar, soybean casein, and Sabouraud dextrose broth were from CDH Fine Chemical, India.

Organoleptic assessment

Brands were inspected for color and clarity against a visual inspection board with a black and white background under a bright light [9].

pH measurement

The pH meter (Mettler Toledo; Type 8603, Switzerland) was calibrated with known standard buffer solutions (4, 7, and 10) before analysis. The electrode of the pH meter was placed directly into the beaker containing a portion of the eye drops and allowed to run until a constant reading was achieved [9]. This analysis was repeated thrice.

Viscosity test

The viscosity of timolol eye drops was determined using a Brookfield viscometer (NDJ-85). About 5 mL of the solution was placed in the plate and the spindle dipped in it and the viscosity was recorded at 50rpm. This was done in triplicate.

Assay test

A 2.5 mL volume of the eye drop (equivalent to 12.5 mg of timolol maleate) was measured and diluted with 25 mL of distilled water. To the 2.5 mL, 7.5 mL of carbonate buffer pH 9.7 was added and it was extracted with 35 mL of Toluene. Thereafter, each extract was washed with 5 mL carbonate buffer. The toluene extract was further extracted with 40 mL of 0.05 M sulfuric acid and diluted to 50 mL volume with distilled water. It was then filtered and the absorbance was measured at 295 nm with the aid of a Cary 60 UV/vis spectrophotometer. A blank solution was as well prepared following the above procedure but with 2.5 mL of distilled water in place of 2.5 mL timolol. The percent content of timolol was extrapolated using a specific absorptivity of 279 [10].

Sterility testing

Prior to the sterility assay, strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* were obtained from a commercial culture collection and maintained in the department of microbiology and biotechnology, NIPRD. A loop full of the various organisms were sub-cultured in a bottle containing sterile peptone water. A further dilution was carried out until it matches the McFarland standard concentration of $1x10^{5}$ CFU/mL [9]. One (1) mL from a freshly opened timolol eye drop was aseptically taken into 20 mL of fluid thioglycolate agar, soybean casein digest medium, and Sabouraud dextrose broth with the aid of a sterile micropipette and incubated for 72 h at room temperature. Twenty (20) mL each of thioglycolate agar, soybean casein digest medium, and Sabouraud dextrose broth were inoculated with 0.1 mL of *Staphylococcus aureus*, 0.1 ml *Pseudomonas aeruginosa* and 0.1 ml of *Candida albicans* to serve as a positive control for anaerobic bacteria, aerobic bacteria, and fungi respectively. This experiment was carried out for each brand [9,11].

Comparative economic analysis

For the vertical and horizontal drops count, bottles were held at 90 and 30 degrees respectively to represent how eye drops are administered to a patient. Bottles were squeezed to expel drops into a graduated 10 mL measuring cylinder calibrated in 0.1 mL increments, followed by a release of pressure between each complete drop. This was repeated until the last drop was expelled, after which the filled volume and drop counts were noted [12].

The number of drops per mL was determined by dividing the number of drops in a bottle by the filled volume, while the drop volume was the reciprocal of the drops per mL [13].

The number of bottles per year was evaluated by multiplying 4 (assuming both eyes receive the medication twice daily) by 364.2 (accounting for leap years) and dividing by the number of drops per bottle [13].

The cost per year was calculated by multiplying the cost price of the medication (in naira) by the number of bottles per year [13].

Cost-effectiveness was extrapolated by dividing cost per year (in naira) by IOP reduction in mmHg (using 3.22 mm Hg as the mean difference in IOP reduction between timolol eye drop and placebo) [2].

RESULTS

Except for T1, all the Timolol eye drop brands used in this study have their country of origin, manufacturing date, expiration date, batch number, NAFDAC number, strength, and label claim volume printed on their package (Table 1). They were all within their expiration date, with a strength of 0.5 % w/v. The label volume was either 5 mL or 10 mL. Preservatives were benzalkonium chloride 0.01 % w/v in all brands. All eye drops were clear and colorless. pH values across brands were between 6.80 and 7.50, while their viscosities range from 0.80-0.85 cp, and assay values were found to be within 92.68-104.16 % (Table 2).

The sterility results for the tested brands cultured for aerobic, anaerobic, and fungi organisms are presented in Table 3. Growth was absent across all brands after 72 h of culturing.

Table 4 and 5 denotes the actual fill volume, drops per bottle, drops per mL, drop volume (mL), the total number of bottles of timolol eye drops required per year assuming no drop was wasted and the total cost per year, and their cost effectiveness when dispensed either vertically or horizontally. Among brands, variations in fill volumes were negligible irrespective of the dispensed method. The average volume of each brand tested was either less than or equal to the label fill volume. The average number of drops in a bottle varies among brands, while the standard deviation of the drops in a bottle differs statistically among brands. Similarly, the standard deviations of drops in an mL were not too different among brands., with their mean drops per mL ranging from 29.4 to 33.8. The average yearly cost for T1 was N 14,400 at an exchange rate of N1 =$ 0.0022. T2 was the least expensive with a yearly cost of N 4,500.

DISCUSSION

Surgical procedure has been proven to be a more effective way of managing glaucoma; however, the high surgical and outpatient costs in the surgical arm have made medications the primary treatment of choice [2]. Ophthalmologists now have a variety of eye drops to choose from in managing IOP. Interestingly timolol is favored over other eye drops due to its availability and mild side effects, but selecting an ideal brand from a wide range of generics could be challenging for the pharmacist.

All products examined in this study passed the integrity test for packaging. A well-packaged eye drop with intact closure and seal is necessary to prevent contamination by microorganisms [14]. They were all preserved with benzalkonium chloride- a known preservative that could inhibit the growth of microbes by ensuring continued sterility and stability upon storage and usage.

We could attribute the clarity, colorlessness, and absence of particulate matter in all samples to the efficiency of the membrane filtration process during the eye drops production [9, 11].

The pH of all brands tested (6.8 -7.5) was comparable to that of tear fluid (6.5-8.0), and also within the acceptable pH range for eye preparations (6.6-7.8). An extreme pH could ocular discomfort and increased lacrimation due to possible drug degradation that could result from the altered pH of the eye preparation and could lead to a condition called epiphora [9].

Although all brands tested met the 90-110 % BP specification for assay for timolol ophthalmic, our data still necessitate the need for routine quality assessment for generic eye drops to

scrutinize for counterfeiting and possible deviation from the standards [10].

Some works have reported the ideal viscosity for ophthalmic preparations to be < 10 cp [15, 16]. Mammo et al in 2010; compared the viscosities of generic timolol eye drops in Canada and USA, and has reported values in the range of 0.11-0.15 cp and 0.11-0.21 cp respectively [17]. These values did not deviate much from our findings. A high viscosity could improve resident time for eye drops, but could as well cause blurring, and ocular discomfort and eventually may damage the ocular epithelium as a result of increased frictional rate between the eye drop and ocular surface during blinking, while a less viscous eye drop will enhance the comfort of the patient as well as decrease friction-related inflammation [16].

The sterility study confirmed that all test samples were devoid of bacteria and fungi contamination, thereby establishing their safety for topical use according to the USP standard [11]. Aside the risk of infection, microbial contamination of eye drops could alter the pH of the solution and as such reduce the efficacy of the drug [18].

Several techniques have been employed by manufacturers to reduce eye drops wastage, like overfilling of the bottles, the design of the bottle, medication dispensing mechanisms, and administration techniques [13]. This study revealed disparities in drops number, filled volumes, and yearly costs across brands tested based on the position in which the medications are dispensed. In prescribing a brand of timolol eye drop with a label volume of 5 mL to a patient residing in Abuja and its environs, we could anticipate a range of 141-169 and 122-139 drops per bottle in vertical and horizontal positions respectively; while for brands with 10 mL label volume, it could range from 305-321 and 299-309 drops per bottle for vertical and horizontal dispensing respectively. A previous study reported similar values of 123-209 and 115-165 drops per bottle for vertical and horizontal positions respectively among 7 brands of timolol eye drops with label volume of 5 mL each [19]. From our findings, if timolol eye drop was to be instilled on both eyes and twice daily without any drop wastage, a 5 mL bottle is expected to last for a period of 35-42 days and 30-34 days for vertical and horizontal instilling; and a 10 mL bottle should sustain the patient for 76-80 days and 74-77 days if instilled vertically and horizontally respectively. At the time of this study, a patient placed on brand T1 for instance would need two bottles less in a year if the medication were to be dispensed vertically, which will amount to N 3,200.00 reduction in treatment cost (more than twice the household daily consumption level of two-third of the Nigerian population) [20], and 45 % improvement in cost-effectiveness per IOP reduction per year. Similarly, T5 and T6 will improve effectiveness by 4.35 and 9.09 % respectively if instilled vertically. Some authors have suggested that administering artificial tears eye drops horizontally could save the patient $ 1.93 (~ N 877.27) per bottle [15]. In another study, vertical administration favored bimatoprost and latanoprost eye drops, while the horizontal instillation method was found to be more cost-effective for travasprost; just as in evaluating the variability in the mean number of drops in 192 different types and brands of glaucoma eye drops from 32 manufacturers, 22 out of the 32 were shown to differ significantly in drops number per bottle in the vertical and horizontal positions, while their adjusted mean drops per mL range from 20.9-40.8 which is in consonant with our findings of 29.4 to 33.8 drops/mL [13, 19]. Products with higher actual volume, small drop size, and larger drop per mL may be more cost-effective; whereas, some preparations may be cheaper but due to the large drop size and the method of administration, they may end up being less cost-effective.

Despite the non-existence of regulatory guidelines on the design of the bottle or the number of drops expected to be available in a mL of medication, the Food and Drug

Administration (FDA) suggests a rough guideline of 0.05 mL/drop or 20 drops/mL to the pharmacist [8]. This however implies that all brands of timolol eye drops tested in this study had more drops per mL and fewer mL per drop than recommended irrespective of the dispensing method; hence they did not meet the FDA guideline. The drop size of any eye drop will depend on the design of the dropper bottle and its tip, the viscosity of the solution, the dispensing angle, the surface area around the tip of the bottle, the surface tension of the solution, and the force required to squeeze the bottle. These factors make it practically difficult to design an ideal bottle for eye drops [8]. However, it has been suggested that utilizing a dropper tip with a smaller orifice diameter will provide a consistent surface area for a smaller-volume drop to fall.

Key limitations of our study were the fact that only two dispensing positions (90 and 30 º) were tested which may inaccurately reflect some of the patient-related factors in dosing, and some patients may experience more variability in the number of drops in bottle since most eye drops are not even intended to be dispensed in a strictly horizontal manner. Secondly, we only tested all generic timolol eye drops available within the Abuja metropolis and not all generics available on the market, hence our results can only be applied to those we tested. Finally, we did not factor in the National Health Insurance (NHIS) coverage plan enrolled by some citizens while evaluating the cost-effectiveness.

CONCLUSION

Our study re-established how brands and dispensing positions could significantly affect drops per bottle which in turn leaves the prescribers and pharmacists unable to correctly estimate the quantity of eye drops to be dispensed, leading to patients running out of medication early or being left with excess and associated costs. However, a larger sample size will be needed to validate these findings.

Table 1. Some information about brands of timolol eye drop tested

	Country	Mfd. Date	Exp. Date	Batch no.	NAFDAC no.	Claim vol.(mL)
T1	UK	-	09/24	-	04-5719	5
T2	India	07/20	06/23	X006009	A4-7179	10
T3	India	08/20	07/23	UE0075	B4-6715	10
T4	Nigeria	05/22	04/24	F1922002	A11-0228	10
T5	India	09/20	08/23	AC20024	C4-0504	5
T6	Spain	01/21	12/23	IFMD1A	04-7061	5
T7	India	04/21	03/23	1EA03107	B4-0470	10

Table 2. Some organoleptic and physicochemical properties of brands of Timolol eye drops tested (n=3).

	Color	Clarity	pH	Viscosity (cp)	Assay (%)
T1	Colorless	Clear	7.20±0.51	0.84±0.00	96.82±0.84
T2	Colorless	Clear	7.40±2.04	0.84±0.00	99.24±0.96
T3	Colorless	Clear	6.80±0.04	0.85±0.01	102.14±0.07
T4	Colorless	Clear	7.30±1.98	0.80±0.00	95.60±0.08
T5	Colorless	Clear	7.50±2.22	0.83±0.00	92.68±0.22
T6	Colorless	Clear	6.90±0.38	0.83±0.00	104.16±0.24
T7	Colorless	Clear	6.90±0.01	0.83±0.01	100.15±0.11

Table 3. Sterility testing results for brands of Timolol eye drops tested

	Liquid thioglycolate medium	Soyabean casein medium	Sabouraud dextrose broth
T1	-	-	-
T2	-	-	-
T3	-	-	-
T4	-	-	-
T5	-	-	-
T6	-	-	-
T7	-	-	-

Table 4. Drop volume ratio and yearly cost Timolol eye drops tested vertically (n=3).

	Vol. (mL)	Drops/bottle	Drops/mL	Drop vol.	Bottles/yr.	Yearly cost(N)	Cost-effectiveness (N)
T1	5.0±0.11	169.0±2.20	33.8±0.02	0.030±0.17	9	14,400	4,472.03
T2	9.9±0.10	305.6±0.80	30.9±0.11	0.032±0.11	5	4,500	1,397.52
T3	10.0±0.01	316.5±2.90	31.7±1.01	0.032±0.51	5	6,000	1,863.35
T4	10.0±0.14	321.2±5.10	32.1±0.66	0.031±0.98	5	8,250	2,562.11
T5	4.8±0.00	141.2±7.20	29.4±0.21	0.034±1.22	11	7,150	2,220.50
T6	4.8±0.00	149.8±2.30	31.2±0.04	0.032±2.00	10	11,500	3,571.43
T7	10.0±0.02	311.6±5.10	31.2±1.16	0.032±0.14	5	4,750	1,475.16

Table 5. Drop volume ratio and yearly cost Timolol eye drops tested horizontally. (n=3).

	Vol. (mL)	Drops/bottle	Drops/mL	Drop vol.	Bottles/yr.	Yearly cost(N)	Cost-effectiveness (N)
T1	5.0	138.5±5.9	27.7±0.04	0.036±0.28	11	17,600	5,465.84
T2	9.9	299.2±3.8	30.2±0.28	0.033±1.11	5	4,500	1,397.52
T3	10.0	305.0±6.9	30.5±2.01	0.033±0.26	5	6,000	1,863.35
T4	10.0	309.0±2.2	30.9±0.15	0.032±0.01	5	8,250	2,562.11
T5	4.8	125.1±3.2	26.1±0.81	0.038±1.10	12	7,800	2,422.36
T6	4.8	122.7±3.3	25.6±2.21	0.039±0.29	12	13,800	4,285.71
T7	10.0	309.3±1.9	31.2±5.01	0.032±0.01	5	4,750	1,475.16

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