Hypohidrosis and hyperthermia during topiramate treatment in children

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Topiramate is one of the newer generation antiepileptic drugs with a beneficial clinical effect on various seizure types. In this study, we present the clinical findings of hypohidrosis and hyperthermia with topiramate in pediatric patients. The data were collected retrospectively on 173 patients diagnosed as epilepsy on topiramate treatment, and hypohidrosis-related symptoms induced by topiramate were found in 22 patients. Their mean age was 64.45±56.63 months. The mean duration of topiramate treatment was 7.09±2.46 months, and the mean dose was 5.37±1.75 mg/kg/day. All of the patients complained of hypohidrosis and hyperthermia. Six (27.2%) of them had facial flushing, 4 (18.1%) had heat sensation and only 1 (4.5%) had lethargy. Hypohidrosis-related symptoms resolved after discontinuation of the medication. In conclusion, children treated with topiramate should be cautioned regarding these potential adverse effects and advised to avoid its use during the hot summer season.

Key words: topiramate, hypohidrosis, hyperthermia, children.

Topiramate (TPM) is an anticonvulsant drug with a broad spectrum of antiepileptic activity that is used in both children and adults to treat generalized or partial refractory epilepsy, Lennox-Gastaut syndrome, refractory infantile spasms, myoclonic-astatic epilepsy, childhood absence seizures, and refractory status epilepticus in children[1-3].

It is a sulfamate-substituted monosaccharide with multiple mechanisms of action[4]. TPM has a favorable safety profile and is well tolerated in pediatric epileptic patients. The adverse effects are somnolence, difficulties in concentration, behavioral changes, anorexia, weight loss, paresthesia, metabolic acidosis, and nephrolithiasis. Recently, hypohidrosis (and related symptoms, often hyperthermia) has been reported as a rare and reversible adverse effect, mostly in children[5,6].

The aim of this study was to evaluate the incidence of hypohidrosis and hyperthermia in pediatric patients with epilepsy treated with TPM.

Material and Methods

We retrospectively analyzed the records of 173 epileptic children on treatment with TPM between January 2008 and June 2010 at the University of Çukurova Hospital, Adana, Turkey. We detected hypohidrosis and hyperthermia induced by TPM in 22 (12.7%) patients. The information included sex, age, dosage, treatment duration, use of other antiepileptic drugs (AEDs), sweat test, and the presence of hypohidrosis-hyperthermia-related symptoms, such as anhidrosis, oligohidrosis, facial flushing, heat sensation or intolerance, lethargy, itching, or irritability.

Topiramate (TPM) was administered as 1 mg/kg/day for the first week, followed by a slow increase of dose over two-week intervals until the seizures stopped. The 19 patients were also treated with another AED, such as valproic acid, carbamazepine, oxcarbazepine, phenobarbital, lamotrigine, clonazepam, or vigabatrin.

Sweat test was done in all patients. The procedure is based on the activation of sweat glands in a localized area by the iontophoretic introduction of 0.5% pilocarpine nitrate gel. After the sweat glands were stimulated, the electrodes were removed, the skin cleaned,

and sweat was collected over the exact region where the pilocarpine was iontophoresed. Sweat electrolytes were then measured. The test was performed firstly during the TPM treatment, and then a second test was performed after discontinuation of the medication.

Results

We identified 22 patients (15 boys, 7 girls) who had developed hypohidrosis and hyperthermia-related symptoms due to TPM treatment. The mean age of the children was 64.45±56.63 months (range: 8–192 months). Fifteen patients (68.2%) were <6 years of age. Nineteen patients (86.4%) had taken polytherapy medication, while 3 (13.6%) were under TPM monotherapy.

In the study, the duration of TPM management was 7.09±2.46 months (range: 2-11 months), and the mean TPM dose was 5.37±1.75 mg/kg/day (range: 2-8 mg/kg/day). Thirteen patients (59.1%) had taken <6 mg/kg/day, and 9 (40.9%) had taken >6 mg/kg/day. All of the patients complained of hypohidrosis and hyperthermia. Six (27.2%) had facial flushing, 4 (18.1%) had heat sensation, and only 1 (4.5%) had lethargy in addition to hyperthermia. Hypohidrosis-related symptoms are summarized in Table I.

In the polytherapy medication group, the additional AEDs were valproic acid, carbamazepine, oxcarbazepine, lamotrigine, vigabatrin, phenobarbital, and clonazepam. Ten (45.5%) patients used two AEDs, 8 (36.4%) used three AEDs, and 1 (4.5%) used four AEDs.

Sweat test was performed with pilocarpine iontophoresis in all patients during the treatment, but sweat could not be collected. Then TPM was stopped, and the sweat test was repeated after one month. The mean sweat chloride concentration was 47.14±6.88 mEq/L (range: 40-65 mEq/L) in those measurements. The demographic details, seizure type, duration and dose of the medication, and additional AEDs are shown in Table II. All hypohidrosis-related symptoms disappeared after discontinuation of TPM.

Discussion

Topiramate (TPM) is an anticonvulsant medication indicated for treatment of various types of seizures, especially in refractory focal and secondarily generalized seizures. TPM has demonstrated a good safety profile. The most common side effects are somnolence, cognitive dysfunction, confusion, and nervousness, whereas the less frequent side effects include lability of mood, weight loss, metabolic acidosis, paresthesia, and nephrolithiasis. Recently, hypohidrosis and heat intolerance, with or without febrile episodes, have been reported in children under TPM treatment[7,8]. Hypohidrosis has been described in all ages of childhood and in adjunctive therapy, and seems to be rare and generally reversible. Among the less frequent side effects of TPM, hyperthermia has been reported in approximately 10% of treated children[6].

Sweating is an important function in the regulation of body temperature. Physiologic sweating is a complex function regulated by the sympathetic system as well as factors and neurotransmitters (e.g., acetylcholine, calcitonin gene-related, histidine, methionine) localized in the periglandular nerves or within human sweat glands. In addition, immunohistochemical studies have demonstrated that isoenzymes of carbonic anhydrase I and II have been identified in human eccrine sweat glands[4,5]. Hypohidrosis is inability to produce or deliver sweat to the surface of the skin, and thus may lead to hyperthermia or heat stroke. It is important to note that pediatric patients are more sensitive to hypohidrosis than adults.

Topiramate (TPM) consists of a sulfamate-substituted monosaccharide that acts by blocking the sodium channel, enhancing GABA-

Table I. Clinical Symptoms of our Patients (n = 22)

	Number	%
Hyperthermia	22	100
Facial flushing	6	27.2
Heat sensation	4	18.1
Lethargy with hyperthermia	1	4.5

Table II. Demographic Details of our Patients

No	Sex	Age (months)	Dose (mg/kg/day)	Duration (months)	Seizure type	Additional AED (n)
1	F	60	7	8	CP	-
2	M	84	6	7	CP	OBZ
3	M	51	5	8	GTC, M	VPA
4	M	24	2	2	GTC, M	PB+VPA+LTG
5	M	18	7.5	9	SP, CP	VPA+OBZ
6	F	168	5	7	SP, CP	CBZ
7	F	40	7.4	10	CP, SG	CBZ
8	M	132	6.7	11	CP, SG	VPA+OBZ
9	M	120	7.3	10	CP	VPA+CBZ
10	M	8	3.5	4	IS	PB+VPA
11	F	60	3.7	5	GTC, M	VPA+LTG
12	M	156	4.4	5	CP, SG	CBZ
13	M	24	8	7	SP, CP	VPA+CBZ
14	M	24	8	8	M	VPA
15	M	40	5.5	10	SP, CP	OBZ
16	M	48	3	7	SP, CP	VPA
17	F	18	4	5	IS	-
18	F	10	5	4	IS	-
19	M	21	6	5	SP, CP	OBZ
20	M	72	5	5	CP	VPA
21	M	48	3	4	GTC, M	VPA+CLN
22	F	192	5	6	CP, M	VPA

F: Female. M: Male. AED: Antiepileptic drugs. CP: Complex partial seizure. SP: Simple partial seizure. IS: Infantile spasms. GTC: Generalized tonic-clonic seizure. SG: Secondarily generalized seizure. M: Myoclonic. CBZ: Carbamazepine. CLN: Clonazepam. PB: Phenobarbital. LTG: Lamotrigine. VGB: Vigabatrin. VPA: Valproic acid. OBZ: Oxcarbazepine.

induced influx of chloride, inhibiting kainate/AMPA glutamate receptors, reducing L-type currents in voltage-activated calcium channels, and inhibiting carbonic anhydrase enzyme[4,9]. These may contribute to its anticonvulsant activity. Although the mechanism of the hyperthermia and hypohidrosis associated with TPM is unclear, it is speculated that the inhibition of carbonic anhydrase and sweat dysfunction may be responsible for this side effect. TPM might affect electrolyte channels or transporters in sweat glands as well as in neurons; however, it is not clear whether the sodium channels in sweat glands are structurally similar to the neuronal channels[4].

In our study, the most common hypohidrosis-related symptoms were hyperthermia, facial flushing, and heat sensation. In one study, Kim et al.[8] reported their patients who presented with facial flushing (34.4%), heat sensation (30.5%), hypohidrosis (27.2%), and lethargy (6.0%) with hyperthermia. The symptoms occurred more frequently in the younger age group (<6 years) than the older age group. In our symptomatic group, we established 15 (68.2%) patients aged <6 years and 7 (31.8%) aged >6 years.

The recommended dosage of TPM ranges from 3 to 9 mg/kg/day in children. In the literature, several studies have found a relationship between TPM dose and hypohidrosis. In contrast, some studies have not identified any such association. Ziad et al.[10] reported risk factors for hypohidrosis, and the TPM dose was >6 mg/kg/day. In another study, Kim et al.[8] detected no relationship between TPM dose and hypohidrosis. In our patients, TPM was started at 1 mg/kg/day with a slow titration, and the dose was increased until the seizures stopped. We found hyperthermia and hypohidrosis in 22/173 (12.7%) patients. TPM was given as <6 mg/kg/day dose in 13 (59.1%) patients, and >6 mg/kg/day dose in 9 (40.9%) patients in our study. We found no significant relationship between dose and symptoms.

Topiramate (TPM), acetazolamide and zonisamide have a structural resemblance. TPM acts as a carbonic anhydrase inhibitor. In the literature, the incidence of hypohidrosis was reported to range between 17% and 25% in children treated with zonisamide[11]. We used anticonvulsants other than TPM; however, we did not use zonisamide or acetazolamide. To our knowledge, there were no reports of hypohidrosis in epileptic children treated with other AEDs. We thought that the hypohidrosis developed due to TPM treatment since the hypohidrosis was absent before TPM treatment, and recovered to normal when the drug was discontinued.

In conclusion, hypohidrosis can be seen in patients treated with TPM, especially in those living in warmer countries such as ours. Its mechanism is not clearly understood, but the probable mechanism is the inhibition of carbonic anhydrase enzyme and dysfunction of electrolyte channels. We recommend that clinicians must remember this reversible side effect in patients under TPM treatment especially during the hot seasons.

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