COMMENT

Evaluation of Insulin Sensitivity in Healthy Volunteers Treated with Olanzapine, Risperidone, or Placebo: A Prospective, Randomized Study Using the Two-Step Hyperinsulinemic, Euglycemic Clamp

MARGARET SOWELL, NITAI Mukhopadhyay, PATRIZIA CAVAZZONI, CHRISTOPHER CARLSON, SUNDER MUDALIAR, SITHIPHOL CHINNAPONGSE, AMY RAY, TRENT DAVIS, ALAN BREIER, ROBERT R. HENRY, AND JAMIE DANANBERG

Lilly Research Laboratories, Eli Lilly & Co. (M.S., N.M., P.C., C.C., A.B., J.D.), Indianapolis, Indiana 46285; and Section of Diabetes, Endocrinology, and Metabolism, Veterans Affairs Medical Center (S.M., S.C., A.R., T.D., R.R.H.), San Diego, California 92161

The primary objective of this study was to evaluate insulin sensitivity in healthy subjects treated with olanzapine or risperidone. Subjects were randomly assigned to single-blind therapy with olanzapine (10 mg/d), risperidone (4 mg/d), or placebo for approximately 3 wk. Insulin sensitivity was assessed pre- and posttreatment using a 2-step, hyperinsulinemic, euglycemic clamp. Glucose and insulin responses were also assessed by a mixed meal tolerance test. Of the 64 subjects randomized, 22, 14, and 19 in the olanzapine, risperidone, and placebo groups, respectively, completed the study procedures. There were no significant within-group changes in the glucose disposal rate or the insulin sensitivity index for the active therapy groups. Further, the results of the mixed meal tolerance test did not demonstrate clinically significant changes in integrated glucose metabolism during treatment with these medications. In summary, this study did not demonstrate significant changes in insulin sensitivity in healthy subjects after 3 wk of treatment with olanzapine or risperidone. (J Clin Endocrinol Metab 88: 5875–5880, 2003)

A TYPICAL ANTIPSYCHOTICS ARE effective therapy for schizophrenia and generally appear to be better tolerated than the conventional agents. Recently, concerns have been raised about a possible association between some atypical antipsychotic medications and new-onset diabetes mellitus (1–3).

Although treatment with many psychotropic medications may be temporally associated with weight gain, reports of severe hyperglycemia with ketoacidosis in the absence of weight gain or shortly after initiation of treatment have led to speculation that some of the atypical antipsychotics may have a rapid, direct effect that impairs insulin secretion or insulin action (1–3). A number of hypothetical mechanisms for such an effect have been postulated based on the receptor binding profiles of the medications, including drug-related decreases in insulin secretion or insulin sensitivity (2, 3).

Previously, we conducted a prospective, randomized study using the hyperglycemic clamp for determining the insulin secretory responses of healthy volunteers before and after 15–17 d of treatment with therapeutic doses of olanzapine or risperidone (4). In that study we did not find that insulin responses to a hyperglycemic challenge were decreased after treatment with these two atypical antipsychotics.

The objective of the current study was to test whether healthy subjects treated with olanzapine or risperidone experienced decreased insulin sensitivity, as assessed by a two-step, hyperinsulinemic, euglycemic clamp.

Subjects and Methods

This was a 3-wk, randomized, placebo-controlled, parallel study of healthy volunteers. Subjects were males or females between 18–65 yr of age, with body mass index (BMI) between 20–27 kg/m², fasting glucose level of 100 mg/dl (5.6 mmol/liter) or less, and no personal or family history of diabetes. Subjects with significant comorbid medical illnesses or using medications associated with alterations in insulin secretion or insulin sensitivity were excluded, as were pregnant or lactating females and sexually active females not actively practicing birth control. In addition, subjects with prior exposure to antipsychotic medications or using medications with primary central nervous system activity or recreational drugs were excluded. All subjects provided written informed consent after study procedures and possible adverse effects of treatment were explained. The protocol was approved by the University of California-San Diego institutional review board.

Screening studies, physical examination, and laboratory tests were administered, and medical history was collected to determine eligibility for study enrollment. Subjects underwent a 3- to 7-d outpatient period of diet stabilization, followed by hospitalization. After undergoing baseline testing, subjects were randomized at a 1:1:1 ratio for treatment with olanzapine (10 mg/d), risperidone (4 mg/d), or placebo for approximately 3 wk. Study medications were begun at half-maximal doses and titrated over 4 d. Subjects were allowed up to three passes (72 h each) during the study, but were required to be readmitted to the in-patient unit 72 h before the final metabolic testing. The mixed meal tolerance test (MMTT) and euglycemic clamp...
were performed on each subject 1 and 2 days after admission, respectively. These measures were repeated sequentially at the end of the treatment period. Investigative staff performing the MMTT and clamp procedures were blinded to treatments.

**Hyperinsulinemic, euglycemic clamp**

A 5-h, two-step, hyperinsulinemic, euglycemic clamp (5) was used to assess peripheral insulin sensitivity in subjects after a 12-h fast. Blood glucose levels were clamped at approximately 90 mg/dL (5 mmol/liter). Insulin action was assessed at two insulin infusion rates: 20 pmol/m²/min (120 pmol/m²/min, low dose) and 120 pmol/m²/min (720 pmol/m²/min, high dose). Clamp studies were initiated by infusing low dose insulin for 3 h to detect changes in insulin sensitivity, followed by the high dose insulin for an additional 2 h to detect changes in maximal responsiveness (6). These insulin infusion rates result in steady state serum insulin concentrations that approximate the ED$_{50}$ (low dose) and the maximum (high dose) concentration for stimulation of peripheral glucose uptake in nonobese, nondiabetic subjects. For this analysis, low insulin, steady state concentrations were defined as the values at the 140- to 160-min interval of the clamp, and the high insulin concentrations as the values at the 240- to 260-min interval. Insulin sensitivity was quantitated as M/I, where M was the steady state glucose disposal rate during the time interval, and I was the mean concentration of steady state insulin during the same time interval.

**MMTT**

An MMTT was conducted to provide an assessment of overall integrated glucose metabolism. After a 12-h fast, subjects were given two standard meals (breakfast and lunch) 4 h apart; each meal consisted of 33.3% of total daily calories and the following caloric distribution: 55% carbohydrates, 30% fat, and 15% protein. Blood glucose and insulin levels were measured hourly beginning 1 h before the first meal and continuing for 3 h after the second meal. The integrated glucose and insulin responses were measured by the area under the curve (AUC) for both the total area as well as the area above the fasting level and were analyzed by F test using an ANOVA model.

**Analysis of blood samples**

Insulin was assayed using the IMMULITE 2000 insulin assay (Diagnostic Products, Los Angeles, CA), which has an intraassay coefficient of variation of 2.5–8.3% and an interassay coefficient of variation of 4.4–8.6%. Plasma venous glucose was assayed using a glucose oxidase-coupled assay (YSI, Hong Kong). Free fatty acids (FFA) were assayed using an enzymatic assay (Wako Chemicals, Richmond, VA) by acetylation of coenzyme A. End products were measured on a Hitachi 717 Analyzer (Hitachi High Technologies, San Jose, CA).

**Statistical analysis**

Patient demographics information, age, and baseline BMI were analyzed by an F test, and count data for sex and ethnicity were compared using Fisher’s exact test. An ANOVA model was used to analyze the primary outcome measure (i.e., mean change from baseline to end point in insulin sensitivity index), and other continuous data were used to assess the overall differences among the three treatment groups (using an F test). Pairwise comparisons of the individual active therapies to placebo were examined using a t test. The ANOVA linear regression model examining baseline to end point changes between groups in fasting glucose, insulin, and FFA included baseline values as covariates. A paired t test was used to evaluate the treatment effect within each group. All tests of hypothesis were performed at a two-sided 5% level of significance. The Statistical Analysis System version 8 (SAS Institute, Inc., Cary, NC) was used to perform all analyses.

**Results**

**Subject disposition and demographics**

A total of 64 subjects were randomized in the study; 9 subjects discontinued after randomization. A statistically significant difference in overall subject disposition was observed between the olanzapine and risperidone treatment groups ($P = 0.004$), as 7 of 21 subjects in the risperidone treatment group were discontinued from the study. In the risperidone group, 3 subjects withdrew consent: 1 subject due to patient unwillingness to return to center, 1 subject due to anxiety, and 1 subject due to discomfort with the clamp procedure. In addition, 4 subjects in the risperidone group were discontinued because they did not meet the protocol criteria or were not compliant with the protocol: 1 subject had a positive drug screen, and 3 subjects were noncompliant with the study drug-dosing regimen. In the placebo group, 2 subjects discontinued because they did not meet the protocol criteria or were not compliant with the protocol: 1 subject had a positive drug screen, and 1 was noncompliant with the study drug-dosing regimen. No subjects discontinued in the olanzapine group. Of the 55 subjects who completed the protocol, 22 received olanzapine, 14 received risperidone, and 19 received placebo treatment for 21–23 d.

There were no significant between-treatment group differences in the mean age (olanzapine, 35.6 ± 15.7; risperidone, 32.9 ± 10.4; placebo, 31.9 ± 12.9 yr) or percentage of male subjects (olanzapine, 77.3%; risperidone, 57.1%; placebo, 68.4%). The percentage of Caucasian subjects was significantly greater in the olanzapine group (90.9%) compared with the placebo group (57.9%; $P = 0.027$), but not compared with the risperidone group (78.6%; $P = 0.357$). There were also no significant between-treatment group differences in BMI (olanzapine, 22.70 ± 2.26; risperidone, 22.8 ± 2.73; placebo, 23.83 ± 2.28 kg/m$^2$).

**Change in weight and levels of fasting glucose, insulin, and FFA**

Subjects in the olanzapine (1.95 ± 1.29 kg) and risperidone (1.61 ± 1.29 kg) groups gained significantly more weight ($P < 0.001$ within olanzapine and risperidone groups and vs. placebo) during the study period than subjects in the placebo group (−0.22 ± 0.90 kg). However, there was no significant difference between the olanzapine and risperidone treatment groups in mean weight gain.

Table 1 summarizes findings for baseline and end-point levels of fasting glucose, insulin, and FFA. Fasting glucose and fasting insulin levels were significantly different among the three groups at baseline, with the subjects randomly assigned to risperidone having higher levels of both compared with the olanzapine and placebo groups (Table 1). Fasting insulin increased in both the olanzapine and placebo groups. However, only the change within the olanzapine group was statistically significant ($P = 0.009$, olanzapine; $P = 0.071$, placebo within group). Overall, there were no significant differences in the end-point fasting insulin ($P = 0.824$) and baseline to end-point changes in fasting insulin between the treatment groups ($P = 0.325$). There was a small, but statistically significant, within-group change in fasting glucose level observed for the olanzapine group ($P = 0.023$, Table 1); however, this change was not significantly different from the small variations in fasting glucose observed for the placebo ($P = 0.281$, olanzapine vs. placebo) and risperidone ($P = 0.384$, olanzapine vs. risperidone) groups. In addition,
End-point fasting glucose levels were not significantly different among the three treatment groups \( (P = 0.413) \). End-point fasting FFA concentrations decreased significantly within all three treatment groups compared with baseline values \( (P = 0.031) \); however, no significant differences were observed among treatment groups.

**Hyperinsulinemic, euglycemic clamp**

**Low insulin phase.** In all treatment groups, the mean glucose levels during the low insulin steady state achieved the target glucose level of approximately 90 mg/dl (5 mmol/liter), with the mean steady state insulin level at approximately 27 \( \mu U/\text{m}^2\text{-min} \) (162 pmol/liter) in both the pre- and posttreatment clamp studies. The glucose disposal rate \( (M) \) was slightly higher at end-point for the placebo group (data not shown; \( P = 0.019 \), within group). The small decrease in glucose disposal in the risperidone group was statistically significant compared with placebo (data not shown; \( P = 0.045 \)), but was not different from the change observed for the olanzapine group (data not shown; \( P = 0.215 \)). There was no significant difference in the mean change in the glucose disposal rate between the olanzapine and placebo groups (data not shown; \( P = 0.332 \)).

Results for baseline and end-point insulin sensitivity index

![Fig. 1. Insulin sensitivity, M/I. A, Low insulin steady state. B, High insulin steady state. Results are expressed (M/I ± SD) for the three treatment groups at the low insulin (A) and high insulin (B) steady states. PLC, Placebo; OLZ, olanzapine; RIS, risperidone. PLC, Placebo; OLZ, olanzapine; RIS, risperidone. Conversion to Systeme International units for glucose, mg/dl ÷ 18 = mmol/liter; for insulin, \( \mu U \times 6 = \text{pmol/liter} \).](https://academic.oup.com/jcem/article-abstract/88/12/5875/2661496)

**TABLE 1. Levels of fasting glucose, insulin, and FFA**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (( \mu U/\text{m}^2\text{-min} ))</th>
<th>FFA (mEq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change to end point</td>
<td>End point</td>
</tr>
<tr>
<td>PLC (n = 19)</td>
<td>87.2 ± 6.2(^a)</td>
<td>0.3 ± 5.0</td>
<td>87.5 ± 6.7</td>
</tr>
<tr>
<td>OLZ (n = 22)</td>
<td>86.4 ± 4.7(^a)</td>
<td>2.3 ± 4.4(^b)</td>
<td>88.7 ± 6.7</td>
</tr>
<tr>
<td>RIS (n = 14)</td>
<td>91.4 ± 6.7(^e)</td>
<td>-0.8 ± 6.7</td>
<td>90.6 ± 5.9</td>
</tr>
</tbody>
</table>

Baseline, change (baseline to end point), and end point means ± SD for fasting glucose, insulin, and FFA for the three treatment groups are shown. PLC, Placebo; OLZ, olanzapine; RIS, risperidone. Conversion to Systeme International units for glucose, mg/dl ÷ 18 = mmol/liter; for insulin, \( \mu U \times 6 = \text{pmol/liter} \).

\( a \ P < 0.05 \) overall.

\( b \ P < 0.031 \) within group.

\( c \ P = 0.023 \) within group.

\( d \ P = 0.009 \) within group.

\( e \ P = 0.003 \) overall.
(M/I) for the three treatment groups are shown in Fig. 1A. No significant within- or between-treatment differences were noted in the change (absolute value or percent change from baseline) in the insulin sensitivity index at the low insulin concentration after 3 wk of treatment. Ranges for the change in M/I ([mg/kg × min] per μU/ml) at low insulin steady state were 0.147 to 0.212 among olanzapine-treated subjects, 0.110 to −0.112 among risperidone-treated subjects, and 0.414 to −0.102 among subjects receiving placebo.

High insulin phase. The mean glucose levels during high insulin steady state achieved the target glucose level of approximately 90 mg/dl (5 mmol/liter) with mean steady state insulin levels near 200 μU/m²·min (1200 pmol/liter) in both the baseline and end-point clamp studies. There were no significant differences in the mean change in glucose disposal rate within each treatment group (data not shown; P = 0.966, olanzapine; P = 0.166, risperidone; P = 0.271, placebo) or among the three treatment groups (data not shown; P = 516, overall). There were also no significant differences within group or between the treatment groups in the mean change in M/I at the high insulin steady state (Fig. 1B). The changes in M/I ([mg/kg × min] per μU/ml) ranged from 0.072 to 0.039 among olanzapine-treated subjects, 0.023 to −0.036 among risperidone-treated subjects, and 0.014 to −0.026 among placebo-treated subjects.

The mean percent change in M/I at the high insulin steady state was as follows: subjects in the olanzapine group, 6.9% ± 24.5%; subjects in the risperidone group, −0.7% ± 21.4%; and subjects in the placebo group, −4.7% ± 17.9%.

MMTT

Glucose responses. Mean glucose levels sampled at each time point during the MMTT are shown in Fig. 2A, and integrated AUC for glucose is presented in Table 2. Peak glucose levels after the first meal did not significantly change in any of the treatment groups, whereas a small increase in peak glucose was noted in all treatment groups after the second meal (lunch). Although the mean within-group increase [7.3 mg/dl (0.41 mmol/liter)] in peak glucose during meal 2 for the olanzapine group was statistically significant (P = 0.039), this change was not different from the mean increases observed for either the risperidone [2.4 mg/dl (0.13 mmol/...
TABLE 2. Integrated glucose and insulin responses from the MMTT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glucose AUC (mg/dl·min (×10^3))</th>
<th>Insulin AUC (µU/min (×10^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change at end point</td>
</tr>
<tr>
<td>PLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52.7 (3.5)</td>
<td>−0.18 (2.88)</td>
</tr>
<tr>
<td>Above fasting</td>
<td>5.5 (2.6)</td>
<td>0.32 (2.84)</td>
</tr>
<tr>
<td>OLZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50.9 (3.0)</td>
<td>1.85 (3.42)</td>
</tr>
<tr>
<td>Above fasting</td>
<td>5.0 (3.2)</td>
<td>0.80 (3.19)</td>
</tr>
<tr>
<td>RIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53.1 (3.1)</td>
<td>0.47 (2.25)</td>
</tr>
<tr>
<td>Above fasting</td>
<td>5.8 (2.7)</td>
<td>0.050 (2.94)</td>
</tr>
</tbody>
</table>

Results are expressed as the mean (sd) baseline and mean change (baseline to end point) AUC. The AUC was calculated as the total AUC and as the AUC above the baseline fasting level. Conversion to Systeme International units: for glucose, mg/dl ÷ 18 = mmol/liter; for insulin, µU × 6 = pmol/liter. PLC, Placebo; OLZ, olanzapine; RIS, risperidone.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a P</td>
<td>0.018 OLZ within group; P = 0.033, OLZ vs. PLC.</td>
</tr>
</tbody>
</table>

The glucose responses during the MMTT were also evaluated as both the total AUC and the AUC above the fasting glucose level (Table 2). For the placebo group, the total AUC declined slightly, whereas the AUC above the fasting level was slightly increased at end point. For both active therapy groups, the integrated glucose response (total AUC and AUC above fasting level) was slightly higher at end point. The small increase in total glucose AUC (but not AUC above fasting) in the olanzapine group did achieve statistical significance (P = 0.180 within group; P = 0.033 vs. placebo). However, there were no significant overall between-group differences in the end-point integrated glucose AUC (data not shown; P = 0.674) or in the baseline to end-point change in integrated glucose response (Table 2; P = 0.092).

Insulin responses. Mean insulin levels at each time point sampled during the MMTT are shown in Fig. 2B and integrated area under curve for insulin in Table 2. Peak insulin levels after meal 1 were not significantly changed in any of the treatment groups. The mean changes in insulin levels after the second meal were significantly increased within both active therapy groups [olanzapine, 7.64 µU/m²·min (45.84 pmol/liter), P = 0.009; risperidone, 9.27 µU/m²·min (55.62 pmol/liter), P = 0.036]. Neither of these changes was different from the increase [2.00 µU/m²·min (12.00 pmol/liter)] observed in the placebo group (olanzapine vs. placebo, P = 0.194; risperidone vs. placebo, P = 0.138). The integrated insulin responses (total AUC and AUC above baseline) were slightly increased in all treatment groups at end point (olanzapine, 10.9%; risperidone, 5.6%; placebo, 7.9%), although none of the changes was statistically significant.

Discussion

Treatment-emergent abnormalities of glucose metabolism have been reported in patients treated with atypical antipsychotics. These include reports of newly identified cases of diabetes, hyperglycemia, diabetic ketoacidosis, and hyperosmolar, hyperglycemic, nonketotic syndrome (1–3). In some instances, newly identified cases of diabetes were reported in the absence of weight gain or other known risk factors for diabetes or shortly after initiation of the antipsychotic. These observations have led to a suggestion that some of the atypical antipsychotic medications may have an acute, direct effect on insulin secretion or insulin sensitivity.

We have previously reported the results of a prospective study in which we found no significant weight-independent effects on insulin secretion or insulin sensitivity, as assessed by a 4-h hyperglycemic clamp in healthy subjects treated for 2.5 wk with olanzapine or risperidone (4). Using a two-step hyperinsulinemic, euglycemic clamp in the current study, we found that the 3-wk treatment with olanzapine or risperidone was not associated with a significant change in insulin sensitivity or in maximum tissue responsiveness to insulin.

The absence of a significant decrease in insulin sensitivity during olanzapine or risperidone treatment is in contrast to results reported for several other medications that have been associated with treatment-emergent diabetes. For example, euglycemic clamp studies of patients with hypertension treated between 4 and 8 wk with β-adrenergic antagonists revealed a 22–23% decrease in the insulin sensitivity with atenolol (7, 8) and a 28% decrease in insulin sensitivity with metoprolol (7). In a study of 10 healthy, normal weight volunteers, after only 7 d of exposure to prednisone (30 mg/d), a 2-fold decrease in insulin sensitivity was assessed by glucose disposal rate at steady state using the euglycemic clamp (9). Treatment of healthy men with the antihuman immunodeficiency virus protease inhibitor, indinavir, was also shown to decrease insulin sensitivity by 17% after 4 wk (10) and by 34% after a single oral dose (11) using euglycemic clamps. The results of this study suggest that olanzapine and risperidone, unlike the medications described above, do not have an acute, direct effect that promotes insulin resistance.

Some small, but statistically significant, changes in glucose and insulin responses were observed during the final MMTT. In general, the directions of the observed changes were similar between the two active therapy groups. Although the magnitude of the changes varied, no significant differences between the olanzapine and risperidone groups were demonstrated. The results of this study cannot, however, resolve whether there were subtle qualitative or quantitative differences in postprandial glucose or insulin responses in subjects treated with olanzapine or risperidone. Nevertheless, results from the euglycemic clamps strongly suggest that the small changes in postprandial glucose and insulin observed during the MMTT in subjects treated with olanzapine or risperidone were not clinically significant and were unlikely to be due to a change in insulin sensitivity.

Potential limitations of the current study include the relatively short duration of exposure (~3 wk) and evaluation of a relatively small number of subjects. The main objective of this study was to evaluate a potential acute direct effect of olanzapine or risperidone on insulin sensitivity. At the time this study protocol was drafted, 6 of 35 published case reports of diabetes temporally associated with atypical antipsychotic treatment occurred within 30 d of exposure. As also noted above, marked effects on insulin sensitivity have
been detected with prednisone and indinavir after short exposures. Therefore, a 3-wk exposure seemed reasonable, particularly with the use of the highly sensitive, two-step, hyperinsulinemic, euglycemic clamp to quantitate insulin action. The results of the current study cannot address potential effects of olanzapine or risperidone after longer-term treatment or with higher doses of these medications, and caution is warranted in extrapolating these results to larger patient groups or to individuals with different baseline characteristics.

The use of healthy subjects rather than patients with schizophrenia might also be considered a limitation. However, the use of healthy volunteers is important for the identification of any direct effect of these agents on insulin sensitivity that is independent of changes that might be associated with underlying mental illness. For patients with major depressive illness, there is some evidence supporting a state-related decrease in insulin sensitivity (12–14). Although specific data are lacking for patients with psychotic illnesses, it is reasonable to consider that episodes of acute illness in schizophrenia and bipolar disorder may impact insulin sensitivity. Nevertheless, the results of this prospective study using healthy volunteers appear to be consistent with the results of a cross-sectional study that examined insulin sensitivity. Nevertheless, the results of this prospective study using healthy volunteers appear to be consistent with the results of another study that examined glycemic control in patients with schizophrenia. Using the hyperinsulinemic, euglycemic clamp, Newcomer et al. (15) found no significant difference in glucose disposal rates among matched groups of overweight patients with schizophrenia treated with olanzapine, risperidone, or typical antipsychotic medications. They did find significantly lower glucose disposal rates in the overweight patients with schizophrenia treated with antipsychotic medications compared with those in slim healthy controls.

In summary, the results of this prospective, randomized study of healthy volunteers did not demonstrate a significant change in whole body insulin sensitivity or maximal tissue responsiveness to insulin after 3 wk of treatment with olanzapine or risperidone. The results of the MMTT also suggest that treatment with these medications was not associated with clinically significant changes in overall integrated glucose metabolism after the ingestion of a mixed composition meal. Overall, the results of this study do not support the hypothesis that olanzapine or risperidone has an acute, direct effect to decrease insulin sensitivity.

Acknowledgments

Received November 30, 2002. Accepted August 8, 2003.

Address all correspondence and requests for reprints to: Dr. Patrizia Cavazzoni, Lilly Research Laboratories, Eli Lilly & Co., Lilly Corporate Center, Indianapolis, Indiana 46285. E-mail: p_cavazzoni@lilly.com.

This work was supported by Eli Lilly & Co.

Current address for M.S.: GlaxoSmithKline Pharmaceuticals, 1250 South Collegeville Road, Collegeville, Pennsylvania 19426.

References

15. Newcomer JW, Haupt DW, Melson AK, Schweiger J 2002 Indinavir insulin resistance measured with euglycemic clamps during antipsychotic treatment in schizophrenia. Biol Psychiatry 51:2SS.