

Topiramate add-on treatment associated with normalization of prolactin levels in a patient with schizophrenia

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Abstract: Topiramate has been used increasingly in the management of psychiatric conditions. Clinical trials demonstrated that topiramate augmentation was effective in controlling negative symptoms in schizophrenia. This case report presents a case of a 38-year-old man with schizophrenia who achieved full negative symptom remission upon the adjunctive use of topiramate. However, the remarkable finding of this case is the concomitant decrease in the level of prolactin when topiramate (50 mg/day) was started and the rebound after discontinuation of topiramate. Previous studies stated that topiramate could prevent antipsychotic-induced weight gain and adverse metabolic effects. To the authors' knowledge, no study has reported that topiramate augmentation could be a treatment strategy for antipsychotic-induced hyperprolactinemia. This finding could be verified by well-designed clinical trials.

Keywords: topiramate, prolactin, schizophrenia, antipsychotics, dopamine, alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)

Introduction

Hyperprolactinemia is a common adverse event of antipsychotics. Current treatment options for antipsychotic-induced hyperprolactinemia are limited (ie, decrease dose of existing antipsychotic, switch to a prolactin-sparing antipsychotic, dopamine receptor agonist) and carry a high risk of exacerbating psychotic symptoms or a relapse.¹ This case report may provide a new strategy to manage hyperprolactinemia in schizophrenia.

Case report

In February 2011, a 38-year-old man presented with a 6-month history of schizophrenia, characterized by auditory hallucinations, persecutory delusions, and social withdrawal. His past medical history was unremarkable. In the outpatient clinic, hematological examinations and cranial computed tomography were performed to exclude underlying physical diseases. Then, he was commenced on quetiapine with a dose of 800 mg/day. However, he had an unsatisfactory clinical response to quetiapine monotherapy. In May 2011, co-treatment with paliperidone extended-release tablets was started and titrated to a dose of 9 mg/day within a week. During the treatment with quetiapine and paliperidone, his psychotic symptoms, except for social withdrawal, markedly improved. However, laboratory tests in November 2011 revealed hyperprolactinemia (prolactin = 1,085 mIU/L). Prolactin was measured by using electrochemiluminescence immunoassay, with commercial kits recommended by the manufacturer (Siemens

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Immuline® 2000 Systems, Siemens Healthcare Diagnostics Products Ltd., Glyn Rhonwy, Llanberis, Gwynedd, United Kingdom). In January 2012, topiramate 25 mg/day was added to ameliorate his negative symptom (social withdrawal). After 4 weeks of treatment with quetiapine 800 mg/day, paliperidone 9 mg/day, plus topiramate 25 mg/day, his negative symptom was not significantly diminished, and his serum prolactin concentration was 1,384 mIU/L. In February 2012, the topiramate dose was increased to 50 mg/day. Over the next 40 days, all his psychotic symptoms were well controlled. Unexpectedly, his serum prolactin concentration returned to normal (318 mIU/L). However, the γ -glutamyltransferase level had increased to 185 U/L. Subsequently, the topiramate treatment was discontinued. When last seen in April 2012, 1 week after the discontinuation of topiramate, his prolactin level was measured at 687 mIU/L, and γ -glutamyltransferase level was 130 U/L.

This work was approved by the Ethical Committee of the First Affiliated Hospital, China Medical University. The patient's guardian has provided written informed consent to have the case details excluding patient's name published.

Discussion

In general, negative symptoms of schizophrenia are not improved dramatically by current antipsychotics. As a result, more effective pharmacological augmentation strategies are sought. Topiramate, a new antiepileptic drug, has been used increasingly in the treatment of numerous psychiatric conditions.² A randomized, double-blind, placebo-controlled clinical trial demonstrated that topiramate add-on treatment in schizophrenia was effective in controlling the negative symptoms.³ In the present case, the patient also achieved full negative symptom (social withdrawal) remission upon the adjunctive use of topiramate (50 mg/day). Negative symptoms are thought to be due to the hypoactivity of the mesocortical dopamine system. A pharmacological study has revealed that topiramate increased basal and Ca^{2+} -evoked dopamine release in the rat prefrontal cortex.⁴ Furthermore, addition of topiramate to rats being treated with raclopride caused a large increase in dopamine output in the medial prefrontal cortex, which reduced the negative symptoms.⁵ These studies may explain the underlying mechanisms by which topiramate ameliorates negative symptoms in schizophrenics. Also, it has been demonstrated that prolactin-derived vasoinhibins increase depression-related behaviors.⁶ Thus, another possibility of the resolution of negative symptoms was the accompanied declining in prolactin level.

It has been proved that topiramate could prevent antipsychotic-induced weight gain and adverse metabolic

effects (ie, hyperglycemia, hyperinsulinemia, increased insulin resistance, hyperleptinemia, hypercholesterolemia, and hypertriglyceridemia).⁷ However, to the authors' knowledge, no study has reported that topiramate could decrease prolactin level in patients treated with antipsychotics. The remarkable finding of this case is the concomitant decrease in the level of prolactin when topiramate (50 mg/day) was started. No other treatments or medications were used while using topiramate. Considering the rebound in prolactin level after discontinuation of topiramate, it can be concluded that topiramate treatment was responsible for the normalization of prolactin levels.

Hyperprolactinemia is common in patients with schizophrenia. It can be a side effect of both conventional antipsychotics and some atypical antipsychotics (amisulpride, risperidone, and paliperidone), which bind to dopamine D2 receptors on the anterior pituitary gland and block the inhibitory effect of dopamine, released from tuberoinfundibular dopaminergic terminals of the hypothalamus, on the prolactin-producing cells of the lactotroph, thereby resulting in hyperprolactinemia.⁸ With alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist properties, topiramate was associated with an attenuation of glutamatergic excitatory neurotransmission. A previous study found that the AMPA antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), injected into the third ventricle blocked the suckling-induced release of prolactin in plasma,⁹ which indicated that the endogenous glutamatergic system plays an important role in prolactin release. Whether the normalization of prolactin levels in the patient is related to the AMPA antagonist properties of topiramate needs further exploration.

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Disclosure

The authors report no conflicts of interest in this work.

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