

Timing and Clinical Characteristics of Topiramate-Induced Psychosis in a Patient With Epilepsy and Tuberous Sclerosis

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Abstract: Several lines of scientific evidence showed that topiramate may induce psychotic symptoms when used as monotherapy. It has been postulated that this topiramate effect may be caused by the inhibition of frontal and prefrontal areas induced by topiramate. The clinical history of the patient described shows that topiramate may also induce psychosis when used in polytherapy. A 34-year-old man, with epilepsy associated to tuberous sclerosis complex and without a previous history of mental disorders, presented an acute onset of florid psychotic symptoms, including visual and auditory hallucinations, derealization, and depersonalization. These symptoms appeared 1 month after the introduction of topiramate, added to levetiracetam and carbamazepine, when topiramate reached the dose of 200 mg daily. Once topiramate was discontinued, the psychotic symptoms disappeared, with no recurrence in a 4-month follow-up. Psychotic symptoms were associated with topiramate administration. We hypothesized that psychotic symptoms appeared a month after the topiramate introduction because of the slow topiramate titration and protective effect of carbamazepine.

Key Words: topiramate, epilepsy and tuberous sclerosis

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Topiramate is prescribed for a wide range of applications: epilepsy, migraine prophylaxis, bipolar disorders, aggressiveness in borderline personality disorder, posttraumatic stress disorder, weight control secondary to antipsychotic medication, and eating disorders. In epilepsy, topiramate is indicated for the management of partial seizures and generalized tonic-clonic seizures. Its precise mechanism of action is not yet known, but sodium channel blockade, augmentation of γ -amino butyric acid activity, antagonism of glutamate receptors, and carbonic anhydrase inhibition are all believed to play a role. Common adverse events observed in initial clinical trials of topiramate include somnolence (15%–29%), psychomotor slowing (3%–21%), depression (3%–13%), and confusion (4%–14%).¹ Topiramate-induced psychosis has been described in some case reports and occurs in 0.8% to 3.7% of patients with epilepsy.^{2,3} On the basis of this scientific evidence, we hypothesized that topiramate may play a role as a potential trigger for psychosis in epilepsy.

CASE PRESENTATION

We report on a case of a 34-year-old white Italian man with a history of epilepsy secondary to tuberous sclerosis complex and without a previous history of mental disorders. Tuberous sclerosis complex is a genetic multisystem disorder characterized by widespread hamartomas in several organs, including the brain, heart, skin, eyes, kidney, lung, and liver.⁴ Our patient has multiple cortical tubers, localized mainly in the temporal cortex, and cutaneous lesions, without any other localizations, and particularly without renal lesions. Since 2001, he was being treated for epilepsy at the Child Neurology and Psychiatry Unit of “Tor Vergata” University of Rome (Italy). In June 2012, a year before the psychotic symptoms onset, our patient underwent annual medical and psychiatric checkup. Results of hematological and biochemical screening did not reveal alterations in blood counts, kidney, liver, and thyroid functions. Cognitive assessment performed using the Wechsler Adult Intelligence Scale Revised showed a normal IQ (verbal IQ, 95; performance IQ, 126; total IQ, 109). The interview with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I disorders was used to exclude any psychopathological symptom. Moreover, the Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale were used to exclude the presence of anxiety and depression in our patient. Finally, the executive functions as well as selective and divided attention, evaluated by Tower of London and Trail Making Test parts A and B, were normal. The pharmacological antiepileptic therapy was based on levetiracetam (3000 mg/d) and carbamazepine (1600 mg/d). In June 2013, just before the annual checkup, our patient presented focal motor seizures and topiramate was introduced, starting from 50 mg daily and with a slow increase (50 mg/wk) to reach 200 mg daily. In July 2013, one month after topiramate introduction, at 100 mg twice a day for 1 week, our patient presented insomnia, severe anxiety, severe psychomotor agitation, aggressiveness, derealization, depersonalization, as well as visual and auditory hallucinations. After the onset of psychotic symptoms, topiramate was suspended and these symptoms regressed in a few days. After topiramate discontinuation, our patient reported a sense of full well-being without taking antipsychotic drugs. In November 2013, the follow-up at 4 months confirmed no recurrence of psychotic symptoms.

DISCUSSION AND CONCLUSIONS

Psychiatric disorders, including acute psychosis, have been reported in patients with tuberous sclerosis complex, particularly in patients with epilepsy.⁴ Topiramate-induced psychosis is observed mainly in patients with epilepsy, and the risk for developing psychosis in patients with epilepsy is 6 to 12 times higher than that in patients without epilepsy.^{5,6} Potential predictors of topiramate-induced psychosis are a positive history of previous psychiatric disorders, epilepsy, as well as starting dose and fast titration.^{6,7} There are several case reports of topiramate-induced psychosis at dosage exceeding 50 mg daily.^{2,3,8,9} Psychosis may

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be a dose-dependent effect because symptoms improve with discontinuation and return upon reinitiating.^{2,9} Watkin et al¹⁰ have observed a patient with epilepsy with topiramate-induced psychosis, and there was no recurrence of any symptoms in a 15-month follow-up, despite not receiving antipsychotic medication. It has been postulated that topiramate decreases functioning of the frontal and prefrontal areas. Thus, the inhibitory control over irrational thoughts and feelings is blocked, leading to psychosis.^{8,9} We hypothesized that topiramate at 200 mg daily may be responsible for the onset of psychotic symptoms. Furthermore, we hypothesized that slow topiramate titration and concomitant use of carbamazepine may have delayed the psychotic symptoms onset. Indeed, carbamazepine is a potent enzymatic cytochrome P450 inducer and is known to reduce the topiramate plasma concentration.^{11–13} This case report may help to increase the knowledge about the timing and clinical characteristics of topiramate-induced psychosis in epilepsy. It also stresses the protective effect of drug interactions and slow topiramate titration regarding the topiramate-induced psychosis.

REFERENCES

1. Adelman J, Freitag FG, Lainez M, et al. Analysis of safety and tolerability data obtained from over 1500 patients receiving topiramate for migraine prevention in controlled trials. *Pain Med* 2008;9:175–185.
2. Khan A, Faught E, Gilliam F, et al. Acute psychotic symptoms induced by topiramate. *Seizure* 1999;8:235–237.
3. Zesiewicz TA, Tullidge A, Tidwell J, et al. Topiramate-induced psychosis in patients with essential tremor: report of 2 cases. *Clin Neuropharmacol* 2006;29:168–169.
4. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet* 2008;372:657–668.
5. José RJ, Cairns A, Babbs C. Topiramate-induced psychosis in two members of the one family: a case report. *J Med Case Reports* 2008;2:195.
6. Kanner AM, Wu J, Faught E, et al. The PADS investigators: a past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. *Epilepsy Behav* 2003;4:548–552.
7. Mula M, Trimble MR, Lhatoo SD, et al. Topiramate and psychiatric adverse events in patients with epilepsy. *Epilepsia* 2003;44:659–663.
8. Christman DS, Faubion MD. Suicide attempt following initiation of topiramate. *Am J Psychiatry* 2007;164:682–683.
9. Miller AD, Prost VM, Bookstaver PB, et al. Topiramate-induced myoclonus and psychosis during migraine prophylaxis. *Am J Health Syst Pharm* 2010;67(14):1178–1180.
10. Watkin A, Alam F, Javed Q. Topiramate-induced psychosis: the picture at 12 months. *BMJ Case Rep* 2010. doi: 10.1136/bcr.07.2010.3141.
11. Spina E, Pisani F, Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. *Clin Pharmacokinet* 1996;31:198–214.
12. Bourgeois BF. Drug interaction profile of topiramate. *Epilepsia* 1996;37(suppl 2):14–17.
13. Patsalos PN, Frocher W, Pisani F, et al. The importance of drug interactions in epilepsy therapy. *Epilepsia* 2002;43(4):365–385.