Case Report

Iloperidone-induced Galactorrhea in a Middle-aged Female

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ABSTRACT

Iloperidone, a piperidinyl-benzisoxazole derivative, is structurally related to risperidone and approved for treatment in acute stage of schizophrenia. Iloperidone is usually considered as a prolactin sparing atypical antipsychotic thereby offering treatment advantage. We aim to present the first reported case of iloperidone-induced hyperprolactinemic galactorrhea in a middle-aged female. A middle-aged female with the diagnosis of paranoid schizophrenia was treated with iloperidone up to a dosage of 8 mg/day. Three months after starting the medicine, patient developed galactorrhea for which no other medical cause could be ascertained except for increased prolactin level. Iloperidone was stopped and aripiprazole was initiated with which galactorrhea subsided and prolactin level returned to normal. Index case report amply demonstrates that Iloperidone can cause hyperprolactinemic galactorrhea even at low dosage and after considerable period into the treatment.

Key words: *Antipsychotic, galactorrhea, iloperidone, side effect*

INTRODUCTION

The evolution of first generation antipsychotics heralded a new era in the treatment of schizophrenia, but its short-term and long-term disabling extra-pyramidal side effects (EPSE) compelled the researchers to continue their quest for novel antipsychotics devoid of such side effects. As a result, second generation antipsychotics (SGA) were discovered and gradually became the cornerstone in the treatment of schizophrenia.[1,2] But, in last two decades, endocrinal and metabolic side effects of the SGA emerged as a troublesome factor in clinical practice. One of the important concerns is hyperprolactinemia and its consequences, e.g., breast enlargement, acne, hirsutism, galactorrhea, atrophic changes in the urethra and vaginal mucosa, reduced vaginal lubrication and dyspareunia, ovarian dysfunction, infertility, reduced libido so on and so forth.[3] SGAs differ among themselves in their prolactin-elevating effect such as risperidone and amisulpride are associated with a higher level of elevated prolactin compared to olanzapine, clozapine, and quetiapine.[1,4,5] Thus, there is obvious dissociation in the motor and neuroendocrine side effects in this new class of agents. These limitations have geared the scientists to develop more effective and safer antipsychotics that would improve overall quality of life for persons suffering from schizophrenia. This group includes iloperidone, a piperidinyl-benzisoxazole derivative structurally related to risperidone.[6,7] Its efficacy in the treatment of schizophrenia which has been established in clinical trials along with a favorable safety profile (e.g., lack of EPSE, akathisia, not likely to cause clinically significant prolactin elevation) quickly earned it the USFDA approval for use in patients in acute stage of schizophrenia in May 2009.[8]

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We describe a case of iloperidone-induced hyperprolactinemia and resultant galactorrhea in a middle-aged female leading to distressing short-term and potentially harmful long-term consequences including drug noncompliance.

CASE REPORT

A 35-year-old female attended the Psychiatry outpatient department of a tertiary care teaching hospital in eastern part of India with the chief complaints of third person and commanding type auditory hallucination, delusion of persecution, and reference with frequent acting on behavior as well as sudden unprovoked violence, decreased sleep and appetite with marked socio-occupational dysfunction since last two months. Her general physical examination was unremarkable. She weighed 54 kg. Her routine biochemical examinations and computed tomography of brain were normal. Her menstrual cycle was regular and there was no evidence of any hirsutism. On first visit, her Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score was 78. She was prescribed tablet iloperidone, 1 mg twice daily along with tablet clonazepam 2 mg at night. Dose of iloperidone was increased up to 4 mg twice daily within one week. Her symptoms started improving within next two weeks and almost completely resolved within 2 months with the same dose of iloperidone (8 mg/day). Dose of tablet clonazepam were reduced to 0.5 mg at night. Three months after starting Iloperidone, patient developed spontaneous milky discharge from both the nipples and on next menstrual cycle, she missed her date. Patient and her family members became excessively worried because of her new symptoms and wanted to stop all kind of treatment. On liaison with department of Gynecology and General Surgery, detailed work-up was done to search for the causes of galactorrhea and amenorrhea. There was no history of any fever, mastalgia, any visual complaints, and symptoms suggestive of raised intracranial pressure. On systemic examination, there was no tenderness, dimpling, or mass on breast palpation, thyromegaly, adenopathy, hepatosplenomegaly, and no abnormality on examinations of cranial nerve functions. Serum Prolactin was estimated to be 31.70 ng/ml (normal reference range for premenopausal female, 4.79–23.3 ng/mL) and serum TSH was estimated to be 1.26 μIU/ml (normal reference range was 0.27–4.20 μIU/ml). No abnormality detected on renal function test, liver function test, blood glucose levels, lipid profile, mammogram, and MRI brain. Keeping in mind that iloperidone-induced galactorrhea could be the possible reason, tablet iloperidone was stopped and tablet aripiprazole (2.5 mg twice daily) was started. Dramatic resolution of galactorrhea was noted within 1 week of stoppage of iloperidone. Dose of aripiprazole was increased to 5 mg twice daily. Serum prolactin was rechecked, was found to be slightly reduced (25.35 ng/ ml) after one week of stoppage of iloperidone. Her psychotic symptoms remained controlled (PANSS score was 47). Her next menstrual flow was scanty but resumed her normal menstrual bleeding on second month of stoppage of iloperidone when serum prolactin level was rechecked and found to be reverted back to normal range (15.90 ng/ml).

DISCUSSION

After extensive search of electronic databases, no case report of iloperidone-induced galactorrhea was found. Iloperidone binds to the 5-HT2A/D2 receptors between which it has higher affinity for the 5-HT2A receptor than for the D2 receptor and α1 receptor, moderate affinity for 5-HT1A, 5-HT2C, and 5-HT6, and α2C receptor, an antagonist at 5HT2C and 5HT6 receptors, and a partial agonist at 5HT1A.[9] It also showed high affinity for the D3 and moderate affinity for the D4 receptor.[10,11] Owing to the D2 antagonistic activity in tuberoinfundibular pathway which projects from hypothalamus to anterior pituitary, antipsychotics reverse the tonic dopaminergic inhibition of prolactin production in anterior pituitary leading to hyperprolactinemia. In literature, it has been mentioned that iloperidone was associated with a reduction in prolactin levels, whereas there was a significant increase in prolactin with haloperidol and risperidone.[12] Like most antipsychotics, there is a transient increase in plasma prolactin associated with onset of treatment with iloperidone. The mean increase at the highest dose (24 mg/day) was only 2.6 ng/ml (not clinically significant). In a pooled analysis of iloperidone *vs* other active comparators, iloperidone and ziprasidone were not associated with clinically relevant prolactin elevation, whereas haloperidol and risperidone caused significant elevations.[13] Therefore, iloperidone treatment is unlikely to cause clinically relevant problems associated with prolactin elevation (e.g., amenorrhea or galactorrhea in premenopausal women), unlike the index patient who developed hyperprolactinemic galactorrhea. Index case also shows that hyperprolactinemic galactorrhea can occur at a moderate dosage of Iloperidone (8 mg/day) and may develop after some time (3 months in index case) into the treatment. It also showed that there was no direct relationship between serum prolactin level and clinical manifestation of hyperprolactinemia as mild elevation of serum prolactin (31.7 ng/ml) caused galactorrhea and amenorrhea. Also, complete resolution of hyperprolactinemia and its clinical features by replacing iloperidone with prolactin-sparing aripiprazole further confirms our diagnosis and adds to the management of such cases.

CONCLUSION

Despite iloperidone being considered as a prolactin-sparing atypical antipsychotic, iloperidone-induced hyperprolactinemia may rarely be encountered as a side effect in susceptible individuals. Therefore, clinicians should be aware that switching to iloperidone in cases of hyperprolactinemia induced by another atypical antipsychotic may not always produce the desirable outcome. Iloperidone-induced hyperprolactinemia and secondary galactorrhea both seem to subside by reducing the dose or stopping the drug.

FUTURE DIRECTION

At present, there is no satisfactory answer of why some atypical antipsychotics elevate prolactin level more than others. It is unlikely that a difference in the 5-HT2/D2 binding ratio would explain the prolactin differences because risperidone (a prolactin-elevating drug) has a higher 5-HT2/D2 ratio than olanzapine and quetiapine (prolactin-sparing drugs).[14] It is best understood as a manifestation of the differential disposition of the drugs across the blood-brain barrier, resulting in differential pituitary *vs* striatal D2 occupancy. Alternatively, strategies that enhance central penetration of antipsychotics may also alleviate the effect of differential disposition.[15] More studies are needed to address such variation among atypical antipsychotics.

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