



Risperidone Induced Hyperprolactinemia: A Clinical Case Series

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Abstract

Prolactin is a polypeptide hormone (198 amino acid) with molecular weight 23 kDa produced by the lactotrophs of the anterior pituitary under the feedback control of hypothalamus in a diurnal rhythm, highest levels in the night and early morning. Other sites of its production where it acts as paracrine hormones are mammary gland, uterus, prostate, immune cells, placenta and endothelium [1,2]. Its secretion increases in conditions such as sleep, psychological stress, food intake, pregnancy, newborn infants, chest wall stimulation, and trauma [3]. Prolactin plays an important role in the process of reproduction in men and women. Thyrotropin releasing hormone, vasoactive intestinal neuropeptide, opioids, and serotonin [5-hydroxytryptamine (5-HT)] can increase prolactin levels while dopamine can decrease prolactin levels [4,5]. Hyperprolactinemia is clinically defined as a plasma prolactin level of >20ng/mL for men and >25ng/mL for women [5]. Elevated prolactin in men may cause erectile dysfunction, ejaculatory dysfunction, gynecomastia, and decreased libido. In female subjects, abnormally high prolactin levels may cause menstrual disturbances, galactorrhea, gynecomastia, and sexual dysfunction chronic hyperprolactinemia increases risk for osteoporosis, cardiovascular disease, and breast cancer [6]. Neuroleptics such as Fluphenazine, thiothixene, perphenazine, chlorpromazine and thioridazine have been shown to cause hyperprolactinemia by blocking D2 receptor in the brain. Risperidone, however, is a widely used atypical agent that has shown more pronounced and continuous elevations in prolactin levels due to a stronger, more prolonged dopamine receptor blockade [7]. It is used in a variety of psychiatric disorders such as schizophrenia, acute mania, anxiety disorder, delusional disorder, bipolar mood disorder irritability associated with autism. (shriviastva). Hereby we describe five cases of risperidone induced hyperprolactinemia in age range of 20 years to 35 years old with Risperidone.

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Case Report

Case 1

On 02 September 2015, 19-year-old female was admitted to the psychiatry ward with complains of sadness of mood, giddiness, tensed mood, unnecessary fear and suspicion, irrelevant talking, nocturnal awakening and decreased appetite since 2 months. Patient was not having any significant past psychiatric history. She was diagnosed of Major Depressive Disorder with psychotic symptoms. Laboratory Investigations were normal. Urine examination was normal. Following treatment was started: Cap. Fluoxetine 20 mg/day, Tab. Risperidone 2 mg/day, Tab. Benzhexol 2 mg/day, Tab. Diazepam 10 mg/day, Tab. Fa/BC 200 mg/day, Injection. Phenergan 25 mg/ml intramuscularly once on day of admission. With improvement of symptoms patient was discharged on 8th day. On monthly follow-up, patient presented with symptoms of lack of emotions, irritability, sadness of mood, so dose of Tab. Risperidone was increased to 3mg/day on and rest all treatment was continued same as before. On next follow-up visit, Patient had come with complains of milk discharge from both the breast and feeling heaviness in breast and amenorrhoea. Pregnancy test was negative. Past menstrual history was normal. CT and MRI reports were normal without any abnormalities in pituitary or hypothalamus. Other causes galactorrhea was also ruled out. Serum Prolactin level was found to be elevated (200 ng/ml). So suspected drug Tab. Risperidone was withdrawn and was replaced by Tab. Aripiprazole 10 mg/day. Rest treatment was continued same as before. Upon discontinuation of Risperidone, the prolactin level dropped to (16.0 ng/ml) within 2 months. Repeated prolactin levels continued to be normal during treatment.

Case 2

On 29 July 2016, a 27-year-old female was admitted to the psychiatry ward with the complains of runs away from home, wandering, irrelevant talking, aggressive behaviour, suicidal ideas, sleep

Table 1:

Case	S. Prolactin level (ng/ml)	Duration of onset of Hyperprolactinemia after initiation of treatment (Days)	Duration of normalisation of S. Prolactin after dechallenge (Days)
R, 19 yr old female	200 ng/ml	79 days	60 days
R, 27 yr. old female	178.86 ng/ml	39 days	13 days
T, 23 yr. old female	57.50 ng/ml	127 days	22 days
H, 27 yr. old female	80.45 ng/ml	147 days	14 days
A, 30 yr. old female	55.99 ng/ml	67 days	08 days

disturbance and self-harming behaviour since month. Her laboratory investigations were normal. She was diagnosed with border line personality disorder with psychotic symptoms and following treatment was started: Tab. Lithium 900 mg/day, Tab. Risperidone 4 mg/day, Tab. Lorazepam 1 mg/day, Tab. Clonazepam 0.5 mg/day and Inj. HPI+Inj. Phenargan 1 amp (25 mg/ml) intramuscularly was given. Patient was discharged on 7th day. Patient use to come for regular follow-up every 15 days and was improving with treatment. Suddenly on 39th day patient come with complains of milk discharge from both the breast and also of oligo-menorrhoea. Her serum prolactin level was done and it was (178.86 ng/mL) (normal level 2.8 ng/mL to 29.2 ng/mL). Past menstrual history was normal no irregularities. Pregnancy test was negative. CT and MRI findings were normal. Therefore, dose of the suspected drug Risperidone was tapered to 3 mg/day and another drug Ziprasidone 20 mg/day was added as antipsychotic and for prevention of extrapyramidal side effects. 15 days after drug withdrawal, patient come to outpatient department with milk secretion still present sometimes from breast (once in 2-3 days). Again S. Prolactin was repeated and it was found to be (94.0 ng/ml). The suspected drug was completely withdrawn and dose of Ziprasidone was increased up to 40 mg/day. Rest all treatment was continued same as before. After 13 days of discontinuation of drug, discharge was completely stopped. Rest all continued same as previously and rechallenge was never attempted.

Case 3

On 29 March 2014, A 23-year-old female, was admitted to the psychiatry female ward with complains of harassing her relative, abusing others, talking of sadhu, repeat sentences much often talkativeness, slurring of speech, suspicious, frequent hair combing 20 times/day. She was diagnosed of Psychotic disorder with obsessive compulsive disorder. The following treatment was started: Tab. Sodium Valproate 800 mg/day, Tab. Risperidone 4 mg/day, Tab. Benzhexol 4 mg/day, Tab. Diazepam 5 mg/day, Tab. Lorazepam 2 mg/day and Tab. MVBC 5 mg/day. Patient was improving with treatment and was on regular monthly follow-up without complains. On 8th follow-up visit, patient complained of sadness of mood, decrease speech, gets inside room, reports that all laughs on her and suspicious. So Tab. Haloperidol 15 mg/day, Tab. Olanzapine 15 mg/day and Tab. Fluoxetine 20 mg/day was given in addition to previous treatment. On 9th follow-up visit, Patient came with symptoms of excessive worrying about mother, suspicious in nature and complains of excessive salivation, weight gain (6 kg) in 3 months, so the dose of suspected drug Haloperidol was decreased to 10 mg/day and dose of Tab. Benzhexol was increased to 6 mg/day. And rest all treatment was continued same as previous treatment. On 11th follow-up visit, Patient came with complains of milk discharge from breast and dysmenorrhoea. Pregnancy test was negative. CT and MRI findings were normal. Serum Prolactin level was done and it was 57.50 ng/ml (higher). The suspected drug Risperidone and Tab. Haloperidol was omitted and Tab. Escitalopram 20 mg/day and Tab. Aripiprazole

15 mg/day was added to the previous treatment rest were continued as above. Finally, on discontinuation the secretion was stopped. Rechallenge was not attempted.

Case 4

On 29 June 2016, A 27-year-old female presented to a female psychiatry department with the symptoms of self-muttering, use of foul language, decrease sleep and appetite, poor self-care, suicidal tendency, hearing of voices at night irrelevant talking, suspiciousness, does not like anything, lethargic since four months. Patient had past history of such episode and was given Tab. Olanzapine 5 mg/day, Tab. Fluphenazine 1 mg/day. Patient had history of five electro convulsive therapy under short general anaesthesia. She was diagnosed with Depression with psychotic symptoms and was treated with Tab. Risperidone 4 mg/day, Tab. Benzhexol 2 mg/day, Tab. Lorazepam 2 mg/day, Tab. MVBC 200 mg/day, Cap. Omeprazole 40 mg/day. Laboratory parameters were normal. Serum Prolactin level was: 7.3 ng/ml (Normal). Patient was discharged on 6th day. Patient used to come for regular monthly follow-up. On 1st follow-up, Patient presented with complains of giddiness, not able to do work, does not like to talk and generalised weakness, irritable mood. Since psychotic symptoms was aggravated dose of Tab. Risperidone was escalated to 6 mg/day and for prophylaxis of extrapyramidal symptoms dose of Benzhexol was also increased 4 mg/day. Rest all treatment was continued as before. On 5th follow-up visit, Patient presented with complains of milk secretion from both breast and with symptoms of irritability of mood and decrease in sleep, Patient had complained of secretion of breast since 3 days of presentation. Pregnancy test was negative. CT and MRI findings were normal without any pituitary abnormalities. Tab. Risperidone was withdrawn and Tab. Escitalopram 10 mg/day was added and rest all treatment was continued as before. 15 days after 6th follow-up visit, due to aggravation of symptoms such as mood fluctuation, irritability, self-harming behaviour, uncontrollable nature patient went to private PHC hospital for treatment in village (Talaja) and was prescribed again with Tab. Risperidone 2 mg/day, Tab. Escitalopram 5 mg/day, Tab. Diazepam. 5 mg/day, Tab. MVBC 5 mg/day. 15 days after that, Patient again come to psychiatry outpatient department with milk secretion from both the breast. On revealing papers and medications prescribed by private practioner, it was revealed that patient was again expose to Tab. Risperidone. Unfortunately, S. Prolactin was not done due to patient inconvenience. The suspected drug Tab. Risperidone was immediately stopped and dose of Escitalopram was increased and Tab. Aripiprazole 10 mg/day was added. Rest all was continued same as before. Pregnancy test was ruled out. CT and MRI findings were normal. S. Prolactin level was done and it was increased 80.45 ng/ml. Suspected drug Tab. Risperidone was stopped and it was substituted by Tab. Aripiprazole 10 mg/day, rest all treatment was continued same as before. Within 14 days of discontinuation of drug the prolactin level dropped to 16.0 ng/ml. Repeated prolactin levels continued to be normal during treatment. In this patient

both dechallenge and rechallenge was positive. Rechallenge was unintentional by some private medical practitioner.

Case 5

On 19 April 2016, 20-year-old overweight (75 kg) female patient presented to psychiatry department with complains of increased talkativeness, decrease need of sleep, wear new clothes, excessive demanding, abusing, increased appetite, crying spells, excessive happy, excessive laughing, increased religious talking. Patient was asymptomatic 2 months back. She was diagnosed with bipolar mood disorder with maniac episode on day of examination. Patient had no past history of psychiatric illness. Patient's mother was having psychiatric illness and was on treatment. Patient was married and symptoms appear after 1 month of marriage. Patient was treated with Tab. Lithium 900 mg/day, Tab. Risperidone 4 mg/day, Tab. Benzhexol 2 mg/day, Tab. Lorazepam 1 mg/day. On 27 June 2016, on regular monthly follow-up patient presented in outpatient department with complains of secretion from both breast and oligo-menorrhoea. S. Prolactin level as done it was 55.99 ng/ml. Pregnancy test was negative. CT and MRI were normal. Other causes of galactorrhea were ruled out. Within 8 days of discontinuation of drug secretion subsided.

Causality Assessment: All the 5 cases show strong temporal association of hyperprolactinemia with the Risperidone as Serum prolactin in all patients were increased after drug intake and got normalised on withdrawal of the drug. Based on WHO's causality assessment scales all Case-1,2,3,5 were categorized as probable and case-4 was categorized as certain (Table 1). All the cases were mild in severity and definitely preventable as per modified Hart wig and Siegel severity scale and modified Schumock and Thornton scale respectively.

Discussion

Risperidone is a commonly used second generation antipsychotic agent for the treatment of schizophrenia, manic or mixed episodes of bipolar I disorder, psychotic disorders [8]. It is an atypical antipsychotic having D2, 5 HT-2, H1, and alpha adrenergic blocking and weak antimuscarinic action. The main mechanism of Risperidone causing hyperprolactinemia is as follows: Main signal of prolactin secretion is exerted by the inhibiting action of dopamine. Dopamine is secreted in hypothalamic periventricular zone (periventricular nucleus and arcuate nucleus) and released from neuronal projections in the median eminence and reaches the anterior pituitary gland through portal vessels (system known as "Tuber Infundibular Dopamine Pathway" or "TIDA"). The dopamine-mediated inhibition of prolactin secretion of Risperidone occurs through the binding of D2 receptors on the membrane of lactotrophs cells and involves several signal transduction systems, resulting in inhibition of prolactin gene transcription, reduction of prolactin synthesis and release [9]. Also, Risperidone has tight binding properties with D2 receptor as compared with other antipsychotics, which suggests it higher incidence of causing hyperprolactinemia. Also, Risperidone causes dose dependence rise in prolactin level, dose that produces 27% occupancy of D2 receptors causes significant rise in prolactin levels while for haloperidol it requires 80% of receptor occupancy [10]. It is known that Fluoxetine increases concentration of Risperidone by 2.5 fold. Fluoxetine is an SSRI. Serotonin is known to have increase in prolactin level as it is an indirect mediator of prolactin secretion. Serotonergic neurons project from dorsal raphe

nucleus to Paraventricular nucleus of hypothalamus and modulates its effects through 5HT1A and 5HT2 receptors containing different neurosecretory cells such as producing oxytocin, vasopressin, Vasoactive Intestinal Peptide (VIP), Thyrotropin Releasing Hormone (TRH) and other neuropeptides. VIP exerts its effects through lactotrophs cell receptors binding, increasing adenylate cyclase activity and increasing prolactin gene transcription. It is known that serotonin affects prolactin levels through the action of one or more of these PRFs, among which VIP pathway is the best studied. Hence, this can aggravate the prolactin level more in case 1 and case3 [11]. Also all the patients were in age group of 20 years to 30 years, and it is proven that dopamine secretion is maximum in adolescent and decreases with age. Hence risperidone has greater blocking action in adolescent and younger adults [12]. Risperidone is also associated with increase in noradrenaline level which is also responsible for increasing prolactin level.

Hyperprolactinemia can lead to following consequences if not treated timely:

1) **Breast cancer:** Prolactin accelerates the process of carcinogenesis by stimulation of rate of DNA synthesis and increasing cell division, as there is increase in synthesis and expression of prolactin receptors in malignant breast cells. roles of prolactin in the development of mammary tumours is to create mammary gland conditions favourable for the action of carcinogens through its stimulation of the rate of mammary gland DNA synthesis, a measure of the frequency of mammary gland cell proliferation and survival, increasing cell motility and tumour vasculoneogenesis [13,14].

2) **Hypogonadism:** Prolactin receptors are present in kiss 1 neuron located in Hypothalamic arcuate and anteroventral periventricular nuclei. Hyperprolactinemia causes decreased expression of kisspeptin in kiss1 neuron. Suppression of kisspeptin causes decreases GnRH release and results in an ovulatory GnRH surge. Decrease in GnRH causes decreases in LH and FSH secretion resulting in oligomenorrhoea, amenorrhoea, infertility due to anovulatory cycles, hypogonadism. This leads to reduced pituitary gonadotropin (LH and FSH) secretion and loss of ovarian stimulation, which results in hypogonadism, infertility, and amenorrhea [15].

3) **Metabolic disorders:** Hyperprolactinemia also results in carbohydrate and lipid metabolism [16]. Reduced glucose tolerance and hyperinsulinemia have been demonstrated in patients with hyperprolactinemia [17,18]. The simple calculated measure of TG/HDL ratio has been identified as a predictor of insulin resistance and cardiovascular disease, and may also be a useful marker of atherogenic lipoprotein profile, enabling clinicians to identify patients who may be at higher risk of metabolic disturbances [19]. Women show increased sensitivity of the lactotrophs to antipsychotic -induced prolactin stimulation compared with men. For the same dose of antipsychotic, women produce more prolactin than men and it's a dose -dependent response.

4) **Endometrial cancer:** Hyperprolactinemia is associated with the an ovulatory cycles due to inhibition of FSH and LH and chronic an ovulatory cycles prone to the development of endometrial carcinoma [20].

Risperidone may induce extrapyramidal side effects, akathisia and tremors, associated with diminished dopaminergic activity in the striatum.

Conclusion

Although galactorrhea, as a direct consequence of hyperprolactinemia caused by risperidone has mainly been researched with higher doses of this atypical antipsychotic, we have to keep in mind that lower doses could also cause serious adverse events.

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