Population pharmacokinetics analysis of olanzapine for Chinese psychotic patients based on clinical therapeutic drug monitoring data with assistance of meta-analysis

Anyue Yin*[1,2,3], Dewei Shang*[4], Yuguan Wen[4], Liang Li[1,2,3], Tianyan Zhou[1,2,3], Wei Lu[1,2,3,4]

1. School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing, China
2. Peking University/Pfizer Pharmacometrics Education Center, Peking University Health Science Center, Beijing, China
3. State Key Laboratory of Natural and Biomimetic Drugs Peking University, Beijing, China
4. Guangzhou Brain Hospital (Guangzhou Huiai Hospital, the Affiliated Brain Hospital of Guangzhou Medical University), Guangzhou, China
5. Beijing Institute for Brain Disorders, Beijing, China
** Anyue Yin and Dewei Shang contribute equally to this work*

INTRODUCTION & OBJECTIVE:

- Olanzapine is a widely used atypical antipsychotic
- Among plenty of olanzapine PK studies, only a small number of them have built population PK models, but these models have not been evaluated on Chinese patients.
- TDM data are incapable of capturing the complete PK profile. Model-based meta-analysis can be used to make up this deficiency[1].
- We aim to make the best use of retrospective TDM data to build an eligible population PK model for olanzapine in Chinese psychotic patients that would facilitate individualized therapy.

METHODS:

Model-based Meta-analysis

- A structural model were constructed to assist the modeling of TDM data as prior estimates.
- Qualified publications from 1996 to March 2015 were selected from PubMed database and SciFinder database to obtain olanzapine concentrations.
- Inter-arm variabilities (IAV) were considered.
- Residual errors were weighted by the sample size.

$$Y_{obs} = Y_{pred} \cdot \left(1 + \frac{\varepsilon_1}{\sqrt{N}}\right) + \frac{\varepsilon_2}{\sqrt{N}}$$

- Modeling analysis was performed using NONMEM software (version 7.3.0).

TDM data analysis

- TDM data were collected from psychotic patients who were hospitalized in the Guangzhou Brain Hospital during January 2014 to January 2015.
- Model structure was set as the one developed in model-based meta-analysis, and typical values of most PK parameters were fixed to the corresponding estimates except for CL/F.
- Inter-individual variabilities (IIV) were set to be the corresponding IAV multiplied by a factor (θf).

$$P_j = P_{tv} \cdot e^{\eta_j} \qquad \eta_j = \eta_i \cdot \theta_f$$

- Potential covariates were investigated.

Simulation

- The time course of olanzapine serum concentrations at steady state was simulated under regular oral administration of commonly used dose regimens [20 mg every day (QD), 15 mg QD, 10 mg QD, 10 mg twice a day (BID), 5 mg BID, and 5 mg QD plus 10 mg every night (QN)].

RESULTS:

Model-based Meta-analysis

- 390 olanzapine serum concentrations acquired from 23 different studies constituted the data set for this meta-analysis.

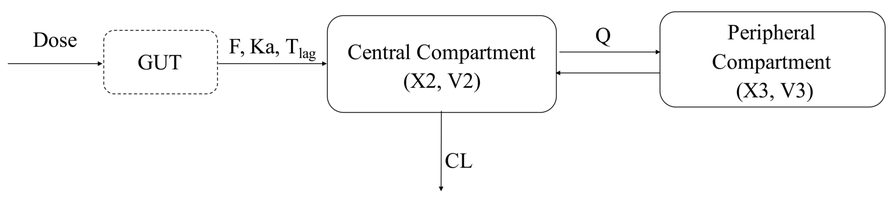

Figure 1. The selected population PK model structure of olanzapine.

Table 1. Population PK parameters estimates and bootstrap results of the final model for meta analysis.

	Final model			Bootstrap		
Parameter	Estimate	RSE (%)	IAV(CV%)	Median	95%CI	RSE(%)
Ka (/h)	0.868	14.4	51.2	0.863	0.602-1.15	16.0
CL/F (L/h)	18.9	7.4	36.7	19.0	16.4-22.5	8.07
V2/F (L)	599	9.6	42.7 (98.2 % correlated)	599	484-744	10.9
Q/F (L/h)	21.3	20.3	0 fixed	21.4	12.7-34.9	24.9
V3/F (L)	174	12.5	0 fixed	173	127-234	15.5
T_{lag} (h)	0.706	6.2	17.9	0.706	0.565-0.787	8.07
Sample size weighted residual error						
PRO (CV%)	26.1	22	-	-	-	-
ADD (SD, ng/ml)	1.47	42	-	-	-	-

IAV, inter-arm variability; CV, coefficient of variation; CI, confident interval; RSE, relative standard errors; PRO, proportional residual error; ADD, additive residual error; SD, standard deviation of the error

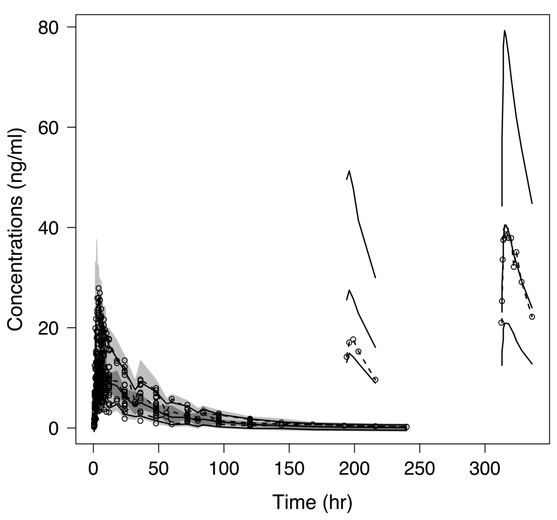

Figure 2. Visual predictive check of the population PK model for meta analysis.

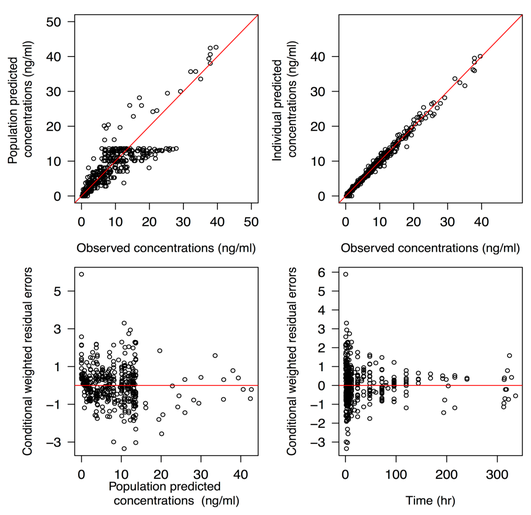

Figure 3. Goodness-of-fit plots of the population PK model for meta analysis.

TDM data analysis

- Data set comprised 543 olanzapine TDM serum concentrations, collected from 128 psychotic patients (68 males and 60 females)
- Gender and smoking habit had a significant influence on CL/F of olanzapine ($p < 0.001$).

Table 2. Population PK parameters estimates of the final PK model for TDM dataset.

	Final model			Bootstrap		
Parameter*	Estimate	RSE(%)	IIV(CV%)	Median	95% CI	RSE (%)
$CL/F_{female\ non\text{-}smokers}$ (L/h)	16.6	6.4	36.7* θ_f	16.7	14.6-18.7	6.13
θ for male smokers	2.25	10	-	2.23	1.85-2.69	10.1
θ for male non-smokers	1.47	8.8	-	1.46	1.25-1.74	8.73
V2/F (L)	599 fixed	-	42.7* θ_f (98.2 % correlation fixed)	599 fixed	-	-
θ_f	1.10	8.4	-	1.07	0.876-1.24	8.66
Residual error						
PRO (CV%)	31.1	5.3	-	-	-	-
ADD (SD, ng/ml)	1.03	120.8	-	-	-	-

IIV, inter-individual variability; *Other parameters were fixed to what obtained in meta-analysis.

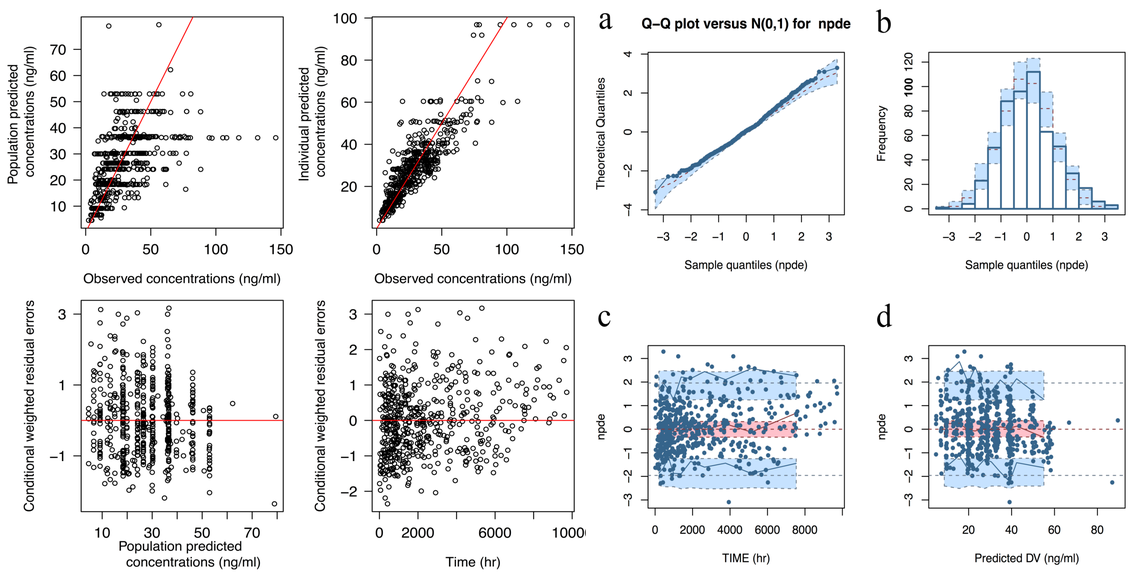

Figure 4. Goodness-of-fit plots of the final population PK model for TDM dataset

Figure 5. NPDE plots of the population PK model built based on TDM concentrations.

Simulation

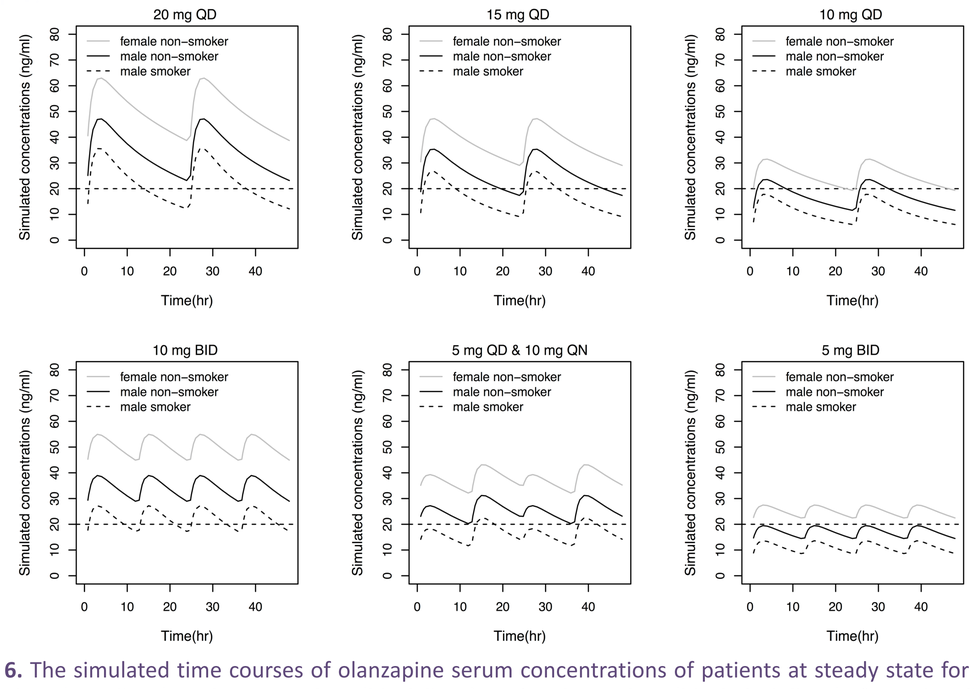

Figure 6. The simulated time courses of olanzapine serum concentrations of patients at steady state for female nonsmokers (grey lines), male nonsmokers (black lines), and male smokers (black dash lines) after using different dose regimens. Horizontal dashed lines represent lower boundary of the recommended therapeutic range for olanzapine[2].

CONCLUSION:

- Model built from meta-analysis could be used as Bayesian priors to assist the modeling of TDM data.
- A two-compartment model with first-order absorption (with a time lag) and first-order elimination, involving the correlation between CL/F and V2/F, was constructed to describe olanzapine concentrations and validated to have good predictability.
- Gender and smoking habit had a significant influence on CL/F of olanzapine.
- The final model could be used as a suitable tool for designing individualized therapy for Chinese psychotic patients.

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