

Aripiprazole is effective in hyperprolactinemia secondary to use of Fluphenazine

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Abstract

Aripiprazole is drug that acts as a partial agonist at D2 and 5-HT1A receptors and antagonist at 5-HT2A receptor. It modulates the neurotransmission over activity on the dopaminergic mesolimbic pathway which is responsible for positive symptoms of Schizophrenia. Dopamine antagonism is the mechanism of action of first generation antipsychotics. In this paper we discuss an interesting case in which Aripiprazole was effective in decreasing Prolactin levels which was elevated secondary to previous Fluphenazine use.

Keywords: Hyperprolactinemia, Fluphenazine, Aripiprazole, Hallucinations, Prolactin.

Introduction

Aripiprazole is drug that acts as a partial agonist at D2 and 5-HT1A receptors and antagonist at 5-HT2A receptor. It modulates the neurotransmission over activity on the dopaminergic mesolimbic pathway which is responsible for positive symptoms of Schizophrenia. Dopamine antagonism is the mechanism of action of first generation antipsychotics. It results in both its side effects and antipsychotic property. Hallucinations and delusions found in partially or untreated Schizophrenia are a result of increased activity in the mesolimbic dopamine pathway. The mechanism by which typical antipsychotics like Fluphenazine reduce psychosis is by blocking Dopamine from binding to D2 receptor, causing inhibition of mesolimbic dopamine pathway and control of psychosis. However, this leads to an elevation in prolactin levels leading to galactorrhea, amenorrhea, visual disturbances and changes in libido among patients.¹

Case Details

Ms. A is a 29-year-old female with history of schizoaffective disorder bipolar type and borderline intellectual functioning who was escorted by police to the inpatient psychiatric facility with symptoms of increased energy, loud and pressured speech, inability to focus associated with command auditory hallucinations, visual hallucinations and endorsing suicidal ideations with a plan to slit her throat or wrists. One day prior to admission, she had presented to a local crisis center with symptoms of depression, psychosis and mania along with increased energy levels and difficulty with concentration after which she was transferred to our inpatient psychiatric facility. In addition she admits to hearing voices that tell her to "slit her wrist or throat" and reports seeing faces of dead people.

Patient is a single mother who lives with her parents and a young daughter. As per parents, Ms. A was incapable of performing her activities of daily living and has an extensive history of noncompliance with medications. Her

hospital stay has been very eventful given her intrusive behavior. Since being transferred she has been more stable but found to be intrusive and hypersexual leading to breaching of boundaries of other patients on the unit.

Patient was started on fluphenazine 10 mg by mouth daily in the morning and 15 mg by mouth at bedtime in addition to her regimen of lithium 300 mg by mouth in the morning and 600 mg by mouth every evening, olanzapine 10 mg by mouth twice a day and trazodone 50 mg by mouth at bedtime for management of her worsening psychosis. Patient was noted to have optimum control of psychosis while being at her baseline intellectual functioning within a week of being started on fluphenazine. However, approximately 30 days of starting fluphenazine, patient reported symptoms of blurry vision, milky discharge from her breasts and menstrual irregularities. Prolactin (PRL) level was found to be elevated at 235 ng/ml. A palpable breast lump was detected over the upper inner quadrant of her right breast. Endocrinology was consulted and recommended discontinuation of fluphenazine and workup including MRI of the brain and periodic monitoring of TSH and Prolactin levels. TSH was found to be 4.65. Pregnancy test was negative. MRI was unsuccessfully attempted secondary to patient's intrusive behavior and severe elopement risk. Patient complained of episodic right retro orbital headache associated with nausea, photophobia, consistent with migraine. Sumatriptan 100 mg PO as needed for breakthrough headache was prescribed for migraine prophylaxis. Ultrasound of the breast demonstrated no discrete abnormality and a decision was made to defer from mammography.

Fluphenazine was tapered down to 5 mg PO QAM and 10 mg PO QHS and eventually discontinued. Patient followed up regularly with endocrinology who advised that TSH and prolactin be serially monitored without

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any surgical or radiological interventions. Patient reported partial resolution of galactorrhea, blurry vision and continued to be amenorrhoeic. After 20 days of discontinuing fluphenazine, aripiprazole 5 mg PO was initiated. Prolactin level progressively dropped down to 59.8 with complete resolution of blurry vision, galactorrhea and resumption of menstruation. Repeat PRL after 2 months of initiation of aripiprazole demonstrated a downward trend to 24.8 ng/ml and TSH of 2.22uIU/mL.

Discussion

Hyperprolactinemia is characterized by elevated serum prolactin levels. Prolactinomas are the most common causes of hyperprolactinemia. Increased prolactin levels are also associated with various common etiologies like physiological hypersecretion in pregnancy, sleep, lactation, sexual activity and stimulation of breast. Various pharmacological agents like hormones (estrogen), anti-hypertensives (verapamil and reserpine) and H2 receptor agonists (cimetidine, ranitidine), amphetamines, opioids and psychotropic drugs and pathological conditions like tumors of pituitary, hypothalamus, sarcoidosis, hypothyroidism, Polycystic Ovarian Syndrome and Cushing's disease have also been associated with it.²

Symptomatically, it is characterized by a syndrome of amenorrhea- galactorrhea associated with infertility in females. Males commonly present with visual disturbances and loss of libido. Prolactin can be raised up to twenty times in pregnancy and return to baseline approximately three weeks after child birth.³ There is evidence that states prolactin levels above 500 mU/L are considered abnormal. Clinical symptoms of hyperprolactinemia usually arise when with levels of prolactin ranging between 600-1200 mU/L.⁴ Serotonin stimulates the release of this hormone while dopamine inhibits its release. Dopamine receptor blockage in the tuberoinfundibular tract results in increased secretion of prolactin. Various antipsychotics are noted to block the dopamine causing hyperprolactinemia.⁵ Fluphenazine (piperazine-phenothiazine) is a first-generation antipsychotic, with antagonistic activity at the Dopamine receptors. Aripiprazole a second-generation antipsychotic, which mediates its action through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors.

As seen above, the patient who previously on Lithium 300 mg orally every morning and 600 mg orally at bedtime, olanzapine 10 mg orally twice daily and Trazodone 50 mg orally at bedtime with worsening psychosis was started on Fluphenazine. Within a week of initiation of Fluphenazine marked improvement in psychosis was noted secondary to its dopamine antagonism. This led to an increase in serum prolactin leading to side effects of amenorrhea- galactorrhea associated with a hyper estrogenic state. Discontinuation of Fluphenazine led to some improvement in serum prolactin levels with no clinical improvement in symptoms.

In order to counteract elevated Prolactin levels along with maintenance of remission of psychosis, we decided to start the patient on Aripiprazole. Secondary to its

blockade of 5 HT2 A receptors Aripiprazole can enhance Dopamine release by improving cognitive and affective symptoms. In addition partial agonism at D2 receptors can theoretically reduce the output of Prolactin and can resolve hyperprolactinemia. Finally, the blockade of 5 HT-2 C and 7 receptors can contribute to antidepressant actions as well. Aripiprazole was chosen over Quetiapine because the later blocks the D2 receptors which can theoretically increase Prolactin levels and potentially exacerbate the already existing hyperprolactinemia.

Initiation of Aripiprazole demonstrated marked improvement in serum prolactin levels secondary to its partial D2 agonism.⁶ A significant reduction in prolactin levels was noticed after addition of aripiprazole versus discontinuation of fluphenazine. Patient's galactorrhea improved significantly and a clinical improvement in psychosis was seen in addition to near-normalization of prolactin levels after addition of aripiprazole (Figure 1). Kinon *et al.* conducted a study wherein 402 patients, being treated with risperidone and other antipsychotics were monitored for a duration of at least three months.⁷ It demonstrated 90% of females (n=362) taking risperidone had hyperprolactinemia in contrast to occurrence of hyperprolactinemia in only 50% of patients (n=201) taking other atypical antipsychotics⁸; highlighting the importance of close monitoring of patients who are being treated with antipsychotics.

In an event of hyperprolactinemia induced by typical antipsychotics like Fluphenazine, we recommend reduction of the dose and eventual discontinuation of the offending drug. Switching to an alternative antipsychotic with least effect on Prolactin levels with periodic monitoring of prolactin levels should be considered. A high index of suspicion for prolactinoma should be maintained if prolactin levels remain unchanged despite the change in medications. There are no guidelines to determine a cut off level for MRI in patients with elevated prolactin level, however prolactinoma should be suspected in women with PRL levels more than 100 ng/ml and in men with levels more exceeding 50 ng/ml and MRI should be performed.⁹

Conclusion

Hereby, we present an interesting case of the use aripiprazole in a patient with fluphenazine-induced hyperprolactinemia. Aripiprazole significantly reduced hyperprolactinemia associated with the use of fluphenazine. A systematic approach should be enforced to thoroughly assess the hypothalamic-pituitary gonadal axis and determine the status of prolactin and thyroid hormones levels before starting patients on antipsychotic medications. The adverse effects associated with hyperprolactinemia should be seriously considered when choosing an antipsychotic for the patient. Conversely, Prolactinomas themselves are responsible for new onset psychiatric manifestations.¹⁰

There is need for more research to highlight the association between antipsychotic medications and its effect on prolactin levels. A high index of suspicion for prolactinoma should be maintained if prolactin levels remain unchanged despite the change in medication.

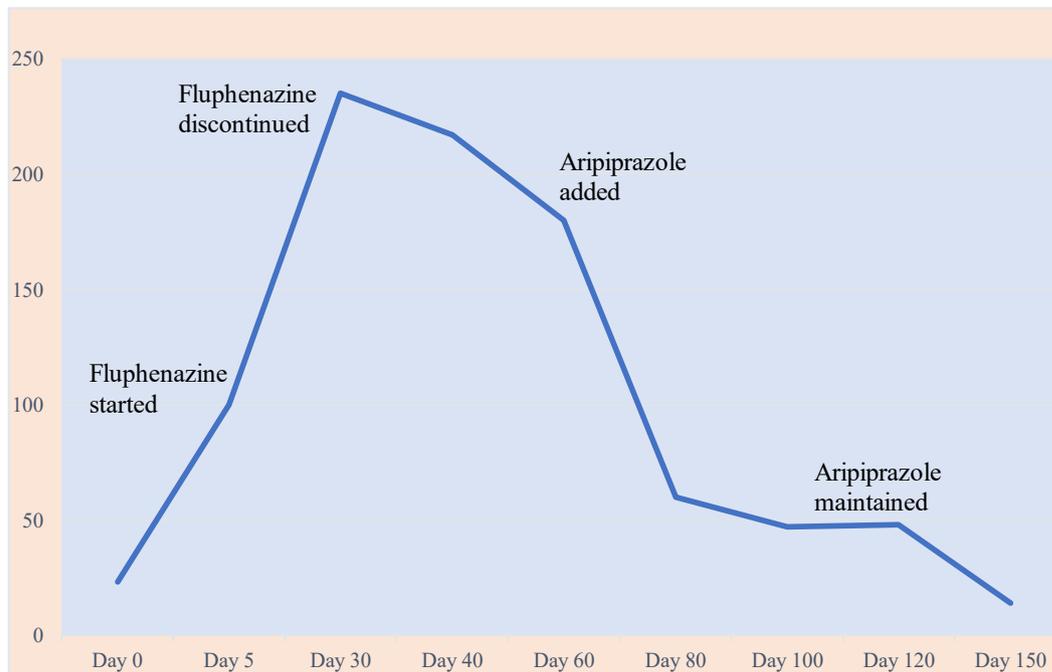


Figure 1: Effect of Aripiprazole on serum prolactin level

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