High-Dose Olanzapine and Prolactin Levels

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Background: This study evaluates whether high-dose olanzapine is associated with elevation of serum prolactin levels.

Method: Twenty-four patients taking daily doses of olanzapine of 20, 25, 30, and 40 mg for DSM-IV schizophrenia or schizoaffective disorder had serum prolactin levels measured. The patients were all from one author's (J.L.K.'s) clinical practice. The mean duration of olanzapine therapy was 15.3 months at a dose of at least 20 mg/day. Data were gathered in 2000 and 2001.

Results: There was no significant correlation between olanzapine dose and prolactin level (Pearson product moment correlation coefficient = 0.09). No significant differences were found between mean prolactin values in each dose group.

Conclusion: There was no significant elevation of prolactin with higher doses of olanzapine. Thus, preliminary evidence suggests that using higher doses of olanzapine is generally safe with regard to prolactin levels.

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In the pharmacologic treatment of schizophrenia, adverse effects often influence what choices are made and whether a medication is continued. Prolactin is a polypeptide hormone whose secretion is influenced by the action of antipsychotics. It is synthesized and released from the anterior pituitary gland. The main physiologic role of prolactin is milk production and secretion in females. As a consequence, excessive prolactin can induce amenorrhea and galactorrhea and may predispose to osteoporosis.[1] In males, excess prolactin can lead to erectile insufficiency and decreased libido.[2]

It is generally accepted that classical antipsychotics may elevate prolactin.[3] With some antipsychotics, such as haloperidol or risperidone, this may be dose related.[4] However, in the treatment of chronic schizophrenia, higher doses of antipsychotics are sometimes necessary for optimal response.

In reviewing the literature, the little information available on the impact of olanzapine on prolactin yields mixed opinions. In a recent review by Stephenson and Pilowsky,[5] the authors stated that based on data from acute-phase trials, there was little increase in prolactin levels. An initial open-label safety trial used only 7 patients treated with 5 to 30 mg of olanzapine.[6] At the end of 4 weeks, 5 subjects had normal prolactin levels. A later international trial used a much larger sample of 431 patients randomly assigned to haloperidol or olanzapine (1–15 mg/day).[7] Although olanzapine was associated with some increase in prolactin concentrations, increases were transient, occurred less often, and were of lesser magnitude than those observed with haloperidol.

A 6-week trial compared 2 doses of olanzapine (1 and 10 mg/day) with placebo using 152 patients.[8] The authors concluded that 10 mg/day of olanzapine did not produce a statistically significant increase in prolactin levels compared with placebo. A long-term study[9] in North America used a double-blind placebo-controlled design comparing haloperidol and 3 dose ranges of olanzapine (5 ± 2.5, 10 ± 2.5, 15 ± 2.5 mg/day) and their effect on serum prolactin. At week 2, for the 10- and 15-mg ranges, there was a statistically significant elevation compared with placebo (but less than haloperidol). However, by 6 weeks, there was no difference from placebo. A large 6-week trial in North America and Europe carried out a double-blind comparison of haloperidol and olanzapine (5–20 mg/day) with 1996 patients.[10] Only mild transient elevation in serum prolactin was noted for the olanzapine groups; however, no hard data are provided in that article. A 28-week, multicenter, double-blind study[11] compared olanzapine with risperidone using 339 subjects. The olanzapine treatment group (10–20 mg/day) demonstrated a lower incidence and less persistent elevation of serum prolactin.

Recently, David et al.[12] reviewed plasma prolactin levels in patients treated with olanzapine, risperidone, or haloperidol. Their conclusions were based on data from 3 multicenter, double-blind, randomized clinical trials, including studies lasting 1 year, 28 weeks, and 54 weeks. They found that prolactin is elevated moderately by olanzapine (mean change, 1–4 ng/mL), and no consistent dose-response relationship was observed. Elevations in

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this range would not be considered clinically significant. By comparison, prolactin elevations for risperidone patients and haloperidol patients were 17 ng/mL and 45 to 80 ng/mL, respectively.

In a small sample of children and adolescents, Alfaro et al.[13] found a correlation between plasma olanzapine concentration and serum prolactin. The mean dose in this sample was 17.5 ± 2.8 mg/day. The generalizability of this finding to an adult population is not clear.

One suggestion of the effects of high-dose olanzapine on prolactin may be found in a study by Kapur et al.[14] A positron emission tomography scan study was conducted on 12 patients randomly assigned to 1, 10, 15, and 20 mg/day of olanzapine. Three other subjects using 30 to 40 mg/day were included. It was found that at the normal clinical dosage of 10 to 20 mg/day, the dopamine-2 (D_2) occupancy ranged from 71% to 80%, and this was hypothesized as an explanation for the lack of prolactin elevation. The high-dose group (≥ 30 mg/day) showed more than 80% D_2 occupancy, leading to the suggestion of increasing likelihood of prolactin elevation, but caution is warranted given the nonrandomization and small sample size.

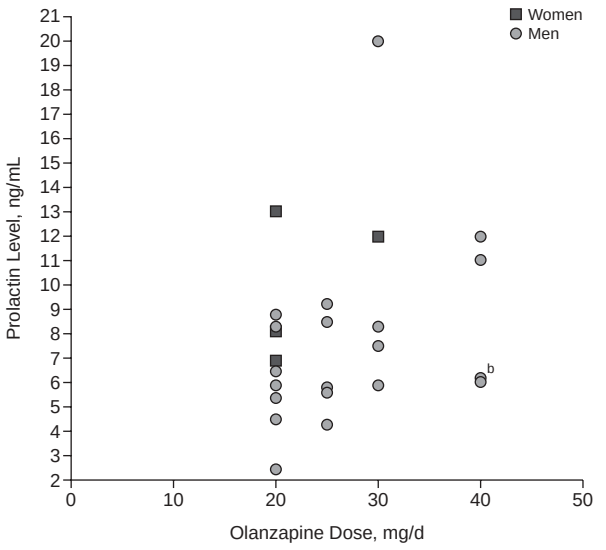
Thus, existing data indicate that olanzapine may produce mild and transient elevation of prolactin. However, this conclusion can only be drawn for doses up to 20 mg/day. There are no data for the effect of doses over 20 mg/day on serum prolactin. Therefore, a retrospective analysis of patients taking higher doses was undertaken. Our hypothesis, based on Kapur and colleagues' work,[14] is that olanzapine taken in a dose of greater than 20 mg/day will produce sustained elevation in prolactin levels.

METHOD

Subjects included men and women taking olanzapine in doses of over 20 mg/day for 4 months or more as treatment for DSM-IV schizophrenia or schizoaffective disorder. Data were gathered in 2000 and 2001. Subjects included all patients except 1 from the senior author's (J.L.K.'s) clinical practice who met these criteria. Only 1 potential subject refused to be included. Excluded were breastfeeding or pregnant women, those with previously documented high prolactin levels, those with any organic conditions known to elevate prolactin, those known to be taking any other medications that could affect prolactin, those who took depot antipsychotics within 6 months or oral classical antipsychotics within 1 month, and those who received electroconvulsive therapy within 8 weeks of a prolactin level assessment.

Twenty-four white patients were included, 20 men and 4 women. Their ages ranged from 21 to 64 years. Serum prolactin level was measured in each patient as a routine part of the patients' clinical care, and 1 male subject was recorded twice at different doses. The numbers of patients per dose were as follows: 10 patients taking 20 mg, 5 taking 25 mg, 5 taking 30 mg, and 5 taking 40 mg (for 1 patient, data were recorded at 30-mg and 40-mg doses). It should be noted that the 20-mg subgroup had the largest number of women (N = 3). Mean duration of treatment with all olanzapine doses was 15.3 months.

Figure 1. Olanzapine Dose and Prolactin Levels in 24 Patients[a]



[a]For 1 patient, data were recorded at 30-mg and 40-mg doses.
[b]Prolactin level was 6.0 in 1 subject and 6.1 in 2 subjects in the 40-mg group.

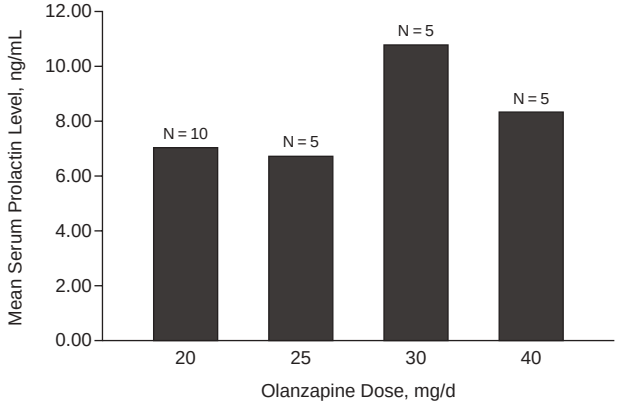
A 1-way analysis of variance (ANOVA) was performed using Minitab 13 for Windows (Minitab Inc., State College, Pa.) to assess differences in mean prolactin values among the dose groups. A Pearson product moment correlation analysis was undertaken to test the correlation between olanzapine dose and prolactin level. The significance level was set at $p < .05$.

RESULTS

Abnormal prolactin levels were found to be mild in nature, with the highest elevation at 20 ng/mL (a man) (Figure 1). Five subjects had elevations above 10 ng/mL, with 19/24 (79%) of the subjects having prolactin levels below the upper limit of normal of 10 ng/mL for men and 11 ng/mL for women.

As outlined in Figure 2, the patients taking a daily dose of 20 mg of olanzapine had a mean ± SD prolactin level of 6.99 ± 2.86 ng/mL. For those taking a dose of 25 mg, the mean was 6.66 ± 2.09 ng/mL. For those taking 30 mg, the mean was 10.74 ± 5.64 ng/mL, including the only outlier in the sample with a prolactin level of 20 ng/mL. Finally, for the 40-mg group, the mean prolactin level was 8.24 ± 3.00 ng/mL.

Figure 2. Olanzapine Dose and Mean Prolactin Level in 24 Patients by Dose Group[a]



[a]For 1 patient, data were recorded at 30-mg and 40-mg doses.

One-way ANOVA showed no significant differences in mean prolactin values among the dose groups. In the ANOVA, the independent variable was olanzapine dose, and the assumptions for normality and equal variance were met within a 95% confidence interval (there was 1 outlying data point). For 25 versus 30 mg (the groups with the biggest difference in mean prolactin levels), $p = .168$, and for 20 versus 40 mg (the biggest differences in doses), $p = .956$.

The Pearson product moment correlation was calculated to be 0.09, which indicated essentially no correlation between olanzapine dose and prolactin level.

DISCUSSION

In the dose range studied, there was no significant correlation between olanzapine dose and prolactin level. Only 2 patients had a sustained elevation of prolactin, providing little support for our hypothesis. None of the subjects reported impotence, decreased libido, amenorrhea, or galactorrhea in response to systematic inquiry.

This study may have some limitations. The sample size in each dose group may be too small to confidently pick up intergroup differences. The study was not powered a priori to detect differences. The time of day when prolactin was drawn was not controlled for, leading to possible confounding influence from the natural circadian rhythm of endogenous prolactin levels. Variations in prolactin associated with the menstrual cycle were not controlled for in female subjects. However, such variations would not be expected to cause elevations of serum prolactin beyond the normal range.

Every drug we use in medicine has its own unique strengths and weaknesses. The relative lack of prolactin elevation by high-dose olanzapine has positive long-term implications for treatment. While caution is always advisable in using drugs in doses beyond the usual range, the initial research evidence for olanzapine thus far suggests that there may be a relatively low risk of sustained hyperprolactinemia and its associated sequelae. Based on available data, olanzapine-associated prolactin elevation seems to be mild, transient, and with little clinical symptomatology. However, it should be noted that the evidence thus far supporting this conclusion is preliminary. Clinicians should remain aware of the possibility of prolactin elevation with all antipsychotic drugs. Further studies with more subjects and more frequent prolactin sampling, controlled for time of day, would be helpful in ascertaining the impact of higher doses of olanzapine on serum prolactin levels.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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