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Acute psychotic symptoms induced by topiramate

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The incidence of psychosis during clinical trials of topiramate was 0.8%, not significantly different from the rate for placebo or reported rates of psychosis in patients with refractory epilepsy. We observed psychotic symptoms in five patients soon after initiation of topiramate therapy. We performed a retrospective chart review of the first 80 patients who began on topiramate after approval for clinical use, between January and April 1997. Symptoms suggestive of psychosis, including hallucinations and delusions, were sought for analysis. Cognitive effects such as psychomotor slowing, confusion, and somnolence were not included. Five patients developed definite psychotic symptoms 2 to 46 days after beginning topiramate. Dosages at symptom onset were 50–400 mg/day. Symptoms included paranoid delusions in four patients and auditory hallucinations in three. Symptoms of psychosis and other psychiatric symptoms resolved quickly with discontinuation of topiramate in three patients, dose reduction from 300 to 200 mg/day in one and with inpatient treatment and neuroleptics in another. One patient had a history of auditory hallucinations, one of aggressive and suicidal thoughts, but three had no significant psychiatric history. Physicians should be aware of the possibility of psychotic symptoms, even in patients without a previous psychiatric history, when prescribing topiramate. Symptoms resolve quickly with discontinuation.

Key words: epilepsy; topiramate; adverse effect; psychosis; resolution.

INTRODUCTION

Various central nervous system side-effects are common with the use of antiepileptic drug therapy in patients with epilepsy. Symptoms suggestive of psychosis in some patients with epilepsy have been attributed to the use of vigabatrin[1], carbamazepine, valproic acid, ethosuximide[2] and phenacemide[3]. Topiramate is a highly effective new antiepileptic drug when used as an adjunctive therapy in patients with refractory partial seizures. Mild to moderate cognitive impairments have been described as the main side-effects of this drug. The incidence of psychosis was not significantly different among treatment groups compared to placebo groups in premarketing clinical drug trials. We discuss five patients treated with topiramate who developed symptoms of psychosis. These included the sudden onset of various combinations of paranoid delusions, auditory hallucinations and a feeling of depersonalization. Suicidal thoughts, aggressive and agitated behavior and thoughts, severe mood swings or cognitive problems were often present as well, but were not considered evidence of psychosis by themselves.

MATERIALS AND METHODS

We performed a retrospective chart review of the first 80 patients with partial seizures put on topiramate after approval for clinical use from 16 January 1997 to 15 April 1997 at the University of Alabama at Birmingham Epilepsy Center. Patients who developed symptoms of psychosis such as hallucinations and delusions were included. Patients with cognitive impairment such as slowed thinking, psychomotor slowing, language impairment, confusion, symptoms of depression, crying spells, and impairment of sleep were not included. Five patients with a history of partial seizures, aged 27 years to 62 years, three men and two women, met criteria for a diagnosis of psychosis.

Case 1

A 27-year-old woman had a history of refractory complex partial seizures since birth secondary to an hypothalamic hematoma. She had no history of psychiatric illness. Her seizure frequency was 1–2 per day despite treatment with optimal doses of carbamazepine

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and lamotrigine. Topiramate was added to her regimen beginning with 50 mg q.d. with a titration rate of 50 mg every week. At a dose of 150 mg/day, she had the sudden onset of paranoia with fear of being observed and being followed all the time. Because of this, the patient was afraid to leave her house. Other side-effects included worsening unsteadiness of gait, dizziness, and impairment of concentration and memory. Her seizure frequency improved during treatment with topiramate. The symptoms of paranoid ideation resolved completely within 48 hours after discontinuation of topiramate.

Case 2

A 62-year-old woman had a history of complex partial seizures since five years of age. She had no history of psychiatric illness. She had been seizure-free for 2.5 years on phenytoin before a seizure two days before topiramate was introduced. Topiramate was begun at 25 mg q.d. and increased at a rate of 25 mg each week for the first four weeks. Symptoms of psychosis and paranoia developed at a dose of 150 mg b.i.d. (300 mg/day). These consisted of remaining awake all night hearing voices, and accusing her husband of attempting to kill her. She repeatedly complained of intruders within the house. Six weeks after the introduction of topiramate she developed onset of psychotic symptoms while she continued to be seizure-free during this period. Resolution of symptoms was seen with reduction of the topiramate dose to 100 mg twice a day (200 mg/day), and she was continued on topiramate.

Case 3

A 50-year-old man had a history of post-traumatic secondarily generalized tonic–clonic seizures since the age of six years. He had a long standing history of auditory hallucinations and mild depression that had never been treated. His last seizure was 2.5 months prior to topiramate therapy. Topiramate was added to phenytoin at a dose of 50 mg q.d. In the fourth week of therapy, clinically overt hallucinations developed and his depression worsened. He heard voices that spoke against him and told him to hurt his wife, that had never happened before. He also had worsening of symptoms of depression including suicidal thoughts. He remained seizure-free during topiramate therapy. A marked improvement in these symptoms of psychosis was noted within 24 hours after discontinuation of topiramate and treatment with haloperidol.

Case 4

A 46-year-old man had a 12-year history of post-traumatic complex partial seizures. He had no history of psychiatric illness. His seizure frequency was one per month on no antiepileptic medication. Topiramate was begun at a dose of 50 mg q.d. with a titration rate of 50 mg increase each week. Symptoms of psychosis developed at a topiramate dose of 75 mg b.i.d. (150 mg/day). He had recurrent thoughts and voices urging him to yell at people and slap his wife. Other symptoms consisted of sudden onset of severe, violent and hostile moods, agitation and feeling that he was another person. He also experienced excessive sedation, restlessness, confusion and fear. These symptoms resolved completely within 48 hours after discontinuation of topiramate.

Case 5

A 30-year-old man had a 15-year history of post-traumatic complex partial seizures. He had a history of aggressive and agitated behavior with suicidal thoughts over the past few years, but had repeatedly refused treatment for these symptoms. He was averaging 2–3 CPS/day. Topiramate was added at an initial dose of 50 mg q.d. to a treatment regimen of vigabatrin, phenobarbital, and phenytoin. Topiramate side-effects developed at a dose of 200 mg b.i.d. (400 mg/day) at a time when his seizures had been totally controlled for over three weeks. These consisted of confusion, agitation, bizarre thinking, obsession, hearing voices, suicidal ideation, thinking Jesus was behind the mass suicide which had just occurred in California and that he came to pick up all dead Catholics. He secretly started carrying a gun. He was admitted to a psychiatric hospital involuntarily. A partial resolution of the symptoms occurred with neuroleptic medication. Treatment with topiramate was continued since he was seizure-free on topiramate.

He was discharged from the psychiatric hospital after one month and when seen in the Epilepsy Clinic one month later was calm, pleasant, and free of all psychotic symptoms. At that time he was receiving antipsychotic medications as well as topiramate 200 mg b.i.d. and phenytoin. He has remained seizure-free and stable for the next six months. An increase of dose of topiramate from 400 mg/day to 600 mg/day later resulted in the recurrence of above symptoms.

DISCUSSION

An association between psychosis and epilepsy has been recognized for a long time. Some of the antiepilep-

tic drugs (AEDs) have also been implicated in various psychiatric symptoms including symptoms of psychosis in patients with and without a prior history of psychiatric illness. Three of our patients had no history of psychiatric illness. The time of onset of psychotic symptoms in our patients was variable although a similar slow titration method was used in all cases, in no case faster than 25–50 mg increases per week. The recommended initial dose and titration rate of topiramate during the immediate post-marketing period was 50 mg per day to be increased every week by 50 mg per day and as tolerated.

The symptoms of psychosis were unlikely to be postictal psychosis for two reasons: first, in four patients the onset of symptoms was rather slow and evolved over 1–2 weeks, and secondly, there was no history of a seizure for at least three weeks before the onset of psychotic symptoms in three patients. One patient never had any seizures while on topiramate therapy and one other patient had only one complex partial seizure during 18 days of topiramate treatment. Complex partial status epilepticus was not a consideration based on clinical examinations. Two patients had normal EEGs at the time of symptoms.

Carbamazepine has been implicated in the development of psychosis in four patients in one report[2]. Only one of our five patients was on carbamazepine at the time of topiramate treatment. One patient who had a history of psychiatric disease was on three AEDs including vigabatrin. Vigabatrin has been reported to have psychosis as a side-effect[1]. Two other patients were not on any AEDs when topiramate treatment was begun. These facts suggest that a combination of topiramate with other AEDs, implicated in the development of psychosis in the past, may not be the sole explanation for the development of symptoms of psychosis in our patients. Topiramate shares a GABAergic action with vigabatrin, gabapentin, and tiagabine, along with its other actions as a sodium channel blocker and antiglutamatergic activity. Vigabatrin has been reported to be responsible for the development of psychosis along with various other psychiatric symptoms. Gabapentin has been reported to cause significant cognitive impairment in children[4]. However, the underlying mechanism for these side-effects is unclear.

The concept of forced normalization has been debated substantially in the literature as a hypothesis for the development of psychiatric symptoms in epileptic patients[5]. This concept is mostly concerned with the normalization of EEG in patients with previous EEGs showing epileptiform abnormality who develop clinical behavioral abnormality[6,7]. We were unable to record serial EEGs in our patients, therefore this possibility was considered but could not be excluded or confirmed. Patients 3 and 4 had a normal EEG at the onset of symptoms of psychosis. Patient 4 also had a normal 24-hour long term video/EEG study three week prior to onset of these symptoms. Three patients had no history of psychiatric illness. Only one patient with a history of psychiatric illness was having frequent seizures and did achieve complete seizure control concomitant with the development of psychosis. Improvement of symptoms on reduction of dose in one patient and recurrence of the symptoms in another patient on increasing the dose of topiramate may suggest dose related effects of this medication on symptoms of psychosis and other psychiatric symptoms in some patients.

CONCLUSIONS

Although the underlying mechanism and precipitating factors for the development of symptoms of psychosis are not clear in these patients treated with topiramate, physicians should be aware of this potential side-effect. It has also been recently reported by others[8]. Psychosis resolves completely with discontinuation or reduction of topiramate dose, and can also respond to appropriate neuroleptic medications.

Although it may be judicious to avoid the use of topiramate in patients with a history of psychosis, this adverse effect can develop in patients with no psychiatric history.

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