Olanzapine pharmacokinetics are similar in Chinese and Caucasian subjects

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Aim To compare the pharmacokinetic profiles and dose proportionality of olanzapine in Chinese and Caucasian subjects.

Methods Randomized, three-period study with 12 Chinese and 12 Caucasian, healthy, male subjects administered 2.5, 5 and 10 mg olanzapine. Noncompartmental pharmacokinetic parameters were derived.

Results No statistically significant racial differences in the weight-normalized pharmacokinetic parameters were observed except for V_z/F_{norm} , which was 17% lower at the 5- and 10-mg dose in the Chinese group (95% confidence interval 8.49, 10.1 and 8.05, 9.73, respectively), compared with the Caucasian group (9.53, 12.8 and 9.39, 12.0, respectively). Olanzapine's pharmacokinetics were linear and dose proportional in both racial groups.

Conclusion The pharmacokinetics of olanzapine are similar in both Chinese and Caucasian racial groups.

Keywords: CYP1A2, olanzapine, pharmacokinetics, race

Introduction

Olanzapine is an antipsychotic agent with a favourable safety profile, and has greater promise among nonresponders when compared with the conventional antipsychotic drug, haloperidol [1]. Olanzapine is well absorbed following oral administration in both the fed and fasted states, and is extensively metabolized with higher clearance in males than in females [2]. Glucuronidation of olanzapine is the major metabolic pathway forming the largest metabolic fraction, though only the formation of *N*-desmethyl olanzapine via CYP1A2 is correlated with the clearance of olanzapine [2].

The importance of CYP1A2 in the disposition of olanzapine has been demonstrated in a number of studies. Co-administration of olanzapine and fluvoxamine, a potent CYP1A2 inhibitor, resulted in higher serum concentrations of olanzapine [3]. Co-administration of carbamazepine and olanzapine resulted in an increase in the clearance and volume of distribution of olanzapine, which was attributed to carbamazepine induction of

CYP1A2 [4]. Furthermore, smoking, which also induces CYP1A2, resulted in higher olanzapine clearance when compared with nonsmokers [2].

Racial differences in the genetic polymorphic distribution of phenotypes for CYP1A2 have been reported [5], with lower catalytic levels of CYP1A2 present in Orientals compared with Caucasians [6]. Due to these potential racial differences in CYP1A2 activity, it was considered important to study the pharmacokinetics of olanzapine in different racial groups. Therefore, the objective of this study was to compare the pharmacokinetic profile and dose proportionality of olanzapine in Chinese and Caucasian subjects.

Methods

Subjects and clinical protocol

Twenty-four healthy males, from Chinese ($n = 12$) and Caucasian ($n = 12$) racial groups, gave written informed consent to participate in this study. Although the subjects did not necessarily reside in their country of origin, each subject reported to have an ancestral background from a single racial group for two generations. The study was approved by the Research and Ethics Committee of the National University Hospital, Singapore and performed in accordance with the Declaration of Helsinki.

Each of the three open-label study periods had a minimum washout interval of 4 days. Subjects were

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instructed not to consume alcohol, cruciferous vegetables, and foodstuffs containing caffeine or xanthine 72 h prior to dosing until 72 h after the final pharmacokinetic sample was taken. Subjects were fasted 8 h prior to dosing and for 4 h subsequently. Depending on the random dosing sequence, subjects initially received a single oral dose of either 2.5, 5, or 10 mg of olanzapine (Eli Lilly and Co., Indianapolis, IN, USA). During each period, venous blood samples (7 ml) were collected from the forearm at time 0 (pre-olanzapine dose) and then at 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 96, and 120 h post-olanzapine dose. These procedures were repeated until the subject had received all three different doses of olanzapine. Subjects were monitored with regard to their clinical and laboratory safety.

Drug assay

Plasma obtained from the centrifuged blood samples was stored at -20°C . Based on a previously described method using LY170222 (Lilly Research Laboratories, Indianapolis, IN, USA) as an internal standard [7], olanzapine concentrations were assayed using high-performance liquid chromatography with electrochemical detection. Peak heights were proportional to the olanzapine concentration in human plasma over the concentration range $0.25\text{--}100\text{ ng mL}^{-1}$. The mean $\pm$ SD recovery of olanzapine was $78.3 \pm 10.4\%$ for six determinations each at 80, 40, 0.64 ng mL^{-1} concentration levels. The intraday and interday variability was $\leq 7.8\%$.

Pharmacokinetic analysis

Noncompartmental pharmacokinetic parameters were derived using actual sampling times for analysis (Win-Nonlin Professional ver. 2.1). The parameters determined were; peak concentration (C_{max}), time to reach C_{max} (t_{max}), apparent clearance (CL/F), apparent volume of distribution (V_z/F), half-life ($t_{1/2}$) and area under the plasma concentration–time curve from time of dosing to infinity (AUC) calculated using the log-linear trapezoidal rule. Dose and body weight normalized values (AUC_{norm} and $C_{\text{max, norm}}$) were derived by dividing by dose per kg body weight. Body weight normalized parameters ($\text{CL}/F_{\text{norm}}$ and V_z/F_{norm}) were calculated by dividing by the body weight.

Statistical analysis

Assuming intrasubject coefficient of variation (CV) of approximately 20%, 12 subjects provides 80% power to detect a 20–30% difference in critical pharmacokinetic variables at a 0.05 α level.

For normally and non-normally distributed data, the Student's t -test and the Wilcoxon rank sum test were

used, respectively, to compare the pharmacokinetic parameters between groups. Dose proportionality of AUC and C_{max} vs. the weight-normalized dose (dose $\times$ 70 kg/body weight) was assessed using a weighted linear least squares regression analysis.

Results

The Chinese and the Caucasian groups were well matched in terms of age range (21–32 years and 21–31 years, respectively) and mean $\pm$ SD body mass index ($22.1 \pm 1.8\text{ kg m}^{-2}$ and $22.8 \pm 1.8\text{ kg m}^{-2}$, respectively). The Chinese group had a statistically significant 8.4% lower mean body weight compared with the Caucasian group ($65.3 \pm 6.7\text{ kg}$ and $71.3 \pm 6.8\text{ kg}$, respectively; $P = 0.049$).

The olanzapine pharmacokinetic parameters at each dose for both racial groups are summarized in Table 1. In general, AUC, C_{max} , $t_{1/2}$ were not significantly different between the two racial groups for all doses. Although the untransformed C_{max} values at the 5-mg dose and the AUC values at the 10-mg dose showed statistically significant differences between the racial groups, after normalizing these parameters by dose/weight, these differences were not statistically significant.

Both the V_z/F and V_z/F_{norm} in the Chinese subjects were significantly lower (approximately 16–24%) than in the Caucasian subjects at all doses, with the difference more pronounced at higher doses. The CL/F was significantly lower at the 10-mg dose in the Chinese, although when normalized by body weight, the 13.9% difference in the mean was not statistically significant.

Linear and dose-proportional pharmacokinetics were established in both racial groups. The linear regression of AUC and C_{max} for the Chinese and Caucasian groups is illustrated in Figure 1. A common slope hypothesis passing through the origin for both racial groups was accepted for AUC ($\text{AUC} = 62.59 \times (\text{dose}/70\text{ kg})$) and C_{max} ($C_{\text{max}} = 1.51 \times (\text{dose}/70\text{ kg})$). Linear pharmacokinetics were also consistent with a lack of significant changes in CL/F and V_z/F with increasing dose (Table 1).

Somnolence was the most frequent adverse event reported, with a trend toward a higher incidence after the larger doses. There were no apparent differences in the severity or frequency of adverse events between racial groups.

Discussion

The pharmacokinetic characteristics of olanzapine in both the Chinese and Caucasian groups were linear and dose proportional. There were no statistically significant racial differences in weight-normalized pharmacokinetic parameters with the exception of the weight-normalized

Table 1 Mean (95% confidence interval) pharmacokinetic parameters after orally administered doses of olanzapine in the Chinese ($n = 12$) and Caucasian ($n = 12$) groups.

Parameter	Chinese ($n = 12$)			Caucasian ($n = 12$)		
	2.5 mg	5.0 mg	10.0 mg	2.5 mg	5.0 mg	10.0 mg
$C_{\max}$ (ng mL ⁻¹)	4.49 (3.42, 5.56)	8.03 (7.46, 8.59)	17.3 (15.3, 19.2)	3.86 (2.94, 4.78)	6.94 (5.97, 7.91)*	15.3 (13.2, 17.5)
$C_{\max, \text{norm}}^{\dagger}$ (ng mL ⁻¹)/(mg kg ⁻¹)	117 (91.7, 142)	105 (94.5, 116)	113 (101, 126)	109 (85.5, 133)	99.1 (86.3, 112)	108 (96.5, 120)
$t_{\max}$ (h)	6.0 (4.0–8.0)	6.0 (2.0–8.0)	4.0 (2.0–12.0)	8.0 (4.0–10.0)	6.0 (4.0–10.0)	7.0 (4.0–10.0)*
AUC (ng mL ⁻¹ h ⁻¹)	179 (147, 211)	351 (304, 397)	712 (608, 816)	146 (126, 167)	293 (242, 344)	578 (486, 669)*
AUC _{norm} [†] (ng mL ⁻¹ h)/(mg kg ⁻¹)	4680 (3930, 5430)	4600 (3960, 5230)	4700 (3990, 5420)	4190 (3590, 4790)	4190 (3490, 4880)	4110 (3490, 4730)
CL/F (L h ⁻¹)	14.9 (12.5, 17.2)	15.0 (12.9, 17.1)	14.6 (12.8, 16.5)	18.0 (15.1, 20.9)	18.5 (14.7, 22.3)	18.5 (15.2, 21.8)*
CL/F _{norm} [‡] (L kg ⁻¹ h ⁻¹)	0.228 (0.187, 0.268)	0.230 (0.195, 0.266)	0.223 (0.191, 0.255)	0.252 (0.210, 0.295)	0.257 (0.206, 0.308)	0.259 (0.213, 0.305)
V_z/F (L)	611 (513, 710)	608 (557, 660)	587 (526, 647)	727 (664, 790)*	805 (665, 944)*	765 (660, 870)*
$V_z/F_{\text{norm}}^{\ddagger}$ (L kg ⁻¹)	9.32 (7.94, 10.7)	9.32 (8.49, 10.1)	8.89 (8.05, 9.73)	10.1 (9.65, 10.6)	11.2 (9.53, 12.8)*	10.7 (9.39, 12.0)*
$t_{1/2}$ (h)	30.0 (24.0, 36.1)	29.1 (25.3, 32.9)	28.7 (24.6, 32.8)	29.5 (24.8, 34.2)	31.2 (26.8, 35.6)	29.6 (25.5, 33.7)

Time to peak concentration ($t_{\max}$) given as the median (range). *Significantly different between the two racial groups at the same dose ($P < 0.05$).

[†]Normalized by dose/weight. [‡]Normalized by weight.

apparent volume of distribution, which was 17% lower in the Chinese at the higher doses. Weight normalization of the pharmacokinetic parameters was applied since Caucasian subjects had higher body weight than the Chinese. From these results, no substantial differences in the absorption or elimination of olanzapine between these racial groups would be expected.

Differences in hepatic drug metabolism have been commonly cited as a major factor influencing the pharmacokinetics of drugs in various ethnic populations. Since smoking and gender both affect the pharmacokinetics of olanzapine [2], this current study sought to enrol only nonsmoking males. Assuming that the study design permitted a careful assessment of any difference in the pharmacokinetics of olanzapine related to the intrinsic factors of each racial group, the results suggest that there is no difference in the olanzapine catalytic activity of CYP1A2 between the two racial groups studied.

The results of this current study are consistent with previous literature that also showed no major interracial differences with CYP1A2 activity. Phenacetin, which is eliminated almost entirely by CYP1A2, showed no significant differences in CYP1A2-related activity between Chinese and Caucasians [8]. A study using the caffeine metabolic ratio as a marker of CYP1A2 also showed

no difference between Caucasian and Chinese subjects [9].

Direct glucuronidation via the UGT1A4 isoenzyme is a known enzymatic pathway for olanzapine [10]. Since there were no significant racial differences in the weight-normalized apparent total clearance, the glucuronosyl-transferase activities of the two ethnic groups appear to be comparable.

At the higher doses of olanzapine administered, the weight-normalized apparent volume of distribution in the Chinese group was approximately 17% lower than in the Caucasian group. Other lipophilic compounds such as diazepam have also shown a smaller volume of distribution in Chinese when compared with Caucasians [11]. Although these differences are not clinically significant, to elucidate further any racial differences in olanzapine distribution, examination of differences in protein binding and body composition would be required.

It is of interest to note that both the apparent clearance and apparent volume of distribution values obtained in this study were approximately 30% lower than the mean values published by Callaghan *et al.* [2]. Their study was conducted in a large population ($n > 470$) predominantly consisting of Caucasians, with an even distribution of smokers and nonsmokers, and a small proportion of females. Although this present study was not designed to

Figure 1 The dose proportionality relationship between (a) the area under the olanzapine plasma concentration–time curve to infinity and dose ($\text{mg } 70 \text{ kg}^{-1}$) and (b) the maximum observed plasma concentration of olanzapine and dose ($\text{mg } 70 \text{ kg}^{-1}$), in healthy, male Chinese (○) and Caucasian (●) subjects. The solid and dashed lines represent the linear regression line for Chinese and Caucasians, respectively.

explore such differences, it appears that pharmacokinetic differences attributable to factors such as smoking and gender might be larger than interracial differences defined by the current findings.

In conclusion, the pharmacokinetic characteristics of olanzapine in Chinese and Caucasian subjects are similar.

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