Population pharmacokinetics of clozapine in schizophrenia patients: sex differences and impact of fluvoxamine coadministration

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Background

Clozapine is the primary choice for treatment-resistant schizophrenia, it effectively alleviates symptoms and reduced hospitalizations and mortality. However, its use can cause serious side effects. Therapeutic drug monitoring can be used to balance efficacy and side effects. Due to a significant interindividual variability (IIV), the same dosage results in varying exposures among patients. To optimize the dosing strategy for the individual patient, an explanation of the causes of this IIV is essential. This study aims to develop a pharmacokinetic model and to evaluate the effect of covariates on pharmacokinetic parameters to reduce the IIV.

Methods

A retrospective analysis was conducted on the plasma concentration of clozapine obtained from 32 patients at the Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany, between June 2020 and October 2021. The plasma concentration samples were analyzed using a point-of-care whole blood test. Nonlinear Mixed Effects Modelling (NONMEM) was used to perform the pharmacokinetic analysis establishing a model and evaluate the effects of various covariates. These covariates included sex, age, smoking status, caffeine consumption, serum creatinine, gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT/GPT), fluvoxamine coadministration, paraxanthine/caffeine ratio, norclozapine/clozapine ratio (NCLZ/CLZ), and the CYP1A2 genotypes wild type, *1F/*1F, *1F, *1D/*1E.

Results

The plasma concentration data of clozapine were best described by a one-compartment model with first-order absorption. The population estimate for distribution volume (V) was 905 L and clearance (CL) estimate was 44.4 L/h. Implementation of the covariates sex and fluvoxamine coadministration significantly reduced the IIV on CL with 8.9% and 7.8% respectively. Female patients demonstrated a median CL that was 50% lower compared to male patients, while those using concomitant fluvoxamine showed a 25.5% reduction in median CL.

Conclusions

Females and fluvoxamine users showed a significantly lower clozapine CL. These findings contribute to understanding a part of the IIV observed in plasma concentrations of clozapine, which could enhance dosing strategies within this patient population.

Key Words

clozapine, population pharmacokinetic model, schizophrenia, NONMEM