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Evaluation of Prolactin Levels in Patients Treated for Schizophrenia

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Abstract: ***Hyperprolactinaemia is a common side-effect of antipsychotic treatment and the clinical consequences associated with this can have a negative impact on patients compliance. The aim of this study was to investigate the frequency of hyperprolactinemia in patients with schizophrenia treated with antipsychotics. This was a descriptive study conducted at the Polyclinic of Speciality Nr.3, Tirana, Albania over a period of two years. It included 76 patients, 23 (30.3%) of whom were females and 53 (69.7%) males. Baseline fasting serum prolactin levels were taken followed by administration of haloperidol and olanzapine respectively. The rise in serum prolactin levels in second measurement was significantly higher in both, males M=445.6 (±534.3) µIU/l and females M=534.9 (±595.6) µIU/l (p<0.01). The mean level of prolactin among females is significantly higher as compared to males (p<0.01). Appropriate investigations and effective management should reduce the burden of adverse effects and prevent long-term consequences.***

Keywords: serum prolactin level, atypical antipsychotics, haloperidol, hyperprolactinemia.

1. Introduction

Prolactin plays a vital role in proper functioning of the reproductive system (1). Prolactin, a polypeptide hormone secreted by lactotroph cells of the anterior pituitary gland, is involved in many biological functions, including reproduction, pregnancy and lactation, and growth and development. Blood prolactin levels could be affected by several variables, including sex, sexual activity, childbirth, stress, smoking, and some medications (2,3). Prolactin in excess can have effects on fertility in women and sexual function in men (4), which in turn can have a profound effect on an individual. Hyperprolactinemia over a long duration has serious negative results on the overall health of the patient. A variety of studies over the past four decades have examined other facts of the relationship between prolactin and schizophrenia and call for a reappraisal of this relationship. Some recent studies have found increased prolactin concentrations in antipsychotic-naive psychotic patients (5–10), whereas other studies of previously treated but drug-free patients reported concentrations that are normal or lower than those of controls (11–13). This also applies to the drugs chosen to treat patients. Although atypical antipsychotic agents have a lower incidence for elevating prolactin levels, an increase is still seen. Most available antipsychotic drugs can therefore cause elevations in prolactin secretion. This increase is associated with a variety of adverse effects: lack of libido and erectile dysfunction in men (5), amenorrhoea and galactorrhoea in women (6), acceleration of osteoporosis in women (7), weight gain (8), and—potentially—an increased risk of cancer, particularly breast cancer in women (9). The association of prolactin with male sexual dysfunction is complex and has been challenged by some authors (10) but is supported by research showing that antipsychotics which cause greater elevations in prolactin also have more marked sexual adverse effects (11). Besides this, a variety of studies over the past four decades have examined other facets of the relationship between prolactin and schizophrenia and call for a reappraisal of this relationship. This paper, highlights the findings pertaining to prolactin and schizophrenia. The aim of this study was to determine whether there is a significant rise in serum prolactin level in patients with schizophrenia treated with antipsychotics.

2. Material and Methods

This is a descriptive study conducted over the period 2014 - 2017 including 76 patients in prolonged treatment with schizophrenia and bipolar disorders. The mean age of patients was 39.3(±13.0) years with a range 14 to 73 years. 23 (30.3%) of patients were females and 53 (69.7%) males.

Blood collection and examination were performed at laboratory in Polyclinic of Speciality Nr.3, Tirana with Immunoassay autoanalyzer MAGLUM 800 fully-auto cheminiluminescence immunoassay analyzer. Baseline fasting serum prolactin levels were taken followed by administration of treatment. A second serum prolactin level was then taken and assessed two years after the first examination by the same prolactin measuring kit. Reference range of serum prolactin as 54-340 mlU/l were fixed for this study. Blood samples were collected using standard procedures.

3. Statistical analysis

Descriptive statistics were reported as frequencies and percentages for categorical variables and mean and standard deviation for continuous variables. Distribution of data was evaluated by using the One-Sample Kolmogorov-Smirnov test. Differences between the measurements were assessed by Wilcoxon test, whereas students t test was used to compare the differences by treatment and gender. A p value ≤0.05 was considered statistically significant.

4. Results and Discussion

The mean of baseline serum prolactin levels of all subjects was 306.4 (±446.6) µIU/l (table 1). No significant difference

was found by gender (t= 1.01 p=0.6) whereas by type of treatment the level of prolactin was significantly higher among patients treated with haloperidol 746.0 (±864.0) µIU/l compared to other antipsychotics 198.4 (±121.9), (t=2.5 p=0.03)

A second measurement of prolactin levels was done two years after the treatment resulting in a significant increase of prolactin levels (M=554.2±548.5) µlU/l with a range 234 – 3104 as compared to baseline levels (Wilcoxon p<0.01) (table 2). Similar as in first measurement the mean prolactin level of patients treated with haloperidol M=874.1 (±653.4) µIU/l was significantly higher as compared with the mean prolactin level of patients treated with other atypical antipsychotics such as olanzapin, risperidon, leponex, etc. M=373.9 (±479.3) µIU/l, (t= 2.8 p<0.01). The rise in serum prolactin levels in second measurement was significantly higher in both, males M=445.6 (±534.3) µIU/l and females M=534.9 (±595.6) µIU/l (p<0.01). The mean level of prolactin among females is significantly higher as compared to males (p<0.01). Overall, 15 (19.7%) patients were treated with haloperidol and 61 (80.3%) of them with other antipsychotics. Eight from 15 patients who initially started the treatment with haloperidol interrupted the treatment with this medicament and subsequently were administered other antipsychotics, namely olanzapin. The mean prolactin level in these patients showed a significant decrease after the change of treatment from M=828.3 (±671.1) µIU/l and range 96.0-2218.0 to M=558 (±547.2) µIU/l with a range 58.0 – 1693.0 (p<0.01). (figure 1).In the rest of seven patients who continued the treatment with haloperidol the mean prolactin level showed a significant increase from M=478.23 (±658.2) µIU/l and range 107-1936 to M=783.4 (±715.4) µIU/l with a range 293 – 2356 (p<0.01).

Eighteen patients who changed the treatment from Olanzapin to Leponex the mean prolactin level showed a significant decrease from M=411.0 (±400.9) µIU/l and range 111-1848 to M=189.6 (±121.7) µIU/l with a range 78 – 512 (p<0.01).

Hyperprolactinemia is one of the most common side effects associated with antipsychotics and occurs in 40-50% of subjects (12). The clinical consequences of hyperprolactinemia include galactorrhea and hypogonadotropic hypogonadism, the later manifesting as oligomenorrhea or amenorrhea in women, erectile dysfunction in men, and loss of libido and infertility in both the sexes. It is important to differentiate medication induced hyperprolactinemia from pathological causes, such as PRL-producing tumors (prolactinomas), hypothalamic disease, hypothyroidism, and renal insufficiency. In psychoactive medication–induced hyperprolactinemia, treatment strategies include switching to an alternative medication that does not cause hyperprolactinemia, using estrogen or testosterone replacement, or cautiously adding a dopamine agonist (13). The question to be considered is whether elevated prolactin levels are related to specific symptoms or subtypes of schizophrenia, which is a multidimensional entity. Low testosterone and high prolactin levels have been reported in male patients with schizophrenia, and it was noted that prolactin levels were positively correlated with the severity of negative symptoms (14).

The majority of the other atypical antipsychotic agents elicit significantly lower elevation of prolactin than haloperidol, most likely due to the lower dopamine D2 binding affinities (15).

In a study by Melkersson K (16), PRL levels were assessed in patients receiving risperidone, olanzapine and clozapine. Elevated prolactin levels were found in 89% of the patients receiving risperidone and 24% of the patients receiving olanzapine, but in none of the patients receiving clozapine. There was a significant difference in median PRL level among the treatment groups, in that the PRL level was higher both in patients treated with risperidone and olanzapine, compared to those treated with clozapine. Elevated prolactin levels may be detected shortly after the initiation of antipsychotic treatment and its effect may persist for a long time (17). Prolactin and some antipsychotics themselves have a direct effect on the hypothalamic neurons controlling gonadotropin secretion (17). Antipsychotic-induced hyperprolactinemia is evident among patients with schizophrenia, and research suggests that elevations in prolactin levels may account for specific mental and physical health problems that are often observed in hyperprolactinemic patients. In particular, conventional antipsychotics and risperidone are consistently associated with ‘prolactin-raising’ effects, whereas other atypical antipsychotics are more likely to have ‘prolactin-provent’ properties. During second generation antipsychotics treatment prolactin concentrations can rise upto ten times normal levels and existing data indicate that 17-78% of female patients have amenorrhoea with or without galactorrhoea. In males, prolactin elevations have been linked specifically to diminished libido, impotence, and sterility (18).
In another study comparisons were made between olanzapine, risperidone and haloperidol on the level of PRL. Magnitude of response, dose dependency, time course, effects of age and sex and response to switching from haloperidol to olanzapine were assessed. Patients with haloperidoq induced hyperprolactinaemia may benefit from a switch to olanzapine. This finding is of significance because atypical antipsychotic agents are recommended in current guideline as first line treatment for patients with newly diagnosed schizophrenia.8 This finding therefore calls for a cautious approach while administering olanzapine. While serum PRL levels and clinical evaluation for associated clinical findings correlate such as gynecomastia is looked for in patients on haloperidol while the same is not done for patients on atypical antipsychotics. A similar caution is also called for in the light of present study, when switching patients with high serum PRL levels following haloperidol use. The finding suggests that olanzapine in our population may have an effect on PRL inhibiting factor albeit less marked than haloperidol. Certain antipsychotics have a lower potential for increasing prolactin levels, and this should be considered when prescribing an antipsychotic. Previous studies have shown that aripiprazole has a minimal effect on prolactin and is associated with lower prolactin levels when compared with other prolactin-provident antipsychotics. Current treatment options for antipsychotic-

induced hyperprolactinemia include a decrease in antipsychotic dose or switching to a prolactin provident medication. Further controlled studies and relevant guidance are essential to increase awareness and understanding of the impact of antipsychotic-induced hyperprolactinemia on mental and physical health in schizophrenia (19). Thus, prolactin should be measured before starting a patient on a new antipsychotic. Essentially, the risk-to-benefit analysis should favor prolactin-sparing antipsychotics as a treatment alternatives (20). Otherwise, before antypsycotic treatment is begun, and also at regular intervals there after, patients should be questioned about potential clinical signs of hyperprolactinemia. If clinical symptoms occur, switching to a prolactin-provident antipsychotic may be necessary. Generally hyperprolactinemia in schizophrenic patients should be taken into consideration much more seriously in a clinical approach (21).

5. Conclusion

Antipsychotic-induced hyperprolactinaemia should become a focus of interest in the drug treatment of psychiatric patients, particularly given the introduction of PRL-sparing antipsychotics. Appropriate investigations and effective management should reduce the burden of adverse effects and prevent long-term consequences. Atypical antipsychotics as a group cause less hyperprolactinemia than conventional ones, yet there is considerable variation among the drugs. Clinicians should ask questions to detect hyperprolactinemia before starting treatment and during follow-up and should give patients relevant information. A decrease of the dose of antipsychotic medication (minimum effective dose) with caution might have a beneficial effect for patients with schizophrenia and negative symptoms. Alternatively, switching to a serotonin dopamine antagonist drug may be helpful since they cause less hyperprolactinemia than conventional antipsychotic drugs. In conclusion, this study indicates that the assessment of prolactin levels could be an important biological marker for the severity of negative symptoms in schizophrenia and these findings may change the present pharmacotherapy for negative symptoms based on prolactin levels of patients with schizophrenia.

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Table 1: Baseline serum prolactin levels by gender and type of treatment

Variables	M (SD)	Range	P
Gender			
Males	293.6 (±462.6)	42-3104	0.6
Females	336.1 (±415.8)	58-1936	
Type of treatment			
Haloperidol	746.0 (±864.0)	58-3104	0.03
Other antipsychotics	198.4 (±121.9)	42-539	
Total	306.4 (±446.6)	42-3104	

Table 2: Baseline and after treatment serum prolactin levels by gender and type of treatment

Vriables	Baseline	Second measurement	P
	M (SD)	M (SD)	
Gender			
Males	293.6 (±462.6)	445.6 (±534.3)	<0.01
Females	336.1 (±415.8)	534.9 (±595.6)	<0.01
Type of treatment			
Haloperidol	746.0 (±864.0)	874.1 (±653.4)	<0.00
Other antipsychotics	198.4 (±121.9)	373.9 (±479.3)	<0.01
Total	306.4 (±446.6)	554.2 (±548.5)	<0.01

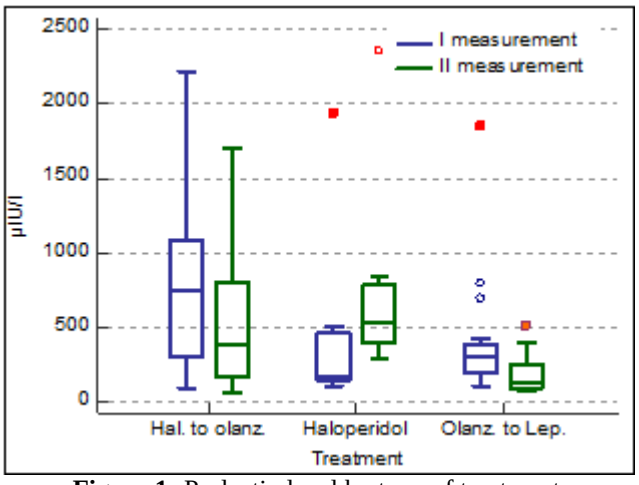

Figure 1: Prolactin level by type of treatment