RESEARCH ARTICLE

Assessment of prevalence of hyperprolactinemia in patients taking antipsychotic drugs in a tertiary care hospital in eastern India

Suhena Sarkar¹, Birupaksha Biswas², Soutrik Roy³, Agnidipa Sanyamath¹, Soumika Biswas⁴, Manab Nandy¹

¹Department of Pharmacology, Medical College and Hospital, Kolkata, West Bengal, India, ²Department of Pathology, Burdwan Medical College and Hospital, Burdwan, West Bengal, India, ³Department of Biochemistry, North Bengal Medical College and Hospital, Siliguri, West Bengal, India, ⁴Department of Biochemistry, Medical College and Hospital, Kolkata, West Bengal, India

Corresponding: Soumika Biswas, E-mail: soumikabiswas0292@gmail.com

Received: March 19, 2024; Accepted: April 16, 2024

ABSTRACT

Background: Researches done over different parts of the world show that hyperprolactinemia in psychotic patients is dependent on many factors such as age, gender, any thyroidal abnormality, drugs such as antipsychotics or antidepressants, psychological stress, and genre of psychosis. In patients taking antipsychotic treatments, prolactin blood levels may rise up to 10 times the normal values. It is very important to differentiate between prolactin-secreting tumor in pituitary and antipsychotic-induced hyperprolactinemia. There has been fewer researches on this topic in Eastern India, so it aims to properly estimate the amount of prolactin rise; a patient has to face after taking anti-psychotic medications and might also help the psychiatrists to adjust the dosage of anti-psychotics or to add some other drugs to lower the prolactin level along with the anti-psychotics in Eastern India.

Aim and Objectives: The aims and objectives of the study are to estimate serum prolactin in diagnosed psychiatric patients taking antipsychotic drugs for at least 3 months and to study the difference in serum prolactin between recently diagnosed psychiatric patients taking antipsychotic drugs for at least 3 months and age and gender-matched mentally healthy patients without any psychiatric complication and without any history of in taking antipsychotic drugs. Materials and Methods: The study was conducted over a period of 4 months at Central Laboratory, Dept of Biochemistry, MCK. Before the conduct of the study, informed consent was taken. Patients diagnosed with psychiatric illness and consuming at least one antipsychotic drug for at least 3 months were enrolled after going through inclusion–exclusion criteria. Serum prolactin was measured with help of CLIA (ADVIA CENTAUR). Results: As per our study done in Eastern Indian population, in the female group of psychiatric patients (aged between 18 and 45 years) taking antipsychotics, the prolactin level was 23.6 ± 4.5 ng/ml, and in age-matched control female group, prolactin level was 9.2 ± 3.1 ng/mL, the difference is statistically significant (P < 0.001). Moreover, in male psychiatric patients (aged between 18 and 45 years) taking antipsychotics, the prolactin level was 14.3 ± 1.7 ng/ml, and in age-matched control male group, prolactin level was 8.5 ± 1.5 ng/mL, the difference is statistically significant (P < 0.001).

Conclusion: As per our study, psychiatric patients of both gender taking antipsychotic drugs had higher serum prolactin level than age and gender-matched mentally healthy persons not taking antipsychotic drugs. While the limitation of this study was its small sample size, another issue that must be taken into consideration is the fact that prolactin levels can also depend on menstrual cycles in women. In our study, there were 40 (57%) females who were still menstruating.

KEY WORDS: Psychiatric Patients; Antipsychotic Drugs; Prolactin

INTRODUCTION

Pituitary gland secretes prolactin under the influence of hypothalamus by dopamine (i.e., prolactin inhibiting factor) and thyrotropin-releasing hormone, which act as release factor. Some factors resulting in increased serum prolactin levels are physiologic such as stress, sleep, pregnancy, and lactation.
Moreover, the pathologic conditions behind hyperprolactinemia are some brain and systemic diseases. Researches done over different parts of the world show that hyperprolactinemia in psychotic patients is dependent on many factors such as age, gender, drugs like antipsychotics or antidepressants, psychological stress, and genre of psychosis. In patients taking antipsychotic treatments, prolactin blood levels may rise up to 10 times the normal values. It is very important to differentiate between prolactin-secreting tumor in pituitary and antipsychotic-induced hyperprolactinemia, and a simple proven rule is that prolactin levels over 250 ng/mL are generally indicative of prolactinomas, while drug-induced hyperprolactinemia seldom exceeds 100 ng/mL. Researches done in recent past in Spain mainly highlighting on antipsychotic drug-induced hyperprolactinemia suggest that whenever prolactin levels are over 50 ng/mL with/without clinical symptoms the researchers needed to adjust the dosage of antipsychotic medication (e.g., lowering doses, changing the drugs, concurrent use of aripiprazole, which reduces prolactin level). If there is severe hyperprolactinemia (over 100 ng/mL) and even there is an absence of clinical symptoms, drugs lowering prolactin level should must be added because of the medium and long-term risk of osteoporosis, cardiovascular complications, and possible increase in breast or endometrial cancer. Dopamine D2 receptor occupancy by antipsychotics determines the clinical response and hyperprolactinemia, both becoming prominent when D2 receptor occupancy exceeds 65%, and 72% respectively. However, researches proved that the amount of serum prolactin elevation correlates with clinical response. By contrast, Eberhard and collaborators found no significant correlations between prolactin levels and positive or negative symptoms in schizophrenia as per their research un-medicated women with schizophrenia appear to have lower mean daily prolactin levels than healthy controls. Remitted patients, who relapse, show lower neuroleptic and prolactin serum levels before the relapse episodes than before the stable periods. Thus, prolactin levels may reveal the pathogenic process (the psychosis-related hyperdopaminergic state) and, in patients receiving treatment, the antipsychotic biological activity. The response to treatment depends on several factors such as patient and family characteristics (plasma dopamine metabolite homovanillic acid) and changes in ventricle volume. Researchers showed that patients in remission receiving antipsychotic treatment have a normal hypothalamic-pituitary-adrenal (HPA) axis function, while newly diagnosed psychosis patients have an activated HPA axis along with a larger pituitary. Conversely, a smaller pituitary volume was found in treated patients with chronic schizophrenia, which may be due to repeated episodes of HPA axis hyperactivity. However, it is also postulated that smaller pituitary volumes found in patients with schizophrenia may be the consequence of neurodevelopmental impairment. Chronic schizophrenia is associated with low dopamine activity. Some researches also show that the decreased prolactin response to antipsychotics can be due to tolerance of the dopamine receptors. This hospital-based, cross-sectional, non-interventional Eastern Indian population-based study aims to investigate the amount of prolactin rise to antipsychotic treatment in patients with psychosis taking antipsychotic drugs for at least 3 months. This kind of study has been previously done worldwide, but not so commonly done in Eastern Indian population so it aims to properly estimate that the amount of prolactin rise a patient has to face after taking antipsychotic medications and might also help the psychiatrists to adjust the dosage of antipsychotics or add some other drugs to lower the prolactin level along with the antipsychotics in Eastern India.

Aims and Objectives

With this background, we conducted this study with the following objectives:

1. To estimate serum prolactin in diagnosed psychiatric patients taking antipsychotic drugs for at least 3 months
2. To study the difference in serum prolactin between recently diagnosed psychiatric patients taking antipsychotic drugs for at least 3 months and age and gender-matched mentally healthy patients without any psychiatric complication and without any history of intaking antipsychotic drugs.

MATERIALS AND METHODS

Study Design

A Cross-sectional, descriptive, non-interventional, hospital-based study.

Place of Study

Medical College and Hospital, Kolkata.

Study Population

Known diagnosed psychiatric patients taking antipsychotic medications for at least 3 months who will come to central laboratory, MCH, Kolkata, after going through the inclusion–exclusion criteria.

Target Sample Size

Target sample size – considering the prevalence (P) of hyperprolactinemia among psychiatric patients as 61.1%. So, Q=100-P and Margin of error (d) = 20% (absolute value). Z =1.96 in 95% CI

Sample size (N)=[((1.96)^2×PQ)/d^2] =[(1.96)^2×61.1×(100-61.1)]/(20% of 61.1)^2=61

- Minimum sample size will be 61 in each group. We took 70 patients in each group.
Sampling Method
Systematic random sampling will be done to select the cases under study.

Study Durations
4 months.

Ethical Clearance
Proper ethical clearance was obtained from the Institutional Ethics Committee.

Inclusion and Exclusion Criteria

Inclusions
The criteria for including the patients in the case group of this study were patients (aged between 18 and 45 years) diagnosed with psychiatric complications as per ICD 10 and taking antipsychotic medications for more than 3 months. For control group, age and gender-matched mentally stable healthy volunteers without having any apparent cause for hyperprolactinemia and without any history of taking antipsychotic drugs were taken.

Exclusion criteria
Patients suffering from any carcinoma, comorbidity, and patients suffering from conditions other than taking antipsychotic medications which are associated with increased serum prolactin, like presence of prolactin secreting tumor, thyroidal abnormality, physiological causes of hyperprolactinemia like pregnant patients, and lactating patients were excluded. Post-psychological evaluation, if a patient is found to be psychologically stable but under acute stressful condition was also excluded as stress is a powerful factor behind increased prolactin level. Post-menopausal females were excluded as the reference range for prolactin is different in that age group.

Data Collection
Serum of patients was collected from central laboratory in Medical College and Hospital after taking proper consent from willing patients.

Prolactin Measurement
Serum Prolactin was measured with the help of CLIA (ADVIA CENTAUR). The ADVIA Centaur Prolactin assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses constant amounts of two antibodies. The first antibody, in the Lite Reagent, is a polyclonal goat anti-prolactin antibody labeled with acridinium ester. The second antibody, in the Solid Phase, is a monoclonal mouse anti-prolactin antibody, which is covalently coupled to paramagnetic particles.

Reference range for non-pregnant females – 2.8–29.2 ng/mL.
Reference range for adult males – 2.1–17.7 ng/mL.

RESULTS
Findings of the present study are summarized in Table 1.

DISCUSSION
As per our study done in Eastern Indian population, in the female group of psychiatric patients (aged between 18 and 45 years) taking antipsychotics, the prolactin level was 23.6 ± 4.5 ng/mL, and in age matched control female group, prolactin level was 9.2 ± 3.1 ng/mL, the difference is statistically significant ($P < 0.001$).

Moreover, in male psychiatric patients (aged between 18 and 45 years) taking antipsychotics, the prolactin level was 14.3 ± 1.7 ng/mL, and in age-matched control male group, prolactin level was 8.5 ± 1.5 ng/mL, the difference is statistically significant ($P < 0.001$).

The result of our study is in accordance with Liana Dehelean et al. (2019) whose study on over 170 patients showed that hyperprolactinemia was present in 120 (70.6%) patients, among which 80 (66.7%) were females and 40 (33.3%) were males. The average increase in prolactinemia was 2.46 times the maximum value in women, and 1.59 times in men. Gender, type of antipsychotic medication, and the duration of psychosis over 10 years significantly predicted prolactin levels.[25]

Hyperprolactinemia is attributable to two major causes, one of which is frank neoplasia/paraneoplastic syndromes and the other is due to medications, the latter being our area of interest, out of which, anti-psychotic pharmacotherapeutics cater for 70% of the excessive PRL secretion as documented.[26-28]

Excessive secretion of the PRL is explicable to both typical (haloperidol, prochlorperazine, loxapine, molindone, pimozide, trifluoperazine to name a few which are vividly used) and atypical antipsychotics also known as the SGA or the second-generation antipsychotics (aripiprazole, olanzapine, risperidone, quetiapine, clozapine, ziprasidone to

| Table 1: Serum prolactin level among participants |
|-----------------|----------------|-----------------|
| Groups        | Gender | Serum prolactin level (ng/mL) |
| Control       | Male   | 8.5±1.5 ng/mL |
| Control       | Female | 9.2±3.1 ng/mL |
| Case          | Male   | 14.3±1.7 ng/mL |
| Case          | Female | 23.6±4.5 ng/mL |
name a few), where atypicals are mostly deciphered to be the offending agent for causing hyperprolactinemia.\textsuperscript{[29-31]}

The main pharmacodynamics would be the longer duration of receptor association of the atypicals and a subsequent increase in the permeability of the blood–brain barrier, with an excess molecular interaction in the pituitary gland, both the above mechanisms would be responsible for such an uncanny effect. The molecule risperidone which is one atypical and generously used, houses the most in the pituitary gland as per Tewksbury and Olander with even aripiprazole, which is often used to cater for hyperprolactinemia, goes haywire and causes the latter at an estimated rate of OG 3.1–9.0\%,\textsuperscript{[32]} which looks surprising. While we discuss the antipsychotics, where psychiatry and psychiatric pharmacotherapy is rather more of a dilemma warranting a difficult understanding, even selective serotonin reuptake inhibitors may be offending to cause an abnormal PRL secretion, through inhibiting the tuberoinfundibular pathway which is primarily dopaminergic, but such rates are less to an approximation of 10.9\% with respect to the atypicals.

Due to the aforesaid problem, algorithms must be essentially derived to combat the complications, switching of antipsychotics in accordance with the PRL levels, which must be rigorously monitored, may be a possibility. Lu et al.\textsuperscript{[33]} write that judicious use of Vitamin B6 or pyridoxine would benefit the PRL problem with fewer side effects.\textsuperscript{[34-37]} Switching from a drug (X) to quetiapine or aripiprazole has been shown to reduce prolactin levels with good clinical outcomes. From this dialect, aripiprazole augmentation or in simple words would be the judicious use of aripiprazole would be beneficial for addressing the high PRL levels due to atypicals along with a fantastic improvement in the psychiatric domain of the patient which is evaluated using the Positive and Negative Syndrome Scale (PANSS), CI>95\%. Noteworthily, aripiprazole augmentation would not be efficacious for patients on sulpiride or amisulpiride which are benzamide antipsychotics, where hyperprolactinemia was significantly seen with the use of risperidone.\textsuperscript{[38]} Reduction of the antipsychotic dose could also be a treatment of choice. A further measure that could be advocated is the use of a full or a partial dopamine agonist such as bromocriptine, pramipexole, or cabergoline. Miller et al.\textsuperscript{[39]} liberally suggest the use of bromocriptine at 2.5–10 mg/day for 8 weeks to reduce the stigmata of hyperprolactinemia. Though it must be noted that reports of worsening psychosis after the initiation of dopamine agonists have been documented.\textsuperscript{[39]}

It is therefore of utmost importance to judiciously monitor the serum prolactin levels to predict the nature of the complication. The NICE guideline recommends documenting a baseline prolactin level where the sample must be collected at fasting or an hour after the first meal before initiation of any antipsychotics. One can further proceed to 3 or more samples to be taken in a time interval of 20–30 mins with the help of an indwelling vascular cannula to avoid stress-induced rise in PRL levels due to venipuncture by the needle. Some researchers further recommend a serial measurement for every 3 months pertaining to the course of the antipsychotic to predict the PRL alterations. Since the antipsychotic pharmacology would involve the central nervous system, it must be carefully noted that serum PRL levels of >3000 ng/dL at any instance would need an MR imaging of the head as it may straightaway point to a neoplastic entity in the brain tissue, essentially a prolactinoma.

As our study addresses a quite raging issue that what to do after taking antipsychotics and the patient is having hyperprolactinemia after that, and as our study on both genders in Eastern India suggested that there was evidence of hyperprolactinemia after taking antipsychotics, the rationale of this study is that whether the dosage should be lowered, atypical antipsychotics should be added or not, and when to start treatment to lower serum prolactin level, and to further nurture these issues more studies should be done with larger sample size and prospective cohort study design.

**CONCLUSION**

As per our study, psychiatric patients of both genders taking antipsychotic drugs had higher serum prolactin level than age and gender-matched mentally healthy persons not taking antipsychotic drugs. Although the limitation of this study was small sample size and another issue that must be taken into consideration is the fact that prolactin levels can also be dependent on menstrual cycles in women, our sample contains 40 (57\%) females that were still menstruating. Furthermore, several medical issues related to hyperprolactinemia (such as sexual dysfunctions and risk of osteoporosis) were not assessed in the present study. The results were interpreted in the absence of thyroid function assessment. However, literature data show that antipsychotic-induced hyperprolactinemia tends to persist despite correction of either subclinical or overt hypothyroidism.

**REFERENCES**

Hyperprolactinemia in patients taking antipsychotic drugs


How to cite this article: Sarkar S, Biswas B, Roy S, Sanyamath A, Biswas S, Nandy M. Assessment of prevalence of hyperprolactinemia in patients taking antipsychotic drugs in a tertiary care hospital in eastern India. Natl J Physiol Pharm Pharmacol 2024;14 (Online First). DOI: 10.5455/nnjppp.2024.14.04157202416042024

Support of Source: Nil, Conflicts of Interest: None declared.