

Risperidone-Induced hyperprolactinemia in a Pre-menopausal Woman: A case report

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ABSTRACT

A common side effect of antipsychotic medications used to treat psychotic patients is hyperprolactinemia. Its occurrence leads to dysfunction of the reproductive, endocrine and metabolic systems. This side effect which may be symptomatic or asymptomatic, is commonly under reported and under treated and may result in poor compliance. We present the case of a 35year old patient treated for psychotic depression with atypical antipsychotics (Risperidone) and antidepressant (Amitrypyline), who presented with galactorrhea and amenorrhea which caused her to stop her medications and consequently, a resurgence of the primary illness. Hormonal assay showed elevated Prolactin level which reduced significantly with institution of dopamine receptor agonist Bromocriptine and a switch in medication to Aripiprazole. These are examples of treatment strategies suggested in literatures reviewed. We recommended that clinicians pay more attention to hyperprolactinemia as an important side effect seen in patients taking antipsychotics which may reduce compliance.

Key words: Hyperprolactinemia, Antipsychotic, Risperidone

INTRODUCTION

Antipsychotic medications are known to be associated with elevation of prolactin levels in the body. This abnormality leads to dysfunction of the reproductive, endocrine and metabolic systems.^{1,2}

Prolactin is a 199-amino acid polypeptide secreted from the lactotrophs in the anterior pituitary gland. Prolactin is controlled by both stimulatory and inhibitory factors. Its secretion is regulated mainly by hypothalamic hormones through the portal vessels. The regulation is a result of balance between stimulation mediated mainly via TSH and serotonin, and the inhibition by dopamine. Other neuropeptides such as oxytocin, vasoactive intestinal peptides and peptide histidine-methionine promote prolactin secretion and are under the control of the neurotransmitter, serotonin. The main physiologic prolactin inhibitory factor is dopamine and it acts by stimulating D2 receptors in the pituitary gland. It causes tonic suppression of prolactin secretion by the lactotrophs in the pituitary. Any blockage of

endogenous dopamine receptors and obstruction of dopamine transportation to the pituitary gland leads to increase secretion of prolactin.

Serotonin stimulates prolactin secretion from the pituitary and also controls the activity of other Prolactin releasing factors such as TSH, Oxytocin, Vasoactive intestinal peptides and peptide histidinemethionine. It also modulates dopamine and its endogenous secretion inhibits dopamine activity. The blockage of 5HT_{2A} serotonin receptor causes an increase in dopamine concentration.^{2,4}

Elevated prolactin secretion disturbs the pulsatile secretion of GnRH and production of FSH and LH. The main function of prolactin in the body is to assist in the development and maturation of the breast during pregnancy and in production of milk during lactation. The increase in prolactin levels that is seen with antipsychotic drugs is commoner with the typical than the atypical antipsychotics. Amongst the atypical antipsychotic drugs, this increase is commoner with risperidone and paliperidone.^{1,2}

The difference seen between typical (First Generation Antipsychotics, FGAs) and atypical (Second Generation Antipsychotics, SGAs) antipsychotic drugs lies in the differential binding properties of each drug to the pituitary D₂ receptors and also the serotonin blockade.⁵ Typical antipsychotics like haloperidol, act by blocking dopamine D2 in a non-selective manner and this blockage causes a reduction in dopaminergic inhibition, which results ultimately in an increased prolactin production. Atypical antipsychotics, on the other hand, have in addition to their potent serotonin 5HT₂ antagonism, a lower D2 affinity so, they cause a lower and transient elevation of prolactin.⁵ Risperidone is an atypical antipsychotic that has more pronounced serotonin antagonism compared to dopamine antagonism. However, it has a high affinity for D2 receptor that blocks in the tubero-infundibular system and as such produce a rise in prolactin.

Hyperprolactinemia is clinically defined as a plasma prolactin level of > 20ng/ml for men and >25ng/ml for women.^{3,6} The elevation of prolactin levels as a result of the antipsychotic use may be as high as 10 or more times pretreatment levels.⁷ The elevated prolactin levels may be symptomatic or asymptomatic in both males and females.^{7,8} Hyperprolactinemia is also reported to develop more frequently in females and younger patients and the risk

increases with higher dosages.^{8,9}

High prolactin level in the body has short and long-term effects. The short-term effects may include menstrual irregularities, galactorrhea, sexual dysfunction and gynaecomastia. The long-term effects include infertility, weight gain, mood changes, reduced bone density leading to osteoporosis, endometrial cancer and breast cancer.^{1,4,5,7,10} Patients often fail to bring up issues relating to these side effects unless they are asked by clinicians who often fail to ask questions about some of the symptoms^{11,12}

It has been reported that about 42%-93% of premenopausal women and about 18%-72% of men taking antipsychotics have hyperprolactinemia.¹² These figures represent the incidence in other climes and to the best of our knowledge and despite extensive searches, there had not been any report of these consequences of hyperprolactinemia with antipsychotic drug use in our environment.

We present the case of symptomatic hyperprolactinemia following use of risperidone in a young woman of childbearing age and the treatment options she was offered. We also reviewed existing literatures on elevated prolactin levels as a consequence of antipsychotic medication and treatment strategies. The case highlights the importance of clinicians taking time to ask, investigate and monitor side effects of medications that may influence compliance with treatment. This is particularly important in low- and middle-income countries where treatment is often out of pocket and clinicians need to tailor management to fit into patients' needs.

Case summary

The patient was a 35yr old, married woman with four children (all alive) who presented about two and a half years prior to presentation with complaints of undue sadness, decreased energy, loss of interest in formerly pleasurable activities, recurrent suicidal thoughts of six weeks duration, as well as hearing voices of unseen people in clear consciousness, seeing things not seen by others in clear consciousness, poor sleep and poor appetite of four weeks duration. This was her second documented episode of mental illness occurring at 9months puerperium and her first contact with orthodox medicine having, previously been treated by a traditional healer. The psychosocial stressors included her then recent relocation from the northern part of the country, unemployment, inability of the husband who is the main caregiver to receive salaries owed him and poor housing.

A diagnosis of severe depressive episode with psychosis was made. The following investigations were done and all were within normal limits--FBC, FBS, Electrolytes, Urea and Creatinine, and ECG (eletrocardiography). The patient was placed on

- i) Tabs Amitryptiline 25mg mane and 50mg nocte
- ii) Tabs Risperidone 2mg nocte.

The Risperidone dose was increased to 1mg mane, 2mg nocte because of complaints of persistence of the psychotic symptoms. The dosages of Amitryptiline and Risperidone were later reduced to 50 mg nocte and 2mg nocte respectively at about eight weeks into treatment, when she became clinically stable.

At about 6 months into treatment with the aforementioned drugs, the patient complained of weight gain for which she received dietary advice and was encouraged to increase physical activities. At about 10 months into treatment, she noticed milky secretions from both breasts even though she

had long stopped breastfeeding. The possibility of drug side effect was discussed and Risperidone was further reduced to 1mg nocte. She stopped using her medication because of these side effects of medication which also included cessation of her menses since last childbirth. She was made to believe that her weight gain was related to her inability to washout impurities from her body with regular menses by a spiritualist.

Patient had a relapse of depressive illness about 9 months after stopping her medications characterized by symptoms similar to previous episode; she was re-commenced on her former medications (Risperidone 2mg, and Amitryptiline 50mg nocte) and was treated on in-patient basis. In the 3rd week of admission, the patient's clinical state had improved but she started complaining of milky secretion from both breasts which was persistent and moderate in quantity. She was also still amenorrhagic despite a negative pregnancy test. A serum prolactin assay done showed elevated Prolactin level of 150ng/ml (about 7 times of normal). This prompted request for further investigations which included a repeat serum Prolactin assay, Fasting Blood Sugar (FBS), Fasting Lipid Profile (FLP), Thyroid function tests, Luteinizing Hormone Assay (LH), Follicle Stimulating Hormone Assay (FSH), Serum Calcium, Breast Ultrasound as well as a Magnetic Resonance Imaging (MRI). This was necessary to rule out other causes of hyperprolactinemia such as hypothyroidism, pituitary tumour and kidney diseases.

Breast ultrasound showed no abnormal findings. Lutenizing Hormones, Follicular Stimulating Hormone, Oestrogen, Serum Calcium and Fasting Blood Sugar were all within normal limits. The Fasting Lipid Profile showed mild hypercholesterolemia. The patient was placed on tabs Bromocriptine which was gradually increased to 2.0mg b.d. The repeat Prolactin done following three weeks treatment on Bromocriptine showed a significant reduction in Prolactin level to 73.2ng/ml but patient complained of re-emergence of auditory hallucination and insomnia. At this point, a decision was taken to change her antipsychotic medication to a Prolactin-sparing one given that Bromocriptine, a dopamine agonist, can only suppress Prolactin production but does not cure the hyperprolactinemia and its continued usage can worsen patient psychosis. Aripipazole was the alternative atypical antipsychotic chosen because of the patient's weight, socioeconomic status and drug availability. The patient and primary caregiver were counseled appropriately with a view to continue to monitor the decline in Prolactin levels and the clinical status of patient.

Patient has remained clinically stable. Her menses returned two weeks after discontinuation of Risperidone and commencement of Aripipazole. Prolactin level at three weeks after stoppage of Risperidone was 12.7ng/ml, which was within normal limit.

DISCUSSION

This case demonstrates the clinical relationship between use of Risperidone and symptomatic hyperprolactinemia. The Prolactin level rose significantly above normal but reduced significantly with use of adjuvant dopamine agonist, Bromocriptine and a switch to Prolactin-sparing antipsychotic medication Aripipazole. Although, Risperidone is an atypical antipsychotic with less extrapyramidal side effects (EPS) compared to the FGAs, it is known to be associated with symptomatic prolactinemia.¹³

Studies have found that a higher percentage of women on Risperidone developed hyperprolactinemia compared to those taking conventional FGAs.^{3,4} The elevation with Risperidone was dose dependent. The elevation associated with Risperidone was also higher in females than males^{3,4}. Risperidone is a monoaminergic antagonist that has a high affinity for D2 receptors as well as 5HT_{2A}, 5HT₇, H₁, 5HT_{2D}, alpha 1 and alpha2 receptors. Its poor blood-brain barrier penetration allows it to bind longer and heavier with D2 receptors in the pituitary glands rather than the striatum.^{3,14,15} It is believed that 9-Hydroxyl-risperidone, a metabolite of Risperidone that contributes significantly to its therapeutic effect may also contribute to the elevation of Prolactin seen with use of Risperidone. The 9-Hydroxy risperidone has a high D2 affinity and a longer half-life than Risperidone, accounting for the symptomatic effects of elevated Prolactin seen with use of Risperidone.^{4,12,15,16} Prolactin levels are elevated within a few hours after initiation and may persist for long even after cessation of therapy.³ Studies have shown that about 72-100% of females on oral Risperidone and about 53-67% on long acting depot injection developed hyperprolactinemia.^{12,16} Some of the side effects of Risperidone are due to direct Prolactin effect on the target organs while others are due to hypogonadism as a result of disruption of normal functioning of the hypothalamic-pituitary-gonadal axis and subsequent inhibition of normal pulsatile secretion of GnRH leading to reduction in LH and FSH secretions. Reduction in the LH and FSH may cause a decrease in Oestrogen and Progesterone secretion leading to menstrual irregularities, amenorrhea and galactorrhea,^{3,17,18} all of which were seen in our patient. In the case of our patient, it was not possible to ascertain if the normal estrogen level found was a result of the recent reduction in Prolactin levels with use of Bromocriptine as we did not have a pre-Bromocriptine use level of gonadotrophic hormones to make any comparisons. Strategies recommended for dealing with hyperprolactinemia include; reduction of antipsychotic dosage, administration of adjunctive dopamine agonists such as Amantadine, Bromocriptine or sex steroids, or the discontinuation of current treatment with a switch to a Prolactin sparing second-generation antipsychotic such as Olanzapine, Quetiapine or Clozapine.^{1,19-21} In our patient, the administration of Bromocriptine reduced the Prolactin level but led to a worsening of symptoms. A switch to other Prolactin-sparing drugs like Olanzapine, Quetiapine and Clozapine was not considered in this patient because the use of Olanzapine, in particular, had a potential of further increasing the weight gain and of causing diabetes. Quetiapine and Clozapine were not readily available and affordable, and the use of Clozapine meant more financial burden would be incurred from the investigations to monitor risk of agranulocytosis. Aripipazole has been found to be safe and well tolerated in people with prior antipsychotic exposure. It has an agonist/ antagonist activity which enables the dissociation of the receptor and help normalize dopamine function in striatum.² Aripipazoles is a potent partial dopamine D2 and serotonin 5HT_{1A} agonist, and a serotonin 5HT_{2A} antagonistic. Under hyperdopaminergic conditions, it is a dopamine D2 antagonist and under hypodopaminergic conditions, it exhibits agonistic properties leading to decrease Prolactin levels.^{20,22} Another explanation for the suitability of Aripipazole in patients previously exposed to potent dopamine antagonist for long period is that Aripipazole binds to the remaining free supersensitive

dopamine receptors thus stabilizing dopamine response and decreased Prolactin secretion.²² Marrag et al in their study, found a prevalence of 23.9 % hyperprolactinemia with atypical antipsychotics which included Amisulpride (13%), risperidone (5.4%), Clozapine (1.1%) and no case with use of Aripipazole.²

The index patient had a score of 5 on the Naranjo scale²³ and this made the likelihood of development of hyperprolactinemia secondary to Risperidone probable. On the Naranjo scale, a probable prediction means that the reaction followed a reasonable temporal sequence after the administration of the drug. It followed a recognized response to the suspected drug which was confirmed by withdrawal but not exposure to the drug. Also, it could not be reasonably explained by the known characteristic of the patient's clinical state and the laboratory findings confirmed this. As seen in this patient, women of reproductive age, particularly parous ones appear to be at higher risk of Risperidone induced hyperprolactinemia than postpartum women.^{7,24} There is no consensus, however, as to whether to screen and follow up the Prolactin levels in patients on antipsychotics.¹⁰ The Psychiatric Association of Turkey Schizophrenic Treatment Guidelines however recommend checking baseline Prolactin level of all patients and to repeat after 3months in those who have no signs of hyperprolactinemia in follow ups but use Risperidone or Paliperidone or Amisulpride or typical antipsychotics. Also, in moderate elevation in Prolactin level, the recommendation is to question symptom progression and effects and to repeat Prolactin test every 6months. Lastly, in case of a significant elevation in Prolactin level, the recommendation is to either change medications or to treat hypogonadism.¹⁰ However, the Pituitary Society recommends the retesting of Prolactin levels after 72hrs of temporarily stopping antipsychotics to ascertain if elevation is related to the medication or otherwise. This is however not possible in some cases because of patient's clinical state.¹⁹ When assessing women with hyperprolactinemia, especially if uncertain of its etiology, it is important to carefully take proper history of drugs and clinical state of patient, do a detailed physical examination and detailed laboratory workup.^{3,7,10} Investigations to do should include MRI or contrast CT which would show presence of pathology in the hypothalamus-pituitary region, blood tests, renal, hepatic, thyroid function tests as well as sexual hormonal assays.^{3,7}

Although it is recognized that hyperprolactinemia is a common side effect of antipsychotic medication which occurs in both women and men, it is still widely under recognized and under treated.^{3,11} This maybe particularly true in environments like ours where treatment is often out of pocket, where patients may not divulge information on side effects because they were not asked and where physicians may be constrained to limit investigations done to those they count very essential. We found no existing literature on this important side effect of antipsychotic medication in Nigeria in our search for information regarding this despite the multitude of literatures in other climes.

We therefore recommend taking baseline history of menstrual, sexual function, and pretreatment Prolactin level, and asking about potential side effects of antipsychotic medications at interval during treatment to allow for proper monitoring of side effects like hyperprolactinemia, especially with high risk drugs like Risperidone. This also decreases the need to do other

unnecessary workup to rule out other possible causes as the temporal relationship with such drug use is clearly established. It allows one to institute patient specific treatment once this is confirmed because symptoms may have profound negative health outcomes and may lead to non-compliance in patients.^{4,18}

Attending psychiatrists should therefore have a higher index of suspicion in female premenopausal patients who present with stoppage or reduction in menstrual flow with antipsychotic use and/or galactorrhea as well as male patients who present with gynaecomastia. This will further help in early detection of hyperprolactinemia as well prompt institution of appropriate treatment in order to prevent further complications and improve the quality of life of the patients.

Conflict of interests:

There are no conflicts of interest connected to writing this paper.

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We declare that we have not received any financial inducement while preparing or writing this paper.

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