

论著·临床研究

基于生理药物代谢动力学模型预测氯氮平联合用药的药物相互作用

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[摘要] **目的**·以氯氮平-氟伏沙明合用为例, 通过构建针对中国群体的生理药物代谢动力学 (physiologically based pharmacokinetic, PBPK) 模型, 预测氯氮平联合用药的药物相互作用 (drug-drug interaction, DDI) 并对氯氮平进行剂量优化。**方法**·通过文献及药理学相关数据库获取氯氮平及氟伏沙明的基本理化性质参数, 药物吸收、分布、代谢及排泄 (absorption, distribution, metabolism and excretion, ADME) 相关参数及中国群体的生理解剖相关参数, 利用 PK-Sim[®] 软件构建 2 种药物的 PBPK 模型。以平均百分比误差 (mean percentage error, MPE) 和平均绝对百分比误差 (mean absolute percentage error, MAPE), 或者预测药时曲线下面积 (area under the curve, AUC) 或峰浓度 (peak concentration, C_{max}) 与实测 AUC 或 C_{max} 的比值为判断指标, 并通过真实世界血药浓度数据进行模型验证。在此基础上结合氟伏沙明对氯氮平的抑制作用参数构建氯氮平-氟伏沙明联合用药的 PBPK 模型, 预测氯氮平的药物代谢动力学变化。以药时曲线下面积比值 (area under the curve ratio, AUCR) 或峰浓度比值 (peak concentration ratio, $C_{max}R$) 的 90% 置信区间为评价指标判断是否存在临床显著的 DDI (无效应边界为 80%~125%)。根据 PBPK 模型量化氯氮平-氟伏沙明联合用药后氯氮平的药物代谢动力学变化, 并制定氯氮平的剂量优化方案。**结果**·构建的氯氮平、氟伏沙明模型验证的 MPE 绝对值 $\leq 10\%$ 且 $MAPE < 25\%$, 说明预测的药时曲线是准确的。氯氮平-氟伏沙明合用的 PBPK 模型的 AUC 预测值与实测值的比值在 1.25 以内, 可准确地预测药物代谢动力学参数。氯氮平-氟伏沙明联合用药模型的预测结果提示, 氯氮平-氟伏沙明联合用药的 AUCR 和 $C_{max}R$ 的 90% 置信区间均不完全位于无效应边界内, 说明两药合用会发生临床显著性的 DDI。此外, PBPK 模型的剂量优化结果提示: 受试者联合服用氯氮平及氟伏沙明时, 氯氮平的剂量减少至原本剂量的 50%, 可使氯氮平的暴露水平与单药治疗时保持一致。**结论**·研究建立的 PBPK 模型可以较好模拟联合用药对氯氮平药物代谢动力学的影响, 对于预测药物可能的相互作用及剂量优化方案有参考意义。如果治疗过程中需要合用氯氮平和氟伏沙明, 须警惕临床显著的 DDI, 并应优化氯氮平的剂量。

[关键词] 氯氮平; 联合用药; 药物相互作用; 生理药物代谢动力学模型**[DOI]** 10.3969/j.issn.1674-8115.2024.11.008 **[中图分类号]** R749.053 **[文献标志码]** A

Prediction of drug-drug interactions in clozapine combination therapy based on physiologically based pharmacokinetic model

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[Abstract] **Objective**·To develop physiologically based pharmacokinetic (PBPK) models specifically designed for the Chinese population by utilizing the combination of clozapine and fluvoxamine as a case, and predict the drug-drug interaction (DDI) associated with the combination medication of clozapine, ultimately optimizing the dosage of clozapine. **Methods**·By obtaining the physicochemical parameters, absorption, distribution, metabolism, excretion (ADME)-related parameters, and physiologically relevant parameters of the Chinese population through literature and pharmacology-related databases, PBPK models for the clozapine and fluvoxamine were constructed by using PK-Sim[®] software. The models' accuracy was evaluated by comparing predicted values of the

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area under the curve (AUC) and peak concentration (C_{\max}) to observed data, using the mean percentage error (MPE) and mean absolute percentage error (MAPE) as evaluation indicators. The models were validated against real-world plasma drug concentration data. Additionally, combining the inhibitory effect of fluvoxamine on clozapine, models for the combination therapy of clozapine and fluvoxamine were developed to predict the pharmacokinetic changes of clozapine. The presence of clinically significant DDI was determined by using the 90% confidence interval of the AUC ratio (AUCR) or C_{\max} ratio (C_{\max} R) as evaluation metrics, with a non-effect boundary set at 80%–125%. The pharmacokinetic changes of clozapine upon co-administration with fluvoxamine based on PBPK models were quantified, and a dosage optimization for clozapine was developed. **Results** The constructed model of clozapine and fluvoxamine was considered accurate if the absolute value of the MPE was $\leq 10\%$ and the MAPE was $< 25\%$ during validation, indicating that the predicted concentration-time curves were accurate. The PBPK model for the co-administration of clozapine and fluvoxamine was able to accurately predict pharmacokinetic parameters if the ratio of predicted AUC to observed AUC was within 1.25. The prediction of PBPK model for the co-administration showed that the 90% confidence intervals for AUCR and C_{\max} R of the combination therapy of clozapine and fluvoxamine were not entirely within the ineffective effect boundary, indicating a clinically significant DDI when these two drugs were used concomitantly. Moreover, the dose optimization according to the PBPK models indicated that when subjects were co-administered with clozapine and fluvoxamine, reducing the dose of clozapine to 50% of the original dose could maintain the exposure levels of clozapine consistent with monotherapy. **Conclusion** The established PBPK model can effectively simulate the impact of combination therapy on pharmacokinetic changes of clozapine, providing valuable insights for predicting potential DDI and optimizing dosage regimens. If clozapine needs to be co-administered with fluvoxamine during the treatment, clinicians should remain vigilant for clinically significant DDI and contemplate optimizing the dosage of clozapine accordingly.

[Key words] clozapine; combination medication; drug-drug interaction; physiologically based pharmacokinetic model

氯氮平是难治性精神分裂症优先考虑的药物。氯氮平与其他药物联合使用时,可能会影响氯氮平的血药浓度,甚至会导致癫痫发作、代谢综合征等药物不良反应(adverse drug reaction, ADR)的发生^[1-2]。氟伏沙明是细胞色素P450成员1A2(cytochrome P450 1A2, CYP1A2)的强抑制剂,与氯氮平合用会发生药物-药物相互作用(drug-drug interaction, DDI),从而增加药物不良反应的发生风险^[3-4]。美国食品药品监督管理局(Food and Drug Administration, FDA)的药物标签建议合用氟伏沙明时减少氯氮平的剂量^[5],该结论是针对高加索人群得出的,是否适用于中国群体尚无明确的证据^[6-7]。生理药物代谢动力学(physiologically based pharmacokinetic, PBPK)模型是药物代谢动力学研究的重要工具,能用于研究合并用药、种族等因素对药物体内给过程的影响^[8-10]。若能针对中国群体构建PBPK模型,对合用氟伏沙明后氯氮平的血药浓度进行预测,并以此为依据提出血药浓度剂量优化建议,可降低氯氮平的治疗风险^[11-13]。

综上,本研究希望通过针对中国群体的氯氮平-氟伏沙明合用的PBPK模型,量化合并用药对氯氮平血药浓度的影响,以期在临床存在合用氟伏沙明的需求时,为调整氯氮平剂量提供参考。

1 材料与方法

1.1 PBPK模型的建立与验证

1.1.1 PBPK模型的软件平台 PK-Sim®软件(10.0

版)用于PBPK模型的建立以及参数的优化,由德国拜耳公司研发。WebPlotDigitizer软件(4.5版)用于提取临床数据中时曲线数据的信息,由美国圣母大学开发完成。OriginPro®(9.5.5版)对输出的结果进行数据分析以及图形编辑,由美国OriginLab公司研发。

1.1.2 建模步骤与数据来源 PBPK模型的建模数据主要来自文献及数据库,PK-Sim®软件将模型分为群体、药物、给药方案及剂型共4个模块,它们共同模拟了药物在体内的过程。

(1) 群体模块。生理及解剖相关参数用于构建个体模块,这类参数主要来自PK-Sim®软件自带的数据库。细胞色素P450(cytochrome P450, CYP450)亚型的酶含量是影响药物代谢的重要因素,在不同种族、不同国家或地区间存在差异。从PubMed、Google Scholar等数据库中收集中国人群各常见CYP450亚型的酶含量参数,以加权平均值(weighted mean, WM)对数据进行整合(详见表1)^[14-16]。

$$WM = \frac{\sum_{j=1}^J n_j \times x_j}{\sum_{j=1}^J n_j} \quad (\text{公式1})$$

其中,WM是数据的加权平均值, n_j 指每个数据的样本量, x_j 指每个数据中的酶的平均丰度。

从相应的临床试验中获取年龄、性别、身高及体重等人口学特征的信息以构建虚拟群体;若缺乏相关信息则从美国国家健康与营养调查(National Health and Nutrition Examination Survey, NHANES)

表1 中国人群各CYP450亚型的酶含量

Tab 1 Enzyme content of CYP450 subtypes in Chinese population

CYP450	Sample 1 ^[14]	Sample 2 ^[15]	Sample 3 ^[16]	WM
CYP1A2/(pmol·mg ⁻¹)	42.48	42.00	42.30	42.31
CYP2A6/(pmol·mg ⁻¹)	15.63	—	—	15.63
CYP2B6/(pmol·mg ⁻¹)	4.62	—	—	4.62
CYP2C9/(pmol·mg ⁻¹)	98.60	—	87.20	87.19
CYP2C19/(pmol·mg ⁻¹)	8.45	60.00	8.10	8.25
CYP2D6/(pmol·mg ⁻¹)	20.50	—	—	20.50
CYP2E1/(pmol·mg ⁻¹)	102.04	—	—	102.04
CYP3A4/(pmol·mg ⁻¹)	49.34	120.00	93.00/70.30	49.34
CYP3A5/(pmol·mg ⁻¹)	42.45	—	145.40/82.10	42.45

Note: Sample 1, Sample 2, and Sample 3 were from three clinical studies, each containing measurement data of CYP450 enzyme levels in the Chinese populations. CYP450—cytochrome P450; WM—weighted mean; “—” indicating missing data.

数据库中获取。

(2) 药物模块及给药方案模块。在药物数据库 (DrugBank) 等药理学数据库、FDA 以及文献中收集药物的基本理化性质参数及药物吸收、分布、代谢及排泄 (absorption, distribution, metabolism and excretion,

ADME) 相关参数来建立药物模块。经文献检索和各药理学数据库检索收集的氯氮平及氟伏沙明的基本理化性质参数与 ADME 相关参数详见表2。氯氮平的给药方案有 2 种, 分别是: 150 mg/次, 2 次/d; 100 mg/次, 2 次/d。

表2 氯氮平和氟伏沙明的基本理化性质及 ADME 相关参数

Tab 2 Basic physicochemical properties and ADME-related parameters of clozapine and fluvoxamine

Parameter	Clozapine	Source	Fluvoxamine	Source
LogP	3.23	DrugBank	3.68	Fitted
f _u	0.02	FDA, fitted	0.20	DrugBank, fitted
Molecular weight/(g·mol ⁻¹)	326.83	DrugBank	318.34	DrugBank
pKa	7.50	DrugBank	9.40	Fitted
Solubility/(mg·mL ⁻¹)	0.19	ALOGPS	0.07	Fitted
CL _h /(mL·h ⁻¹ ·kg ⁻¹)	2.28	Fitted	1.21	Fitted
CL _r /(mL·h ⁻¹ ·kg ⁻¹)	0.01	Fitted	0.02	FDA, fitted

Note: Fitted represents the parameters obtained from fitting the PBPK model. LogP—logarithm of octanol/water partition coefficient; f_u—fraction unbound; pKa—negative decadic logarithm of acid dissociation constant; CL_h—hepatic clearance; CL_r—renal clearance.

(3) 剂型模块。当给药途径为口服时需要建立剂型模块以模拟药物在胃肠道内的溶出过程, 该过程一般通过威布尔模型描述^[17]。

$$m=1-\exp[-(t-T_{lag}^b)/a] \quad (\text{公式2})$$

其中, a 为尺度参数, b 为形状参数, m 为 t 时药物溶解的百分比, T_{lag} 为药物溶出的迟滞时间 (单位 h)。

1.1.3 模型验证 (1) 模型验证的评价指标。PBPK 模型可以从 2 个方面进行验证。一是以平均百分比误差 (mean percentage error, MPE) 和平均绝对百分比误差 (mean absolute percentage error, MAPE) 为评价依据, 当 MPE 绝对值 ≤ 10% 且 MAPE < 25% 时模型预测的药时曲线是准确的 (公式 3、4)^[18]。二是以预测药时曲线下面积 (area under the curve, AUC) 或峰浓度 (peak concentration, C_{max}) 与实测 AUC 或 C_{max} 的比值

为判断指标, 当预测值与实测值的比值在 1.25 倍内可认为预测药物代谢动力学参数的准确度较高。

$$MPE = \frac{100\%}{n} \sum_{i=1}^n \left(\frac{\hat{y}_i - y_i}{y_i} \right) \quad (\text{公式3})$$

$$MAPE = \frac{100\%}{n} \sum_{i=1}^n \left| \frac{\hat{y}_i - y_i}{y_i} \right| \quad (\text{公式4})$$

$$R_{\text{pre/obs}} = \frac{\text{Model predicted AUC or } C_{\text{max}}}{\text{Clinical observed AUC or } C_{\text{max}}} \quad (\text{公式5})$$

其中, n 为样本量, \hat{y}_i 表示预测值, y_i 表示实测值, R_{pre/obs} 为预测值与实测值之比。

(2) 模型验证的数据来源。内部验证数据集的数据来自文献报道的既往氯氮平及氟伏沙明的药物代谢动力学相关的临床试验数据^[19-23]: 其中用于氯氮平内部验证的数据来自一项含有 18 名健康受试者多次

给药后的氯氮平的药时曲线数据的临床研究^[19]；氟伏沙明的内部验证数据则来自一项含有健康受试者单次口服 50 mg 氟伏沙明后的血药浓度数据的临床试验^[20]。外部验证数据集的数据来自上海交通大学医学院附属精神卫生中心病历系统，选取了 2018—2019 年期间与模型构建的虚拟群体性别、年龄、氯氮平给药方案相匹配的患者，提取氯氮平的血药浓度数据。

1.2 氯氮平-氟伏沙明联合用药的 PBPK 模型

1.2.1 DDI 模型的构建与验证 根据文献报道的氟伏沙明对 CYP1A2 的抑制作用参数 ($K_{ic}=10.00$ nmol/L, $K_{iu}=10.00$ nmol/L) 和对 CYP3A4 的抑制作用参数 ($K_i=1.60$ μ mol/L) 来整合氯氮平与氟伏沙明的 PBPK 模型^[24-26]。研究构建了 2 种给药方案：受试者分别口服 100 mg 或 150 mg 氯氮平片 (2 次/d) 以及 50 mg 的氟伏沙明 (1 次/d)。DDI 模型构建完成后，根据既往氯氮平与氟伏沙明合用的临床试验中的药物代谢动力学参数数据进行外部验证^[23]。

1.2.2 基于 PBPK 模型的 DDI 预测 (1) DDI 预测的过程及评价指标。以氯氮平单用时与合用氟伏沙明时的药时曲线下面积比值 (AUC ratio, AUCR) 或峰浓度比值 (C_{max} ratio, C_{max} R) 为依据判断氯氮平暴露量的变化在临床上是否具有显著性 (无效应边界为

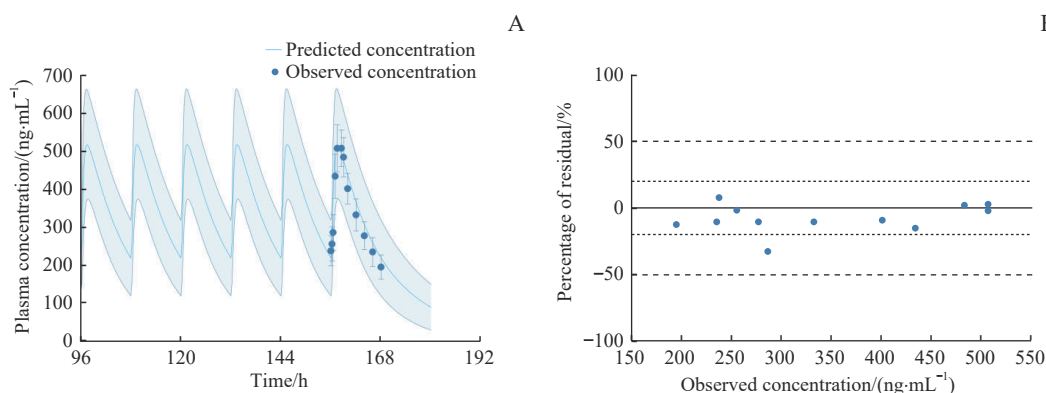
80%~125%)^[27]。当 AUCR 或 C_{max} R 的 90% 置信区间完全处于上述无效应边界范围之内，则可认为不会出现具有临床显著性的 DDI。此外，氯氮平的谷浓度 (trough concentration, C_{trough}) 超出推荐治疗范围 (C_{trough} : 350~600 ng/mL) 时也提示出现 ADR 的风险增加^[28]。

(2) 氯氮平的剂量优化。氯氮平与氟伏沙明合用后，以氯氮平在稳态情况下的 C_{max} 以及 C_{trough} 为依据调整氯氮平剂量。当两药合用后氯氮平的 C_{max} 及 C_{trough} 均与单用氯氮平保持一致时，此时氯氮平的剂量为优化剂量。

2 结果

2.1 单药的 PBPK 模型及验证结果

2.1.1 氯氮平的 PBPK 模型及验证结果 研究模拟多次口服氯氮平 (100 mg/次, 2 次/d) 的 PBPK 模型并进行验证。内部验证的结果显示，氯氮平的血药浓度达到稳态后 AUC 均值为 4 388.90 ng·h/mL, C_{max} 均值为 516.89 ng/mL, C_{trough} 均值为 129.57 ng/mL (图 1)。内部验证的结果表明，模型预测的 MPE 值为 -7.66%，MAPE 为 9.71%，表明 PBPK 模型预测氯氮平的药物代谢动力学参数准确度较高。



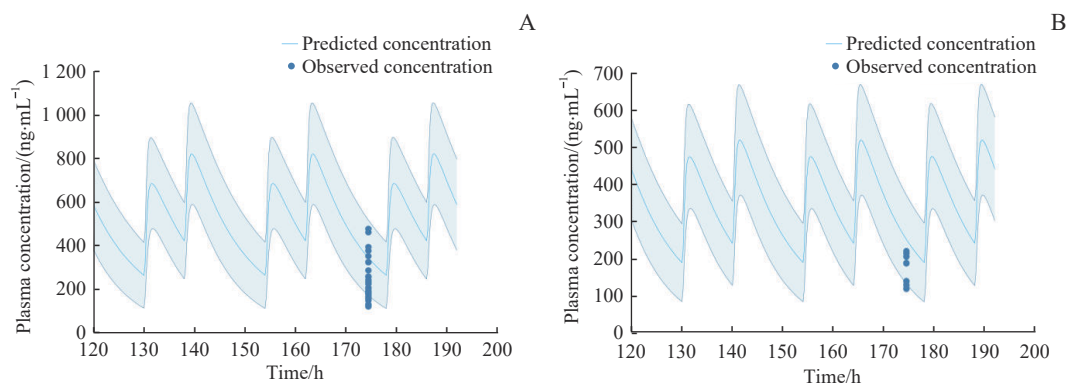
Note: A. Plasma concentration-time curve profiles of clozapine after the administration of multiple oral 100 mg tablets in healthy adults. B. Residue plot for the model prediction of clozapine plasma concentrations in healthy adults.

图 1 健康受试者多次口服 100 mg 氯氮平后氯氮平的药时曲线及残差图

Fig 1 Plasma concentration-time curve profiles and residue plot of clozapine after multiple oral doses of 100 mg in healthy adults

外部验证数据来自上海交通大学医学院附属精神卫生中心病历系统，用于进一步评价 PBPK 模型的预测能力。模型预测了 2 个给药方案 (150 mg/次, 2 次/d; 100 mg/次, 2 次/d)。前一个给药方案的 AUC 均值为 4 402.18 ng·h/mL, C_{max} 均值为 817.08 ng/mL,

C_{trough} 均值是 271.27 ng/mL; 后一个给药方案的 AUC 均值为 3 597.09 ng·h/mL, C_{max} 均值为 522.93 ng/mL, C_{trough} 均值为 150.34 ng/mL (图 2)。外部验证数据中符合 2 个给药方案的血药浓度数据共 32 个, 74.36% 的数据位于预测值的 95% 置信区间内。



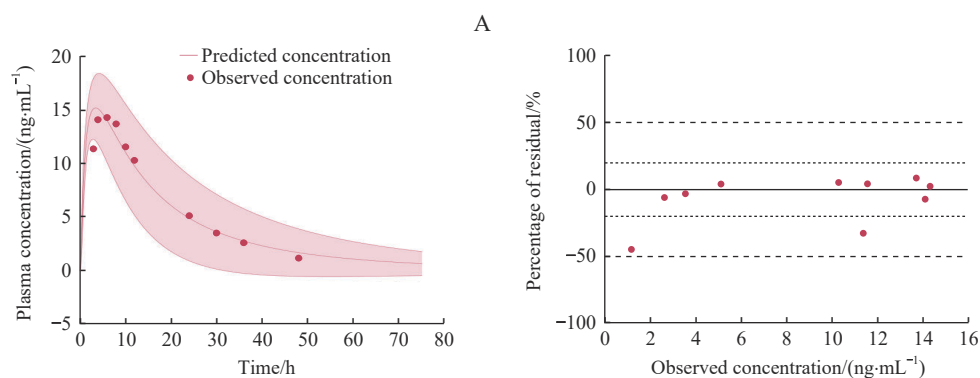
Note: A. Plasma concentration-time curve profiles of clozapine after the administration of multiple 150 mg oral tablets in patients. B. Plasma concentration-time curve profiles of clozapine after the administration of multiple 100 mg oral tablets in patients.

图2 患者多次口服氯氮平片后的药时曲线

Fig 2 Plasma concentration-time curve profiles of clozapine after the administration of multiple oral tablets of clozapine in patients

2.1.2 氟伏沙明的PBPK模型与验证结果 研究模拟了单次口服50 mg 氟伏沙明的PBPK模型, 预测的AUC均值为353.89 ng·h/mL, C_{\max} 均值为15.92 ng/mL。

模型内部验证结果表明, 模型预测的MPE值为-6.99%, MAPE为11.81%, 说明PBPK模型预测氟伏沙明的药物代谢动力学参数的准确度高(图3)。



Note: A. Plasma concentration-time curve profiles of fluvoxamine after the administration of a single 50 mg dose of fluvoxamine in healthy adults. B. Residue plot for the model prediction of fluvoxamine plasma concentrations in healthy adults.

图3 健康受试者单次50 mg口服氟伏沙明后的药时曲线及残差

Fig 3 Plasma concentration-time curve profiles and residue plot of fluvoxamine after the administration of a single 50 mg dose of fluvoxamine in healthy adults

2.2 氯氮平-氟伏沙明联合用药

2.2.1 氯氮平-氟伏沙明联合用药的PBPK模型与验证 氟伏沙明-氯氮平的联合用药模型预测了氯氮平血药浓度达到稳态后的暴露水平, 2个给药方案的AUC均值分别为10 380.99 ng·h/mL和10 288.17 ng·h/mL, C_{\max} 均值分别为1 049.12 ng/mL和1 663.57 ng/mL, C_{trough} 均值分别为712.49 ng/mL和1 460.93 ng/mL。PBPK模型的模拟结果表明合用氟伏沙明的AUCR为2.11, 既往临床试验的AUCR为2.3^[23], 即 $R_{\text{pre/obs}}$ 为0.92 (<1.25), 说明DDI的预测效果佳。另一项临床研究结果^[3]表明氯氮平合用氟伏沙明后, 氯氮平的血药浓度/剂量比值(plasma concentration/dose, C/D)较单

药使用时增加了117.9%, 模型预测结果显示氯氮平的C/D为111.4%, 也侧面验证了模型预测的准确性。

2.2.2 基于PBPK模型的DDI预测结果及剂量优化

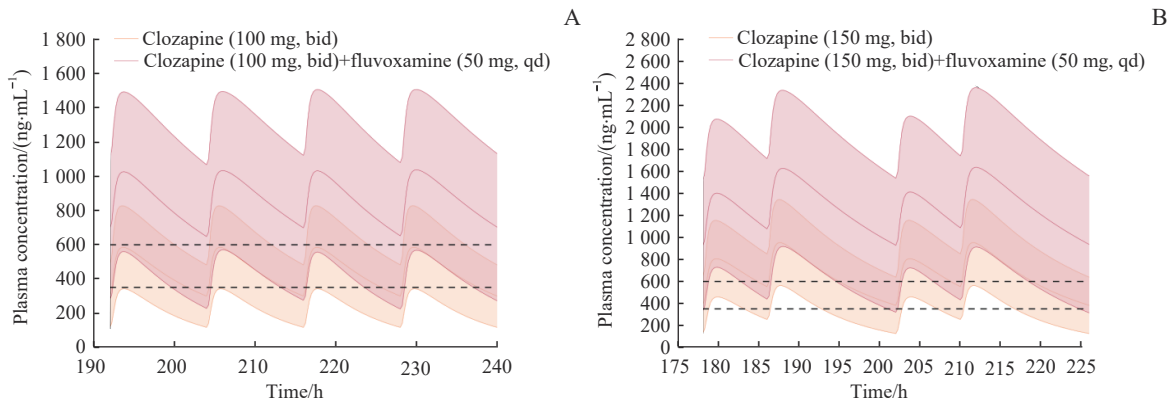
(1) 氯氮平-氟伏沙明合并用药的DDI预测结果。根据氯氮平-氟伏沙明合并用药的PBPK模型得到的2个给药方案中AUCR均值分别为197%和189%, C_{\max} R均值分别为180%和175%(表3)。氯氮平-氟伏沙明合并用药的AUCR和 C_{\max} R的90%置信区间均部分位于无效应边界内, 说明两药合用会发生临床显著性的DDI。同时, 氯氮平的稳态血药浓度超过了推荐治疗范围(C_{trough} : 350~600 ng/mL), 也说明存在风险(图4)。

表3 氯氮平-氟伏沙明 PBPK 模型药物代谢动力学参数比较

Tab 3 Comparison of pharmacokinetic parameters of clozapine-fluvoxamine PBPK model

Drug administration	Pharmacokinetic parameter	Combination therapy/monotherapy		No effect boundary
		mean/%	90%CI	
Administration 1	C _{max} /(ng·mL ⁻¹)	180	111%–223%	80%–125%
	AUC/(ng·h·mL ⁻¹)	197	105%–204%	
Administration 2	C _{max} /(ng·mL ⁻¹)	175	110%–240%	
	AUC/(ng·h·mL ⁻¹)	189	100%–277%	

Note: Administration 1 and 2 respectively involved subjects taking oral clozapine at either 100 mg or 150 mg twice daily, and 50 mg once daily. CI—confidence interval.



Note: A. Plasma concentration-time curve profiles of clozapine (100 mg) before and after combination with fluvoxamine (50 mg). B. Plasma concentration-time curve profiles of clozapine (150 mg) before and after combination with fluvoxamine (50 mg). bid—twice a day; qd—once a day.

图4 氯氮平-氟伏沙明合用前后氯氮平的药时曲线的比较

Fig 4 Comparison of plasma concentration-time curve profiles of clozapine before and after combination with fluvoxamine

(2) 剂量优化。以受试者口服氯氮平 100 mg/次、2 次/d 及氟伏沙明 50 mg/次、1 次/d 为例，经模型拟合制定的剂量调整建议是：受试者在加用 50 mg 氟伏沙明后氯氮平片的剂量从 100 mg（2 次/d）可以减为 50 mg（2 次/d）。在这种情况下，加用氟伏沙明后氯氮平的暴露水平与单药使用氯氮平时保持一致（图 5）。

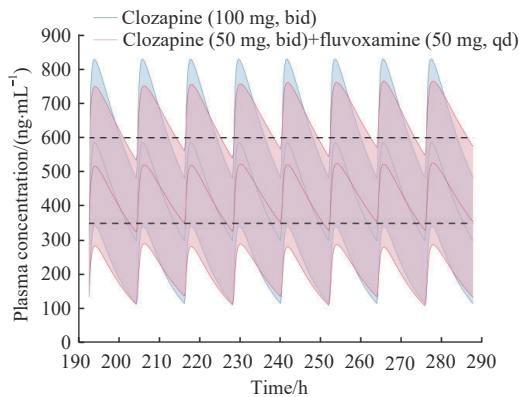


图5 剂量优化前后氯氮平的药时曲线比较

Fig 5 Comparison of plasma concentration-time curve profiles of clozapine before and after dose optimization

3 讨论

在难治性精神分裂症的治疗过程中，若出现氯氮平的单药治疗效果不好等情况时，可能需要考虑加用氟伏沙明^[29-30]。研究者在多项临床研究中发现，与氯氮平的单药治疗相比，氯氮平与氟伏沙明合用可以改善精神分裂症的阴性症状，提高氯氮平/去甲基氯氮平的比例等^[4]。同时，有研究^[31]提出合用氟伏沙明导致的氯氮平/去甲基氯氮平的比例增加，除了可以增强氯氮平的疗效外，还可以减少氯氮平治疗过程中体质量增加和代谢紊乱等 ADR 的发生。但氟伏沙明是 CYP1A2 的强抑制剂，可能会显著增加氯氮平的血药浓度。两者合并用药时的安全性是临床医师十分关注的问题。

研究构建了针对中国群体的氯氮平、氟伏沙明及两药合用的 PBPK 模型，建立的模型均能较为准确地预测药物在体内的药物代谢动力学过程。在模型验证中，研究通过上海交通大学医学院附属精神卫生中心病历系统，选取了 2018—2019 年期间与模型的虚拟

群体相匹配的患者,提取了氯氮平的血药浓度数据进行外部验证,更为有力地证明了PBPK模型可以较好地预测中国群体的氯氮平的体内过程。在构建的模型基础上,研究对氯氮平-氟伏沙明合并用药进行了DDI预测,结果提示两药合用存在显著的DDI。因此若需合用氟伏沙明,应减少氯氮平的剂量以提高用药安全性。FDA的药物标签提出氯氮平与氟伏沙明合用时应减至原始剂量的1/3^[5]。需要注意的是,该结论主要基于高加索人群的数据,而氯氮平是一个在种族间存在显著代谢差异的典型药物。亚洲人对于氯氮平的代谢能力更弱,在合并氟伏沙明时更应警惕血药浓度的变化^[32-33]。研究结果提示,在中国群体中,若将氯氮平的剂量调整为原来的50%,可以使加用氟伏沙明后氯氮平的暴露水平与单药治疗时一致。

与传统的DDI临床研究相比,基于PBPK模型的DDI预测在伦理方面所受的限制更少,且经济效益高,具有重要的临床意义^[34-35]。同时,针对中国群体构建的氯氮平-氟伏沙明合用模型,更适合用于研究中国群体中合并用药对氯氮平体内过程的影响。

此外,本研究也具有局限性:首先,氯氮平是多代谢途径以及多代谢产物的药物,代谢过程十分复杂,是研究氯氮平体外代谢的难点之一。因此研究构建氯氮平的PBPK模型只对氯氮平药物代谢动力学进行了预测。未来需要通过体外试验或者大量的临床数据拟合不同的代谢酶催化生成各代谢产物的过程。其次,虽然PBPK模型的内部验证与外部验证结果均提示模型预测性能较好,但是作为一个预测模型的研究,还需要更多的临床试验数据来对预测结果进行验证和修正。

综上,本研究基于中国群体,从药物代谢动力学角度提出了氯氮平-氟伏沙明联合用药时的剂量优化方法,为临床试验或者临床给药方案的制定提供了参考。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclosed no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

本研究涉及的所有项目均已通过上海交通大学医学院附属精神卫生中心伦理委员会的审核批准(伦理号:2022-79)。受试对象或其家属均已签署知情同意书。

All experimental protocols in this study were reviewed and approved by the Ethics Committee of Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine (Approval Letter No. 2022-79). All the subjects or their families have signed informed consent forms.

作者贡献/Authors' Contributions

禹顺英设计并指导整个课题研究,牟凡参与研究设计并完成数据收集、模型构建及验证和论文撰写,黄志伟参与模型构建及验证的指导,程渝、赵雪参与数据收集与整理,黄志伟、李华芳和禹顺英参与论文修改。所有作者均阅读并同意了最终稿件的提交。

YU Shunying designed and supervised the entire research project; MOU Fan participated in research design, and completed data collection, model construction, validation, and paper writing; HUANG Zhiwei participated in guiding model construction and validation; CHENG Yu and ZHAO Xue participated in data collection and organization; HUANG Zhiwei, LI Huafang and YU Shunying participated in paper revisions. All the authors have read the last version of the manuscript and consented to submission.

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参 · 考 · 文 · 献

- [1] VERDOUX H, QUILES C, DE LEON J. Optimizing co-prescription of clozapine and antiseizure medications: a systematic review and expert recommendations for clinical practice[J]. *Expert Opin Drug Metab Toxicol*, 2024, 20(5): 347-358.
- [2] VERDOUX H, QUILES C, DE LEON J. Risks and benefits of clozapine and lithium co-prescribing: a systematic review and expert recommendations[J]. *Schizophr Res*, 2024, 268: 233-242.
- [3] AUGUSTIN M, SCHORETSANITIS G, PFEIFER P, et al. Effect of fluvoxamine augmentation and smoking on clozapine serum concentrations[J]. *Schizophr Res*, 2019, 210: 143-148.
- [4] RAFIZADEH R, SOOCH A, RISI A, et al. Impact of patient-specific factors on clozapine metabolism in individuals with treatment-resistant schizophrenia or schizoaffective disorder[J]. *J Psychopharmacol*, 2024, 38(6): 526-531.
- [5] DAILYMED. Label: clozapine tablet [EB/OL]. [2023-03-30]. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=25c0c6d5-f7b0-48e4-e054-00144ff8d46c>.
- [6] DE LEON J, RAJKUMAR A P, KAITHI A R, et al. Do Asian patients require only half of the clozapine dose prescribed for caucasians? A critical overview[J]. *Indian J Psychol Med*, 2020, 42(1): 4-10.
- [7] HASSAB ERRASOUL A, ALARABI M A. Factors predicting serum clozapine levels in Middle Eastern patients: an observational study[J]. *BMC Psychiatry*, 2022, 22(1): 269.
- [8] CHO C K, KANG P, JANG C G, et al. PBPK modeling to predict the pharmacokinetics of venlafaxine and its active metabolite in different CYP2D6 genotypes and drug-drug interactions with clarithromycin and paroxetine[J]. *Arch Pharm Res*, 2024, 47(5): 481-504.
- [9] ZHANG Z C, HU M, XUAN D L, et al. Physiologically based

- pharmacokinetic (PBPK) modeling of BDE-209 following oral exposure in Chinese population[J]. Food Chem Toxicol, 2022, 169: 113416.
- [10] LIN W, CHEN Y, UNADKAT J D, et al. Applications, challenges, and outlook for PBPK modeling and simulation: a regulatory, industrial and academic perspective[J]. Pharm Res, 2022, 39(8): 1701-1731.
- [11] WILLCOCKS I R, LEGGE S E, NALMPANTI M, et al. Clozapine metabolism is associated with absolute neutrophil count in individuals with treatment-resistant schizophrenia[J]. Front Pharmacol, 2021, 12: 658734.
- [12] VAQUERO-BAEZ M, DÍAZ-RUIZ A, TRISTÁN-LÓPEZ L, et al. Clozapine and desmethylclozapine: correlation with neutrophils and leucocytes counting in Mexican patients with schizophrenia[J]. BMC Psychiatry, 2019, 19(1): 295.
- [13] VERDOUX H, QUILES C, DE LEON J. Optimizing antidepressant and clozapine co-prescription in clinical practice: a systematic review and expert recommendations[J]. Schizophr Res, 2024, 268: 243-251.
- [14] ZHANG H F, WANG H H, GAO N, et al. Physiological content and intrinsic activities of 10 cytochrome P450 isoforms in human normal liver microsomes[J]. J Pharmacol Exp Ther, 2016, 358(1): 83-93.
- [15] SHU Y, CHENG Z N, LIU Z Q, et al. Interindividual variations in levels and activities of cytochrome P-450 in liver microsomes of Chinese subjects[J]. Acta Pharmacol Sin, 2001, 22(3): 283-288.
- [16] AN X X, YU Y C, LI G F, et al. Abundance and associated variations of cytochrome P450 drug-metabolizing enzymes in the liver of East Asian adults: a meta-analysis[J]. Eur J Drug Metab Pharmacokinet, 2021, 46(2): 225-233.
- [17] ZHU J Y, ZHOU S F, WANG L, et al. Characterization of pediatric rectal absorption, drug disposition, and sedation level for midazolam gel using physiologically based pharmacokinetic/pharmacodynamic modeling[J]. Mol Pharm, 2024, 21(5): 2187-2197.
- [18] OWEN J S, FIEDLER-KELLY J. PK/PD 建模实践: NONMEM 软件入门[M]. 北京: 化学工业出版社, 2020: 69.
- OWEN J S, FIEDLER-KELLY J. Introduction to population pharmacokinetic/pharmacodynamic analysis with nonlinear mixed effects models[M]. Beijing: Chemical Industry Press, 2020: 69.
- [19] TASSANEYAKUL W, KITTIWATTANAGUL K, VANNAPRASAHT S, et al. Steady-state bioequivalence study of clozapine tablet in schizophrenic patients[J]. J Pharm Pharm Sci, 2005, 8(1): 47-53.
- [20] ORLANDO R, DE MARTIN S, ANDRIGHETTO L, et al. Fluvoxamine pharmacokinetics in healthy elderly subjects and elderly patients with chronic heart failure[J]. Br J Clin Pharmacol, 2010, 69(3): 279-286.
- [21] MALLIKAARJUN S, SALAZAR D E, BRAMER S L. Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers[J]. J Clin Pharmacol, 2004, 44(2): 179-187.
- [22] FUKASAWA T, YASUI-FURUKORI N, SUZUKI A, et al. Effects of caffeine on the kinetics of fluvoxamine and its major metabolite in plasma after a single oral dose of the drug[J]. Ther Drug Monit, 2006, 28(3): 308-311.
- [23] LU M L, LANE H Y, CHEN K P, et al. Fluvoxamine reduces the clozapine dosage needed in refractory schizophrenic patients[J]. J Clin Psychiatry, 2000, 61(8): 594-599.
- [24] KARJALAINEN M J, NEUVONEN P J, BACKMAN J T. *In vitro* inhibition of CYP1A2 by model inhibitors, anti-inflammatory analgesics and female sex steroids: predictability of *in vivo* interactions[J]. Basic Clin Pharmacol Toxicol, 2008, 103(2): 157-165.
- [25] YAO C, KUNZE K L, KHARASCH E D, et al. Fluvoxamine-theophylline interaction: gap between *in vitro* and *in vivo* inhibition constants toward cytochrome P4501A2[J]. Clin Pharmacol Ther, 2001, 70(5): 415-424.
- [26] OLESEN O V, LINNET K. Fluvoxamine-clozapine drug interaction: inhibition *in vitro* of five cytochrome P450 isoforms involved in clozapine metabolism[J]. J Clin Psychopharmacol, 2000, 20(1): 35-42.
- [27] KIKUCHI R, CHOTHE P P, CHU X Y, et al. Utilization of OATP1B biomarker coproporphyrin-I to guide drug-drug interaction risk assessment: evaluation by the pharmaceutical industry[J]. Clin Pharmacol Ther, 2023, 114(6): 1170-1183.
- [28] SCHORETSANITIS G, KANE J M, CORRELL C U, et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American society of clinical psychopharmacology and the therapeutic drug monitoring task force of the arbeitsgemeinschaft für neuropsychopharmakologie und pharmakopsychiatrie[J]. J Clin Psychiatry, 2020, 81(3): 19cs13169.
- [29] BEREL C, MOSSÉ U, WILS J, et al. Interest of fluvoxamine as an add-on to clozapine in children with severe psychiatric disorder according to CYP polymorphisms: experience from a case series[J]. Front Psychiatry, 2021, 12: 669446.
- [30] XU J J, XIAO C F, PAN Y L, et al. Utilizing plasma drug levels and genetic testing to achieve optimal treatment response in a patient with treatment-resistant schizoaffective disorder[J]. Bipolar Disord, 2024, 26(1): 95-97.
- [31] BELLON A, NGUYEN K. Selective serotonin reuptake inhibitors and risk reduction for cardiovascular disease in patients with schizophrenia: a controversial but promising approach[J]. World J Psychiatry, 2021, 11(7): 316-324.
- [32] DE LEON J, RUAN C J, SCHORETSANITIS G, et al. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology[J]. Psychother Psychosom, 2020, 89(4): 200-214.
- [33] DE LEON J, SCHORETSANITIS G, KANE J M, et al. Using therapeutic drug monitoring to personalize clozapine dosing in Asians[J]. Asia Pac Psychiatry, 2020, 12(2): e12384.
- [34] ROWLAND YEO K, GIL BERGLUND E, CHEN Y. Dose optimization informed by PBPK modeling: state-of-the art and future[J]. Clin Pharmacol Ther, 2024, 116(3): 563-576.
- [35] GILL J, MOULLET M, MARTINSSON A, et al. Comparing the applications of machine learning, PBPK, and population pharmacokinetic models in pharmacokinetic drug-drug interaction prediction[J]. CPT Pharmacometrics Syst Pharmacol, 2022, 11(12): 1560-1568.

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