Tear Film Break-up Time in Bipolar Disorder

Parvin Dibajnia, MD[1]
Mohadeseh Mohammadinia, MSc[2]
Maryam Moghadasin, PhD[3]
Mohammad Aghazade Amiri, PhD[2]

1 Shahid Beheshti University of Medical Sciences, Faculty of Rehabilitation Sciences,Tehran, Iran
2 Shahid Beheshti University of Medical Sciences,Faculty of Rehabilitation Sciences,Department of Optometry, Tehran, Iran.
3 Allameh Tabatabaie University, Tehran, Iran.

Corresponding author:
Parvin Dibajnia MD,
Hossien Sq. Damavand Ave. Faculty of Rehabilitation, Shahid Beheshti University of Medical Sciences. Tehran 16169-13111, Iran.
Tel: +98-21-77542057
Fax: +98-21 -77561406
Email**:** pdibaj@gmail.com

Objective: Ocular dryness is a well-recognized adverse side effect of many topical and systemic medications. In psychiatry, patients who have consumed such drugs as lithium carbonate and sodium valproate frequently experience dry eye symptoms. The purpose of this study was to compare tear film stability between patients who use these drugs with those patients who are not on medication.
Methods: After obtaining informed consent, the tear film break up time (TBUT) test was performed in 96 eyes of 48 subjects. The subjects were placed in to three groups. Participants included two groups of euthymic bipolar disorder patients (16 cases each) with history of pharmacotherapy for more than two years. Patients in each group were taking only one type of mood stabilizer (lithium carbonate or sodium valproate). In addition,16 age-matched bipolar patients who did not take any topical or systemic medications were included in a control group. Values of TBUT were compared between the three groups using the student's t-test.
Results: The mean tear film break up time (TBUT) in test groups were 4.88 seconds± 0.34(lithium group), 4.81 seconds ± 1.60 (valproate group) and 15seconds± 2.0(control group), respectively. No statistically significant differences were observed between the first and the second groups in TBUT values, but significant differences were found between the two groups and the control group (P< 0.0001).
Conclusion: The results of this study show that lithium carbonate and sodium valproate contribute to decrease of tear film break up time, resulting from dryness of the eyes.

Key words: *Bipolar disorder, Dry eye syndromes, Lithium, Tears, Valproic acid*

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Dry eye syndrome or keratoconjunctivitis sicca is a very common eye condition that affects quality of life as an important and common public health problem(1,2,3). Dry eye can be caused by different mechanisms(4). Many systemic drugs have been associated with ocular and visual side effects that require patient management.[5]Some drugs used in psychiatry are known to cause ocular drying[6]. Studies showed that these drugs also contribute to decrease of tear film production(7,8). Lithium carbonate and sodium valproate are two of the most popular drugs to treat bipolar disorders. Patients who do not respond to or who cannot tolerate conventional lithium therapy (normally the therapy of choice for bipolar disorder) can be treated with valproate. Bipolar disorder, e.g., manic depression is a chronic disease that warrants long-term treatment strategies(9).The purpose of this study was to compare tear film stability in patients who take these drugs with those patients who are not on medication.

Materials and Method

Tear film break-up time (TBUT) is a method for determining the stability of the tear film and checking evaporative dry eye. In testing for TBUT, sodium fluorescein dye is added to the eye and the tear film is observed under the slit lamp while the patient avoids blinking until tiny dry spots develop. Generally, >10 seconds is thought to be normal,(10,11,12) 5 to 10 seconds, marginal, and < 5 seconds is considered low.
A short tear break-up time is a sign of a poor tear film and the longer it takes the more stable the tear film.
In this study, tear film stability was evaluated in 96 eyes of 48 subjects who were placed into three groups. Thefirstgroupincluded16 patients who were taking900 mg of lithium carbonate per day; the second group included16 patients who were taking600 mg of sodium valproate per day for more than 2 years; and the third group (control group) comprised of 16 age matched untreated bipolar patients who did not taketopical and systemic medications.
The protocol for this study was approved by the ethics review board of the institute (Shahid Beheshti University of Medical science). Written informed consent was obtained from all the participants. For evaluation of tear film stability, TBUT test was performed and the time required for dry spots to appear on the corneal surface after blinking was measured. The test was repeated three times for each eye. The

Table 1. The Mean Tear Film Break-up Test in the Bipolar Disorder and Control Groups

Test groups	Gender		Age	TBUT
	Male (%)	Female(%)	Mean(SD)	Mean(SD)
Group 1 (Lithium)	7 (44)	9 (56)	30.69 (10.28)	4.88 (0.34)
Group 2 (Valproate)	6 (38)	10 (62)	31.50 (10.86)	4.81 (1.60)
Group 3 (Control)	9 (56)	7 (44)	30.63 (8.01)	15.00 (2.00)

mean values of TBUTs were compared among 3 groups by the student's t test.

Results

Descriptive statistics for the variables examined in this study including age, sex and TBUT are presented in table 1. The mean TBUT in the test groups were 4.88 seconds ± 0.34 (group 1), 4.81 seconds ±1.60 (group 2) and 15 seconds ± 2.0(group 3), respectively. There were no statistically significant differences between the first and the second groups in TBUT values. However, significant differences were observed between the two groups and the control group (P<0.0001).

Discussion

TBUT is a method for determining the stability of the tear film and checking for evaporative dry eye (10). Our study revealed that long term lithium carbonate and sodium valproate therapy reduced the results of the time for tear film break–up. The TBUT results for both lithium-treated and valproate-treated patients were similar. The average TBUT observed in control group was 15 ± 2.0 seconds. This value is similar to that reported by several previous studies,(10,13) but lower than that reported by some others(14,15). According to these studies, the TBUT value may vary in different populations. The differences in findings may also be partly due to different methods of investigation, or differences based on geography and climate, or itmay be due to the age range of subjects(13).

Although long-term treatment with lithium/ valproate is an effective way to reduce the frequency, severity and duration of manic and depressive episodes in patients with bipolar disorder, studies show that these drugs have been associated with many systemic and ocular side effects (13). The effect of lithium and valproate on the visual system has been previously reviewed (5,8,16,17).However, during our review of the literature we could not find any previous studies evaluating the effects of lithium carbonate and sodium valproate on tear film function. Only in one document by Ben-Aryeh H et al., lowered tear secretion was reported in 22 patients with bipolar disorder on lithium therapy (7).The lithium and valproate mechanisms in the body have not been specially identified, but their therapeutic benefits are probably related to their effects on the other electrolytes such as sodium, potassium, magnesium and calcium(16). During our Medline review, we could not find any previous study about pharmacologic and pathophysiologic reasons for the effects of these drugs or the bipolar condition itself on the tear film stability. Of course, evidence shows that lithium is rapidly and completely absorbed and is distributed widely throughout the body although the rate and extent of entry into tissues varies(16).The mechanisms of lithium and valproate which effect the tear film are probably related to their effects on the tear components and electrolytes replacement such as sodium, potassium, and calcium. Further studies on determining the possible mechanisms of these medications on the ocular surface and tear film function are needed.

Dry eye is one of the ocular side effects of psychiatric drugs. Many ophthalmologic effects of psychiatric medications can only be identified with a complete examination and since the eye is an organ system frequently ignored by therapists, these effects are considered in frequently. Since the patients in our study were under monotheapy, it seems likely that incidence of ocular side effects increases sharply with the use of polypharmacy that is very common in psychiatric patients. Psychiatrists, ophthalmologists and patients need to be aware of and prepared for any associated medication-induced adverse effect such as dry eye. Clinicians should try to use the lowest dose possible to achieve the desired therapeutic effect.

TBUT is a method for determining the relative stability of precorneal tear film, because it is a simple test, it has been widely used as a clinical diagnostic test for dry eyes. However, the best quantitative way to evaluate the precorneal tear film is the tear film break–up time (TBUT) concurrent with shirmer test.

Our study has several limitations. First, the sample size was fairly small and the results obtained should be replicated in larger samples. Another potential limitation relates to our assessment of tear film using only TBUT test.

Conclusion

The results of this study show that lithium carbonate and sodium valproate contribute to the decrease of tear break up time, resulting from dryness of the eyes. Psychiatrists, eye care professionals and patients need to be aware of and prepared for any associated medication-induced adverse effects such as dry eye. Clinicians should try to use the lowest dose possible to achieve the desired therapeutic effect.

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