Prolactin Levels in Schizophrenia and Schizoaffective Disorder Patients Treated With Clozapine, Olanzapine, Risperidone, or Haloperidol

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Background: Prolactin levels are elevated to varying degrees by antipsychotics. Prolactin elevations may result in sexual and other adverse effects, and they may be related to antipsychotic effects. We used the data collected in a trial of antipsychotics to study the differential effect of these drugs on prolactin level, to explore the relation between clinical effects and prolactin level, and to determine the relationship between plasma levels of antipsychotics and prolactin level.

Method: Treatment-resistant patients (133 men, 24 women) diagnosed with DSM-IV schizophrenia or schizoaffective disorder participated in a double-blind, randomized, 14-week trial comparing clozapine (N = 40), olanzapine (N = 39), risperidone (N = 41), and haloperidol (N = 37). Plasma levels of prolactin and antipsychotics were determined at baseline and at weeks 5, 8, 10, 12, and 14 during the trial. Clinical effects were measured with the Positive and Negative Syndrome Scale and the Extrapyramidal Symptom Rating Scale. Statistical analyses were limited to the 75 men for whom repeated prolactin levels were available. Data were gathered from June 1996 to December 1999.

Results: Risperidone caused significant elevation of prolactin levels ($p < .05$) that appeared to be dose-dependent. Clozapine and olanzapine were associated with decreases of prolactin, whereas haloperidol led to a minor, nonsignificant increase. Plasma olanzapine and prolactin levels were correlated. Prolactin levels were not related to clinical improvement or extrapyramidal side effects.

Conclusion: Antipsychotics show major differences in their effects on prolactin, and risperidone has clearly the most robust effect.

(J Clin Psychiatry 2004;65:57–61)

Received March 3, 2003; accepted June 26, 2003. From the Nathan Kline Institute, Orangeburg, N.Y. (Drs. Volavka, Czobor, Lindenmayer, and Citrome and Mr. Cooper); New York University School of Medicine, New York (Drs. Volavka, Czobor, Lindenmayer, and Citrome and Mr. Cooper); Dorothea Dix Hospital, Raleigh, N.C. (Dr. Sheitman); University of North Carolina, Chapel Hill (Drs. Sheitman and Lieberman); John Umstead Hospital, Butner, N.C. (Dr. McEvoy); and Duke University, Durham, N.C. (Dr. McEvoy).

Grant R10 MH53550 from the National Institute of Mental Health, Bethesda, Md., provided the principal support for this project. Additional support was provided by grant MH MH33127 from the University of North Carolina Mental Health and Neuroscience Clinical Research Center, Chapel Hill, and the Foundation of Hope, Raleigh, N.C. Antiserum for radioimmunoassay was donated by the National Hormone and Pituitary Program, Torrance, Calif. The authors thank Janssen Pharmaceutica Research Foundation, Titusville, N.J.; Eli Lilly and Company, Indianapolis, Ind.; Novartis Pharmaceuticals Corporation, East Hanover, N.J.; and Merck and Co., Inc., West Point, Pa., for their generous gifts of medications. Eli Lilly and Company contributed supplemental funding that covered approximately 18% of the total cost of the study. However, overall experimental design, data acquisition, statistical analyses, and interpretation of the results were implemented with no input from any of the pharmaceutical companies.

Financial disclosure appears at the end of this article.

The authors acknowledge Linda Kline, R.N., M.S., C.S., who was the chief coordinator of the entire project.

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Therapeutic doses of conventional antipsychotics elevate plasma prolactin levels; hyperprolactinemia may lead to amenorrhea and galactorrhea in women, gynecomastia in men, and sexual dysfunction in both genders. Hyperprolactinemia develops because these medications block dopamine D_2 receptors in the tuberoinfundibular pathway. Prolactin secretion by the anterior pituitary is tonically inhibited by dopamine, and dopamine blockade thus disinhibits the secretion. Therefore, plasma prolactin level may be used as an indicator of blockade of D_2 receptors and thus as a measure of the bioavailability of conventional antipsychotics. This bioavailability aspect was concurrently validated by the finding of a significant correlation between plasma levels of prolactin and haloperidol.[1]

Therapeutic effects of conventional antipsychotics are believed to depend on their dopamine-blocking activity.[2]

Therefore, one may expect that prolactin levels will be related to the efficacy of conventional antipsychotics. Prolactin response to low or moderate doses of haloperidol was associated with better clinical response, particularly with improvement of positive symptoms.[1] A similar finding was reported for risperidone.[3]

Risperidone, but not clozapine, has been associated with a significant increase of prolactin levels in schizophrenia patients.[4] Plasma levels of prolactin were measured in 16 male schizophrenic patients during treatment with haloperidol (mean dose = 23.3 mg/day) and 6 weeks later after switching to treatment with risperidone (mean dose = 11.8 mg/day).[5] The patients' psychopathology improved, and prolactin levels were significantly increased from 39.5 to 58.9 ng/mL. Prolactin levels did not correlate with psychopathology changes.[5] In contrast, olanzapine raised the level of prolactin in a dose-dependent manner during the first 2 weeks of treatment, but these elevations subsided by week 6.[6]

Prolactin levels collected during 3 multicenter double-blind randomized clinical trials were used to examine the comparative effects of olanzapine, risperidone, and haloperidol.[7] The olanzapine doses ranged between 5 and 20 mg/day, risperidone doses ranged between 4 and 14 mg/day, and haloperidol doses ranged between 5 and 20 mg/day. Prolactin was increased moderately by olanzapine (mean change, 1–4 ng/mL), intermediately by haloperidol (mean change, approximately 17 ng/mL), and strongly by risperidone (mean change, 45–80 ng/mL). In haloperidol- and risperidone-treated patients, the mean change in prolactin was greater in women than in men. No consistent dose-response relationship was observed.[7]

In another trial, clozapine treatment did not elevate prolactin, while olanzapine yielded a moderate elevation, haloperidol was associated with marked elevation, and risperidone was associated with a maximal elevation of prolactin.[8] Prolactin levels from 4 large, randomized, double-blind studies of risperidone in patients with chronic schizophrenia were analyzed.[9] Both risperidone and haloperidol produced dose-related increases in plasma prolactin levels in both men and women. Risperidone-associated increases in serum prolactin levels were not significantly correlated with the emergence of possible prolactin-related side effects.

Thus, there are considerable differences among clozapine, risperidone, olanzapine, and haloperidol in their effects on prolactin levels; however, these differences have not been studied in a single, randomized, double-blind trial including blood levels of medications as well as clinical assessments. The principal goal of our study was to test the following hypotheses.

1. Differences among medication effects on prolactin levels exist.
2. Plasma levels of prolactin and of the 4 antipsychotic medications are related, and that relationship is different among drugs.
3. Plasma levels of prolactin and improvement in Positive and Negative Syndrome Scale (PANSS)[10] total score (and PANSS positive symptoms) are related, and that relationship is different among drugs.
4. Plasma levels of prolactin and change in Extrapyramidal Symptom Rating Scale (ESRS)[11] score are related, and that relationship is different among drugs.

METHOD

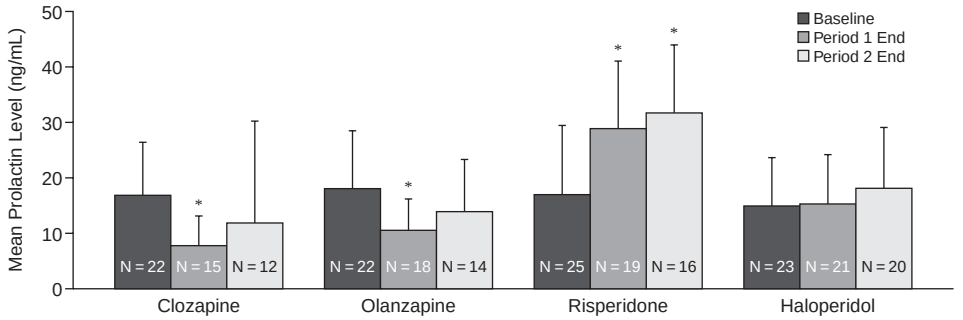
The methods and principal results of this trial were published elsewhere.[12] In brief, 157 patients (133 men, 24 women) with chronic DSM-IV schizophrenia or schizoaffective disorder were randomly assigned to treatment with clozapine (N = 40), olanzapine (N = 39), risperidone (N = 41), or haloperidol (N = 37) in a double-blind, 14-week study. After the procedures were fully explained, all patients provided written informed consent conforming to each institution's review board guidelines, and institutional review board approval was obtained. Data were gathered from June 1996 to December 1999. Before enrollment, the patients were on treatment with a variety of antipsychotics; the doses were reduced during the prestudy screening period and then gradually discontinued after randomization while the doses of the study drugs were being escalated to their target levels.

During the first 8 weeks of the study (period 1), the target fixed doses were 500 mg/day for clozapine, 20 mg/day for olanzapine, 8 mg/day for risperidone, and 20 mg/day for haloperidol; the doses actually achieved were slightly lower. In the last 6 weeks of the study (period 2), the doses were allowed to vary according to clinical judgment. Mean (SD) dose levels (mg/day) achieved during this second period (last observation carried forward) were 526.6 (140.3) for clozapine, 30.4 (6.6) for olanzapine, 11.6 (3.2) for risperidone, and 25.7 (5.7) for haloperidol.

Blood levels for the assays of prolactin and the antipsychotic levels were drawn at baseline, week 5, end of period 1 (week 8), and every 2 weeks thereafter (i.e., at weeks 10 and 12 and at the end of period 2 [week 14]). Clinical assessments included the PANSS[10] and the ESRS.[11]

All plasma assays used in this study were validated. Plasma prolactin level was assayed with a double-antibody radioimmunoassay using a standard calibrated against the National Pituitary Agency (NPA) primary prolactin standard.[13] Plasma levels of risperidone, the active metabolite 9-OH risperidone, and olanzapine were assayed by reversed-phase high-performance liquid chromatography with amperometric detection as described by Le Moing et al.[14] and Catlow et al.[15] Plasma haloperidol and clozapine

Figure 1. Prolactin Levels in Men Treated With Clozapine, Olanzapine, Risperidone, or Haloperidol[a]



[a]Bars indicate standard deviations.
*$p < .05$ vs. baseline.

levels were assayed by gas liquid chromatography with nitrogen-specific detection based on Bianchetti and Morselli[16] and Simpson and Cooper.[17]

Statistical Testing of Hypotheses

Hypothesis 1 was tested using 1-way analysis of variance (ANOVA) with change in prolactin levels from baseline to endpoint (last-observation-carried-forward approach) as dependent variable. A separate analysis was performed for change in period 1 and period 2. Treatment group was used as independent variable. If the ANOVA indicated an overall difference among the treatments, post hoc analyses were conducted to investigate pairwise contrasts. Paired t tests were used to investigate whether a change over time in prolactin levels reached statistical significance in a particular treatment group.

Association between blood medication levels and prolactin levels (hypothesis 2) was investigated with bivariate (Pearson) correlations. A separate analysis was done for each treatment group and for each time period.

Hypotheses 3 and 4 were tested with analysis of covariance. For hypothesis 3, change in the total PANSS score from baseline to endpoint was used as a dependent variable and for hypothesis 4, change in ESRS parkinsonism score was used as a dependent variable, with baseline severity as a covariate. Treatment group and change in blood prolactin level were used as independent variables; interaction between these 2 independent variables was included in the model. A separate analysis was conducted for periods 1 and 2.

RESULTS

Prolactin levels at baseline and at least 1 timepoint during the randomized treatment trial were available in 15 women and 75 men. In view of the small number of women, data analyses were limited to male patients. The averages of prolactin levels in the male patients in the 4 treatment groups at baseline and at the ends of periods 1 and 2 are shown in Figure 1. As indicated in the figure, clozapine and olanzapine treatments were associated with decreases in prolactin levels (statistically significant at period 1). Risperidone resulted in highly statistically significant increases of prolactin in both periods. Haloperidol treatment was associated with smaller increases of prolactin that failed to reach statistical significance.

For the fixed-dose part of the study, hypothesis 1 was tested in 73 male subjects by an ANOVA that used the difference between the prolactin levels at baseline and at the end of period 1 as the dependent variable and medication type as the independent variable. The analysis demonstrated a statistically significant effect of medication type on prolactin levels ($F = 14.76$, $df = 3$, $p < .0001$). Pairwise comparisons using least square means for medication effect indicated that risperidone treatment was associated with significantly greater change in prolactin level than each of the 3 other medications ($p < .002$) and that haloperidol differed from clozapine ($p < .003$) and olanzapine ($p < .026$); no significant differences were detected between olanzapine and clozapine.

Analogous analyses were performed to test hypothesis 1 for the variable-dose part of the study in 62 male subjects; these analyses used the difference between the prolactin levels at the baseline and at the end of period 2 as the dependent variable. The medication effect was significant ($F = 5.26$, $df = 3$, $p < .0028$). Pairwise comparisons again showed significantly higher elevations of prolactin with risperidone treatment than with the other 3 drugs ($p < .034$); the other pairwise comparisons showed no statistically significant differences.

Thus, as predicted by hypothesis 1, there were significant differences among the medications in their effects on prolactin levels. Risperidone was associated with the highest increases of prolactin.

To test hypothesis 2 in male subjects for whom data were available, correlation coefficients between the plasma levels of medications and the plasma levels of prolactin were computed separately for each of the medi-

cations. Olanzapine was the only medication for which plasma levels were significantly related to prolactin in period 1 ($r = 0.51$, $p < .013$, $N = 23$) and period 2 ($r = 0.68$, $p < .002$, $N = 18$).

Hypothesis 3 was tested in 68 men by an analysis of covariance using the difference between the PANSS total score at baseline and at the end of period 1 as the dependent variable, the difference between the prolactin levels at these 2 timepoints as an independent variable, medication as another independent variable, and the PANSS total score at baseline as a covariate. The relation between the prolactin level change and the improvement on the PANSS was not significant ($F = 1.43$, $df = 1$, $p < .24$). Thus, hypothesis 3 was not supported. The hypothesis could not undergo valid testing in period 2 since the doses of medications (and thus, to some extent, the prolactin levels) were determined by clinical judgment.

Since it has been reported that prolactin levels may be related to the improvement of positive symptoms, the analyses for hypothesis 3 were repeated using the positive symptom PANSS subscale score instead of the total PANSS score. Again, the result was not significant.

Hypothesis 4 was tested in 73 men using an analysis of covariance that was analogous to that used to test hypothesis 3; the dependent variable was the difference between parkinsonism scores on the ESRS at baseline and at the end of period 1. The relationship between the prolactin level change and the change in parkinsonism was not significant ($F = 0.40$, $df = 1$, $p < .53$). Hypothesis 4 was not supported.

DISCUSSION

Risperidone caused significantly greater increases of prolactin than the other medications; these increases exceeded the upper limit of normal for men (20 ng/mL). This finding is consistent with other reports.[4,7,8] The prolactin increases appeared to be dose-related; they were higher in period 2 when the average risperidone dose was increased from 8 to 11.8 mg/day.

When evaluating the effects of study medications on prolactin levels, it is important to realize that the baseline levels of prolactin were affected by various prestudy medications (there was no medication-free lead-in period). The statistically significant prolactin decreases observed in period 1 in patients assigned to clozapine and olanzapine were probably caused by the reduction of D_2 blocking effect of prestudy medications. The slight, nonsignificant increases of prolactin levels in period 2 in these patients may have been related to a minor increase of the D_2 blocking effects associated with the dose increases of olanzapine and clozapine in period 2.

Olanzapine and prolactin plasma levels were significantly related when the olanzapine dose was 20 mg/day, and that relationship appeared to strengthen when the dose was increased to a mean of 30.4 mg/day. This relationship may be important to consider when using high doses of olanzapine, a practice that has become common in clinical practice.[18] It appears that the dose range of olanzapine used clinically is approaching the threshold for achieving sustained D_2 inhibition in the pituitary and consequent prolactin elevation. Clearly, risperidone is above this threshold, whereas clozapine is not. The lack of significant correlation between plasma levels of risperidone and prolactin was surprising in view of the apparent dose-response relationship (Figure 1).

Prolactin levels were not associated with clinical improvements or with extrapyramidal side effects. It is possible that these relationships could not be demonstrated in our study because the improvements were very modest, and the extrapyramidal side effects were effectively treated by benztropine.[12] In clinical practice, it is important to keep in mind that high levels of prolactin may be elicited by causes unrelated to antipsychotic medication (e.g., pituitary adenoma).

Our study has several limitations. The small number of women enrolled necessitated limiting the analyses to men. Because of the treatment-resistant nature of the patient sample, the doses of medications, particularly risperidone, were higher than those used in most other clinical circumstances. Different results could have been obtained with other dosing strategies.

Furthermore, although we did collect some data on sexual side effects of hyperprolactinemia, the data were incomplete. Such data collection should be an integral, carefully planned part of future studies of antipsychotics.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

Financial disclosure: Dr. Volavka has received honoraria from and participated in speakers/advisory boards for Lilly and Janssen. Dr. Lindenmayer has been a consultant for and received grant/research support from Lilly and Janssen and has participated in speakers/advisory boards for Lilly, Janssen, and Abbott. Dr. Citrome has been a consultant for Abbott and Lilly; has received grant/research support from Janssen, Lilly, Abbott, and Bristol-Myers Squibb; has received honoraria from Lilly, Novartis, Pfizer, Bristol-Myers Squibb, and Abbott; and has participated in speakers/advisory boards for Lilly, Novartis, Bristol-Myers Squibb, AstraZeneca, Pfizer, and Abbott. Dr. McEvoy has been a consultant for Lilly, GlaxoSmithKline, and Bristol-Myers Squibb; has received grant/research support from Lilly, Janssen, GlaxoSmithKline, and Bristol-Myers Squibb; and has received honoraria from Bristol-Myers Squibb, Janssen, and Lilly. Dr. Lieberman has received grant/research support from Upjohn Pharmacia, Bristol-Myers Squibb, Novartis, Lilly, Janssen, Pfizer, Hoechst, and AstraZeneca; has been a consultant for Upjohn Pharmacia, Bristol-Myers Squibb, Novartis, Lilly, Janssen, Pfizer, and AstraZeneca; and has participated in speakers/advisory boards for Lilly and Janssen.

REFERENCES

1. Chou JCY, Douyon R, Czobor P, et al. Change in plasma prolactin and clinical response to haloperidol in schizophrenia and schizoaffective disorder. Psychiatry Res 1998;81:51–55
2. Seeman P, Lee T. Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. Science

1975;188:1217–1219
3. Zhang XY, Zhou DF, Yuan CL, et al. Risperidone-induced increase in serum prolactin is correlated with positive symptom improvement in chronic schizophrenia. Psychiatry Res 2002;109:297–302
4. Breier AF, Malhotra AK, Su T-P, et al. Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. Am J Psychiatry 1999;156:294–298
5. Markianos M, Hatzimanolis J, Lykouras L. Gonadal axis hormones in male schizophrenic patients during treatment with haloperidol and after switch to risperidone. Psychopharmacology (Berl) 1999;143:270–272
6. Tollefson GD, Kuntz AJ. Review of recent clinical studies with olanzapine. Br J Psychiatry Suppl 1999;37:30–35
7. David SR, Taylor CC, Kinon BJ, et al. The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. Clin Ther 2000;22:1085–1096
8. Markianos M, Hatzimanolis J, Lykouras L. Neuroendocrine responsivities of the pituitary dopamine system in male schizophrenic patients during treatment with clozapine, olanzapine, risperidone, sulpiride, or haloperidol. Eur Arch Psychiatry Clin Neurosci 2001; 251:141–146
9. Kleinberg DL, Davis JM, de Coster R, et al. Prolactin levels and adverse events in patients treated with risperidone. J Clin Psychopharmacol 1999;19:57–61
10. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
11. Chouinard G, Ross-Chouinard A, Annable L, et al. Extrapyramidal Symptom Rating Scale [abstract]. Can J Neurol Sci 1980;7:233
12. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in treatment-resistant patients with schizophrenia and schizoaffective disorder. Am J Psychiatry 2002;159:255–262
13. Sinha YN, Selby FW, Lewis UJ, et al. A homologous radioimmunoassay for human prolactin. J Clin Endocrinol Metab 1973;36:509–516
14. Le Moing JP, Edouard S, Levron JC. Determination of risperidone and 9-hydroxyrisperidone in human plasma by high-performance liquid chromatography with electrochemical detection. J Chromatogr 1993;614: 333–339
15. Catlow JT, Barton RD, Clemens M, et al. Analysis of olanzapine in human plasma utilizing reversed-phase high-performance liquid chromatography with electrochemical detection. J Chromatogr B: Biomed Appl 1995;668:85–90
16. Bianchetti G, Morselli PL. Rapid and sensitive method for determination of haloperidol in human samples using nitrogen-phosphorus selective detection. J Chromatogr 1978;153:203–209
17. Simpson GM, Cooper TA. Clozapine plasma levels and convulsions. Am J Psychiatry 1978;135:99–100
18. Citrome L, Volavka J. Optimal dosing of atypical antipsychotics in adults: a review of the current evidence. Harv Rev Psychiatry 2002; 10:280–291