Quetiapine Is Not Associated with Increase in Prolactin Secretion in Contrast to Haloperidol

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Background. Typical antipsychotic drugs frequently cause hyperprolactinemia and even galactorrhea. In addition, these side effects may result in noncompliance with antipsychotic treatment. Capacity to avoid hyperprolactinemia has been accepted as one atypical criterion. The aim of the present study was to compare effects of haloperidol, the most commonly used antipsychotic, and quetiapine, a novel antipsychotic agent used in Turkey, on serum prolactin (PRL) levels.

Methods. The study consisted of 35 females diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Thirty-five patients in a drug-free period for at least 2 weeks were included to randomized quetiapine (n = 18) and haloperidol (n = 17) treatment group. All patients were assessed by Brief psychiatric rating scale (BPRS), Positive and negative syndrome scale (PANSS), and Extrapyramidal symptoms rating scale (ESRS). PRL levels were measured both at the beginning and at the sixth week of the study.

Results. Both treatment groups exhibited significant improvements in clinical signs as evaluated by BPRS and PANSS. While there was no significant difference in PRL level between groups at the beginning of the study, control prolactin (PRL) levels were significantly lower in quetiapine compared to haloperidol group. While no quetiapine group patients exhibited galactorrhea, we observed that two patients from the haloperidol group had galactorrhea related to hyperprolactinemia.

Conclusions. The present study revealed that quetiapine is not associated with increase in PRL secretion in contrast to the conventional antipsychotic haloperidol. © 2002 IMSS. Published by Elsevier Science Inc.

Key Words: Quetiapine, Haloperidol, Prolactin, Hyperprolactinemia.

Introduction

Prolactin (PRL) is a hormone released from the anterior hypophysis and its level is determined by dopamine. Dopamine is secreted by neuron terminals in the hypothalamus median eminence to veins of the pituitary (1). Therefore, PRL is controlled by the dopaminergic system. Typical antipsychotic drugs commonly cause hyperprolactinemia and even galactorrhea. Moreover, increased PRL can cause irregular menstrual cycles, increased risk of osteoporosis, secondary amenorrhea in women, and loss of libido, impotence, and decreased spermatogenesis in men (2). As can be observed, these side effects may result in noncompliance with antipsychotic treatment. Therefore, an important aspect of tolerability of atypical antipsychotic drugs is their propensity to cause hyperprolactinemia. Newer atypical antipsychotic drugs appear to cause less elevation in PRL level (3). This condition is probably associated with their lower dopamine 2 (D2) receptor-binding affinities (4); however, controversial results were reported. Some studies reveal that clozapine has no PRL-increasing effect (3,5,6). It was reported...
that risperidone was associated with PRL elevation in rats (7) and humans (8,9). Quetiapine is one of the newer antipsychotic agents possessing clozapine-like properties. Arvanitis et al. (10) showed quetiapine to be at least as effective as haloperidol in treatment of patients with schizophrenia and not to cause increased PRL levels. The aim of the present study was to compare effects of haloperidol, one of the most commonly used antipsychotics, and quetiapine, a novel antipsychotic agent in Turkey, on serum PRL levels.

Materials and Methods

Patients. The study was comprised of female in- or out-patients (aged 18–45 years) who were attended to for the first time at the Firat University School of Medicine Department of Psychiatry between October and December 2000 and who had been diagnosed with schizophrenia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) (11). After complete description of the study to the subjects, informed consent was obtained from each person. Ethical permission was obtained from the Firat University School of Medicine Local Ethics Committee (September 22, 2001). Exclusion criteria included severe physical illness, history of alcohol and substance abuse or dependence, presence of any endocrinologic state, and taking oral contraceptives; thus, 35 females eventually were included in the study. Patients were randomly assigned to two subgroups: quetiapine (n = 18) and haloperidol (n = 17). Two groups were matched according to previous hospitalization numbers, duration of hospitalization, mean duration of illness, and mean age of onset (p > 0.05). Patients were given quetiapine at a fixed dose of 600 mg/day and haloperidol 10 mg/day: the drugs were initiated after a 2-week washout period.

Instruments: sociodemographic information form. All subjects were evaluated by a semistructured questionnaire form arranged in accordance with clinical experience and available information sources, and included gender, age, marital status, educational status, and duration of illness. In addition, Brief psychiatric rating scale (BPRS) (12), Positive and negative syndrome scale (PANSS) (13,14) and Extrapyramidal symptoms rating scale (ESRS) (15) were administered to all patients.

Determination of PRL levels. Venous blood samples were obtained at 8:00 a.m. after overnight fasting and sera were separated both after washout period and at study end (6 weeks). Serum samples were stored at −70°C. PRL levels were determined by chemiluminoassay method using BIODPC kit (Immulyte 2000, Diagnostic Product Co., Los Angeles, CA, USA). Sensitivity of this assay is 0.60 ng/mL; upper limits of PRL are 15 ng/mL for males and 20 ng/mL for females (16).

Statistical analysis. Statistical analysis was performed by statistical package for social sciences (SPSS/PC 9.05 version, 1998; SPSS, Inc., Chicago, IL, USA). Patient characteristics were compared using independent sample t or chi-square test where appropriate. To compare PRL values or scale scores of repeated measures within and between groups, repeated measurement analysis of variance (ANOVA) according to Bonferroni correction test was used. Correlation analysis between scale scores and PRL levels was performed by Pearson correlation test.

Results

All participating patients completed the study. However, two patients of the haloperidol group exhibited galactorrhea at the third and fourth weeks and both required dose reduction (5 and 7.5 mg/day, respectively). Mean age was 27.62 ± 9.23 years for quetiapine and 29.44 ± 10.08 years for haloperidol group. There was no statistically significant difference between groups with respect to demographic characteristics (p > 0.05).

Both treatment groups exhibited meaningful improvements in clinical signs when evaluated by BPRS and PANSS. There were no statistically significant differences between the two groups in these measurements either at baseline or week 6, suggesting that these treatment regimens were similar with respect to efficacy. While mean ESRS score of quetiapine group at study initiation was similar to the haloperidol group, it was significantly less at the end of the 6-week period than the haloperidol group (p < 0.001). Detailed analysis regarding within and between group differences is presented in Table 1.

At study initiation there was no significant difference in mean PRL level between groups (p > 0.05). When control PRL levels were measured, the quetiapine group had significantly lower levels compared to the haloperidol group (p < 0.001) (Table 1). At 6 weeks, mean level was significantly different from that found at study initiation in haloperidol group (p < 0.001) but not in quetiapine group (p > 0.05).

PRL values exhibited positive correlation with ESRS scores in haloperidol group (r = 0.72, p < 0.01) but not in quetiapine group (r = 0.21, p > 0.05). In both groups, there was no correlation between PRL levels and PANSS, BPRS, or age. While no quetiapine-group patient exhibited galactorrhea, it was observed that two from the haloperidol group had galactorrhea related to hyperprolactinemia.

Discussion

Results of the present study demonstrated that quetiapine had minimal effects on PRL secretion, whereas haloperidol caused significant elevation and even galactorrhea. Newer atypical antipsychotic drugs appear to cause less elevation in PRL level, although contradictory results have been reported (3). Studies exhibited clozapine to have no PRL-increasing effects (3,5,6). It was suggested that olanzapine could cause modest PRL increases compared to risperidone.
and haloperidol (17,18). There are a few studies that examine the effect of quetiapine on PRL secretion. Arvanitis et al. (10) found that haloperidol was associated with significantly greater increase in PRL than placebo, whereas quetiapine had similar effect with placebo. In another study performed with patients previously treated with fluphenazine and who partially responded, PRL levels fell into normal range in 83% of patients treated with quetiapine compared with 21% of patients treated with haloperidol (19).

Lack of PRL elevation reported with atypical antipsychotics is believed due to their greater specificity for dopaminergic pathways, which results in less blockade of D2 receptors in tuberoinfundibular pathway (20). There is some evidence suggesting that olanzapine (21,22) and risperidone (22–24) have dose-related extrapyramidal symptoms that can be considered to cause dose-related increase in PRL secretion. Nevertheless, it was reported that quetiapine does not show such elevations even at highest doses (10). We could not evaluate this condition because we utilized fixed-dose quetiapine. Quetiapine’s low D2 occupancy can explain its freedom from extrapyramidal symptoms and prolactin-level elevation. Data suggest that transient D2 occupancy may be sufficient for its antipsychotic effect (25). Brain imaging studies revealing low D2 receptor occupancy rate in striatum with quetiapine support aforementioned suggestions (26,27). The finding that PRL values exhibited positive correlation with ESRS scores inhaloperidol group— but not in quetiapine group— supports low D2 occupancy because extrapyramidal side effects and elevation of PRL are related to amount of D2 occupancy.

We are aware of the fact that the present study has some limitations. The number of subjects is limited and the study additionally could have assessed association between PRL and related menstrual and sexual disturbances (erectile dysfunction, loss of libido, amenorrhea, hypospermatogenesis, etc.). Nevertheless, the present study clearly revealed that quetiapine is not associated with increase in PRL secretion, in contrast to the conventional antipsychotic haloperidol.

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