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Physiologically based Pharmacokinetic Modeling of Olanzapine in Different Populations

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Abstract

Physiologically based pharmacokinetic (PBPK) modeling permits clinical scientists to reduce practical constraints for clinical trials on patients with special diseases. In this study, simulations were carried out to evaluate the pharmacokinetic parameters of olanzapine using Simcyp® simulator in healthy adults, geriatrics, obese and renal impaired populations A PBPK model was established and validated to predict the pharmacokinetic parameters of olanzapine in different populations. The model used was Advanced, Dissolution, Absorption and Metabolism (ADAM). The PBPK model adequately predicted the pharmacokinetic parameters of olanzapine for the different populations. PBPK modeling could be helpful in the investigation and comparison of the pharmacokinetics in populations with specific disease conditions.

Keywords: Olanzapine, Physiologically based pharmacokinetic modeling, geriatrics, obesity, hepatic impairment

Introduction

Physiologically based pharmacokinetic (PBPK) approach has received value in recent years due to provision of new opportunities for the estimation of systemic drug concentrations in both healthy and diseased populations (1). The PBPK simulation has been used to predict inter-individual changes accompanied with the absorption, distribution, metabolism and excretion (ADME) of administered drugs (2). Not to mention that by allowing an opportunity to associate pathophysiological variabilites associated with a disease, the PBPK model helps the construction of drug–disease models (3).

When a PBPK model is constructed and evaluated, because of to its mechanistic nature, it can easily be extended to special populations and medications (4). Hence, the PBPK approach can be very efficient in predicting ADME of administered drugs in clinically important diseases such as psychosis.

Schizophrenia is a complicated illness with great differences in presentation, response to treatment and trajectory (5) . This suggests the presence of more than one cause and the existence of many interplaying factors which lead to the development of schizophrenia (6). So far, etiology of schizophrenia has been still unknown (7). However, a combination of genetic, physiological processes and certain environmental risk factors is believed to contribute to the development of this disease (8). Schizophrenia is regarded as the most dangerous of all psychiatric illnesses, from which approximately 1% of the world's population are affected, regardless to cultures and ethnicities (9). The manifestation of schizophrenia can be attenuating, disturbing the skills of cognition, social affairs which may lead personality to loss (7). As such, schizophrenia presents a huge social and financial burden to patients and health care systems (10).

Olanzapine is an antipsychotic medication used to treat schizophrenia and bipolar disorder. It is usually classed with the atypical antipsychotics, the newer generation of antipsychotics (11). It appears to have slightly greater effectiveness in treating schizophrenia (especially the negative symptoms) and a lower risk of causing movement disorders than typical antipsychotics. Olanzapine, however, has a higher risk of causing metabolic side effects like weight gain and type 2 diabetes than the typical antipsychotics (12).

Olanzapine is structurally similar to clozapine and quetiapine. It is chemically classified as a thienobenzodiazepine. It is believed to work by blocking, or antagonizing, the dopamine D2 receptor which is an action it shares with all presently-approved antipsychotics (13). Like most other atypical antipsychotics olanzapine also strongly antagonizes the 5-HT2A receptor, which may partially underpin its reduced propensity for causing movement disorders. Despite its close structural relation to traditional benzodiazepine anxiety-relieving medications, it possesses no affinity for the GABAA receptor, its anxiety-relieving effect is mediated through its effect on dopamine and 5HT receptors (14).

Olanzapine is practically insoluble in water (15), exhibiting extensive first pass metabolism, such thatonly 40% reaching the circulation. its half-life ranges from 21 to 54 hours, and apparent plasma clearance ranges from 12 to 47 L/hr. Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL,

binding primarily to albumin and α1-acid glycoprotein (16). Olanzapine is metabolized by the cytochrome P450 (CYP) system; principally by isozyme 1A2 (CYP1A2) and to a lesser extent by CYP2D6 (17).

This research aimed to establish and validate the PBPK model, which describes the pharmacokinetic parameters of olanzapine in healthy adults. Also, the effect of age, obesity and liver disease on the pharmacokinetics of the drug was studied.

Methods

PBPK Modeling Approach

PBPK model was applied to compare between the predicted and the reported pharmacokinetic parameters of olanzapine immediate release tablets (10 mg). The software used was Simcyp® Simulator (V17.1; Certara, Sheffield, UK). The applied model was Advanced Dissolution, Absorption and Metabolism (ADAM). ADAM model V16.1 has been described fully by Doki et al. (18), but version 17.1 has been modified to improve the simulation effect. For example, gut transporters have been included which play a key role in determining drug concentrations in the blood, liver, brain, intestine, lung, and kidney.

PBPK drug input parameters

The physicochemical parameters of olanzapine are shown in table1. Most of these parameters were obtained from data available in literature (17) (19) (20). Other parameters like human liver microsomal protein intrinsic clearance (Clint-HLM), blood to plasma partition ratio (P/B), the fraction unbound in plasma (Fu) were experimentally measured by Jones et al (21).

Parameters	Value	Reference
Molecular weight (g/mol)	312.4	19
PKa	7.2	19
Type	Monoprotic Base	19
B/P	0.84	Predicted by Simcyp
Fu	0.07	21
Log P	3	19
Vss (L/Kg)	15	20
CL (L/hr)	26	17
HLM-Clint	3	21
(µL/min/mg protein)		

Table 1: Parameters of olanzapine for PBPK simulation

log P, the oil-water partition coefficients; B/P, Blood/plasma ratio; fu value, Fraction unbound in plasma; CL, oral clearance; Vss, Apparent Volume of distribution; HLM-Clint, human liver microsomal protein intrinsic clearance

Trial Design

Ten simulated trials were done on 10 healthy volunteers, n=100, under fasted conditions to compare the pharmacokinetics parameters with the reported clinical study by Elshafeey et al (22). The dose was set to 10 mg, given once with 150 ml water. Cmax, Tmax, AUC0-24h. The simulation was repeated using geriatric (ages between 65 and 75), obese and patients with hepatic cirrhosis (Child-Pugh, Class C) populations embedded in the Simcyp simulator.

Results and Discussion

The PBPK model was verified by comparing the predicted pharmacokinetics parameters of the drug suspension to the reported clinical data by Elshafeey et al (22). The predicted Cmax, Tmax and AUC-values were within 0.9-fold, 1-fold and 0.6-fold of the reported clinical results, respectively. The results of the pharmacokinetics of olanzapine in healthy adults, elderly, obese and liver impaired populations are present in Tables 2.

Population				
Parameters	**Healthy adults**	**Geriatrics**	**Obese**	**Liver impaired**
Cmax (µg/L)	10.15	17.38	11.88	20.28
Tmax (h)	6.21	5.95	6.54	6.1
AUC 0-24h (µg/L.h)	224.17	375.78	258.69	436.65

Table 2: Comparison of olanzapine Pharmacokinetic Parameters for Different Populations

Regarding the geriatric population, an increase in the values of Cmax and AUC 0-24h by approximately 1.7 folds and was observed. Ageing is a factor that can influence the pharmacokinetic profile of olanzapine due to increase in systematic exposure. As adipose mass increases with ageing, the volume of distribution is higher for lipophilic drugs, such as olanzapine (23). Lipophilic drugs could accumulate in adipose tissue, leading to a prolongation of their half-lives and their duration of action, thus increasing the risk of iatrogenic events in the elderly. Aging is accompanied by decline in hepatic and renal functions and variations in plasma protein concentrations (24). Reduction in hepatic blood flow and deterioration in the activity of hepatic CYP enzymes may lead to reduced clearance of drugs metabolized by the liver in the elderly population (25). Age-related changes in the liver have the potential to impact on the presystemic metabolism (first-pass effect) and therefore the bioavailability of drugs with high hepatic clearance after oral administration (26). Although the effect on bioavailability is unpredictable, the age-related changes in the liver have the potential to result in a significant and variable increase in bioavailability for some medicines after oral administration (27).

In patients with schizophrenia during previous studies, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that

there may be a different tolerability profile in this population compared to younger patients with schizophrenia (28).

Regarding obese populations, AUC and Cmax showed slight increase, compared to the healthy adults. There is limited information on the influence of obesity on drug pharmacokinetics after oral administration. This is a major limitation, given the fact that most drugs are given orally. From the very small number of studies on drug, it seems that drug absorption is rather unaltered (29).

The AUC and Cmax values were increased by approximately 2 folds. The virtual populations of hepatic impaired patients have specific key features. Features include reduction in several elements like kidney weight, blood flow, CYP P450 expression, and serum albumin and hematocrit levels. In addition to reduction of a-1 acid glycoprotein levels, portal hypertension, with consequential blood shunting to bypass the liver, and increased blood flow through the hepatic artery and mesentery (30).

CONCLUSION

Olanzapine seems to be safe in obese and patients, but dose adjustment may be recommended with geriatrics and patients with hepatic impairment to avoid toxicity. In general, olanzapine is well tolerated. Across the available dosage range, olanzapine shows a novel pharmacological profile with a broader antipsychotic profile and reduced frequency of extrapyramidal symptoms in comparison with the older conventional antipsychotic agents.

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