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ORIGINAL ARTICLE

Topiramate-induced paresthesia is more frequently reported by migraine than epileptic patients

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Abstract Topiramate is an approved and effective drug in migraine prophylaxis. Paresthesia is the most commonly reported side effect. The primary objective of this study was to compare the frequency of topiramate-induced paresthesia in migraine headache to epileptic patients. Patients with migraine without aura and epilepsy were enrolled in this observational study. All cases were interviewed by telephone about their history of paresthesia. Confounding factors were controlled through logistic regression. The odds ratio of developing topiramate-induced paresthesia in migraine compared to epilepsy patients was 3.4. Three factors were independent contributors to developing topiramate-induced paresthesia: female sex (odds ratio 2.1), topiramate dosage (odds ratio 0.3) and duration of therapy. Our findings indicate an independent association between migraine and development of paresthesia. Migraineurs were more likely than epileptic patients to report paresthesia as topiramate adverse effects. Female sex, treatment duration and topiramate dosage contribute significantly to subsequent development of paresthesia.

Keywords Migraine · Topiramate · Paresthesia

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Background

Migraine is a common, disabling, and costly disorder with no definite and effective cure.

The aim of therapy, shared with the patient, is to minimize the impact of the illness on the patient's quality of life. Prophylactic treatment decreases not only the number and severity of migraine headache but also its disability and cost burden. The safety and efficacy of medications for migraine prophylactic treatment is also the subject of concern for health care professionals.

As mentioned in an Iranian study, only 49 % of migraineurs consulted a physician, and only 53 % were correctly diagnosed by physicians according to the International Headache Society criteria [1].

Prophylactic treatment could be recommended to approximately 50 % of patients with migraine [2]. Although there are strong evidence-based recommendations and guidelines, the majority of these patients do not receive them. In one study, only 13.0 % of migraineurs reported current use of daily prophylactic treatment [3].

Several randomized controlled trials have demonstrated the effectiveness of beta-blockers, antidepressants, calcium channel blockers, and anticonvulsants on reducing migraine attacks since 1960 [4].

Topiramate is a sulfa derivative monosaccharide, which was originally developed as a hypoglycaemic agent but was found to be devoid of hypoglycaemic activity, and later, it has been widely used for the treatment of epilepsy, migraine, bipolar disorders and alcoholism [5, 6].

The Food and Drug Administration approved topiramate in 2004 for migraine prophylaxis [5]. It is also established as effective prophylactic treatment for migraine by American headache society (AHS) and American Academy of neurology (AAN) guidelines. According to these

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guidelines, topiramate should be offered to patients requiring migraine prophylaxis. According to that guideline, topiramate should be offered to patients who require prophylaxis for migraine [7]. In migraine prophylaxis, the recommended total daily dose of topiramate is up to 100 mg/day in two divided doses [8].

Most of migraine prophylaxis treatments commonly cause weight gain and this adverse effect makes adherence to treatment a troublesome issue for many patients. In contrast, with best evidenced in prophylactic treatment of migraine, topiramate causes weights loss [4, 9]. Topiramate is also attractive prophylactic choice when there are concerns about gaining weight, and in patients who are currently overweight, or who have coexisting epilepsy [9].

Topiramate is completely absorbed through gastrointestinal tract and excreted unchanged through urine. Topiramate has no significant drug interaction or enzyme inducing or inhibiting effect and also easily crosses the CNS [8].

There are several suggested mechanisms explaining the exact topiramate efficacy in migraine prophylaxis [10]. It possibly exhibits its action through the blockade of sodium channels, L-type calcium channels, gamma-aminobutyric acid (GABA) receptor, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) or kainate currents [11]. It is possible that topiramate prevents phosphorylation on some receptors, channels or proteins [11]. Topiramate also inhibits carbonic anhydrase [12]. This inhibitory action results in an overall decrease in excitatory neurotransmission and an increase of inhibitory neurotransmission [13]. This medication possibly reduces neurotransmission through the trigeminocervical complex to prevent migraine [14].

More than forty percent of patients on topiramate achieved at least 50 % reduction in monthly migraine attacks frequency [15]. It also has been demonstrated that the health-related quality of life significantly improves for up to 6 months following initiation of prophylactic treatment by topiramate [2]. The prophylactic effect of topiramate is dose dependent and greater with 50 mg/d (39 %, $P = 0.01$), 100 mg/d (49 %, $P < 0.001$), and 200 mg/d (47 %, $P < 0.001$) vs placebo (23 %) [16, 17].

Apparently topiramate adverse effects like any other medication have been considered one of the major obstacles to the adequate prophylactic treatment of migraine. Topiramate-associated adverse effects of mild or moderate severity have been reported in up to 70 % during migraine prophylaxis [14] and lead to treatment discontinuation in nearly 30 % of patients [18].

The most common topiramate-associated adverse effects are generally mild or moderate in severity and include paresthesia, fatigue, nausea, and difficulty with concentration. The mean body weight significantly decreases in patients compared with placebo. These adverse effects occur more frequently during titration to target doses [17, 19, 20]. The ophthalmological disturbances, paresthesias, and itching are treatment-emergent adverse reactions of topiramate [5].

Paresthesia is positive sensory symptom, defined by patients as a tingling, or burning sensation of the skin, without an apparent stimulus of the fingers or toes. It is the most commonly reported side effect and accounts for 51 % of all topiramate-related adverse events [8]. Nearly 10 % of migraineurs experience paresthesia when using topiramate [2, 10, 15, 18, 21–23].

Many studies have suggested that migraineurs who develop topiramate-induced paresthesia usually have lower headache frequency than those who do not. It is also interesting that paresthesia develops more frequently in those who have a higher response rate and development of paresthesia predicts a favorable response to topiramate in migraine prophylaxis [24]. In a study by Lee et al. the researchers have concluded that migraineurs who report paresthesia would have a significantly better response to migraine prevention with topiramate treatment [24].

The reported risk ratios (RR) for paresthesia in topiramate vs. placebo-treated migraine patients are 5.8 for 50 mg, 8.4 for 100 mg, and 8.5 for 200 mg [25]. Migraineurs usually experienced paresthesia during the titration phase and paresthesia spontaneously subsides after about 2–3 months of treatment [8]. It is usually not necessary to treat topiramate-induced paresthesia as numbness and tingling are self-limiting, but use of potassium supplements may provide relief [26].

It has been reported that frequency of topiramate adverse effects is different in migraineurs and epileptic patients. For example, behavioral changes, upper respiratory tract infection, and headache are less frequent in the migraineurs. In contrast, epileptic patients experience more cognitive changes and taste alteration [25].

According to lack of comparative studies, the primary objective of this study was to compare the frequency of topiramate-induced paresthesia in migraine headache to Epileptic patients.

Methods

We had access to the electronic health records in two clinics and the patients with migraine without aura and epilepsy were asked by telephone to answer our questionnaire, if they agreed.

There was a structured interview, and a questionnaire was administered. The questionnaire covered patients' history of migraine and epilepsy, their demographic data, duration of treatment and topiramate dosage. To consider

clinically significance in our study, paresthesia should last at least more than 24 h.

We excluded patients who had history of cognitive deficit or other comorbidities like diabetes or neuropathy.

The migraine diagnosis was established according to the International Headache Society criteria.

All patients had been examined and documented by two neurologists. All patients consented to participate in our survey and of course were not aware of the aim of the study; they were just asked if they agreed to take part in an epidemiological study on their health matters.

The patient's data were kept secret and Kerman University ethic committee approved our study. Our study protocol was approved by Neurology Research Center of Kerman University of Medical Sciences.

An observational bias could have occurred since the observer was aware of the clinical status of the patients, but the structured questionnaire was designed to overcome this potential bias.

The categorical variables were compared with Pearson's Chi-squared test and, when necessary, Fisher's two-tailed test of exact probability and odds ratio was used as a close approximation to relative risk. Logistic regression analysis was used to determine the association of independent fixed patient factors with the prevalence of topiramate-induced paresthesia. Female sex, age, topiramate dosage and duration of therapy were combined in an equation from which risk of topiramate-induced paresthesia could be estimated.

Hypothesis testing and estimation of 95 % confidence intervals were carried out with the standard error estimate for the logistic coefficient estimates.

Results

In this study, we assessed the frequency of the topiramate-induced paresthesia among the 160 patients who were diagnosed as migraine and same number of patients with diagnosis of epilepsy. Baseline demographic data, duration and dosage of topiramate and frequency of paresthesia are shown in Table 1.

As it is shown in Table 1, the two groups differed significantly according to age, sex, duration of treatment and topiramate dosage. Thus, multivariate logistic regression analyses were employed to evaluate the relationships of those confounding factors and developing paresthesia. Logistic regression allows the prediction of a single dependent variable (outcome) from the values of other explanatory (predictor) variables.

The odds ratio of developing topiramate-induced paresthesia in migraine compared to epilepsy is 6.4 with 95 % confidence interval. But this association changed after we controlled variables for age, sex, duration and dosage of treatment. After considering these confounding factors, the odds ratio was reduced to 3.4 (Table 2).

We found out that two factors were independent contributors to develop topiramate-induced paresthesia, female sex (odds ratio 2.1) and topiramate dosage (odds ratio 0.3) and duration of therapy (0.9). All of these were highly statistically significant ($P < 0.05$).

So it seems that women experience more paresthesia than men as topiramate dosage and duration of treatment increase. Women with migraine had a more than twofold increase in reporting paresthesia compared to epileptic.

Discussion

In this study, we found migraine to be strongly associated with increasing development of paresthesia. There is little explanation for increasing reported paresthesia in migraineurs compare to epileptic patients.

The confounding factors between migraine and epileptic patients probably play major role. One of the most prominent confounding factors is difference in gender distribution between migraine and epilepsy. Migraine is more prevalent in women, who generally have lower body mass index (BMI) than men. When treated with equal topiramate dosages, this BMI difference exposes women into higher milligram dosage per kilogram body weight compared to men [25]. Other probably significant contributing factor caused by gender difference is that men are

Table 1 Demographic data, clinical characteristics and frequency of topiramate-induced paresthesia

Demographic data	Migraine	Epilepsy	*P* value
Number of patients	160	160	
Mean age (years)	34.5 (9.9)	28.9 (13)	<0.05
Age range (minimum–maximum) years	12–61	7–61	
Female (percent)	92.5 %	40 %	<0.05
Duration of treatment (months)	8 (3.4)	10.2 (1.9)	<0.05
Topiramate dosage (mg)	33.2 (12.7)	62.3 (30)	<0.05
Paresthesia	53 %	15 %	<0.05

Numbers showed in parenthesis are standard deviation

Table 2 Contributing factors in developing topiramate-induced paresthesia

Contributing factors	Odd ratio	Lower	Upper	*P* value
Migraine vs Epilepsy	3.45	1.58	7.5	0.002
Age	0.99	0.96	1.0	0.7
Sex	2.1	1.0	4.39	0.04
Duration of illness	1.0	0.99	1.0	0.4
Duration of treatment	0.9	0.83	1.0	0.05
Topiramate 25 mg				
Topiramate 50 mg	0.32	0.11	0.94	0.03
Topiramate 100 mg	0.56	0.19	1.62	0.2

also more likely to use alcohol and other substances which alter the possibility of change in reported adverse effects [25].

Titration protocol also differs between migraine and epileptic patients. In clinical practice the titration protocol is faster in the migraine than epileptic patients, which may have promoted the occurrence of paresthesia [25]. Paresthesia occurs at consistently higher rates during the titration period and slower dosage increases may improve tolerability [23, 27, 28].

It is worth to mention that patients consider epilepsy more threatening than migraine attacks and this raises drug compliance and tolerance in epileptic patients. This could be one of the main causes of bias in reporting paresthesia [25].

Another possible explanation for the increasing paresthesia in migraineurs compared to epileptic patients may be the development of central sensitization [29]. The central sensitization hypothesis proposes that in migraine processing of sensory input in the brainstem has been altered [30].

Luykx J. et al compared adverse drug reactions to topiramate in patients with migraine and patients with epilepsy in a systematic review 2009. They concluded that when treated with the same doses of topiramate, migraineurs might show different adverse drug reactions (ADRs) than patients with epilepsy and were more likely to drop out because of adverse effects. The Relative Risks (RRs) for paresthesia in migraine vs. epilepsy trials were 2.5 for 50 mg, 2.7 for 100 mg, and 3.0 for 200 mg [25].

Statistical methods like logistic regression enabled us to consider these confounding factors. After adjusting these factors migraineurs still have a higher rate of reporting paresthesia than epileptic patients. So these patients have possibly different physiological response to topiramate and its adverse effects.

It is interesting to us that migraineurs on a higher dose of topiramate reported less paresthesia.

Conclusion

These results indicate an independent association between migraine and development of paresthesia. Migraineurs were more likely than epileptic patients to report paresthesia as topiramate adverse effects and higher dose of topiramate caused less paresthesia than lower one.

The study also confirmed that among fixed patient factors, female sex, treatment duration and topiramate dosage contribute significantly to subsequent development of paresthesia.

Compliance with ethical standards

Conflict of interest We declare that we have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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