Original Article

Acute Ocular Side Effects of Topiramate

Ophthalmology Section

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ABSTRACT

Purpose: To evaluate the acute ocular side effects of Topiramate in patients of migraine.

Design: Retrospective study.

Materials and Methods: 296 patients of migraine of all ages and of either sex, who were being treated with Topiramate from January 2010 to January 2011 by the neurologist, were retrospectively studied for severe ocular side effects.

Results: Four patients of different ages and of either sex reported with signs of shallow anterior chamber , bilateral acute myopia and angle closure glaucoma of varying severity. All four patients responded well to conservative treatment and immediate cessation of Topiramate therapy.

Conclusions: Topiramate which is recently being used quite frequently and effectively in the treatment of migraine has rare but potential side effects in the form of bilateral acute angle closure glaucoma which can be effectively managed with prompt stoppage of Topiramate therapy and conservative management.

Key Words: Topiramate, Intraocular pressure, Bilateral acute angle closure glaucoma, Acute myopia, Ciliochoroidal effusion, Shallow anterior chamber

INTRODUCTION

Topiramate is a sulfamate-substituted monosaccharide, related to fructose, a rather unusual chemical structure for an anticonvulsant. It was discovered in 1979 by Bruce E. Maryanoff and Joseph F. Gardocki during their research work at McNeil Pharmaceutical [1, 2, 3]. This antiepileptic medication is also used in the management of depression, and neuropathic pain. Lately, it has gained popularity as a weight reducing agent, and to treat bipolar disorder. It is a Food and Drug Administration (FDA) approved drug for the prevention of migraine. The exact mechanism of action is unknown, however, four properties that may contribute to Topiramate's anti-epileptic and anti-migraine efficacy include a blockage of voltage-dependent sodium channels, an augmentation of gamma-amino-butyrate acid activity at some subtypes of the GABA-A receptors, antagonism of AMPA/ kinate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV.

Ocular side effects with Topiramate are not very common but in literature many studies of rare but serious side effects of Topiramate are published [4]. Banta et al first reported a case of uveal effusion and secondary angle-closure glaucoma associated with Topiramate use in July 2001 [5]. In September 2001, Ortho-McNeil Pharmaceuticals sent out a "Dear Healthcare Professional" letter, indicating 21 cases of acute angle-closure glaucoma had been reported to their safety division, and physicians should be aware of this adverse drug reaction [6]. We have presented here four cases of ocular toxicity out of 296 patients of migraine who were given Topiramate, using the World Health Organization classification system as to causation [7].

MATERIALS AND METHODS

Out of 296 patients 172 were males and 124 were females. The distribution of patients according to age group is as per [Table/Fig-1].

Age group	Total	Males	Females
18–27	102	76	26
28–37	87	43	44
38–47	76	41	35
48–57	31	12	19

[Table/Fig-1]: Age and sex distribution of patients

Out of 296 patients, in 205 patients Topiramate was the first line drug for treatment, in the rest of 91 patients, patients were shifted from other drugs for treatment of migraine. The patients selected for the study were only on Topiramate therapy. The precise description of all the four cases is as follows:

Case 1

A male patient aged 19 years came after 10 days of starting Topiramate 25 mg twice daily for migraine, with acute bilateral diminution of vision and mild dull headache which deteriorated within 36 hours. Patient did not complain of any ocular pain. The visual acuity (VA) in right eye (OD) was finger counting at 3 meters and in left eye it was finger counting at 5 meters. His conjunctiva showed mild congestion. On slit lamp examination there was mild corneal epithelial edema, central as well as peripheral shallow anterior chamber, iris was normal in architecture, pupil was reactive to light. His auto-refr readings were, myopia of –6.00 Diopter in right eye and –5.00 Diopter in left eye. The intraocular pressure (IOP) was 36 mm of Hg and 32 mm of Hg in OD and OS respectively. Immersion A-scan showed the anterior chamber depth (ACD) to be 1.6 mm and 1.8 mm in OD and OS respectively. The crystalline lens was transparent and showed no swelling. The patient was given 200 ml of 20% Mannitol I/V BD for 1 day and was put on topical anti-glaucoma drugs namely Dorzolamide plus Timolol combination TID, Brimonidine eye drops BD, Betamethasone drops QID and Homatropine eye drops BD. Topiramate was stopped immediately.

The IOP was controlled in 3 days while the myopia recovered slowly in 6 days. Patient remained comfortable and had no recurrence of ocular symptoms for about two months .

Case 2

A female patient aged 26 years who was started on Topiramate for her migraine treatment 5 days ago at the dose of 25 mg once daily, reported with a sudden diminution of vision with moderate ocular pain and headache. The snellen's visual acuity was finger counting at 2 meters in both the eyes. Her auto-refr readings were , myopia of –6.00 Diopter in right eye and –6.5 Diopter in left eye.

She had circumcorneal congestion in both eyes, corneal epithelial edema, central and peripheral shallow anterior chamber, normal iris architecture, mid-dilated pupil sluggishly reacting to direct light in both eyes. Intra-ocular pressure (IOP) was 46 and 50 mm Hg in OD and OS respectively. Immersion A-scan showed the anterior chamber depth (ACD) to be 1.6 mm in both eyes. There was no change in the crystalline lens thickness or transparency at presentation and after treatment. Topiramate was stopped immediately. She was given Mannitol (200 ml I/V BD for 2 days), Glycerol (30 ml BD orally for 3 days), Dorzolamide and Timolol combination eye drops (TID for 10 days), Brimonidine eye drops (BD for 10 days), Betamethasone eye drops (QID for 10 days), Cyclopentolate eye drops BD. The symptoms were relieved within 5 days . The visual acuity recovered to 20/20 on snellen chart within 7 days. The patient remained symptom free during two months of follow-up.

Case 3

A 55 years old female was started on 25 mg Topiramate for chronic headache for past 8 days. She developed acute pain in both eyes with severe headache and vomiting. The visual acuity was hand movements close to face in both eyes. Her auto-refr readings were, myopia of –8.00 Diopter in right eye and – 8.25 Diopter in left eye.

On presentation she had circumcorneal congestion, corneal stromal and epithelial edema, and very shallow anterior chamber, boggy iris architecture, mid-dilated and non-reactive pupils. She also had ciliochoroidal effusion evident on slit lamp examination. The intra-ocular pressure (IOP) was 64 and 62 mm Hg in OD and OS respectively. Immersion

A-scan showed the anterior chamber depth (ACD) to be 1.4 mm and 1.5 mm in OD and OS respectively. The lens thickness remained unchanged at presentation and after treatment. She was given Mannitol (200 ml I/V BD for 4 days), Glycerol (30 ml BD orally for 5 days), Atropine eye drops (BD for 6 days), Dorzolamide and Timolol comlaination eye drops (TID for 15 days), Brimonidine eye drops (BD for 15 days), Betamethasone eye drops (QID for 15 days). The symptoms were relieved in 7 days period. The visual acuity recovered to snellen's visual acuity of 20/20 in 8 days. Patient remained symptom free during follow-up for about two months .

Case 4

A 20 years male patient who came with acute headache and diminished visual acuity and correlated it to mild trauma with a rubber cricket ball on forehead. On further enquiry he gave a history of change of medicine for headache from Tab. Flunarizine 10 mg to Tab. Topiramate 25 mg once daily 4 days ago. His Snellen's visual acuity was 20/200 and finger counting at 5 meters in OD and OS respectively. His auto-refr readings were, myopia of –3.00 Diopter in right eye and –2.75 Diopter in left eye.

On examination he had conjunctival congestion, clear cornea, bilateral shallow anterior chamber, normal iris architecture and normal reacting pupils in both the eyes. The intra-ocular pressure (IOP) was 30 and 32 mm Hg in OD and OS respectively. Immersion A-scan showed the anterior chamber depth (ACD) to be 2.2 mm and 2.1 mm in OD and OS respectively. The patient did well after stoppage of Topiramate and instillation of topical anti-glaucoma drops and Cyclopentolate drops. Symptoms and signs improved quickly within 3 days. Patient remained symptom free during follow-up period of about two months.

		Uncorrected VA	Refraction	Anterior Chamber Depth on A-Scan	IOP (in mm of Hg)	Angle Closure Glaucoma	Cilio-choroidal Effusion
Case 1	Presentation	OD: FC 3 M	OD:–6:00 DS	1.6 mm	OD: 36	Yes	Present on B-Scan
		OS: FC 5 M	OS:–5.00 DS	1.8 mm	OS: 32		
	6 days off Topiramate	OD: 20/20	OD: -1.00 DS	3.2 mm	OD: 16	Resolved	Absent on B-scan
		OS: 20/20	OS: -1.00 DS	3.2 mm	OS: 16		
Case 2	Presentation	OD: FC 2 M	OD: -6.00DS	1.6 mm	OD: 46	Yes	Present on B-Scan
		OS: FC 2 M	OS:–6.50 DS	1.6 mm	OS: 50		
	1 week off Topiramate	OD: 20/20	Emmetropia	3.1 mm	OD: 18	Resolved	Absent on B-scan
		OS: 20/20	Emmetropia	3.1mm	OS: 16		
Case 3	Presentation	OD: HM close to face	OD:–8:00DS	1.4 mm	OD: 64	Yes	Severe effusion on B-Scan
		OS: HM close to face	OS: – 8.25DS	1.5 mm	OS: 62		
	8 days off Topiramate	OD: 20/20	OD:+2.00 DS	2.7 mm	OD: 18	Resolved	Resolving on B-Scan
		OS: 20/20	OS:+1.75 DS	2.8 mm	OS: 18		
Case 4	Presentation	OD: 20/200	OD:–3.00 DS	2.2 mm	OD: 30	Yes	Present on B-Scan
		OS: FC 5 M	OS: – 2.75 DS	2.1 mm	OS: 32		
	5 days off Topiramate	OD: 20/20	Emmetropia	2.9 mm	OD: 12	Resolved	Absent on B-scan
		OS: 20/20	Emmetropia	2.8 mm	OS: 14		

[Table/Fig-2]: Comparison of parameters at presentation and after cessation of Topiramate
Abbreviations: OD- right eye, OS- left eye, HM- hand movements, DS- dioptre spherical, DC- diopter cylindrical, IOP- intra-ocular pressure.

Certain	Probable/likely	Possible
Abnormal vision Acute intraocular pressure elevation Acute myopia (up to 8.75 diopter) Diplopia (at high doses) Nystagmus (at high doses) Shallow anterior chamber with angle closure	Blepharospasm Myokymia Oculogyric crisis Suprachoroidal effusions	Congenital ocular abnormalities Periorbital edema Scleritis

[Table/Fig-3]: Adverse Ocular Side Effects Associated with Topiramate Use: World Health Organization (WHO): Classification

RESULTS

A total of 4 patients suffering from acute attacks of angle closure glaucoma of varying severity have been reported here . All patients presented with bilateral symptoms with no previous history of angle closure glaucoma. All patients experienced symptoms within first 10 days of starting of therapy with Topiramate, the earliest being

4 days and latest being 10 days. Two patients were male and two were females. The youngest patients to suffer from the symptoms was 19 years and oldest was 55 years. All the patients resolved with conservative medical management and immediate stoppage of therapy with Topiramate. Out of these 4 patients, 3 patients (case 1,2 and 4) had more prominent symptoms of decreased vision with mild (case2 and 4) or no (case 1) headache. Case 3 had the most severe symptoms in terms of visual loss, headache and recovery time.

All the patients had suprachoroidal effusion which is considered to be the cause of ocular pathology , out of which 3 patients (case 1,2 and 4) had moderate cilio-choroidal effusion as detected on B-scan examination while one patient (case 3) had severe ciliochoroidal effusion that took longer time to resolve and this patient had the severest visual loss, highest myopic reading and maximum increase in intra-ocular pressure. Pilocarpine was not used in any of the cases as it increases the chances of pupillary block instead , mydriatics were used as recommended in literature to relieve ciliary spasm.

DISCUSSION

Topiramate induced angle closure is an idiosyncratic reaction and can occur in otherwise normal eyes with normal anterior chamber angles. Although the mechanism for Topiramate induced myopia and acute angle closure glaucoma is unknown, it may partly be from Topiramate's weak carbonic anhydrase inhibitor activity or a prostaglandin mediated effect. This could cause forward rotation of the iris-lens diaphragm, ciliary body swelling causing relaxation of zonules which in turn causes increased curvature of the lens surfaces, and a spasm of accommodation. The underlying mechanism by which this occurs has been better characterized with ultrasound technology [8]. The ultrasound studies indicate that anterior chamber shallowing is predominantly due to ciliochoroidal effusion, which is supported by recent reports [8,9]. The small change in lens thickness may result from effusion-induced forward displacement. Most glaucoma cases resolve without miotics or iridotomy because pupillary block is not the cause of angle closure. The side effects of Topiramate according to world health organization classification system are listed in [Table/Fig-3].

The management of Topiramate-related acute pressure elevation requires stopping the drug in consultation with the prescribing physician. Topical cycloplegic agents probably lower intraocular pressure by retracting the ciliary processes, along with topical and systemic anti-glaucoma drugs [4].

Topiramate has been shown to be effective in the prevention of migraine headache in adults. Henceforth, it is likely to be prescribed more frequently. Ophthalmologists will have to be aware of this potential complication, since they may be the first to see patients with these symptoms. There is a chance that these cases may be misdiagnosed to be accommodative spasm or more importantly, as primary angle closure glaucoma. If that happens, these patients will be subjected to peripheral iridotomy or at least dilatation, to detect accommodative spasm [10]. The knowledge of this complication and usage of OCT and ultrasound-biomicroscopy would help arriving at the diagnosis and averting inadvertent treatment for glaucoma [11]. Patients who develop blurred vision should promptly discontinue Topiramate to prevent progression to angle closure glaucoma [12].

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