Research Journal of Pharmacology 6 (5-6): 71-77, 2012
ISSN: 1815-9362

Dry Eyes: An Adverse Effect of Systemic Antihistamine Use in Allergic Conjunctivitis Management

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Abstract: Systemic antihistamines are crucial in the management of allergic conjunctivitis in Ghana. This study, therefore, determined the incidence of dry eyes in patients with allergic conjunctivitis and the risk of developing dry eyes associated with the management of allergic conjunctivitis using systemic antihistamines. A retrospective cohort study involving the review of medical records of 738 cases of allergic conjunctivitis before and after treatment in two prominent referral eye care centers in Ghana was conducted. Associations between variables were determined using Binary Logistical Regression and Fisher's Exact Chi-Square (χ^2). The 1 month incidence of dry eyes among Allergic Conjunctivitis (AC) patients was 17.5% (15.1% in those below 45 years and 27.2% in those above 45 years). Age was significantly associated (aOR:1.02, p<0.001) with dry eyes. Seasonal allergic conjunctivitis was the commonest (62.2%) ocular allergy while perennial allergic conjunctivitis patients were the most susceptible (aOR:1.79; p = 0.454) to Dry Eyes (DEs). A significant (p<0.001) association existed between occupation and DEs. Students 304 (41.2%) suffered AC most but were significantly less susceptible (aOR:0.24; p<0.001) to DEs while teachers 29 (3.9%) had the least prevalence of AC but had the highest risk (aOR:1.42; p = 0.483) of DEs. Of 60 (8.1%) AC patients with pterygium, 16 (26.7%) were found to have DEs (aOR:1.16; p = 0.050). Burning sensation was significantly (p<0.001) associated to DEs. Out of 441 (59.8%) patients treated with cetirizine (a systemic antihistamine) on the first visit, 103 (23.4%) had DEs on the second visit. Cetirizine usage was the most significant risk factor (aOR:2.79; p<0.001) for DEs. Allergic conjunctivitis patients treated with systemic antihistamines had a significantly high risk of dry eyes.

Key words: Cetirizine, allergic conjunctivitis, dry eye, pterygium, systemic antihistamines

INTRODUCTION

Dry Eyes (DEs) is a symptomatic ocular surface disorder resulting from tear deficiency or loss of Pre-Ocular Tear Film (POTF) stability causing ocular discomfort (Dry Eye Workshop). POTF overlies the conjunctiva and cornea and performs many functions, including; moistening, protection, antibacterial, nutrition and optical (Lamberts, 1983; Pflugfelder *et al*., 1998; Norn, 1985). Therefore, instability of the POTF could result in ocular surface disorders such as dry eyes, increased susceptibility to allergy and infection (Thoft, 1985; Suzuki *et al*., 2006).

The prevalence of DEs reported by several studies worldwide has provided figures ranging from 5-30% as presented by the DEW. A clinical study by Hikichi *et al*. (1995) revealed that DE was found in 15-30% of new patients reporting to eye centers in Japan. Very few studies have been conducted on dry eyes in Africa. However, a survey by Gillan (2009) which involved convenient sampling of 112 subjects and using questionnaire by the Ocular Surface Disease Index (OSDI) observed that about 64% experienced at least mild dry eye symptoms. Frequently reported complaints of patients suffering from DEs are burning, foreign body sensation, pain, tearing, ocular fatigue and itching (Schiffman *et al*., 2000; Perry and Donnenfeld, 2004). These symptoms affect the quality of life of patients by compromising their ability to read, drive use the computer or watch the television resulting in loss of productivity. In addition to these DEs also imposes huge financial burden on sufferers (Clegg *et al*., 2006).

Allergic Conjunctivitis (AC) is on the increase and accounts for a huge proportion of ocular consultations in Ghana (Abokyi *et al*., 2012). Studies have shown that DEs is often found in patients suffering from allergic conjunctivitis (Abokyi *et al*., 2012; Toda *et al*., 1995; Hom *et al*., 2012). An increase in AC is, therefore,

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presumptive of a higher risk in the prevalence of DEs. About one-half of cases of allergic conjunctivitis treated in Ghana involve the use of systemic antihistamines (Abokyi *et al*., 2012). According to Al-Faris and Al-Taweel (1999), systemic antihistamines were the most prescribed medications by practitioners and accounted for about one-fourth of all prescriptions. It is known, however, that systemic antihistamines decrease mucous and aqueous productions which are two components of the precorneal tear film (Ousler *et al*., 2007) and could, therefore, be implicated in DEs. Hence, despite the significant contribution of systemic antihistamines in managing AC, monitoring is required to prevent ocular complications arising from these drugs.

Although, DEs is a very common ocular surface disorder found in clinical practice not much studies has been conducted in Ghana to estimate its incidence. This study, therefore, sought to determine the incidence of dry DEs in patients with allergic conjunctivitis and the risk of DEs associated with the management of allergic conjunctivitis using systemic antihistamines in Ghana.

MATERIALS AND METHODS

Study area: This study was conducted in the eye clinics of St. Michael Hospital and Our Lady of Grace Hospital both run by the Catholic Health Secretariat, Ghana and supported by the Ghana Health Service. The St. Michael Hospital, located at Pramso in the Bosomtwe District of the Ashanti region of Ghana, serves Kumasi the capital city of the Ashanti region and its environs. The eye clinic of the hospital which has an ophthalmologist, an optometrist, two ophthalmic nurses and one intern optometrist is the biggest in the district.

Our Lady of Grace Hospital, located at Asikuma-Odoben-Brakwa District in the central region of Ghana is the District Hospital designated to serve Asikuma, Odoben, Ahwhiam, Kuntanase, Jamra, Kokoso and Bedum and its environs. Over the years the great expertise of health care providers and staff has made the hospital a very important centre for the people in the district. The eye care team comprises an ophthalmologist, two ophthalmic nurses an enrolled nurse and two ward maids.

Study conduct and design: A retrospective cohort study which involved reviewing of past medical records of newly diagnosed cases of Allergic Conjunctivitis (AC) among the patients aged 12 years and above from January to December, 2011. A total of 1147 cases of AC were seen and managed mainly with anti-allergic medications. All patients were scheduled for a follow-up (a subsequent examination of a patient for the purpose of monitoring earlier treatment) 1 month after the first visit. Out of these, 738 cases were re-examined 1 month after the second visit (409 patients were lost due to absenteeism).

Information regarding patients' demographics (including gender, age and occupation), case history and diagnosis were recorded. All patients underwent a basic eye examination as recommended by protocol. All cases of AC were diagnosed based on patients' complaint of ocular itching in addition to clinical signs which includes discharge, chemosis, hyperemia or papillae of the conjunctiva. Diagnosis of dry eyes syndrome was made on the basis of patients' symptoms such as of ocular irritation and the Tear Break-Up Time (TBUT) as recommended by Toda *et al.* (1995) for patients with AC. Patient's eyes were stained with fluorescein and observed with the cobalt blue filter under the slit-lamp whilst they avoid blinking. The appearance of dark spots on the cornea before 10 sec was diagnosed as dry eyes.

Exclusion criteria:

- New cases of allergic conjunctivitis in children <12 years
- Newly diagnosed cases of allergic conjunctivitis but which were lost during follow-up or not followed up
- New cases of allergic conjunctivitis with concomitant dry eye on the first encounter of examination
- Cases of allergic conjunctivitis that were also suffering from glaucoma, chronic systemic diseases (including hypertension and diabetes) or being managed of these conditions

Ethical considerations: The study was approved by the Ethics Committee of the College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. Permission was also sought from the Hospital Directors of the various eye care facilities. Confidentiality and anonymity was ensured in the use of information retrieved from the patients medical records and the information collected was used solely for the purpose of this study.

Data analysis: Data was compiled using the Statistical Packages for Social Sciences (SPSS) version 17 (SPSS Inc., Chicago, IL in 2008). Descriptive statistics such as measures of central tendencies and dispersion, frequencies and percentages were used in analyzing the patient's demographics and other variables. Both crude Odds Ratios (ORs) and adjusted Odds Ratios (aORs) were computed using logistic regression to determine associations between dry eyes and other variables (such

as; gender, age, occupation, type of ocular allergy, presence or absence of a pterygium and previous medical history of antihistamine exposure). Also, Relative Risks (RRs) and Fisher's Exact Chi-square (χ^2) were computed to determine statistically significant differences between ocular symptoms presented by ocular allergic patients also suffering from dry eyes compared to those without dry eyes. An association was considered to be statistically significant if the p-value was found to be <0.05.

RESULTS AND DISCUSSION

A total of 1147 cases of Allergic Conjunctivitis (AC) were found in patients aged 12 years and above with only 738 (64.3%) cases eligible for the study since the others failed to return within the scheduled follow-up period. The incidence of Dry Eyes (DEs) recorded on the second visit in patients suffering from allergic conjunctivitis in this study was 17.5% (129/738). The coexistence of allergic conjunctivitis and dry eye usually present extreme discomfort to patients, since adequate tear film serves as a barrier to allergens and dilutes them as well as washes away inflammatory mediators. According to Asbell and Lemp (2006), cross sectional prevalence studies are mostly reported in literature due to the challenges in carrying out longitudinal studies on dry eyes on a sufficiently large population. However, cohort studies have the advantage compared to cross-sectional studies in the identification of risk factors since those factors usually preceded the outcome observed (dry eyes). One noticeable hospital based cohort study by Moss *et al.* (2004) in an older population (age range 43-84 years) recorded an incidence of 13.3% for a 5 year study period. A study by Nita *et al.* (2009) also reported of a much higher incidence of 63% but the subjects of their study were among patients that had presented with some symptoms of ocular irritation.

This study showed that males were in the minority 228 (30.9%) of the AC population and were also less susceptible (aOR:0.87; p = 0.558) to DEs compared to females, though this difference was not significant. The role of gender in DEs is slightly controversial with most studies noting a significantly higher susceptibility among women while a few others have observed no significant differences between the two sexes. A study on prevalence of DEs among diabetic patients by Manaviat *et al.* (2008) and the 5 year incidence study by Moss *et al.* (2004) support the assertion that gender is not a significant risk factor. However, Sendecka *et al.* (2004) found out in their study that females were significantly at risk of DEs. The biological factor underlying this preferential susceptibility of females to DEs is due to differences in the level of sex hormones produced by males and females. Davison *et al.* (2005) has shown that there is a very steep decline in the level of androgens with aging in females. Androgens (sex hormones) are known to promote normal functioning of the lacrimal and meibomian glands responsible for tear production (Sullivan *et al.*, 1999). According to Kathleen, a deficiency in these hormones could cause dry eyes. Since males have larger quantities of these hormones compared to females, males are therefore less susceptible to dry eyes.

A total of 591 (80.1%) of the AC patients were below 45 years with 15.1% (89/591) in this age group having dry eyes (in patients above 45 years, 27.2% (40/147) had dry eyes) (Table 1). The mean age±SD (years) of participants was 30.6±16.9. Results from this study reaffirms that age is a significant risk factor (aOR:1.02; p<0.001) of DEs (Table 1) in the AC population as seen in other studies (Moss *et al.*, 2000, 2004; Sendecka *et al.*, 2004). Mathers *et al.* (1996) indicated that ageing was significantly associated with reduction of tear production and increased tear evaporation in the normal eye. Ageing could result in lacrimal gland dysfunction due to obstruction of the secretory ducts of this gland (Damato *et al.*, 1984; Obata *et al.*, 1995).

An individual's occupation may have some impact on the health status of the eye. From the study, occupation was found to be very significantly (p<0.001) related to dry eyes with teachers having the highest risk (aOR:1.42; p = 0.858) of dry eyes (Table 2). However, students were significantly less (p<0.001) susceptible to dry eyes (though farmers also showed borderline decreased risk p = 0.079 before adjustment) (Table 2). Adequate blinking is important in the distribution of tears

Table 1: Univariate and multivariate analysis of potential risk factors relating gender and age to dry eyes

Risk factors	No. (%)	Dry eye present (n = 129)	Dry eye absent (n = 609)	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Gender							
Male	228 (30.9)	31 (24.0)	197 (32.3)	0.77 (0.50-1.17)	0.220	0.87 (0.53-1.40)	0.558
Female	510 (69.1)	98 (76.0)	412 (67.7)	1.00	-	1.00	-
Age							
<45	591 (80.1)	89 (69.0)	502 (84.9)	1.03 (1.02-1.04)	<0.001***	1.02 (1.01-1.04)	0.007**
>45	147 (19.9)	40 (31.0)	107 (72.8)	-	-	-	-

Data is presented as number of individuals with percentage distribution in parenthesis; mean age ±SD (30.6±16.9); OR = Odds Ratio; aOR = adjusted Odds Ratio; CI = 95% Confidence Interval; p≤0.05 was considered statistically significant; ***p≤0.001; **p≤0.01; SD = Standard Deviation

Table 2: Univariate and multivariate analysis of potential risk factors relating occupation to dry eyes

Occupation	No. (%)	Dry eye present (n = 129)	Dry eye absent (n = 609)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Trader	139 (18.8)	35 (27.1)	104 (17.1)	0.85 (0.46-1.55)	<0.001***	0.82 (0.43-1.57)	<0.001***
Student	304 (41.2)	25 (8.2)	279 (45.8)	0.19 (0.10-0.36)	0.587	0.24 (0.12-0.49)	0.815
Farmer	51 (6.9)	10 (7.8)	41 (6.7)	0.45 (0.18-1.10)	<0.001***	0.52 (0.21-1.25)	<0.001***
Teacher	29 (3.9)	8 (6.2)	21 (3.4)	1.09 (0.43-2.73)	0.079	1.42 (0.54-3.74)	0.142
Artisan	80 (10.8)	15 (11.6)	65 (10.7)	0.65 (0.32-1.34)	0.858	0.84 (0.39-1.79)	0.483
Unemployed	53 (7.2)	13 (10.1)	40 (6.6)	0.79 (0.36-1.72)	0.242	0.91 (0.40-2.06)	0.649
Professionals	82 (11.1)	23 (17.8)	59 (9.7)	1.00	0.547	1.00	0.820

Data is presented as number of individuals with percentage distribution in parenthesis; OR = Odds Ratio; aOR = adjusted Odds Ratio; CI = 95% Confidence Interval; ***p<0.001; p<0.05 was considered statistically significant

Table 3: Univariate and multivariate analysis of potential risk factors relating the type of conjunctivitis to dry eyes

Ocular allergy	No. (%)	Dry eye present (n = 129)	Dry eye absent (n = 609)	OR (95% CI)	p- value	aOR (95% CI)	p- value
SAC	459 (62.2)	71 (55.0)	388 (63.7)	2.79 (0.65-11.94)	0.039*	1.26 (0.28-5.71)	0.289
PAC	237 (32.1)	55 (42.6)	182 (29.9)	4.43 (1.03-19.12)	0.166	1.79 (0.39-8.24)	0.765
AKC	10 (1.4)	2 (1.6)	8 (1.3)	1.67 (0.14-20.58)	0.046*	0.57 (0.04-7.51)	0.454
VCK	32 (4.3)	1 (0.8)	31 (5.1)	1.00	0.690	1.00	0.669

Data is presented as number of individuals with percentage distribution in parenthesis; OR = Odds Ratio; aOR = adjusted Odds Ratio; CI = 95% Confidence Interval; SAC = Seasonal Allergic Conjunctivitis; PAC = Perennial Allergic Conjunctivitis; VKC = Vernal Kerato Conjunctivitis; AKC = Atopic Keratoconjunctivitis; p<0.05 was considered statistically significant; *p<0.05

to lubricate and moisten the conjunctiva and cornea. It is found that any activity such as constant reading, writing or working with a computer that tends to decrease the rate of blinking could predispose the individual to dry eyes. The daily activities of a teacher include all of the above which causes them to blink less frequently, increasing the risks of dry eye. Again, teachers are continuously exposed to a health hazard from the dust particles from blackboard chalk in the class room. Chalk is a product of calcium carbonate which is alkaline in nature. Calcium carbonate ($CaCO_3$) is considered toxic to the human eyes causing both chemical and mechanical injury to the eye resulting in redness, pain and inflammation (NIOSH, 1991).

Seasonal allergic conjunctivitis (62.2%) and perennial allergic conjunctivitis (32.1%) were the commonest forms of ocular allergy with no case of giant papillary conjunctivitis found (Table 3). Univariate analysis revealed that the type of ocular allergy was significantly associated (p for trend = 0.039) to dry eyes with Perennial Allergic Conjunctivitis (PAC) showing a significantly higher susceptibility (p = 0.046) (Table 3). Studies have indicated that people suffering from ocular allergy are more prone to dry eye (Toda *et al*., 1995; Hom *et al*., 2012). PAC is mainly caused by House Dust Mite (HDM), animal dander and cockroaches which are indoor allergens. HDM exhibits proteolytic activity capable of causing damage to ocular epithelial cells (Chapman *et al*., 2007). The chronic exposure to these allergens in sensitized individuals results in persistent inflammation of the ocular surface (a prerequisite for DEs) (Choi and Bielory, 2008; Stern *et al*., 1998; Nelson *et al*., 2000).

Of 60 AC patients with pterygium, 26.7% (n = 16) were found to have dry eyes. The uniformity of the ocular surface is vital in allowing an even distribution of tears. The presence of pterygium on the eye compromises this uniform distribution of tears resulting in desiccation of areas of the ocular surface. This study observed that the presence of a pterygium was associated with a significantly higher (OR: 1.82; p = 0.050) risk of DEs (Table 4). Lee *et al.* (2002) noted that pterygium remained a very significant risk factor of DE after adjusted for age and sex. A clinical case-control study by Rajiv *et al.* (1991) observed a decrease in both values of TBUT and Schirmer test in cases of pterygium compared to controls.

Of 441 (59.8%) AC patients managed with Cetirizine (a systemic antihistamine) on the first visit (23.4% (103/441), p<0.001) had dry eyes (Table 4). The high use of systemic antihistamines in allergic conjunctivitis management gives credence to the fact that these medications remain the first line of treatment in the management of ocular allergies due to concurrent nasal symptoms experienced (Del Cuvillo *et al*., 2009). According to Qiao *et al.* (2008), about 90% AC cases were concomitantly associated with allergic rhinitis. The second generation antihistamines (of which cetirizine belong) are much safer and therefore preferred in managing AC. However, evidence suggests that these drugs induce some extent of an ocular drying effect (Ousler *et al*., 2007; Del Cuvillo *et al*., 2009). This study found that patients that had been managed with systemic antihistamines in this short term (mean duration ±SD: 10.4±2.2 days) were almost 3 times much likely to experience symptoms of DEs. Several studies on DEs have tried to determine the effect of systemic

Table 4: Univariate and multivariate analysis of the ocular drying effect of pterygium and systemic antihistamine (cetirizine)

Risk factors	No. (%)	Dry eye present (n = 129)	Dry eye absent (n = 609)	OR (95% CI)	p- value	aOR (95% CI)	p- value
Pterygium							
Yes	60 (8.1)	16 (12.4)	44 (7.2)	1.82 (1.00-3.34)	0.050*	1.16 (0.61-2.21)	0.659
No	678 (91.9)	113 (87.6)	565 (92.8)	1.00	-	1.00	-
Antihistamines							
Yes	441 (59.8)	103 (79.8)	338 (55.5)	3.18 (2.00-5.03)	<0.001***	2.79 (1.76-4.42)	<0.001***
No	297 (40.2)	26 (20.2)	271 (44.5)	1.00	-	1.00	-

Data is presented as number of individuals with percentage distribution in parenthesis crude; OR = Odds Ratio; aOR = adjusted Odds Ratio; CI = 95% Confidence Interval; mean duration of treatment ±SD (10.4±2.2 days); p≤0.05 was considered statistically significant; ***p≤0.001; *p≤0.05

Table 5: Symptoms of ocular irritation presented by AC patients with concomitant dry eye

Symptoms of ocular irritation	Dry eye present	Dry eye absent	RR (95%CI)	p- value
Burning sensation	33 (31.7)***	71 (68.3)	2.08 (1.48-2.92)	<0.001
Foreign body sensation	32 (19.4)NS	133 (80.6)	1.11 (0.77-1.59)	0.641
Tearing	60 (20.7)NS	230 (79.3)	1.33 (0.97-1.84)	0.085
Photophobia	10 (9.8)*	92 (90.2)	0.52 (0.28-0.95)	0.024
Pain	46 (18.2)NS	207 (81.8)	1.04 (0.75-1.45)	0.836

RR = Relative Risk; CI = Confidence Interval; relative risk was computed by comparing AC patients with dry eye to their cohort without dry eye; statistically significant differences between the two groups were established using Fishers Exact Chi-square test and the exact p-value or Monte Carlo p-value was reported for all variables; p<0.05 was considered statistically significant; ***p<0.001; *p<0.05; NS = Not Significant; p>0.05

antihistamines on this ocular condition. Though these studies have been cross-sectional and lacked the ability to establish causation most found a positive correlation between systemic antihistamines use and DEs. One very important cohort population based 10 years dry eyes study by Moss *et al.* (2008) discovered that exposure to systemic antihistamine was significantly associated with 1.24 times risk of DEs. His study only adjusted for age and gender, neglecting other potential risk factors which could have masked the actual risk due to systemic antihistamines. The study therefore reveals that of all significant risk factors of DEs found in sufferers of allergic conjunctivitis, systemic antihistamine exposure was associated with the most risk and may account for the high incidence of DEs.

To diagnose DEs in patients already suffering from allergic conjunctivitis is very essential for appropriate management of their condition. According to the Subcommittee of International Dry Eye Workshop, complaints of ocular symptoms are of outmost importance in diagnosing patients with DEs. However, it is usually challenging to diagnose DEs in patients with AC because apart from itching, AC presents with ocular symptoms (including; tearing, foreign body sensation, photophobia, burning sensation and dryness) which overlap with DEs symptoms. Researchers observed in this study that several symptoms except photophobia frequently occurred among AC patients suffering from dry eye than AC patients without dry eyes. Although, tearing and pain were the commonly presenting symptoms, no statistically significant difference (p>0.050) existed in AC patients also suffering from DEs compared to AC patients without DEs. However, burning sensation was found to be very significantly (p<0.001) related to DEs (Table 5) and therefore could prompt the likelihood of concomitant DEs among AC sufferers. This is consistent to some literatures that have indicated ocular burning sensation as a primary symptom of DEs.

CONCLUSION

Allergic conjunctivitis patients treated with systemic antihistamines have significantly high risk of dry eyes. There is, therefore, the need for practitioners to monitor patients being managed with these anti-allergic medications as DEs further complicates ocular disorders.

ACKNOWLEDGEMENTS

Researchers wish to express profound gratitude to Dr. Ben Ababio-Danso (Ophthalmologist, St. Michael's Catholic Hospital), Dr. Alfred Osafo-Kwaako (Ophthalmologist, Our Lady of Grace Hospital) and entire team of eye care personnel of these eye care facilities for their assistance.

REFERENCES

Abokyi, S., G.A. Koffuor, M. Ntodie, S. Kyei and L. Gyanfosu, 2012. Epidemiological profile and pharmacological management of allergic conjunctivitis: A study in Ghana. Int. J. Pharm. Biomed. Res., 3: 195-200.

Al-Faris, E.A. and A. Al-Taweel, 1999. Audit of prescribing patterns in Saudi primary health care: What lessons can be learned?. Ann. Saudi Med., 19: 317-321.

Asbell, P.A. and M.A. Lemp, 2006. Dry Eye Disease: The Clinician's Guide to Diagnosis and Treatment. Thieme, USA., pp: 6-7.

Chapman, M.D., S. Wunschmann and A. Pomes, 2007. Proteases as Th2 adjuvants. Curr. Allergy Asthma Rep., 7: 363-367.

Choi, S.H. and L. Bielory, 2008. Late-phase reaction in ocular allergy. Curr. Opin. Allergy Clin. Immunol., 8: 438-444.

Clegg, J.P., J.F. Guest, A. Lehman and A.F. Smith, 2006. The annual cost of dry eye syndrome in France, Germany, Italy, Spain, Sweden and the United Kingdom among patients managed by ophthalmologists. Ophthalmic Epidemiol., 13: 263-274.

Damato, B.E., D. Allan, S.B. Murray and W.R. Lee, 1984. Senile atrophy of the human lacrimal gland: The contribution of chronic inflammatory disease. Br. J. Ophthalmol., 68: 674-680.

Davison, S.L., R. Bell, S. Donath, J.G. Montalto and S.R. Davis, 2005. Androgen levels in adult females: Changes with age, menopause and oophorectomy. J. Clin. Endocrinol. Metab., 90: 3847-3853.

Del Cuvillo, A., J. Sastre, J. Montoro, I. Jauregui and I. Davila *et al*., 2009. Allergic conjunctivitis and H1 antihistamines. J. Invest. Allergol. Clin. Immunol., 19: 11-18.

Gillan, W.D.H., 2009. A small-sample survey of dry eye symptoms using the ocular surface disease index. S. Afr. Optom., 68: 188-191.

Hikichi, T., A. Yoshida, Y. Fukui, T. Hamano and M. Ri *et al*., 1995. Prevalence of dry eye in Japanese eye centers. Graefes Arch. Clin. Exp. Ophthalmol., 233: 555-558.

Hom, M.M., A.L. Nguyen and L. Bielory, 2012. Allergic conjunctivitis and dry eye syndrome. Ann. Allergy Asthma Immunol., 108: 163-166.

Lamberts, D.W., 1983. Dry eye and tear deficiency. Int. Ophthalmol. Clin., 23: 123-130.

Lee, A.J., J. Lee, S.M. Saw, G. Gazzard, D. Koh, D. Widjaja and D.T.H. Tan, 2002. Prevalence and risk factors associated with dry eye symptoms: A population based study in Indonesia. Br. J. Ophthalmol., 86: 1347-1351.

Manaviat, M.R., M. Rashidi, M. Afkhami-Ardekani and M.R. Shoja, 2008. Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. BMC Ophthalmol., Vol. 8. 10.1186/1471-2415-8-10.

Mathers, W.D., J.A. Lane and M.B. Zimmerman, 1996. Tear film changes associated with normal aging. Cornea, 15: 229-234.

Moss, S.E., R. Klein and B.E. Klein, 2000. Prevalence of and risk factors for dry eye syndrome. Arch. Ophthalmol., 118: 1264-1268.

Moss, S.E., R. Klein and B.E. Klein, 2004. Incidence of dry eye in an older population. Arch. Ophthalmol., 122: 369-373.

Moss, S.E., R. Klein and B.E. Klein, 2008. Long-term incidence of dry eye in an older population. Optometry Vision Sci., 85: 668-674.

NIOSH, 1991. Registry of toxiceffects of chemical substances database: Calcium carbonate. U.S. Department of Health Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH., USA.

Nelson, J.D., H. Helms, R. Fiscella, Y. Southwell and J.D. Hirsch, 2000. A new look at dry eye disease and its treatment. Adv. Ther., 17: 84-93.

Nita, S., A. Verghese and J. Verghese, 2009. Dry eye-a hospital based incidence study. Kerala J. Ophthalmol., 21: 396-401.

Norn, M., 1985. The effects of drugs on tear flow. Trans. Ophthalmol. Soc., 104: 410-414.

Obata, H., S. Yamamoto, H. Horiuchi and R. Machinami, 1995. Histopathologic study of human lacrimal gland. Statistical analysis with special reference to aging. Ophthalmology, 102: 678-686.

Ousler, G.W., D.A. Workman and G.L. Torkildsen, 2007. An open-label, investigator-masked, crossover study of the ocular drying effects of two antihistamines, topical epinastine and systemic loratadine, in adult volunteers with seasonal allergic conjunctivitis. Clin. Ther., 29: 611-616.

Perry, H.D. and E.D. Donnenfeld, 2004. Dry eye diagnosis and management in 2004. Curr. Opin. Ophthalmol., 26: 299-304.

Pflugfelder, S.C., S.C. Tseng, O. Sanabria, H. Kell and C.G. Garcia *et al*., 1998. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. Cornea, 17: 38-56.

Qiao, T., Y. Hu and Z. Wang, 2008. Pediatric allergic conjunctivitis and allergic rhinitis. J. Nanjing Med. Univ., 22: 183-187.

Rajiv, S. Mithal and A.K. Sood, 1991. Pterygium and dry eye-A clinical correlation. Indian J. Ophthalmol., 39: 15-16.

Schiffman, R.M., M.D. Christianson, G. Jacobsen, J.D. Hirsch and B.L. Reis, 2000. Reliability and validity of the ocular surface disease index. Arch. Ophthalmol., 118: 615-621.

Sendecka, M., A. Baryluk and M. Polz-Dacewicz, 2004. Prevalence and risk factors of dry eye syndrome. Przegl. Epidemiol., 58: 227-233.

Stern, M.E., R.W. Beuerman, R.I. Fox, J. Gao, A.K. Mircheff and S.C. Pflugfelder, 1998. The pathology of dry eye: The interaction between the ocular surface and lacrimal glands. Cornea, 17: 584-589.

Sullivan, D.A., L.A. Wickham, E.M. Rocha, K.L. Krenzer and B.D. Sullivan *et al*., 1999. Androgens and dry eye in Sjogren's syndrome. Ann. N. Y. Acad. Sci., 876: 312-324.

Suzuki, S., E. Goto, M. Dogru, N. Asano-Kato and Y. Matsumoto *et al*., 2006. Tear film lipid layer alterations in allergic conjunctivitis. Cornea, 25: 277-280.

Thoft, R.A., 1985. Relationship of the dry eye to primary ocular surface disease. Trans. Ophthalmol. Soc. UK., 104: 452-457.

Toda, I., J. Shimazaki and K. Tsubota, 1995. Dry eye with only decreased tear break-up time is sometimes associated with allergic conjunctivitis. Ophthalmology, 102: 302-309.