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Plasma concentrations of high-dose olanzapine in a double-blind crossover study

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Olanzapine is structurally similar to clozapine but has not been shown at routine doses to share the superiority of clozapine to traditional antipsychotics in treatment-resistant patients. Olanzapine, however, has been increasingly used in higher doses as clinicians attempt to find a more tolerable therapy for those refractory to conventional agents. This study examined the relationship of high-dose olanzapine plasma concentrations to symptoms, adverse effects, smoking, and gender. Thirteen patients participated in a double blind 16-week crossover study (8 weeks each arm) of olanzapine (50 mg/day) compared to clozapine (450 mg/day). Women had significantly higher plasma olanzapine levels than men at each time point in each arm (weeks 4, 6, and 8). At 8 weeks women had a steady-state olanzapine level of 278 ± 62 ng/ml while men had a steady-state level of 127 ± 47 ng/ml ($p = 0.005$). At week 4, olanzapine levels tended to be higher in those who had been on clozapine previously (205 ng/ml) compared to those who received olanzapine in the first arm (105 ng/ml). Cigarette intake was negatively correlated to olanzapine plasma concentrations (week 8: $r = -0.86$, $p < 0.05$). Plasma levels were significantly higher in those experiencing constipation (176 vs. 82 ng/ml; $p = 0.022$). Plasma levels of olanzapine were not associated with symptom response and anticholinergic effects were seen at greater frequency with higher olanzapine concentrations. In conclusion, this study reports plasma olanzapine levels at high fixed doses of olanzapine (50 mg/day) in relation to side effects, symptoms, smoking, and gender. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — olanzapine; plasma level; smoking; sex; clozapine; gender; high dose

INTRODUCTION

Olanzapine's molecular structure and receptor binding profile are similar to that of clozapine but its efficacy for treatment-resistant schizophrenia at standard doses has been disappointing (Conley *et al*., 1998, 1999). Clinicians, however, are increasingly prescribing olanzapine for treatment-resistant patients at doses higher than 20 mg/day presumably in hope of achieving efficacy with a lower side-effect burden than that of clozapine, or for patients who refuse weekly blood-work (Bronson and Lindenmayer, 2000). In fact, in 2001, over 25% of olanzapine-treated patients in New York State public in-patient facilities were receiving more than 20 mg/day, despite the limited published data concerning the efficacy or safety of such doses (Citrome and Volavka, 2002).

The relationship of olanzapine plasma concentrations to response has not been well characterized and the few published reports have recommended different plasma levels for maximizing efficacy (>9 and >23 ng/ml) (Perry *et al*., 1997, 2001), however different sampling times were noted for these studies. Dopamine$_2$ (D_2) blockade and plasma levels have been found to correlate very well with doses up to 20 mg/day, however, D_2 occupancy and plasma levels above 20/mg day are not well correlated to dose and appear highly variable (Harvey *et al*., 2001). Thus, even less information is available regarding the relationship of side effects and efficacy to plasma levels, especially for the use of higher doses. Likewise, the impact of variables such as gender or smoking status on olanzapine's metabolism and associated plasma levels at higher doses has not been investigated.

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We have completed a prospective, double-blind, randomized, crossover study comparing high-dose olanzapine (50 mg/day) to fixed-dose clozapine (450 mg/day) in 13 patients with treatment-resistant schizophrenia. Efficacy and general side-effect results have been published elsewhere. Here, we report on the relationship of olanzapine plasma levels to gender, smoking status, and side-effect occurrence.

METHODS

All study participants carried a diagnoses of schizophrenia (DSM-IV criteria), and were considered treatment-resistant as evidenced by: persistent positive psychotic symptoms (item score $\geq$4 (moderate)) on at least 2–4 positive symptom items on the BPRS (rated on a 1–7 scale)); at least moderately severe illness at study entrance as defined by a total BPRS score $\geq$45 (18-item scale) and a score of $\geq$4 (moderately ill) on the CGI; documentation of prior failed trials on two different antipsychotics of at least 6 weeks duration at doses of at least 600 mg/day CPZ equivalents; and no period of good social and/or occupational functioning within the last 5 years. Patients who had a documented history of clozapine failure were excluded from the study.

Participants were randomly assigned to either olanzapine or clozapine and were titrated to the targeted doses of 50 or 450 mg/day, respectively, over 2 weeks. After 8 weeks total treatment, subjects were crosstitrated to the other medication over the first 2 weeks of the second 8-week treatment phase. At no time were the patients medication-free. Subjects' weights and blood pressures were measured, and subjects were questioned about side effects on a weekly basis throughout the study. BPRS ratings were completed weekly, and the Simpson Angus Scale (SAS) and the Barnes Akathisia Scale (BAS) were administered biweekly. Routine concomitant medications with primarily CNS activity were not permitted in this protocol.

Plasma samples were obtained prior to morning dosing at weeks 4, 6, and 8 of each treatment period. High-performance liquid chromatography (HPLC) method was then used to measure plasma concentrations olanzapine and all levels were measured at the same time. The amount of cigarette smoking was calculated as mean number of cigarettes daily. This was gathered by daily direct patient questioning, nurse supervision, and treatment-team consensus prior to study completion.

This study was approved by the University of Maryland and the State of Maryland Institutional Review Boards. All subjects were considered able to consent by use of the Evaluation to Sign Consent (DeRenzo *et al*., 1998), and all signed consent before research participation after study procedures and possible side effects were explained to them. Data on efficacy and detailed side effects are presented elsewhere (Conley *et al*., 2003; Kelly *et al*., 2003).

Continuous measures were compared using the Student's *t*-test and the Wilcoxon exact test. The Fisher's exact chi-square test was used for dichotomous variables. Spearman's correlation was used to examine the relationship between smoking intake and plasma concentrations and was evaluated on the 8-week data. A last observation carried forward (LOCF) analysis for patients who dropped out early was performed for analysis of plasma levels. Gender differences were compared using the repeated measures analysis of variance (ANOVA). All tests were two-tailed, and an alpha level of 0.05 was considered significant.

RESULTS

Thirteen patients participated in the study; eight were initially assigned to high-dose olanzapine, and five to standard dosing of clozapine. In the total randomized sample the mean age and the mean age at first hospitalization were 37.6 ± 9.0 years and 20.9 ± 4.7 years, respectively. Eight of 13 (62%) of the subjects were male, 7 (54%) were Caucasian, and the mean number of previous hospitalizations was 11.1 ± 6.8. The subjects assigned to clozapine initially and olanzapine initially were very similar and only differed with regards to race distribution (100% Caucasian on clozapine and 25% Caucasian on olanzapine) (Fisher's exact $p = 0.02$).

Of the eight patients initially assigned to olanzapine, three discontinued during the first 8 weeks (1 experienced falls, 2 lack of efficacy). The remaining five patients completed this phase and the entire clozapine treatment phase as well. Of the five patients initially assigned to clozapine, all completed their initial treatment, but three of the five discontinued after the switch to olanzapine (clinical worsening). Patients who completed at least 2 weeks of treatment in either phase, and thus, had at least one plasma level determination on a medication were included in this analysis. Therefore overall, six patients on olanzapine were discontinued, three of which dropped before week 2 (not included in this analysis) and three dropped after week 2 (data included as LOCF). These

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discontinuations occurred at weeks 5 ($N=2$) and 7 ($N=1$). Thus, for the analysis of side effects in relation to plasma levels with olanzapine, there were 10 patients included for olanzapine for all analyses who had a least 1 plasma level, 8 of which were males and 2 females.

Olanzapine plasma concentrations were significantly higher in women than men for all time points with a significant gender interaction ($F=10.1$, $df=1,8$, $p=0.013$) (see Figure 1). At 8 weeks women had a steady-state olanzapine levels of 278 ± 62 ng/ml while men had a steady-state level of 127 ± 47 ng/ml ($p=0.005$). Greater amounts of cigarette smoking was associated with lower steady-state plasma levels of olanzapine for both sexes (week 8 data used) (Spearman Correlation ($r=-0.86$, $p=0.002$) (see Figure 2). Both females included were nonsmokers and had the highest levels, not affecting the significant correlation seen with the males. Mean weight (BMI) for the females was 201.5 ± 34.6 pounds (32.9 kg/m^2) and was 217.5 ± 40.2 pounds (30.8 kg/m^2) for the males ($p=$ NS). Baseline BMI for women and men were not significantly different (33.8 ± 6.1 vs. 29.7 ± 6.0 kg/m^2, $p=$ NS). There was no trend for body weight to be associated with olanzapine plasma levels.

There were no significant findings for plasma levels in relation to total BPRS change, CGI change, or response rates in this study. At week 4, olanzapine levels tended to be higher in those who had been on clozapine previously (205 ng/ml) compared to those who received olanzapine in the first arm (105 ng/ml). This group that had been on clozapine previously also had higher levels at week 4 than at weeks 6 or 8 (See Figure 3). An equal number of women (1 each) and an equal smoking frequency were noted in each group (4.7 cigarettes/day initial olanzapine; 4.6 cigarettes/day olanzapine following clozapine). Furthermore, all three of the olanzapine dropouts during the study were on olanzapine following clozapine, thus potentially having lower olanzapine levels than would be expected and this still did not confound the findings. Additionally, mean weights were not significantly different between those who were and were not treated initially with olanzapine.

A complete description of side effects and laboratory changes are presented elsewhere (Kelly *et al*., 2003). The most prominent differences between

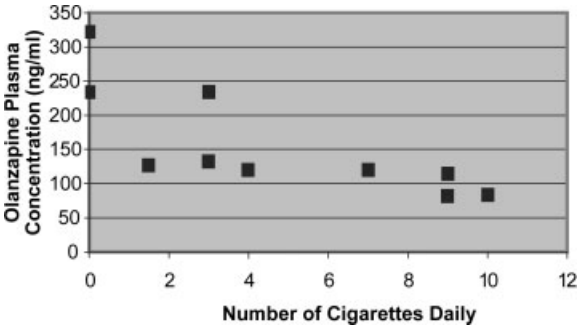

Figure 2. Week 8 plasma concentrations of olanzapine are plotted in relation to mean daily cigarette intake. Spearman Correlation ($r=-0.86$, $p=0.002$)

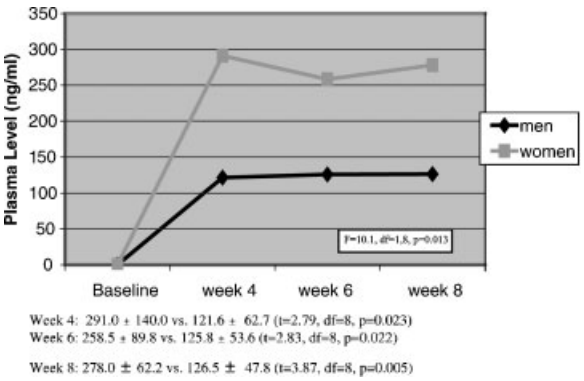

Figure 1. Plasma concentrations of olanzapine in men and women are presented for baseline, 4, 6, and 8 week blood draws. In addition to a significant time by gender interaction ($F=10.1$, $df=1,8$, $p=0.013$), females had significantly higher olanzapine concentrations at weeks 4 ($t=2.79$, $df=8$, $p=0.023$), 6 ($t=2.83$, $df=8$, $p=0.022$), and 8 ($t=3.87$, $df=8$, $p=0.005$) then did men. Eight men and two women were included at all time points, LOCF

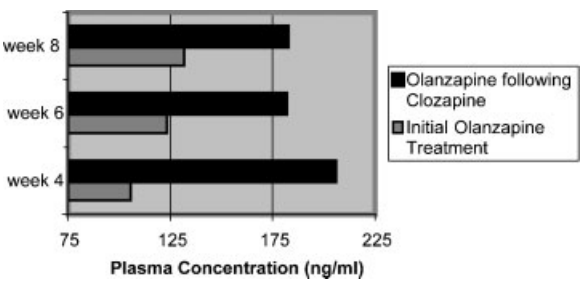

Figure 3. Plasma concentrations are plotted here for weeks 4, 6, and 8 for both patients who were initially treated with olanzapine versus those who were treated with olanzapine following 2 weeks of clozapine. A 2-week taper occurred between treatments and women are equally distributed in the two groups. $N=5$ in each group

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clozapine and olanzapine involved anticholinergic side effects. Eight of 10 (80%) of olanzapine-treated subjects experienced dry mouth while only 2/10 (20%) experienced during clozapine treatment ($p = 0.007$). Likewise, blurry vision was present in 4/10 (40%) patients on olanzapine while none of the clozapine patients ($p = 0.03$). While not statistically significant, tachycardia occurred in 2/10 (20%) on olanzapine while not present on clozapine therapy ($p = 0.14$). Constipation was present in 60% of both treatment groups. Plasma levels are listed in Table 1 for those who did and did not experience some anticholinergic side effects while on olanzapine. Sample sizes are small, however, significantly higher plasma concentrations of olanzapine were observed for those experiencing constipation (Wilcoxon test $p = 0.022$). Plasma levels were not found to be related to weight gain or any laboratory changes and all women in the study complained of dry mouth and constipation.

DISCUSSION

Women, as compared to men, had higher olanzapine concentrations independent of weight. This is most likely due to the differential rate and extent of metabolism by the CYP450 1A2 enzyme system in females, as has been described in the literature (Szymanski *et al*., 1996; Kelly *et al*., 1999; Weiss *et al*., 2005). Even at high-olanzapine doses, as used in this study, women continue to have levels over twice as high as men. Women, particularly nonsmoking, may be at particular risk for some side effects during treatment with high doses of olanzapine and all women in this study experienced dry mouth and constipation. This heightened risk is compounded by the fact that women are less likely to be smokers (as seen in our study) and are more sensitive to medication-related adverse events (Martin *et al*., 1998; Beratis *et al*., 2001). In this study, the only patient who discontinued treatment due to a medication-related adverse event was female.

Table 1. Anticholinergic side effects and steady-state plasma concentrations of high dose (50 mg/day) olanzapine

	Experiencing side effect	No side effect
Constipation*	176 ± 78 ng/ml ($N = 8$)	82 ± 1 ng/ml ($N = 2$)
Dry mouth	169 ± 84 ng/ml ($N = 8$)	108 ± 35 ng/ml ($N = 2$)
Tachycardia	225 ± 138 ng/ml ($N = 2$)	140 ± 61 ng/ml ($N = 8$)

*Wilcoxon test $p = 0.022$.

Cigarette smoking is highly correlated to plasma levels for olanzapine. This is an expected finding as olanzapine and clozapine plasma levels have been reported to be approximately 30%–40% lower in smokers due to the induction of the CYP450 1A2 by cigarette smoking (Seppala *et al*., 1999; Physician's Desk Reference, 2005). One recent report found that lower olanzapine plasma concentrations in smokers were associated with a diminished effect of the medication as compared to the nonsmokers (Carrillo *et al*., 2003). Several case reports have noted the new onset of side effects, including confusion, seizures, severe sedation, 0 and anticholinergic side effects, in olanzapine and clozapine-treated patients who have reduced or discontinued their smoking (McCarthy, 1994; Oyewumi, 1998; Zullino *et al*., 2002; Bondolfi *et al*., 2005; Derennet and Baldessarini, 2005). Therefore, the nonsmoking status of the women in our study most likely contributed somewhat to the higher plasma levels seen in women. Nonetheless, this is reflective of real-world situations where women are less likely to smoke.

Olanzapine concentrations of ≥ 23.2 has been reported to be predictive of olanzapine response in acutely ill patients (Perry *et al*., 2001). No treatment-resistant patients in this current study demonstrated a clinically significant response while on olanzapine, yet all patients' levels were greater than this threshold (Conley *et al*., 2003).

Anticholinergic side effects on olanzapine tended to correspond to higher plasma concentrations (61% higher in patients with tachycardia, 110% higher in patients with constipation, and 56% higher in patients with dry mouth). Others have reported over 20% higher plasma concentrations in patients experiencing side effects (Skogh *et al*., 2002) and more side effects in nonsmokers due to higher plasma concentrations (Carrillo *et al*., 2003; de Leon *et al*., 2005). Furthermore, anticholinergic activity in elderly patients is noted to be higher in than other antipsychotics such as risperidone, a population in which lower dosing is important (Mulsant *et al*., 2004). Clinicians should be aware that higher plasma concentrations may likely be associated with more adverse effects. Also of note, the toxic levels of olanzapine have not been established, however some have suggested that the plasma levels are as low as 100 ng/ml. Most, fatalities from olanzapine toxicity occur at much higher levels or with concurrent disease risks, however, levels of 100–300 ng/ml associated with mortality have been reported in some patients (Chue and Singer, 2003).

Interestingly, olanzapine plasma concentrations tended to be higher in patients who were first treated

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with clozapine and then crosstitrated to olanzapine compared to those who were initially randomized to olanzapine. This does not appear to be an artifact of weight, gender, or smoking differences. Competitive inhibition of the CYP450 1A2 system may explain this finding as olanzapine levels tapered downward after the fourth week. However, no data exists to suggest that clozapine remains in the body for 2 weeks after discontinuation. Another explanation might be that the CYP450 1A2 system does not completely recover in 2 weeks following the discontinuation of clozapine in a sense that it takes awhile to become accustomed to the metabolism of one medication after receiving two during the crossover phase. Whatever the mechanism, this may have important implications for crosstitration and initial dosing when switching from clozapine to olanzapine. One would expect higher than normal plasma concentrations of olanzapine to occur even for a few weeks following the discontinuation of clozapine. Side effect monitoring, especially during this period, should be undertaken. Furthermore, it is possible that initially effective olanzapine doses might become ineffective over time.

This study is limited by its small sample size and may not be widely generalizable, yet, it is the first report of plasma concentrations of high-dose olanzapine therapy utilizing random assignment and clozapine as an active comparator. It is apparent that even at high doses women continue to have plasma levels twice that of males and smoking status is highly correlated to plasma levels. The high-plasma levels in relation to anticholinergic effects is interesting and needs further study as does the possible competitive inhibition and higher olanzapine levels following clozapine discontinuation. Nonetheless, close monitoring for side effects should occur when using higher doses, especially in populations prone to higher plasma levels such as the elderly, women, nonsmokers, and those taking substances which inhibit the CYP450 1A2 enzyme system.

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