Acute effect of flurbiprofen (Ivyflur) on tear production

***[1]Oluwasola M. Ojo, [2]Olusola I. Aremu, and [1]Fatimah O. Mustapha**

[1]Department of Optometry and Vision Science, University of Ilorin, Kwara State, Nigeria.

[2]Department of Pharmaceutics and Industrial Pharmacy, University of Ilorin, Kwara State, Nigeria.

ABSTRACT

Background: Many ocular and systemic conditions detected by eye care givers can be treated by the use of steroidal anti-inflammatory drugs (SAIDs), as well as Non-steroidal anti-inflammatory drugs (NSAIDs). Flurbiprofen is a non-steroidal anti-inflammatory drug usually prescribed in most eye clinic recently for the treatment of some eye diseases. The effect of Flurbiprofen on the tear production of 104 healthy participants was studied using their right eyes.

Methods: The participants with the mean age of 23.36 ± 4.28 years, consisted of 53 male participants and 51 female participants were selected after a thorough case history, external examination and ophthalmoscopy was done to rule out pathology. Schirmer's test was done in all participants before instilling Flurbiprofen drops, the test was repeated at an interval of 30 minutes, for a period of one and half hours.

Results: The mean tear production reduced from baseline tear production 20.22mm to 15.63mm in the first 30 minutes, 13.95mm in 60 minutes and 14.90mm in 90 minutes. This amounts to a reduction of 4.59 (22.70%), 6.27 (31.01%), 5.32 (26.31%) at 30, 60 and 90 minutes respectively. These reductions were found to be statistically significant ($P > 0.05$) showing that Flurbiprofen significantly inhibits tear production.

Conclusion: Flurbiprofen should therefore be used with caution in individuals that have or are predisposed to dry eye syndrome.

Keywords: Synthesis, Flurbiprofen, Schirmer's test, Anti-inflammatory, Tear

1. INTRODUCTION

Many ocular and systemic conditions encountered by practitioners can be treated with topical anti-inflammatory drugs such as corticosteroids, commonly known as steroids (SAIDs), as well as Non-steroidal anti-inflammatory drugs (NSAIDs) [1]. An inflammation can occur in any tissue in the eye, it serves as a protective response of cells to invasion such as pathogens, infection as well as tissue damage. It involves the coordinated communication of different immune cells and blood vessels through an intricate cascade of molecular signals. An acute inflammatory response usually lasts for a few hours or days [2]. Usually, inflammatory response has four phases: inflammatory inducers (infection or tissue damage), inflammatory sensors (mast cells and macrophages), inflammatory mediators and the phase of physical presentation in the tissues that are affected. Each phase has a unique response based on the cause of the inflammation. The five cardinal signs of inflammation are redness (rubor), pain (dolor), heat (calor), swelling (tumour) and loss of function. In order to shorten the duration of the inflammatory process, anti-inflammatory drugs are given to reduce inflammation [2]. Over the years, Non-Steroidal anti-inflammatory drugs (NSAIDS) have been used as safer alternatives to corticosteroids for the treatment of ocular inflammation. They comprise several chemically heterogenous classes of drugs that possess potent cyclooxygenase inhibitory activity [3]. Topical NSAIDS are classified into six groups based on their chemical composition: Indoles, phenyl acetic acids, phenyl alkanoic acids, salicylates, fenamates and pyrazolones. Salicyclates, fenamates and pyrazolones are considered too toxic to be used in the eye (Flach, 2002). The beneficial effects of NSAIDS over corticosteroids include: stabilization of intraocular pressure (IOP), provision of analgesia and reduction in risk of secondary infections [4]. Studies comparing NSAIDS with corticosteroids have demonstrated no significant difference in results between their uses [5]. However, NSAID treatment appears to be more effective than topical corticosteroids in re-establishing the blood-aqueous barrier [6]. Flurbiprofen is a member of the phenylalkanoic acid derivative family of nonsteroidal anti-inflammatory drugs (NSAIDs). It is primarily indicated as a pre-operative anti-miotic, however it is also used in the treatment of swelling and pain caused by cataract surgery. The addition of the fluorine atom imparts important characteristics to the flurbiprofen molecule that distinguishes it from other NSAID, it has been established that in drug design one way of improving metabolic stability is to

* Corresponding author: Email: michosola@gmail.com; Phone: +2347032063614

introduce fluorine at a metabolically labile site [7]. A study was carried out to compare the efficacy of two topical non-steroidal anti-inflammatory drugs, flurbiprofen and diclofenac sodium, for the inhibition of surgically induced miosis. There were no statistically significant differences between the two drugs except at the start of phacoemulsification, when the flurbiprofen treated eyes were more dilated than the diclofenac treated eyes [6]. This may also contribute to the efficacy of flurbiprofen to prevent occurrence of anterior uveitis following surgery done in the anterior aspect of the eyes. Tearing is the secretion of tears, which often serves to clean and lubricate the eyes in response to an irritation to the eyes [8]. The tear film is a unique thin fluid layer of approximately 3µm thick and 3µl in volume that covers the outer mucosal surfaces of the eye [9,10]. The human tear film coats the anterior surface of the eye and is composed of three distinct layers; an inner mucin layer, a middle aqueous component and a lipid overlay [11]. The three-layered tear film inhibits ocular surface invasion, provides an air-tissue interface for gas exchange, supplies essential nutrients and metabolites to maintain a transparent and avascular cornea. A loss or reduction to any layer of this film may lead to dry eye and a potential for significant ocular surface pathology [11]. Non-steroidal anti-inflammatory drugs have been suggested to be an efficient tool in the management of dry eye, due to the fact that inflammation plays a significant role in the ethiopathogenesis of dry eye [12]. Their contribution to the management of dry eye has been explained to be as a result of their anti-inflammatory effect on the ocular surface [13]. Notwithstanding, the effect of a substance on tear production can make it either an efficient or inefficient tool in the management of dry eye syndrome. This study therefore was geared towards finding out whether the observed positive effect of a non-steroidal anti-inflammatory drug (Flurbiprofen) on the management of dry eye is just as a result of its anti-inflammatory effect on the ocular surface or it also has some effect on tear production.

2. MATERIALS AND METHODS

2.1. Materials

2.1.1 Reagents

The following reagents were used in this study; Flurbiprofen (0.03%) as an active ingredient in ivyflur, Benzalkonium Chloride, Disodium Edetate, Sodium Chloride, Sodium Phosphate and Water for injection.

2.1. Equipment

The instruments used for the study were Direct ophthalmoscope (Keeler), Pen light (Reister), Stop clock , 5x 35mm Whatmann no. 41 filter strips (Schirmer strips).

2.1.3 *Biological Materials*

The tear samples used in this study were obtained from the eyes of voluntary human subjects in Optometry clinic, University of Ilorin.

2.2 Methods

This was a prospective study carried out in University of Ilorin, Optometry clinic in which the pre-test, post-test design was employed to determine the effect of Flurbiprofen on tear production. There were 104 participants randomly selected in this study between the age of 16 to 35 years because people within this age range usually have little or no existing ocular or systemic pathological conditions which might give an erroneous result and consent was sought from each subject. All the subjects were free from ocular and systemic diseases. They went through a pre-study measurement of tear production using Schirmer's tear strip. The base line tear production was taken prior to the administration of Flurbiprofen and the induced tear production were taken after stipulated time intervals (30 minutes, 60 minutes and 90 minutes) respectively.

2.2.1 Ophthalmoscopy

The direct ophthalmoscope was used to observe the interior part of the eye. The ocular media fundal background, optic nerve head, retinal vessels and macula were inspected. The disc was observed for size, shape and normal physiological cupping. While the vessels were observed for the ratio of the diameter of veins to arteries and presence of macular reflex, exudates, pigmentation and degeneration, Subjects with pathologies were screened out.

2.2.2 Schirmer's Test

This test was carried out with a 5 x 35mm strip of Whatmann #41 filter paper (Schirmer strips). The paper had a notch located 5mm from one end of the strip. The notched end of the strip was rounded. The test was done by bending the strip at the notch. The rounded end of the Schirmer's sterile paper strip was then inserted into the lower conjunctival sac of the right eye. The right eye was then closed; the strip was progressively wetted by the capillary action drawing up tears as they were produced. The amount of wetting was measured after 5mins. The amount of wetting was measured from the notch of the strip as the zero point. The test was read by removing the strip from the right eye and recording the length of the moistened area. This served as the baseline/control for the experiment. 15 - 30mm of wetting in 5mins was considered normal. After 5mins, when the subject was calm, a

drop of Flurbiprofen (0.03%) was instilled into the right eye. The tear production reading of the right eye (OD) was recorded at 30mins interval for three times (30 minutes, 60 minutes and 90 minutes).

2.3 Statistical Analysis

The results of the studies are expressed as mean ± standard error of the mean (SEM) and the data were represented in tables, figures and analyzed using z-test. The statistical value, $p < 0.05$ was set as the statistically significant difference level.

3.0 RESULTS

In this study, one hundred and four participants were examined, 51% were males and the remaining 49% were females. All participants were within the age range of 16-35years with a mean age of 23.36 ± 4.82 years (Mean ± SD) as shown in table 1.

Table 1: Age Descriptive Statistics of Participants

AGE(YRS)	FREQUENCY(F)	MIDPOINT(x)	Fx	x^2	Fx^2
16-20	37	18	666	324	11988
21-25	33	23	759	529	17457
26-30	25	28	700	784	19600
31-35	9	33	297	1089	9801
Total	104		2422		58846

N	Mean ± SEM	Std. Deviation
104	23.36 ± 0.47	4.82

Table 2 Shows that among the female participants, those in the age range of 16 – 20 years, had the highest frequency (43.1%) and among the male participants, those in the age range of 21 – 25 years had the highest frequency (32.1%). The Table also shows that the male population (53) is higher than the female population (51).

Table 2: Distribution of Participants according to their Age and Gender

Age range	Male	Female	Total
16-20yrs	15 (28.3%)	22 (43.1%)	37(35.6%)
21-25yrs	17 (32.1%)	16 (31.4%)	33(31.7%)
26-30yrs	16 (30.2)	9 (17.6%)	25(24%)
31-35yrs	5 (9.4%)	4 (7.8%)	9(8.7%)
Total	53(100%)	51(100%)	104(100%)

Table 3 below shows the mean decrease and percentage decrease in tear production from baseline tear production at all-time intervals. After 30minutes of administration, there was 4.59 (22.70%) decrease, after 60 minutes, there was 6.27 (31.01%) decrease and after 90 minutes, there was 5.32 (26.31%) decrease.

Table 3: Percentage Mean decrease in tear production (TP) mm of subjects from Baseline at Time Intervals of 30, 60 and 90 minutes after Administration of Flurbiprofen

Mean Baseline Tear Production = 20.22	Mean Tear Production Values	Mean Decrease of Tear Production	Percentage Decrease %
30 minutes	15.63	4.59	22.70
60 minutes	13.95	6.27	31.01
90 minutes	14.90	5.32	26.31

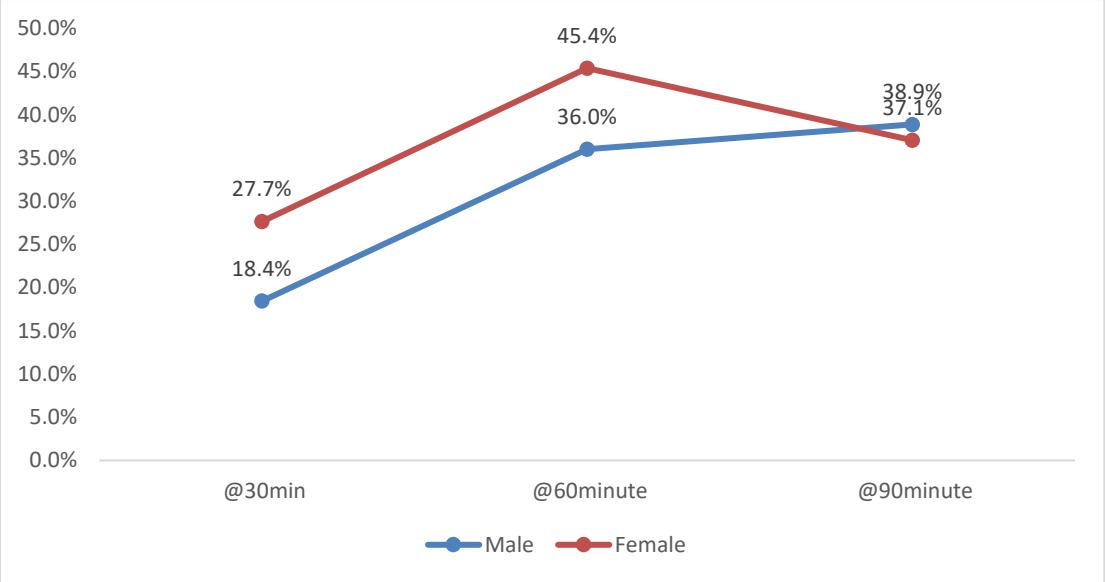

Figure 1: Percentage Decrease in Tear Production by Sex after Administration of Flurbiprofen.

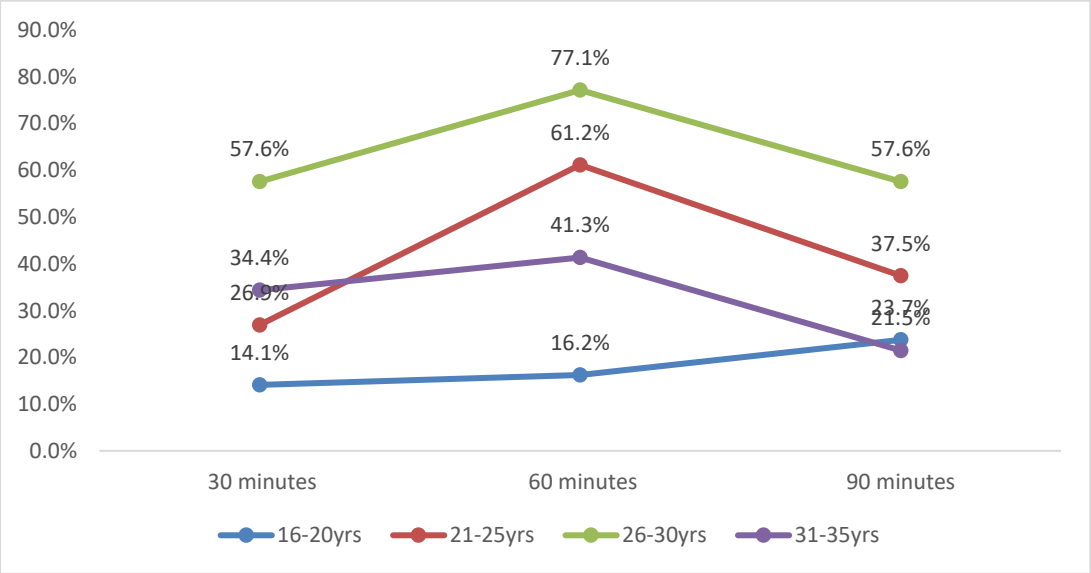

Figure 2: Percentage decrease in Tear Production by Age range after Administration of Flurbiprofen.

Table 4 below shows that male subjects had higher tear production than female subjects at all time intervals but the lowest point of reduction in tear production for both genders was observed at 60 minutes after administration, afterwards there was an increase in tear production after 90 minutes of administration showing a decline in the effect of the drug after 90 minutes.

Table 4: Effect of Flurbiprofen on Tear production from Baseline through Time Intervals 0f 30, 60 and 90 minutes after administration with respect to Gender

Sex	Baseline (mm)	30 minutes (mm)	60 minutes (mm)	90 minutes (mm)
Male	21.15±0.88	17.25±0.94	14.94±0.84	15.34±0.88
Female	19.24±0.94	13.92±0.92	12.92±0.79	14.45±0.76
Total	20.22±0.65	15.63±0.67	13.95±0.58	14.90±0.65

Mean ± SEM; SEM = standard error of mean

Table 5 below shows that participants between the age of 16 to 20years old had the highest tear production than the other age groups at all time intervals and participants aged 31-35 had the lowest tear production. The lowest point of reduction for all age groups is observed at 60 minutes after administration.

Table 5: Effect of Flurbiprofen on Tear production from Baseline through Time Intervals of 30, 60 and 90 minutes after administration with respect to Age

Age range	Baseline (mm)	30 minutes (mm)	60 minutes (mm)	90 minutes (mm)
16-20YRS	22.25±1.49	16.40±1.38	15.65±0.99	15.70±1.14
21-25YRS	21.58±1.00	15.94±1.11	13.39±0.98	15.00±1.99
26-30YRS	18.22±1.73	14.12±1.05	12.56±1.21	14.70±0.96
31-35YRS	18.19±1.06	13.56±1.87	12.89±1.80	14.12±1.24
Total	20.22±0.65	15.63±0.67	13.95±0.58	14.90±0.60

Mean ± SEM; SEM = standard error of mean

Table 6 shows a decrease in tear production from baseline tear production at all time intervals and a slight increase after 90 minutes of administration which can be attributed to wearing off of the drug. The lowest point of the reduction was at 60mins after administration.

Table 6: A comparison of the mean baseline tear production to the mean tear production 30, 60 and 90 minutes after the instillation of Flurbiprofen for each age range

	Baseline	30 minutes	60 minutes	90 minutes
Mean(mm)	20.22±6.57	15.63±6.87	13.95±5.95	14.90±6.13

Using Z-test statistic to test for the difference between the mean baseline Tear Production and Mean Tear Production at Time Intervals (30, 60 and 90 minutes) for a level of significance of p = 0.05, after the administration of Flurbiprofen (Table 7). It was shown topical administration of Flurbiprofen has a significant effect on tear production {p<0.05) (Z =.6.55817)

Table 7: Statistical Data Analysis for the effect of Flurbiprofen on tear production Using Z-Test

	Base line	*Time Interval*
Mean	20.2233	14.82524
Known Variance	42.40645	27.37613
Observations	103	103
Hypothesized Mean Difference	0	
Z	6.55817	
P(Z<= z) one-tail	2.72E-11	
z Critical one-tail	1.644854	
P(Z<=z) two-tail	5.45E-11	
z Critical two-tail	1.959964	

4. DISCUSSION

The aim of this study was to determine the effect of Flurbiprofen on tear production. One hundred and four (104) participants, with a total of 53 male participants and 51 female participants took part in this study, all participants are within the age range of 16-35 years with a mean age of 23.36 ± 4.82 years (Table 1). The Z-test statistical method of analysis was used to show that effect of topical administration of Flurbiprofen on tear production is significant. The result from this study showed a reduction in tear production from baseline 20.22 ± 6.57 to 15.63 ± 6.87, 13.95 ± 5.95 and 14.90 ± 6.13, at 30, 60 and 90 minutes respectively after administration of Flurbiprofen (Table 6). Flurbiprofen is a non-steroidal and inflammatory drug that possesses analgesic, anti-pyretic and anti-inflammatory characteristics and is known to be used for the inhibition of interoperative miosis [14]. This result is in agreement with previous study done by Crandall in 1999, which showed that several classes of drugs decrease aqueous tear secretion including drugs with analgesic effect such as Flurbiprofen [15]. The mean baseline tear production was 20.22 mm and the mean decrease of tear production was 4.59 (22.70%), 6.27 (31.01%) and 5.32 (26.31%) after 30mins, 60mins and 90mins of administration of Flurbiprofen. respectively (Table 3) which revealed the highest mean decrease of tear production at 60mins. The mean distribution of tear production in both genders at the different time intervals after the administration of Flurbiprofen (Table 4), showed that the male participants had higher baseline values and higher tear production values at the different time intervals compared to the female participants. This result is in agreement with the findings of Nicholas *et al.* [16] that conducted a study on the repeatability of clinical measurements of dry eye cornea which showed that females are found to have dry eyes more frequently than males. Following the result of this work, Table 5 shows the influence of age on the effect of Flurbiprofen on tear production from baseline and time intervals of 30, 60 and 90 minutes after

administration of Flurbiprofen, it was found that age range 16-20 years old had the highest baseline mean tear production of 22.25 mm while the age range 31-35 years had the lowest mean baseline tear production of 18.19mm with a difference of 4.06mm between the two age groups. In essence, the results showed that the amount of tear production in teenagers was more than tear production in adults. This is in agreement with the findings of Hirase *et al*., [17] that the volume of tears presents in the surface of the eye declines with age. Also Khisti *et al*., [18] reported that the basal tear production as measured by flourophotometry from the decay fluorescence after administration of flourescein solution in the eye was found to decrease with age.

5. CONCLUSION

This study shows that Flurbiprofen has a significant effect on tear production as a result of reduction in tear volume after a topical administration of Ivyflur and the effect of Flurbiprofen on tear production is also influenced by age and gender. Therefore it is advisable to be cautious in administering Flurbiprofen to Patients prone to dry eyes syndrome.

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Conflict of interest statement

The authors declare no conflict of interest regarding this study.

Contributions of Authors

This research work was conceptualized and designed by O.M. Ojo. Collection of data, writing and editing of the article for publication were collectively carried out by all the authors.

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