Case Report

Mania Induced by Opipramol

Kazhungil Firoz, Asfia Khaleel, Rajmohan V, Manoj Kumar, Raghuram TM

ABSTRACT

Antidepressants have propensity to induce manic switch in patients with bipolar disorder. Opipramol is an atypical anxiolytic and antidepressant drug which predominantly acts on sigma receptors. Although structurally resembles tricyclic antidepressant imipramine it does not have inhibitory action on the reuptake of norepinephrine/serotonin and hence it is not presumed to cause manic switch in bipolar depression. Here, we describe a case of mania induced by opipramol, in a patient with bipolar affective disorder who was treated for moderate depressive episode with lithium and opipramol and we discuss neurochemical hypothesis of opipramol-induced mania.

Key words: *Antidepressants, mania, opipramol, switch*

INTRODUCTION

Opipramol is an atypical anxiolytic and antidepressant drug which has been found to be effective in depressive disorder.[1,2] Although it was developed by Schindler and Blattner in 1961, its use was limited and recently it has regained popularity among psychiatrists all over for the treatment of somatoform and depressive disorders. Structurally its nucleus is similar to that of tricyclic antidepressant imipramine and the attached side chain is identical to that of perphenazine. Although it is structurally similar to tricyclic antidepressants, it does not inhibit the neuronal uptake of norepinephrine and/or serotonin and is a sigma-receptor agonist, primarily at the sigma-1 receptor subtype, but also at the sigma-2 subtype with lower affinity. Sigma-1 agonism is responsible for its antidepressant activity and sigma-2 for the anxiolytic properties.[3] Sigma receptor agonist opipramol is not presumed to cause affective switch because of its relative sparing of monoamine receptors. Hereby, we describe a case of opipramol-induced mania in a patient with bipolar depression.

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CASE REPORT

Mr. A 39-yr-old male was brought to our OPD with 4 weeks history of talking excessively even to unfamiliar people, being irritable to others, overspending, singing, dancing and reduced need for sleep. There was family history of bipolar disorder in a first degree relative.

On exploration it was reported that he had a manic episode with psychotic symptoms 15 years back and was on lithium prophylaxis till 5 years ago. Four months ago, the patient consulted a psychiatrist with history of excessive sadness, inability to sleep, easy fatiquability, anhedonia, not being able to carry out his job and reduced libido, and was diagnosed to have moderate depressive episode and was restarted on lithium 900 mg/day. Two months ago, as patient did not improve on lithium monotherapy with serum lithium level of 0.7 Meq/litre, opipramol 50 mg/day was added along with lithium. And after 1 month on opipramol treatment patient was brought to us with the current symptoms. Patient's investigations showed serum lithium level of 0.7 mEq/litre and thyroid

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function was normal. On mental status examination, he was found to be intrusive and overtalkative with euphoric mood. Patient was diagnosed as a case of bipolar affective disorder, current episode being treatment emergent manic switch due to opipramol as per the International Society for Bipolar Disorders (ISBD) criteria and patient was admitted.

Opipramol was stopped and patient was continued on lithium 900 mg/day and risperidone titrated up to 4 mg/day. His manic symptoms started resolving by second week and remitted by fourth week and the patient was discharged. The total manic score on Young's mania rating scale was 39 at the time of admission and it dropped to 28, 17 and 6 at the end of first, second and fourth week of treatment, respectively.

DISCUSSION

Although being effective, almost all the antidepressants carry a risk of mania/hypomania in bipolar affective disorder. Treatment-emergent affective switch (TEAS) is not well defined and according to the International Society for Bipolar Disorders (ISBD) 2009 criteria, switch can be called as 'definite' treatment emergent manic switch if:

1. It occurs within a window period of 8 weeks from intervention,
2. Full syndromic hypomanic, manic, mixed symptoms emerge and
3. If symptoms last for at least 2 consecutive days with daily occurrence of symptomatic periods lasting more than 50% of time each day.[4]

In the largest multicentre trial of antidepressants in bipolar depression STEP–BD, when patients followed for up to 2 years, transition from depression directly to manic, hypomanic or mixed states was observed in 21% of individuals prospectively observed for a single episode.[5] Tricyclic antidepressants (TCAs) have consistently been associated with a high risk of TEAS compared to other antidepressants; incidence rates ranging from 9% to 69%.[6] The question whether concomitant use of mood stabilizers would reduce the switch inducing property of antidepressants is unanswered and wide variation in rates of TEAS observed in studies is often attributed to concomitant administration of mood stabilizers. Studies show that when mood stabilizers are combined with TCAs risk of switching to mania is significantly reduced.[7] When used along with mood stabilizers very low switch rates ranging from 0% to 3.7% have been observed with SSRIs.[5]

In our case, manic symptoms emerged within 4 weeks of opipramol treatment even though he was on lithium and serum lithium level was optimal. The dose of opipramol in our case was 50 mg/day which indicate that even very low dose of opipramol has propensity to cause switch to mania.

Opipramol has agonistic action on sigma-1 receptor which is responsible for its antidepressant activity.[3] It does not have inhibitory action on reuptake of norepinephrine or serotonin and dopamine unlike other antidepressants. Opipramol also blocks histamine, serotonin, dopamine and alpha-1 adrenergic receptors, on the basis of which switch due to opipramol cannot be explained. SSRIs, TCAs and norepinephrine-dopamine reuptake inhibitor bupropion which are reported to cause switch also have sigma receptor agonism and only factor which is shared between these drugs and opipramol is the affinity for sigma receptors.[8,9] In animal models, sigma-1 receptor mediates stimulant and appetitive properties of cocaine which is similar to hypomanic symptoms and sigma-1 receptor antagonists block the hyperlocomotion and appetitive effect of cocaine.[10] Hence agonistic action on sigma receptor itself may be postulated to cause behavioral activation and manic switch in case of opipramol, though this correlation is yet to be understood in detail.

In summarisation, the above-mentioned case of bipolar depression who developed treatment emergent manic switch due to opipramol while on concomitant treatment with lithium remitted by fourth week of opipramol discontinuation. Sigma-1 receptor agonism of opipramol may be hypothesized as the basis of manic switch due to opipramol. This is the first case of opipramol-induced manic switch published in the literature and further studies are essential to confirm our view.

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