ORIGINAL ARTICLE

EFFECT OF TYPICAL AND ATYPICAL ANTIPSYCHOTICS ON PLASMA PROLACTIN LEVELS IN SCHIZOPHRENIA

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ABSTRACT

Background: 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 compare the frequency of hyperprolactinemia in patients with schizophrenia treated with atypical antipsychotic olanzapine and typical antipsychotic haloperidol.

Material & Methods: This was a cross-sectional, analytical study conducted at the Department of Psychiatry, AFIMH, Rawalpindi over a period of six months. It included 60 patients and 30 healthy controls. All patients underwent a thorough psychiatric evaluation for fulfilling the ICD-10 criteria of schizophrenia. They were then randomly allocated into two groups. Baseline fasting serum prolactin levels were taken followed by administeration of haloperidol and olanzapine respectively. A second serum prolactin level was then taken and assessed by the same prolactin measuring kit. With these two groups being given haloperidol and olanzapine alongside serum prolactin levels were similarly measured for healthy controls.

Results: Elevated Prolactin levels were found in 25(89%) of the patients receiving haloperidol and 12(32%) of patients receiving olanzapine, but in none of the healthy controls. There was a significant difference in median prolactin level among both the treatment groups ($p<0.001$), in that the prolactin level was significantly higher in the patients treated with haloperidol and moderately high in the patients treated with olanzapine, compared to the healthy controls.

Conclusion: The typical antipsychotic haloperidol significantly elevates the prolactin levels while atypical antipsychotic olanzapine only moderately raises the prolactin levels.

KEY WORDS: Serum prolactin level; Typical antipsychotics; Atypical antipsychotics; Haloperidol; Olanzapine; Hyperprolactinemia.

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INTRODUCTION

Prolactin (PRL) is released from the anterior pituitary under the inhibitory control of dopamine, which is secreted from the hypothalamus. Psychiatric patients being prescribed antipsychotic medications for chronic illnesses suffer from endocrine dysfunctions. These dysfunctions among others include the rise of serum prolactin levels with prolonged use of older typical antipsychotics like haloperidol. The use of novel or atypical antipsychotics are thought to be associated with only minor rise of levels of PRL.

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There are the older conventional antipsychotics called typical antipsychotics and the relatively newer ones called atypical antipsychotics. The Serotonin Dopamine Antagonists (SDA's) are also referred to as novel or atypical drugs and include risperidone, olanzapine, quetiapine, clozapine and ziprasidone.[1] Atypical antipsychotics can be defined as those that are effective against psychotic symptoms with lesser tendency to induce neuroleptic induced movement disorders. These act on both dopamine as well as serotonin receptors and partially or completely block them. The other spectrum of side effects believed to be caused by the use of atypical antipsychotics is the so-called metabolic syndrome with derangement in glucose levels, weight changes and alterations in the cholesterol levels.

From the previous studies it is evident that schizophrenia mostly manifests itself in adulthood

with mean age of onset at 18 years and better compliance of the treatment can be procured in that age group by minimizing the adverse effects. Dopamine receptor dysfunction is thought to be part of the pathophysiology of schizophrenia.[2] It is generally accepted that atypical antipsychotics have revolutionized the bio-psychosocial management of schizophrenia. Hyperprolactinaemia is a common side-effect of antipsychotic treatment and the clinical consequences associated with this e.g. sexual dysfunction can have a negative impact on patients compliance.[3] Even atypical antipsychotics give rise to transient drug specific elevations of prolactin levels and the difference between typical and atypical antipsychotics have more to do with the degree and duration of prolactin elevation than to a categorical difference.[4] When developing guidelines for the long-term management of schizophrenia, one approach is to adopt a proactive strategy that sets out clear treatment goals and strategies. This should involve the broad view of embracing overall mental and physical wellbeing rather than simply the absence of illness.

The current research would emphasize on the side-effects of antipsychotics, and comparison between the older typical antipsychotics and newer atypical antipsychotic on the level of PRL. The cascade of dysfunction caused by the abnormally raised serum PRL levels in humans is far too immense to forego.

The aim of this study was to compare the frequency of hyperprolactinemia in patients with schizophrenia treated with atypical antipsychotic olanzapine and typical antipsychotic haloperidol.

MATERIAL AND METHODS

The present research included 90 individuals; 60 psychiatric patients and 30 healthy controls. These healthy controls were age-matched volunteers from paramedical staff of the hospital and the undergraduate students of associated medical college. Patients who reported themselves for treatment or were brought by their relatives or guardians to the mental health tertiary care facility for treatment of their disease were included in this study.

Patients underwent a thorough psychiatric evaluation for fulfilling the ICD-10 criteria of schizophrenia. Only those 60 individuals were included who fulfilled the ICD-10 criteria of schizophrenia and signed the informed consent. The patients who were newly diagnosed as having schizophrenia as their first episode and were not on any antipsychotic medication were only included. Patients with past history of antipsychotic treatment for schizophrenia were excluded from the study. These patients were then randomly allocated into two groups before the commencement of their treatment.

Before the administration of either of the antipsychotics, the pre-treatment fasting serum prolactin levels were taken. Treatment followed with the administration of haloperidol or olanzapine respectively for the two groups. A second serum prolactin level was taken after one month. Prolactin levels were similarly measured for healthy controls who did not receive any medication.

Vitros Immunodiagnostic Prolactin Reagent Pack was used to measure serum prolactin levels. An immunometric technique which involves the simultaneous reaction of prolactin present in the blood sample with a biotinylated antibody sheep polyclonal antiprolactin and a horse radish peroxidase labeled antibody conjugate (mouse monoclonal anti-prolactin). Reference range of serum prolactin as 53-360 mIU/l (0-20 ng/ml) were fixed for this study. Blood samples were collected using standard procedures.

RESULT

The age range was 12 to 78 years and the mean age was 32.31±9.02 years. The mean of serum prolactin levels of all subjects after the treatment was 601.91±493.90. The mean prolactin level of haloperidol group after treatment was 1036.63±633.75, in the olanzapine group 523.47±93.84 and in the healthy controls the mean 245.63±70.90. (Fig. 1)

The three Groups were compared for rise in serum prolactin levels after administration of haloperidol to Group 1, Olanzapine to Group 2, while the Group 3 healthy controls did not receive any medication. Using Independent sample t-test, group 1 was compared with group 2 and 3. Group 2 was compared with group 3.

The rise in serum prolactin levels after treatment of Group 1 was statistically significant compared to both Group 2 and Group 3 ($p<0.001$). Similarly prolactin levels of Group 2 were also significantly raised as compared to Group 3 ($p<0.001$). (Table 1-3)

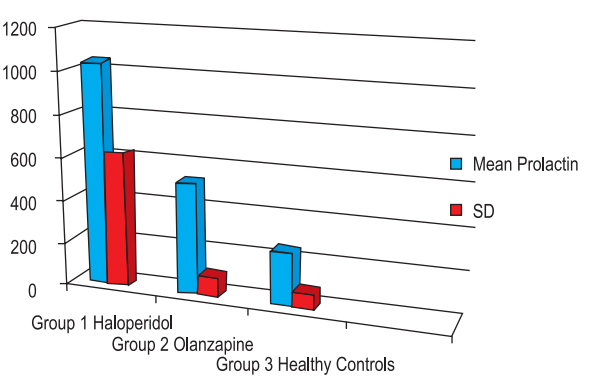

Figure 1: The rise in Prolactin levels in the three groups after treatment.

Table 1: Comparison of serum prolactin levels in Group 1 (haloperidol) and Group 2 (olanzapine) after treatment.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig	t	df	sig. (2-tailed)	Mean Difference	Std. Error Difference	95% confidence Interval of the Difference	
									Lower	Upper
Serurm prolactin levels with treatment	Equal variances assumed	19.923	.000	4.387	58	.000	513.167	116.969	279.028	747.305
	Equal variances not assumed			4.387	30.271	.000	513.167	116.969	274.374	751.959t

Table 2: Serum prolactin levels in group1 and group 3 after treatment.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig	t	df	sig. (2-tailed)	Mean Difference	Std. Error Difference	95% confidence Interval of the Difference	
									Lower	Upper
Serurm prolactin levels with treatment	Equal variances assumed	21.639	.000	6.794	58	.000	791.000	116.429	557.942	1024.058
	Equal variances not assumed			6.794	29.726	.000	791.000	116.429	553.129	1028.871

Table 3: Serum prolactin levels in group 2 and group 3 after treatment.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig	t	df	sig. (2-tailed)	Mean Difference	Std. Error Difference	95% confidence Interval of the Difference	
									Lower	Upper
Serurm prolactin levels with treatment	Equal variances assumed	1.022	.316	12.938	58	.000	277.833	21.474	234.848	320.819
	Equal variances not assumed			12.938	53.969	.000	277.833	21.474	234.779	320.888

DISCUSSION

The paramount finding of this research was that treatment with haloperidol and olanzapine raised the serum prolactin levels. However the prolactin rise associated with haloperidol was greater olanzapine.

Atypical antipsychotic drugs in clinical doses, occupy 5-HT2 receptors near saturation, while D2 dopamine receptors assessed in striatum by single photon emission computed tomography (SPECT) or positron emission tomography (PET) are occupied to different degrees. Critical to the understanding of the ways in which medications affect PRL secretion is the neuroendocrine regulation of PRL secretion. The hypothalamus predominantly influences PRL secretion through one or more PRL inhibitory factors that reach the pituitary via hypothalamic/pituitary portal vessels. Disruption of the pituitary stalk leads to moderately increased PRL secretion and decreased secretion of other pituitary hormones. Dopamine is the predominant physiological inhibitory factor; blockade of endogenous dopamine receptors by various drugs, including antipsychotic agents causes PRL secretion to increase.[5]

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.[5]

In a study by Melkersson K[6], 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. The prevalent concept that olanzapine is a prolactin sparing antipsychotic may not hold ground in the light of the findings of this study.

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.[7]

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 haloperidol 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 gynaecomasia is looked for in patients on haloperidol while the same is not done for patients on atypical neuroleptics. 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.

Several adverse effects are associated with the use of most of the antipsychotics over long duration. The subjects in a research were studied for their serum PRL, leptin, cholesterol, triglyceride, high density lipoprotein (HDL) and low density lipoproteins (LDL).[9] Treatment of patients with olanzapine caused marked increase in serum prolactin, LDL, triglyceride and leptin levels. No changes in HDL concentration were seen in this study.

In a study by Wyszogrodzka-Kucharska,et al[10] the prevalence of hyperprolactinaemia and its clinical symptoms were studied in three groups in which the first group was treated with risperidone, second with olanzapine and the third control group. In all subjects a fasting morning blood sample was obtained for serum PRL and the investigators did not establish any statistically significant difference in the prevalence of hyperprolactinaemia diagnosed with laboratory tests. In patients treated with different atypical neuroleptics clinical symptoms of hyperprolactinaemia were established only in a part of the subjects with hyperprolactinaemia diagnosed with laboratory tests. Data from yet another study concluded that atypical antipsychotics do elevate prolactin levels but more transiently than typical antipsychotics.[11] Therefore, simply classifying the conventional and novel antipsychotics into prolactin-raising and prolactin-sparing respectively may not be accurate.

In another study the effects of acute, sub-chronic and chronic olanzapine and risperidone administration on prolactin levels were determined and the study showed that olanzapine and risperidone

display similar-effects on prolactin levels following acute and chronic administration but differ in their prolactin response over a 24 hour period.[3]

Polish investigators in a study did not establish any statistically significant difference in the prevalence of hyperprolactinemia diagnosed with laboratory tests in patients treated with different atypical neuroleptics. Hyperprolactinemia was established in 92.3% patients treated with risperidone and in 76.5% patients treated with olanzapine as compared to 2.6% of controls.[10] These findings point out that olanzapine may not raise the PRL levels to those at par with the conventional antipsychotics, but olanzapine considerably raises the prolactin levels, unlike the previously held belief.

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. Risperidone at higher doses has been shown to produce increases in PRL similar to conventional antipsychotics. At the other end of the spectrum, clozapine and quetiapine produce minimal sustained increases in PRL.[12]

The results of the present study showed that treatment with haloperidol was associated with profound hyperprolactinaemia whereas PRL elevation was moderate in patients receiving olanzapine. It is of paramount importance that clinicians who prescribe the atypical olanzapine should be aware that olanzapine is not free from prolactin rise. It is further recommended that regular monitoring of PRL levels may be made a part of long term treatment of patients on olanzapine. The common misconception that dopaminergic pathway is totally spared by olanzapine may need to be reviewed and future studies are needed on this area.

We acknowledge several limitations of our study. This study was conducted in a tertiary care military hospital where a specific subgroup of patients report, and the majority of patients were males; which may have inadvertently influenced the results.

CONCLUSION

The typical antipsychotic haloperidol significantly elevates prolactin levels while atypical antipsychotic olanzapine only moderately raises the prolactin levels.

All patients on antipsychotics should undergo clinical and whenever required laboratory assessment for raised serum prolactin levels. This may save patients from potentially hazardous and embarrassing side-effects of antipsychotic treatment leading to non-adherence to treatment. Such an approach may enhance compliance to treatment and thus have a positive impact on prognosis in patients with schizophrenia.

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