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Pharmacokinetics of olanzapine in Chinese male schizophrenic patients with various smoking behaviors

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ABSTRACT

Tobacco consumption has been recognized as a factor mediating the interindividual variations in olanzapine's pharmacokinetics and pharmacodynamics. The primary objective of this study was to describe the dose effect of smoking on the dose–plasma concentration relationship and the pharmacokinetics of oral olanzapine in male schizophrenic patients using high-performance liquid chromatography coupled with electrochemical detector. Twenty-seven male schizophrenic inpatients were recruited and were stratified into the following groups according to smoking behaviors: non-smokers ($n=9$), light-smokers (1–4 cigarettes per day; $n=9$), and heavy-smokers (≥5 cigarettes per day; $n=9$). Plasma olanzapine concentrations were determined up to 120 h following a single oral dose of 10 mg olanzapine. The pharmacokinetic parameters were calculated by the non-compartment method using WinNonlin software. Results show that there was a significant correlation among non-smokers ($n=9$; 0.79; $p=0.01$) or combined with light-smokers ($n=18$; 0.62; $p<0.01$) between peak plasma olanzapine concentrations (C_{max}) and their individual dose-corrected by body weight, but this correlation did not appear in heavy-smokers. There were no significant differences between non-smokers and light-smokers except for significant decreased $AUC_{0\rightarrow120}$ by 45.1% in light-smokers. The mean C_{max} and the mean area under the plasma concentration–time curve from time zero to 120 h ($AUC_{0\rightarrow120}$) of the heavy-smoking patients was 9.3±4.3 ng/ml (65.2% reduction compared to the non-smokers) and 302.4±167.8 h ng/ml (67.6% reduction compared to the non-smokers), respectively. In summary, a daily consumption of 5 cigarettes is probably sufficient for induction of olanzapine metabolism. Smoking cessation is recommended for olanzapine therapy to have better prediction for therapeutic dosages particularly in heavy-smokers. Compared to non-smokers, heavy-smokers therefore require a 50–100% increase in olanzapine doses. Therapeutic drug monitoring will need to be considered when schizophrenic patients change their smoking behaviors.

1. Introduction

Olanzapine is effective in treating patients with schizophrenia and bipolar manic episodes in numerous controlled clinical trials (Beasley et al., 1997; Tollefson et al., 1997). Following oral administration, olanzapine is mainly metabolized to 10-*N*-glucuronide, 4'-*N*-desmethylolanzapine, olanzapine-*N*-oxide through uridine diphosphate glucuronyltransferase (UGT), cytochrome P450 (CYP) 1A2 isoenzymes and a flavin-containing monoxygenase, respectively (Ring et al., 1996; Callaghan et al., 1999). Metabolism to 2-hydroxymethylolanzapine through CYP2D6 is a minor pathway (Callaghan et al., 1999). Many psychotropic drugs undergo glucuronidation by a superfamily of UGT, of which the families 1 and 2 are most important for glucuronidation of drugs (Kiang et al., 2005). In vitro study showed that the A4 subform of the UGT 1 family (UGT1A4) is primarily involved in the glucuronidation of olanzapine (Linnet 2002). Cigarette smoking has influence on the activity of UGT (Villard et al., 1998). The CYP1A2 activity is influenced by various factors, such as genetic variability, gender differences, tobacco

Abbreviations: CYP, cytochrome P450; k, elimination rate constant; $t_{1/2}$, half-life; T_{max}, time to reach the peak plasma concentration; C_{max}, peak plasma concentration; $AUC_{0\rightarrow120}$, area under the plasma concentration–time curve from time of dosing to the last sampling time; $AUC_{0\rightarrow\infty}$, area under the plasma concentration–time curve from time of dosing to infinity; V_z/F, apparent volume of distribution; CL/F, apparent clearance; TDM, Therapeutic drug monitoring.

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consumption, and drug interactions, which have been recognized to mediate the intraindividual and interindividual variations in the pharmacokinetics of olanzapine (Skogh et al., 2002; Carrillo et al., 2003; Gex-Fabry et al., 2003).

Cigarette smoke constituents can induce hepatic microsomal CYP isoenzymes, which play a key role in drug metabolism. Polycyclic aromatic hydrocarbons in cigarette smoke are powerful inducers of hepatic microsomal enzymes and can serve to increase the rate of metabolism of certain drugs (Zevin and Benowitz, 1999). Other constituents of tobacco smoke may also play a role (Desai et al., 2001). In animal studies, nicotine induces the activities of several enzymes, including CYP2E1, CYP2A1/2A2 and CYP2B1/2B2 in the brain, but whether this effect is clinically significant remains unknown (Zevin and Benowitz, 1999).

Patients with psychiatric diseases are thought to smoke more heavily than those without psychiatric diseases due to the quantity of cigarettes that they smoke and how deeply they inhale (Hughes and Frances, 1995). Proposed reasons for high incidence of smoking among these patients include that smoking has anxiolytic effects and reduces therapeutic drug-related adverse effects. The result of meta-analysis showed that the odds that schizophrenic patients smoke are 5.3 times higher than people in the worldwide general population (de Leon et al., 2005). Such high rates of smoker in schizophrenia occurred world widely (de Leon et al., 2002), particularly among the institutionalized patients (Dalack et al., 1998). In Taiwan, an epidemiological study reported that 70.9% and 11.5% of male and female schizophrenic inpatients, respectively, are current smokers (Liao et al., 2002). Compared to the prevalence of smoking in the general population (46.8% of men and 4.3% of women in 2001 in Taiwan) (Wen et al., 2005), smoking was slightly more prevalent in male schizophrenic patients than in the general population of males but was double in female patients (Liao et al., 2002). One major limitation of this study is that the sample was collected from chronic inpatients with more severe psychopathology; accordingly, the results may not be representative of all patients with schizophrenia. In fact, schizophrenic smokers also favor stronger cigarettes and extract more nicotine from their cigarettes than normal smokers (Olincy et al., 1997). Interestingly, nicotine has been reported to induce oxidative stress (Solak et al., 2005) or reduce lipid peroxidation in patients with schizophrenia (Zhang et al., 2007). Whether nicotine or smoking provides benefits or harms in tardive dyskinesia, positive–negative symptoms and cognitive function in schizophrenic patients is still controversial (Binder et al., 1987; Yassa et al., 1987; Goff et al., 1992; Chong and Choo, 1996; Liao et al., 2002). Cigarette smoking may selectively enhance visuospatial working memory and attention deficits in schizophrenic smokers, which may depend on nicotinic acetylcholine receptors stimulation (Sacco et al., 2005). Most western surveys have found a correspondingly higher antipsychotic daily dose administered to smokers than to non-smokers (Goff et al., 1992; Desai et al., 2001). That antipsychotic usage in Chinese subjects may be relatively insensitive to the effects of smoking as compared to Caucasians, racial differences in hepatic microsomal enzymes have been proposed as an explanation for these findings (Chong et al., 1996; Liao et al., 2002).

The reduced plasma levels of olanzapine and exacerbated clinical symptoms are suggested to relate to significantly increased consumption of cigarettes (Chiu et al., 2004a,b; Bigos et al., 2008). When the patient smokes four or fewer cigarettes per day, his CYP1A2 activity is found to be similar to that observed in non-smokers (Kalow and Tang, 1991). To provide evidence on the need of dosage adjustment for patients with limited cigarette smoking or heavy-smokers to maintain olanzapine's clinical efficacy, we conducted current study to determine the pharmacokinetic profiles of male Chinese schizophrenic inpatients with different habits of smoking.

2. Methods

2.1. Study subjects

This study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2000). The study was approved by the Institute of Review Board. The Structured Clinical Interview for DSM-IV was conducted for the diagnosis. All enrolled patients fulfilled the DSM-IV diagnosis of schizophrenia and were male Taiwanese inpatients. Those who received any medication with inducing or inhibiting activities of cytochrome P450 enzyme were excluded from this study. All participants (n=27) received written information of this study and signed an informed consent before any assessment was done. The hospital staff reported the amount of patients' tobacco consumptions. Light-smokers were defined as individuals who smoked four or fewer cigarettes per day during the past year, whereas heavy-smokers smoked five or more cigarettes per day, and non-smokers had never smoked.

2.2. Study design and analyses

All subjects received a single oral dose (10 mg) of olanzapine (Zyprexa, Eli Lilly and Company, Indianapolis, USA) in the morning. We collected serial blood samples to determine the plasma olanzapine concentrations from each patient before dosing and at 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96 and 120 h after administration. Plasma was separated by centrifugation and stored at −20 °C. The plasma concentrations of olanzapine were done by using a modified high-performance liquid chromatography coupled with electrochemical detector (Chiu et al., 2004a,b). The parameters determined were elimination rate constant (k), half-life ($t_{1/2}$), time to reach the peak plasma concentration (T_{max}), peak plasma concentration (C_{max}), area under the plasma concentration–time curve from time of dosing to the last sampling time ($AUC_{0\rightarrow120}$), area under the plasma concentration–time curve from time of dosing to infinity ($AUC_{0\rightarrow\infty}$), apparent volume of distribution (V_z/F), and apparent clearance (CL/F). The AUC values were calculated by using the log-linear trapezoidal rule. The values of $C_{max\text{-}norm}$ were derived from C_{max} divided by dose per kilogram body weight.

2.3. Statistical analyses

The correlation of maximum drug concentration and the dose-corrected by body weight were analyzed by Pearson product moment

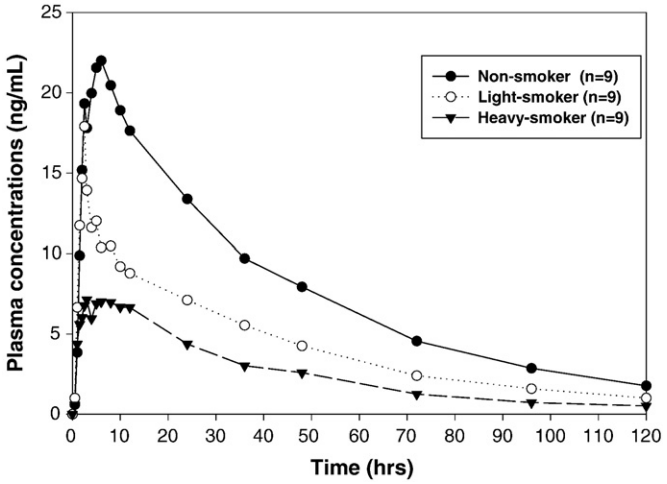

Fig. 1. Mean plasma concentration–time curves for a single 10 mg dose of olanzapine in non-smokers (●), light-smokers (○) and heavy-smokers (▼).

correlation method. The pharmacokinetic parameters were calculated using non-compartment methods by using WinNonlin®5.2 software. Statistically significant differences among groups were analyzed by one-way ANOVA with post hoc analysis using SigmaStat® 2.03. The differences between the groups were considered significant if the *p*-value was smaller than 0.05.

3. Results

Overall, all subjects tolerated the study procedure well, and they completed all aspects of the study. The most prevalent treatment-emergent adverse events included sedation ($n=10$) and accommodation disturbances ($n=7$). Those events were all mild in severity and tolerable, and they disappeared spontaneously.

The age (in mean±standard deviation) of non-smokers, light-smokers and heavy-smokers was 34.9±6.8 years, 40.9±12.5 years, and 44.4±7.6 years, respectively. The body weight (in mean±standard deviation) of non-smokers, light-smokers and heavy-smokers was 59.0±5.1 kg, 63.2±9.7 kg, and 65.4±10.4 kg, respectively.

Fig. 1 shows the relationship of the olanzapine plasma concentrations versus time in a 120h sampling of non-smokers, light-smokers and heavy-smokers. The correlation coefficient between peak plasma olanzapine concentrations (C_{max}) and their individual dose-corrected by body weight among these twenty-seven patients were 0.54 and significant correlated ($p<0.01$). There was a significant correlation among non-smokers ($n=9$; 0.79; $p=0.01$) or combined with light-smokers ($n=18$; 0.62; $p<0.01$). However, there was no significant correlation among heavy-smokers or all smokers.

Table 1 summarizes the C_{max} per dose (C/D) corrected by body weight and other mean pharmacokinetic parameters of plasma olanzapine of each group. In general, there was no statistically significant difference among three groups of patients in k, $t_{1/2}$ and T_{max}; however, C_{max} and $C_{max\text{-}norm}$ were significantly lower in the heavy-smokers ($p<0.001$) than non-smokers. The mean $C_{max\text{-}norm}$ of heavy-smokers was also significantly decreased compared to light-smokers ($p<0.05$). The values of $AUC_{0\rightarrow120}$, $AUC_{0\rightarrow\infty}$ were in the rank: non-smoker>light-smokers>heavy-smokers while the values of V_z/F, CL/F were in the rank: heavy-smokers>light-smokers>non-smoker. There were statistically significant differences in AUCs, V_z/F and CL/F among all pairwise comparison between patients with various smoking habits ($p<0.05$). Similar significance statistical results for CL/F normalized by body weight (CL/F_{norm}) were also observed among all pairwise comparisons between patients with various smoking habits except for the one of light-smoker and non-smoker.

Table 1
Main pharmacokinetic parameters of a single dose 10 mg olanzapine in patients with different cigarette consumptions

	Non-smoker ($n=9$)	Light-smoker ($n=9$)	Heavy-smoker ($n=9$)
k (1/h)	0.021±0.005	0.021±0.005	0.022±0.004
$t_{1/2}$ (h)	34.5±7.2	35.2±9.5	32.8±6.9
T_{max} (h)	5.0±2.8	3.3±1.4	6.4±4.9
C_{max} (ng/ml)	26.7±13.7	19.7±7.4	9.3±4.3§§
$C_{max\text{-}norm}$ (ng ml^{-1}/mg kg^{-1})	153.1±64.1	121.3±41.1†	59.6±26.7§§
$AUC_{0\rightarrow120}$ (h ng/ml)	933.5±459.4	512.2±120.2*†	302.4±167.8§
$AUC_{0\rightarrow\infty}$ (h ng/ml)	1026.0±489.7	568.2±141.8*†	335.8±184.4§
V_z/F (l)	550.2±191.1	913.1±194.1*†	2763.7±2754.4§
CL/F (l/h)	11.2±3.9	18.8±5.4*†	49.7±48.4§
CL/F_{norm} (l/h/kg)	0.19±0.1	0.30±0.1†	0.76±0.7§

All the data were expressed as mean±SD (standard deviation).
k, elimination rate constant; $t_{1/2}$, half-life; T_{max}, time to reach the peak plasma concentration; C_{max}, peak plasma concentration; $C_{max\text{-}norm}$, C_{max} divided by dose per kilogram body weight; $AUC_{0\rightarrow120}$, area under the plasma concentration–time curve from time of dosing to the last sampling time; $AUC_{0\rightarrow\infty}$, area under the plasma concentration–time curve from time of dosing to infinity; V_z/F, apparent volume of distribution; CL/F, apparent clearance.
Statistically significant for each comparison group was indicated as * ($p<0.05$) for light-smoker vs. non-smoker; § ($p<0.05$) or §§ ($p<0.001$) for heavy-smoker vs. non-smoker; † ($p<0.05$) for light-smoker vs. heavy-smoker.

4. Discussion

Therapeutic drug monitoring (TDM) is an important tool in the clinical practice of antipsychotic treatment (Baumann et al., 2004a,b). Information from TDM helps clinician make patient's individual dose adjustment. Therefore, knowledge about individual factors (e.g., age, gender, smoking status, concomitant drugs, and genetics) that influence the pharmacokinetic variability of a specific drug makes it possible to adjust for these differences. In fact, TDM is "strongly recommended" for olanzapine (Baumann et al., 2004a,b) to minimize adverse events or to optimize clinical efficacy (Theisen et al., 2006). In order to examine whether there is linear correlation between peak plasma concentrations of olanzapine and dose-corrected by body weight as expected from nine patients of each smoking group, Pearsons correlation test, instead of Spearman rank test, was the chosen method for statistical analysis. In this study, we gave evidence that individual peak plasma olanzapine concentration (C_{max}) and dose-corrected by body weight were significantly correlated between non-smoking patients and non-smokers plus light-smoking patients following a single dose of 10 mg olanzapine. Such results suggest that the linearity between two variables might be able to provide dose–concentration prediction for non-smoker and light-smoking patients once the model is established. The mean ratios of C/D, mean C_{max}, and mean $C_{max\text{-}norm}$ of light-smokers were similar to the ones of non-smokers. The similar plasma olanzapine levels and half-life in our study support the previous reports which did not show any differences in CYP1A2 activity among the patients without or with smoking four or fewer pieces of cigarettes per day (Kalow and Tang, 1991; Chiu et al., 2004a,b). To our best knowledge, we first report that patients who smoked four or fewer pieces of cigarettes per day may not need to adjust their therapeutic doses of olanzapine.

Haslemo et al. (2006) reported that a daily consumption of 7–12 pieces of cigarettes is probably sufficient to maximally induce olanzapine metabolism. We here added further pharmacokinetic information for the patients who received olanzapine and smoked fewer cigarettes than those in the study done by Haslemo et al. (2006). As indicated in our study, we found that patients smoked more than four pieces of cigarettes per day decreased significantly in C_{max}, proportionality of C_{max} vs. body weight-corrected dose, and increased significantly in the rate of clearance. Based on our and Haslemo's findings, we suggest that the threshold of tobacco consumption to induce olanzapine metabolism may be four pieces of cigarettes per day.

Even though the disposition data of olanzapine in our study were similar to those reports of Callaghan et al.'s (1999) study, Sathirakul et al.'s (2003) study and Lane et al.'s (2000) study as single 10 mg oral dose studies of olanzapine in mixed smoking-behavior patients, there is still a limitation present in our study. For example, since the bioavailability (F) of olanzapine was not available for each individual patient, the given increase of CL/F for our study patients was an interpretive number and the V_z/F was then also obtained hypothetically. In fact, the commonly used equations may also yield a flaw estimation for distribution of volume in certain studied system (Berezhkovskiy, 2007). The unmeasured interindividual bioavailabilities of olanzapine might contribute to varieties in C_{max}, AUC or V_z/F parameters of each group with various smoking behaviors. Because administered drug may possibly enter to other compartments in addition to plasma, the pharmacokinetic parameter volume in steady state (V_{ss}) has been addressed to be superior or more reliable than V_z (the volume in the terminal state) by several reports (Gobburu and Holford, 2002; Sevcik 2006).

In addition, another important factor worth to be raised is that the variations of CYP1A2 activity within the study individuals. This factor

may also account for the observed wide interindividual variability in certain pharmacokinetic parameters. The genetic polymorphism of CYP1A2 has been shown to influence the inducibility (Sachse et al., 1999) of CYP1A2 isoenzyme, resulting in having a significant effect on the clozapine metabolism (Melkersson et al., 2007). In the present study, differences in patients' CYP1A2 genotypes may have contributed to the individual variability in olanzapine's pharmacokinetics. The involvement of the CYP1A2 activity of our patients with various smoking habits in the differences of olanzapine distribution needs more evidence to further characterize.

A therapeutic window has been proposed for olanzapine plasma concentrations (Perry et al., 1997, 2005). A 24h post-dose olanzapine plasma concentration of 9.3 ng/ml has been identified as a predictor of clinical response in acutely ill patients with schizophrenia (Perry et al., 1997). And a threshold dose-weighted 24-hour post-dose plasma concentration of 20.6 ng/ml was associated with an increased likelihood of clinically significant weight gain during olanzapine treatment (Perry et al., 2005). Patients who were well-treated and then discharged from the acute inpatient setting may require olanzapine dosage adjustments and clinical response assessment for tailored therapy to prevent psychotic relapse if their smoking consumptions would return to be more than four pieces of cigarettes per day. Patients who were willing to quit smoking should be encouraged to decrease their olanzapine dosage gradually to avoid side effects or toxicity with excessive plasma olanzapine concentration. Therefore, the smoking patients who are treated with olanzapine should be regularly monitored for their cigarette consumption, body weight, other side effects, clinical efficacy, and, if possible, olanzapine plasma concentrations.

The generalization of the findings of our study should be cautious because it had some limitations. First, our data were derived from the pharmacokinetic study of the single dose 10 mg of olanzapine, but not that of the steady state after continuous dosing. Second, the sample size of our study was small and all subjects were male. Third, drugs were administered orally and the used non-compartmental system would introduce bias. For better strength of the data, further exploring the pharmacokinetics of olanzapine up to 240 h post-dose sampling, or at steady state coupled with employing other analytical methodology such as area/moment analysis, compartmental modeling, and allometric scaling to man (Samtani et al., 2004) for olanzapine may be needed to clarify the influence of tobacco consumption on the pharmacokinetics of olanzapine.

5. Conclusions

The current study provides evidence of dose-dependent effect of the tobacco consumption in olanzapine's pharmacokinetics. Daily consumption of five or more pieces of cigarettes significantly changed the peak plasma olanzapine concentrations and the linearity of dose and drug concentrations. Since smoking is an important health concern of psychiatric patients, clinicians should take this into consideration when assessing olanzapine dose requirement and clinical response. Compared to non-smokers, heavy-smokers therefore require a 50–100% increase in olanzapine doses. Further studies on the relationship between plasma olanzapine concentration and various dosages for each group of non-smokers or smokers are warranted to obtain equations for prospective dosing adjustments.

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