The Apparent Effects of Ziprasidone on Plasma Lipids and Glucose

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Background: We examined the effects of ziprasidone on body mass index (BMI) and serum levels of glucose, cholesterol, and triglycerides.

Method: As part of a multicenter study examining different strategies for switching to ziprasidone from other antipsychotics, we evaluated weight and serum glucose, cholesterol, and triglyceride measurements at baseline and following 6 weeks on ziprasidone treatment in 37 patients at our site.

Results: Short-term treatment with ziprasidone appeared to lead to significant reduction in serum cholesterol ($p < .001$) and triglyceride levels ($p = .018$) independent of changes in BMI. Ziprasidone treatment appeared to have no significant effect on BMI or glucose level, perhaps due to the small number of subjects.

Conclusion: Ziprasidone appears to independently lead to a lowering of serum lipid levels.

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With the introduction of clozapine and other new, "atypical" antipsychotic medications, there has been a dramatic reduction in extrapyramidal side effects (EPS) and a concomitant increased focus on other side effects during treatment with antipsychotic medications.[1] Dramatic increases in weight,[2] increasing incidence of diabetes,[3] and other metabolic changes[4] have received increasing attention. For example, with clozapine, the oldest and most studied of the atypical antipsychotics, significant weight gain has been found along with an increase in glucose levels related to the plasma levels of clozapine.[2,5] Increased triglyceride levels and, less consistently, increased cholesterol levels have also been reported.[6] In addition, weight gain, new-onset diabetes, and ketoacidosis have apparently been associated with olanzapine.[7] The effects of these changes on long-term health status and compliance have been increasingly discussed.

Ziprasidone is a new antipsychotic that has recently been introduced to the market.[8] As with other atypical antipsychotics, it has a high serotonin-2 ($5\text{-}HT_2$)/dopamine-2 (D_2) ratio, acting as an antagonist at these receptors. However, it is a weak antagonist for the histamine H_1 receptor, and it is unique among the atypical antipsychotics by showing agonist activity at the $5\text{-}HT_{1A}$ receptor. Like other recently introduced antipsychotics, it shares a low liability for causing EPS, but unlike those agents (clozapine, risperidone, olanzapine, and quetiapine), it does not appear to produce any change in weight, perhaps due to its $5\text{-}HT_{1A}$ activity and its low H_1 activity. Due to concerns about the effects of other atypical antipsychotics on weight and lipid and glucose levels, the effects of ziprasidone on these measures have already received preliminary examination, although that study[9] did not examine these effects independent of weight change. It would be expected that for some patients switching from a drug that causes weight gain to a weight-neutral drug, weight loss alone could affect plasma lipid and glucose levels.

The purpose of this analysis was to examine the short-term association of treatment with ziprasidone and changes in serum levels of cholesterol, triglycerides, and glucose while controlling for weight changes.

METHOD

Data were available from 37 patients at the University of Southern California Medical Center (Los Angeles, Calif.) who participated in a multicenter study of ziprasidone that examined different strategies for switching stable outpatients from other medications to ziprasidone. The patient group described in the present study included all subjects who completed this 6-week trial. The study was approved by our local institutional review board, and all participants gave written informed consent. Only relevant details of this switch study will be described.

Adult outpatients with schizophrenia or schizoaffective disorder by DSM-IV criteria who had been on treatment with a single antipsychotic for at least 3 months were switched to open-label ziprasidone using 1 of 3 randomly assigned strategies. In all 3 strategies, patients were started on ziprasidone, 40 mg p.o. b.i.d., on day 1, and discontinued their previous antipsychotic by day 7. After week 1, patients received flexible doses between 40 and 80 mg p.o. b.i.d. Since all subjects had been off their previous medication for a minimum of 5 weeks before the 6-week collection, the specific switch strategy was ignored for the purposes of the analysis described in this article. No other chronically administered psychotropic medication was permitted for 1 month before the study or during the 6-week study period. Further, patients with significant laboratory abnormalities or unstable or significant medical conditions were excluded. No dietary changes were required, and no patients were dieting during the study period. Physical examination and laboratory testing including measurements of height, weight, and nonfasting (random) serum glucose, cholesterol, and triglyceride levels were performed at baseline and week 6.

Weight was converted to body mass index (BMI) using the formula weight (kg)/(height [m])^2. Subjects were also grouped by whether their previous medication had been olanzapine, risperidone, or a typical antipsychotic. Since age and sex of subjects were not significantly associated with change in BMI alone or by interaction, these were not reported in the analyses for this study. Further, age and sex of subjects were used with change in BMI in multiple regressions against changes in serum glucose, cholesterol, and triglyceride levels. In none of these analyses was age or sex significantly associated with changes in these serum levels (analyses available upon request).

Changes in BMI and in serum glucose, cholesterol, and triglyceride levels were each analyzed with a repeated-measures analysis of variance (ANOVA), using baseline and week 6 data as the repeated measure and previous medication (olanzapine, risperidone, or typical antipsychotics) as a grouping variable. Since previous medication was not significantly associated with outcome changes in study variables, the changes in BMI and laboratory values were explored with Pearson product moment correlations. All analyses were performed using SYSTAT 8.0.[10]

RESULTS

Although outside the scope of the present report, psychopathology was stable or improved in the majority of patients (36/37). Full data were available for all 37 subjects. By the end of the 6-week trial, the subjects were receiving a mean ± SD of 62.16 ± 13.97 mg b.i.d. of ziprasidone, a moderate dose. Their relevant data are summarized in Table 1.

Table 1. Patient Characteristics and Baseline and Week 6 Values for Outcome Variables in 37 Patients Switched to Ziprasidone Treatment

Characteristic		Value
Sex, M/F		26/11
Age, y, mean (SD)		35.88 (11.16)
Race, N		
Black		5
White		6
Hispanic		23
Asian		2
Other		1
Height, m, mean (SD)		1.70 (0.07)
Previous medication, N		
Olanzapine		15
Risperidone		12
Typical antipsychotics		10
Outcome variable[a]	Week 0	Week 6
BMI	30.06 (7.11)	29.82 (6.69)
Glucose	104.97 (34.84)	100.97 (20.65)
Cholesterol	210.65 (51.74)	183.08 (47.47)
Triglycerides	262.68 (193.49)	176.30 (101.24)

[a]All outcome variables shown as mean (SD).
Abbreviation: BMI = body mass index.

Analysis showed no differences in BMI based on previous medication ($F = 0.04$, $df = 2,34$; $p = .96$). Further, there was no significant change in BMI during the 6-week trial ($F = 1.69$, $df = 1,34$; $p = .20$), nor were there differential changes based upon patients' previous medication ($F = 90$, $df = 2,34$; $p = .42$).

Similarly, serum glucose levels did not significantly change during this 6-week trial, as determined by a repeated-measures ANOVA with previous medications as a grouping variable. Neither previous medications ($F = 1.39$, $df = 2,34$; $p = .263$), the 6-week trial ($F = 0.183$, $df = 1,34$; $p = .672$), nor the interaction of previous medications with the 6-week trial ($F = 2.50$, $df = 2,34$; $p = .098$) significantly affected glucose levels.

Serum cholesterol levels did significantly decrease from baseline to week 6 ($F = 20.48$, $df = 1,34$; $p < .001$). The previous medication patients had been taking did not significantly affect cholesterol levels, either independently ($F = 0.20$, $df = 2,34$; $p = .82$) or differentially over the 6-week trial ($F = 1.84$, $df = 2,34$; $p = .18$).

Serum triglyceride levels also decreased significantly from baseline to week 6 ($F = 6.24$, $df = 1,34$; $p = .018$). Again, neither previous medications alone ($F = 0.298$, $df = 2,34$; $p = .74$) nor in interaction with the 6-week trial ($F = 1.41$, $df = 2,34$; $p = .26$) significantly affected triglyceride levels.

To further explore the change in BMI and changes in glucose, cholesterol, and triglyceride levels, change scores for each measure were computed by subtracting the 6-week value from the baseline value of each. Then the change in BMI was correlated with the change in glucose levels, the change in cholesterol levels, and the change in triglyceride levels. The correlations between

change in BMI and the change in glucose levels (Pearson r = 0.222, N = 37, p = .186) and the change in cholesterol levels (Pearson r = 0.11, N = 37, p = .514) were not significant. This suggests that the decrease in cholesterol levels was independent of change in BMI. Although the correlation between change in BMI and change in triglyceride levels was significant (Pearson r = 0.409, N = 37, p = .018), the amount of variation in triglyceride levels predicted by this relationship is small ($r^2 = 0.167$), suggesting that a large part of the change in triglyceride levels is independent of change in weight.

DISCUSSION

These results suggest that a 6-week trial of ziprasidone leads to lower levels of cholesterol and triglycerides independent of changes in weight (BMI). However, changes in weight also independently affect glucose and triglyceride levels.

Since this study is preliminary, a number of limitations must be noted. First, in the absence of a placebo control group, it is unclear whether these changes are due to ziprasidone or to the withdrawal of the previous medications. Second, the serum samples were nonfasting. Collection in a uniform manner would decrease a possible source of error and could decrease the variance of our measurements, decreasing the chance of type 2 errors. In addition, our sample was small, especially for evaluating the effects of the specific previous medications. Small sample size may also explain why our results regarding weight loss when switching from other medications are discrepant from results obtained from larger samples.[9] Finally, this was a short-term study and therefore could not address whether these improvements in lipid levels would be sustained over time.

Despite these caveats, the present results are intriguing. Ziprasidone may be the only atypical antipsychotic that does not lead to weight gain and may decrease levels of cholesterol and triglycerides. Patients with schizophrenia comprise a population at higher risk for certain medical comorbidities and increased mortality. An antipsychotic that has a potential beneficial effect on hyperlipidemia, a known cardiovascular risk factor, may have a positive impact on general health status. However, there are also concerns about ziprasidone leading to corrected QT prolongation. Clearly, these results need replication and extension.

Drug names: clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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