Multiple dose pharmacokinetics of quetiapine and some of its metabolites in Chinese suffering from schizophrenia

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ABSTRACT

AIM: To study the multiple dose pharmacokinetics of quetiapine and its sulfoxide-, 7-hydroxy-, 7-hydroxy-*N*-dealkyl-metabolites in Chinese suffering from schizophrenia. **METHODS:** Twenty-one patients (11 females and 10 males) were given quetiapine twice daily to control the symptoms. After the dose reached 200 mg twice daily, blood were sampled to study the pharmacokinetics. The plasma concentrations of quetiapine and its metabolites were assayed by HPLC-MS. **RESULTS:** The main pharmacokinetic parameters of quetiapine, 7-hydroxy-*N*-dealkyl-quetiapine, quetiapine sulfoxide, and 7-hydroxy-quetiapine were as follows: t_{max} were 2.0 (0.3-5.0), 4.0 (1.5-6.0), 3.0 (0.5-5.0), and 3.0 (0.5-5.0) h respectively; $t_{1/2}$ were (7±3), (9.4±2.7), (7±3), and (8±5) h, respectively; C_{max}^{SS} were (678±325), (19±5), (451±216), and (58±22) µg/L, respectively; C_{min}^{SS} were (51±68), (3.3±1.6), (35±36), and (5±4) µg/L, respectively; C_{av}^{SS} were (295±144), (13±4), (209±71), and (28±9) µg/L, respectively; AUC_{0-12} were (3 538±1 728), (153±44), (2 512±854), and (335±104) µg·h·L^{-1}, respectively; $AUC_{0-\infty}^{SS}$ were (5 534±4 198), (287±107), (3 858±2 012), and (529±262) µg·h·L^{-1}, respectively; K_e were (0.11±0.03), (0.079±0.019), (0.11±0.03), and (0.103±0.028) h^{-1}, respectively; CL/*F* and *V*/*F* of quetiapine were (67±25) L·h^{-1} and (672±394) L, respectively. The plasma concentrations for the four compounds reached a steady state within 48 h at the dose of 200 mg initiation. These parameters were not statistically different between genders. **CONCLUSIONS:** Quetiapine was absorbed quickly, distributed widely, and metabolized mainly to be quetiapine sulfoxide. The elimination speeds of quetiapine and its three metabolites were similar. Gender had no effect on the pharmacokinetics of quetiapine and its metabolites. The clinical dosage regime caused no drug accumulation.

INTRODUCTION

Quetiapine (QTP) is a novel atypical antipsychotic which is as effective as traditional antipsychotics. It causes less extrapyramidal side effects, hyperprolactinmia, QT interval prolongation, and agranulocytosis than other neuroleptics[1-3]. The commonly used

effective dose ranged from 25 to 300 mg per day and even over to 750 mg per day.

In vivo, quetiapine sulfoxide (QTP-SF) is the major inactive metabolite. 7-Hydroxy-quetiapine (QTP-H) and 7-hydroxy-*N*-dealkyl-quetiapine (QTP-ND) are active metabolites[4]. Davis *et al* have studied the multiple dose pharmacokinetics of QTP, QTP-H, and QTP-ND in Caucasian in dose of 150 mg per 8 h. For QTP-ND, because of the limit of detecting method, only C_{max}^{SS} and t_{max} were achieved[5]. The multiple dose pharmacokinetics of QTP-SF is not reported at present.

The purpose of the study was to evaluate the

multiple dose pharmacokinetics of QTP and its metabolites (QTP-SF, QTP-H, and QTP-ND) in Chinese suffering from schizophrenia.

MATERIALS AND METHODS

Drugs and reagents Quetiapine tablets (Batch No: LOT AM 188; 25, 100 or 200 mg/tablet), QTP-SF (purity=74 %), QTP-H (purity=77 %), and QTP-ND (purity=55 %) standards were donated by AstraZeneca Pharmaceuticals (London, UK). QTP standard (purity> 99.6 %) was kindly provided by Hu-nan Dongting Pharmaceutical Co Ltd (Changde, Hunan, China). Carbamazepine (IS, purity >99.9 %) was provided by National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Other AR grade and HPLC grade reagents were obtained from Chemical Reagent Factory of Hu-nan province (Changsha, Hu-nan, China).

Apparatus Waters 2690 high performance liquid chromatography equipment system, micromass ZQ mass spectrometer (Wythenshawe, Manchester, UK), Oasis™ HLB extraction cartridge (1CC/10 mg) (Waters Corporation, Milford, Massachusetts, USA) were used.

Subjects Twenty-one Chinese in-patients (11 females, 10 males, ages from 18 to 45 a, weighing from 41 to 77 kg) were recruited in the study. All subjects were diagnosed as schizophrenia, or schizophreniform disorder (criteria of CCMD-III). According to medical history, physical examination and routine laboratory tests, all patients have no hepatic, renal, cardiac, hematologic, or other diseases. All patients took no drugs two weeks before the trial, but were permitted to take alprazolam, inosine, and propranolol during the trial. Cigarettes and alcohol were restrained. Written informed consent was obtained from each parent or patient's legal guardian. The Ethical Committee of Xiangya Second Hospital of Central South University approved the protocol.

Experimental protocol All subjects were given quetiapine twice daily from a started dose of 25 mg to control the schizophrenia symptoms. After 4 d, all patients reached the dose of 200 mg twice daily. This dose continued for 3 d to get steady-state plasma concentrations. On d 8, after the 200 mg daily dose at 8:00 am, blood samples were collected before and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 h. To confirm steady-state concentrations of QTP and its metabolites, blood samples for trough plasma concentrations were collected before the morning dose of QTP

on d 6 and d 7. Plasma was separated by centrifugation and stored at -10 ºC. During the trial, all subjects had the same diet.

Analytical procedures Plasma concentrations of QTP and its metabolites were determined by a validated procedure involving extraction of QTP and its metabolites with Oasis™ HLB extraction cartridges and detection by high-performance liquid chromatography – electrospray ionization mass spectrometry[6].

Pharmacokinetic analysis The peak plasma concentration (C_{max}^{SS}) and time to reach the peak concentration (t_{max}) were get directly from the plasma concentration-time curve. The terminal elimination rate constant (K_e) was calculated from the slope of regression line of the last four natural log-transformed plasma concentrations-time curve. The terminal-phase elimination half-life ($t_{1/2}$) was calculated as $0.693/K_e$. AUC_{0-12}^{SS} was calculated by linear trapezoidal rule. CL/*F* and *V*/*F* were calculated as dose/AUC_{0-12}^{SS} and dose/($K_e \cdot AUC_{0-12}^{SS}$), respectively. The trough plasma concentration (C_{min}^{SS}) was represented by the plasma concentration of the sample collected before QTP administration on d 8. The average plasma concentration for a 12-h dosing interval (C_{av}^{SS}) was calculated as $AUC_{0-12}^{SS}/12$.

Statistical methods All statistical evaluations were performed with SPSS statistical software (Version10.0, USA). The gender difference of pharmacokinetics were assessed by comparing pharmacokinetic parameters, where t_{max} data were analyzed using a nonparametric Wilcoxon signed rank test, and for the other variables, log-transformed data were compared using independent-samples *t* test. Achievement of a steady state was determined using one-way ANOVA to compare trough levels on d 6, 7, and 8. $P<0.05$ was considered to be significant.

RESULTS

The trough plasma concentrations of QTP and its metabolites on d 6, 7, and 8 have no statistically difference ($P>0.05$), indicating the steady-state concentrations of QTP and its metabolites were achieved (Tab 1). The steady-state plasma concentration versus time curves of QTP and its metabolites were shown in Fig 1.

The mean pharmacokinetic parameters of QTP and its metabolites were presented in Tab 2. There was no statistically difference between male and female in pharmacokinetic parameters of QTP and its metabolites (Tab 3), which showed that gender had no effect on these parameters. $t_{1/2}$ of QTP, QTP-SF, and QTP-ND were

Tab 1. The trough plasma concentrations of QTP and its metabolites on d 6, 7, and 8. *n*=21. Mean±SD. QTP-SF: quetiapine sulfoxide; QTP-H: 7-Hydroxy-quetiapine; QTP-ND: 7-hydroxy-N-dealkyl-quetiapine.

| | Trough plasma concentration/$\mu g \cdot L^{-1}$ | | | |
	QTP	QTP-ND	QTP-SF	QTP-H
d 6	131±65	6±4	106±71	14±7
d 7	140±131	6±3	118±103	15±10
d 8	147±142	6±4	109±53	15±8
P	0.898	0.895	0.881	0.965

largely different between individuals. The variations of $t_{1/2}$ were about 4.1 times (16 h/4 h), 4.3 times (18 h/4 h), and 2.7 times (16 h/6 h) for QTP, QTP-SF, and QTP-ND, respectively. One patient's $t_{1/2}$ of QTP-H was about 30 h, which was largely deviated from the common value (5-10 h, Fig 2).

DISCUSSION

After oral administration, QTP is rapidly absorbed with a mean t_{max} of about 2 h. The main *V/F* is 672 L, which indicates QTP is widely distributed throughout the body. The mean $t_{1/2}$ of QTP is 7 h, which is similar to literature reports, and the mean t_{max} and *V/F* obtained in this study were consistent with those reported for QTP in Caucasian schizophrenics in the clinical dose range[5,7,8]. The plasma concentrations of QTP were variable and the CV for C_{max}^{SS} and AUC_{0-12}^{SS} were more

Tab 2. Main multiple dose pharmacokinetic parameters of QTP and its metabolites. *n*=21. Mean±SD. QTP-SF: quetiapine sulfoxide; QTP-H: 7-Hydroxy-quetiapine; QTP-ND: 7-hydroxy-N-dealkyl-quetiapine.

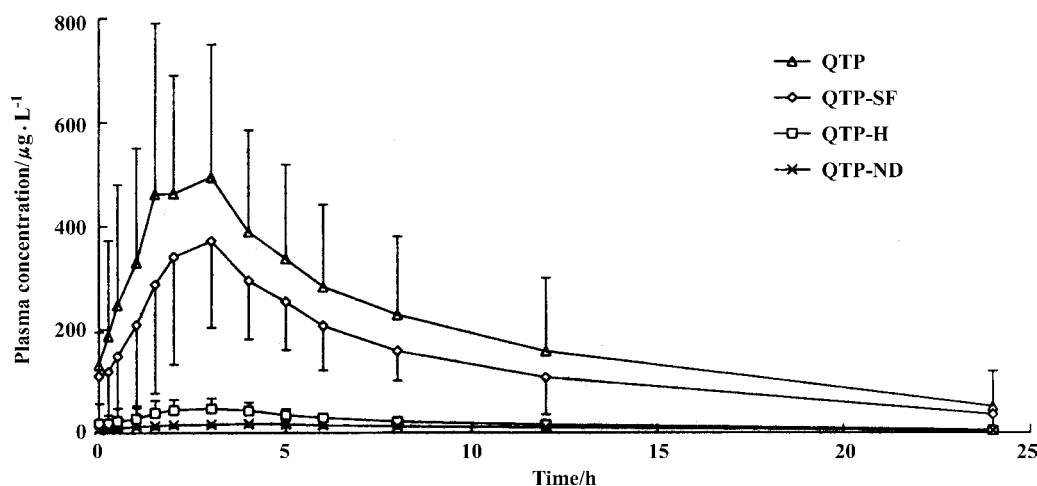| Parameter	QTP	QTP-ND	QTP-SF	QTP-H
t_{max} (h)	2.0 (0.3-5.0)	4.0 (1.5-6.0)	3.0 (0.5-5.0)	3.0 (0.5-5.0)
C_{man}^{SS} ($\mu g \cdot L^{-1}$)	678±325	19±5	451±216	58±22
C_{min}^{SS} ($\mu g \cdot L^{-1}$)	51±68	3.3±1.6	35±36	5±4
C_{av}^{SS} ($\mu g \cdot L^{-1}$)	295±144	13±4	209±71	28±9
AUC_{0-12}^{SS} ($\mu g \cdot h \cdot L^{-1}$)	3538±1728	153±44	2512±854	335±104
$AUC_{0-\infty}^{SS}$ ($\mu g \cdot h \cdot L^{-1}$)	5534±4198	287±107	3858±2 012	529±262
$t_{1/2}$ (h)	7±3	9.4±2.7	7±3	8±5
K_e (h^{-1})	0.11±0.03	0.079±0.019	0.11±0.03	0.103±0.028
V/F (L)	672±394			
CL/*F* ($L \cdot h^{-1}$)	67±25			

Fig 1. Mean plasma concentration-time curves of QTP and its metabolites after multiple doses of QTP on d 8. *n*=21. Mean±SD.

Tab 3. Main multiple dose pharmacokinetic parameters of QTP and its metabolites in different gender. Mean±SD.

Parameter	QTP			QTP-ND			QTP-H			QTP-SF		
	Female (n=11)	Male (n=10)	P	Female (n=11)	Male (n=10)	P	Female (n=11)	Male (n=10)	P	Female (n=11)	Male (n=10)	P
t_{max}/h	3.0 (1.5-4.0)	2.0 (0.5-5.0)	0.32	2 (1-3)	3 (1.5-3.5)	0.22	2 (1-3)	3 (1.5-4)	0.21	3 (1-4)	3 (1.5-4)	0.64
C_{max}^{SS} /μg·L^{-1}	707±386	646±257	0.80	18±4	20±7	0.78	60±21	56±25	0.51	482±231	418±205	0.59
C_{min}^{SS}/μg·L^{-1}	47±31	55±96	0.19	3.5±1.8	3.1±1.4	0.85	5±4	5±5	0.86	37±35	32±40	0.28
AUC_{0-12}^{SS}/μg·h·L^{-1}	3626±1686	3442±1860	0.28	156±50	150±37	0.95	339±85	330±126	0.90	2688±910	2319±789	0.16
$AUC_{0-\infty}^{SS}$/μg·h·L^{-1}	5466±2658	5609±5594	0.55	280±97	294±121	0.81	520±183	539±340	0.79	4114±1956	3577±2140	0.21
$t_{1/2}$/h	8±3	7±4	0.57	10±3	8.6±1.7	0.41	7.0±1.8	9±7	0.23	6.8±2.5	7±4	0.90
K_e/h^{-1}	0.11±0.04	0.12±0.03	0.57	0.073±0.021	0.082±0.015	0.41	0.105±0.023	0.10±0.03	0.23	0.11±0.04	0.11±0.03	0.90
V/F (L)	731±523	607±177	0.50									
CL/F (L·h^{-1})	63±22	71±29	0.21									
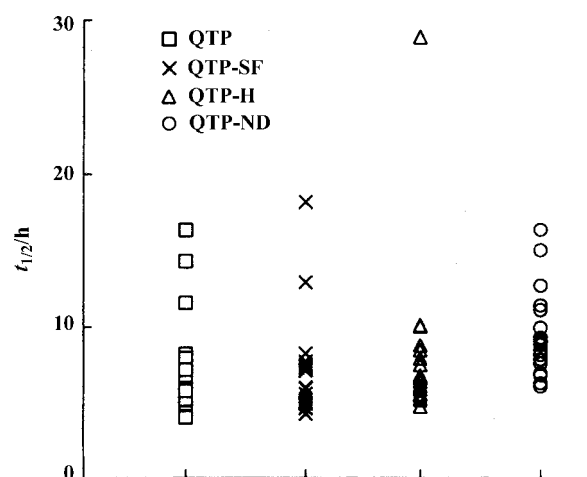
Fig 2. Individual difference for $t_{1/2}$ of QTP and its metabolites. n=21.

than 50 %, and the results in Fig 2 showed high individual differences of metabolism for QTP and its metabolites, so monitoring plasma concentration for QTP is necessary to optimize the treatment protocol during clinical use of QTP.

In addition, DeVane *et al*[8] reported that the metabolism of QTP was mainly catalyzed by CYP3A4 *in vitro* and our study evaluated the activity of CYP3A4 by assaying the plasma concentration ratio of 1'-hydroxy-midazolam to midazolam (1'-OH-MDZ/MDZ). There was negative correlation between AUC_{0-12}^{SS} and 1'-OH-MDZ/MDZ (r=-0.734, P<0.05) and positive correlation between CL/F and 1'-OH-MDZ/MDZ (r=0.891, P<0.05). These mentioned above show that gene polymorphism of CYP is a main factor for the individual differences of metabolism for QTP and its metabolites.

Although QTP-H and QTP-ND are active at the dopamine and serotonin receptor sites, Gefvert *et al*[4] reported that QTP-SF was the major metabolite, and QTP-H and QTP-ND were the minor metabolites *in vivo*. This study also shows that QTP-SF is the major metabolite (69.7 %), and QTP-H (9.6 %) and QTP-ND (5.2 %) are the minor metabolites. The mean t_{max} of QTP-H and QTP-ND, and the common $t_{1/2}$ value of QTP-H in the study are similar to previous reports[5,7,8]. But one patient's $t_{1/2}$ of QTP-H largely deviates from the common value, and the $t_{1/2}$ of QTP and QTP-SF are the longest in the 21 patients. The ratio of 1'-OH-MDZ/MDZ of the patient (0.12) also largely deviates from the common value (0.66). So it indicates the $t_{1/2}$ deviation of QTP-H, QTP-SF, and QTP may resulted from the low activity of CYP3A4 in the patient. In addition,

the mean $t_{1/2}$ of the four compounds are about 7 to 9 h. This suggests the clinical dose range and interval do not cause accumulation of QTP and its metabolites.

In conclusion, the pharmacokinetics of QTP is similar to literature reports. The clinical dosage regime causes no drug accumulation.

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