Use of Three-Compartment Physiologically Based Pharmacokinetic Modeling to Predict Hepatic Blood Levels of Fluvoxamine Relevant for Drug–Drug Interactions

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ABSTRACT: Using a three-compartment physiologically based pharmacokinetic (PBPK) model and a tube model for hepatic extraction kinetics, equations for calculating blood drug levels (C_bs) and hepatic blood drug levels (C_{hb}s, proportional to actual hepatic drug levels), were derived mathematically. Assuming the actual values for total body clearance (CL_{tot}), oral bioavailability (F), and steady-state distribution volume (V_{dss}), C_bs, and C_{hb}s after intravenous and oral administration of fluvoxamine (strong perpetrator in drug–drug interactions, DDIs), propranolol, imipramine, and tacrine were simulated. Values for C_bs corresponded to the actual values for all tested drugs, and mean C_{hb} and maximal C_{hb}-to-maximal C_b ratio predicted for oral fluvoxamine administration (50 mg twice-a-day administration) were nearly 100 nM and 2.3, respectively, which would be useful for the predictions of the DDIs caused by fluvoxamine. Fluvoxamine and tacrine are known to exhibit relatively large F values despite having CL_{tot} similar to or larger than hepatic blood flow, which may be because of the high liver uptake (almost 0.6) upon intravenous administration. The present method is thus considered to be more predictive of the C_{hb} for perpetrators of DDIs than other methods. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: bioavailability; compartment model; distribution; drug interactions; fluvoxamine; hepatic blood level; hepatic clearance; pharmacokinetics; physiological model; simulation

INTRODUCTION

Fluvoxamine is known to be a strong perpetrator in CYP1A2- and CYP2C19-involved drug–drug interactions (DDIs).[1–4] However, prediction of DDIs caused by fluvoxamine is difficult. The area under the blood drug level (C_b) curve (AUC) for ramelteon (CYP1A2 substrate) increased by almost 130-fold with coadministration of fluvoxamine.[3] This large-magnitude DDI was predicted by a conventional static model [AUCR (fold increase in AUC) = $1+I_u$ (unbound inhibitor level)/K_i (overall inhibition constant)],[5] assuming the inhibition of plural CYP molecules and I_u relative to the maximal portal-vein drug level (C_{portal}).[6] However, the prediction required I_u ($1.63 \times 11\,\mu M$) being nearly 50 times as high as the maximal unbound C_{portal}, and several hundred times as high as the maximal unbound C_b. It is possible that, in addition to the inhibitory activity of fluvoxamine, the large hepatic extraction ratio (E_h) of ramelteon has an effect on DDIs. The AUC of mephenytoin (CYP2C19 substrate) also reportedly increased by almost 7-fold with fluvoxamine [62.5 mg, QD (once-a-day administration)] with a nearly 40-fold gap between the *in vitro* $K_{i,u}$ and *in vivo* $K_{i,i.v.,u}$ values of fluvoxamine toward CYP2C19, when mephenytoin was administered 16 h after fluvoxamine.[4] Thus, the maximal C_{portal} concept, in which the peak levels emerge no later than 0.5 h, is not applied to this DDI. Nonetheless, the hepatic blood unbound perpetrator level is relative to the hepatic cellular unbound perpetrator level, which should regulate metabolic inhibition. Therefore, determination of C_{hb} is essential for the prediction of DDIs.

With regard to physiologically based pharmacokinetic (PBPK) models, several dynamic methods that allow prediction of dynamic changes in blood victim drug levels in response to the metabolic inhibition by a perpetrator have been reported, for example, the common PBPK[7–9] and the three-compartment (3-Comp) PBPK.[10] Currently, these methods are recommended in the regulatory guidelines of DDI studies,[11] but they have various issues. First, most of the published DDI predictions highlight increases in blood victim drug levels without introducing hepatic blood inhibitor levels (C_{hb}s). These methods commonly assume that the E_hs for any drug are determined by the well-stirred model. Nonetheless, they overestimate the E_hs, and therefore underestimate the C_{hb} if the drug is eliminated rapidly from the liver. It is also difficult to review these predictions, as the methods employ specialized computer tools and employ numerous input parameters to compute blood drug levels. However, the use of numerous parameters, while neglecting possible interrelations between them, leads to incorrect estimation of total body clearance (CL_{tot}) and steady-state distribution volume (V_{dss}).

Fluvoxamine[12] has unique PK characteristics that enhance DDIs. It has a large V_{dss} (around 25 L/kg), which is a common characteristic in cationic amphiphillic drugs (pKa > 8 and log P > 3). It exhibits almost the same CL_{tot} as hepatic blood flow (Q_h, 21 mL min^{-1} kg^{-1}), despite having moderate oral bioavailability (F; around 0.5). This deviates from the common hepatic extraction kinetic: $CL_{h,b} = Q_h \times E_h$.[13] Therefore, it is important to establish new hepatic extraction kinetics to interpret this phenomenon.

Abbreviations used: AUC, area under the curve of blood drug level; BID, twice-a-day administration; C_b, blood drug level; C_{hb}, hepatic blood drug level; CL_{tot}, total body clearance; DDI, drug–drug interaction; F, bioavailability; PBPK, physiologically based pharmacokinetic; QD, once-a-day administration; V_{dss}, steady-state distribution volume.

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The 3-Comp PBPK method is more convenient than the common PBPK method for predicting C_b and C_{hb}, as it uses minimal input parameters and the equations for C_b and C_{hb} can be solved mathematically.[13] The tube model is more accurate and simpler for determining the E_h of a drug when compared with any other model.[14] Thus, the objectives of the present study were to derive the equations for C_b and C_{hb} mathematically using the 3-Comp PBPK and tube models, to predict the time-dependent C_b and C_{hb} after oral administration of fluvoxamine in relation to DDIs caused by fluvoxamine, and to clarify the unusually large CL_{tot} observed for fluvoxamine.

MATERIALS AND METHODS

3-Comp PBPK Model

The 3-Comp PBPK model was as shown in Figure 1a. Comp 1 represents the central drug pool, including the extrahepatic systemic blood drug pool and the extrahepatic organ-and-tissue drug pool. Comp 2 represents the hepatic drug pool, including the hepatic blood drug pool, the hepatic intracellular unbound drug pool (= cytosolic unbound drug pool) and the hepatic intracellular bound drug pool (= organelle and cytosolic bound drug pool). Comp 3 represents the peripheral drug pool (deep tissue drug pool). C_i (i = 1, 2, and 3) represents the blood–drug concentration , whereas V_i represents the blood–drug level-based volume of Comp i. C_1 corresponds to the C_b and is the same as the drug concentration in the influx to the liver (hepatic artery plus the portal vein) ($C_{b,in}$), but is dissimilar from the hepatic blood drug concentration immediately after the drug enters into the liver ($C_{2,in}$), depending on the drug distribution in the liver (Fig. 1c). C_2 represents the average concentration of the drug in the hepatic blood pool (C_{hb}) (Fig. 1c). V_2 is the C_2-based distribution volume (different from the C_1-based distribution volume, see Eq. (A17) and is also defined as the product of the hepatic tissue-to-hepatic plasma partition coefficient (K_{ph}) and the actual volume of the liver (V_h, 0.02 L/kg). Accordingly, the actual hepatic drug level ($C_{2,actual}$) is expressed as: $C_{2,actual} = K_{ph} \times C_2$. Hepatic blood flow and peripheral blood flow are represented by Q_h and Q_p, respectively. Drug elimination occurs only from the liver ($CL_{tot,b} = CL_{h,b}$), by metabolism, depending on the unbound drug concentration in the hepatic cellular unbound drug pool (Fig. 1d). The unbound drug concentration in the hepatic cellular pool (C_{hcu}) may be higher than the hepatic blood unbound drug concentration ($fu_b \times C_{hb}$, with fu_b being the blood unbound fraction), depending on the contribution of

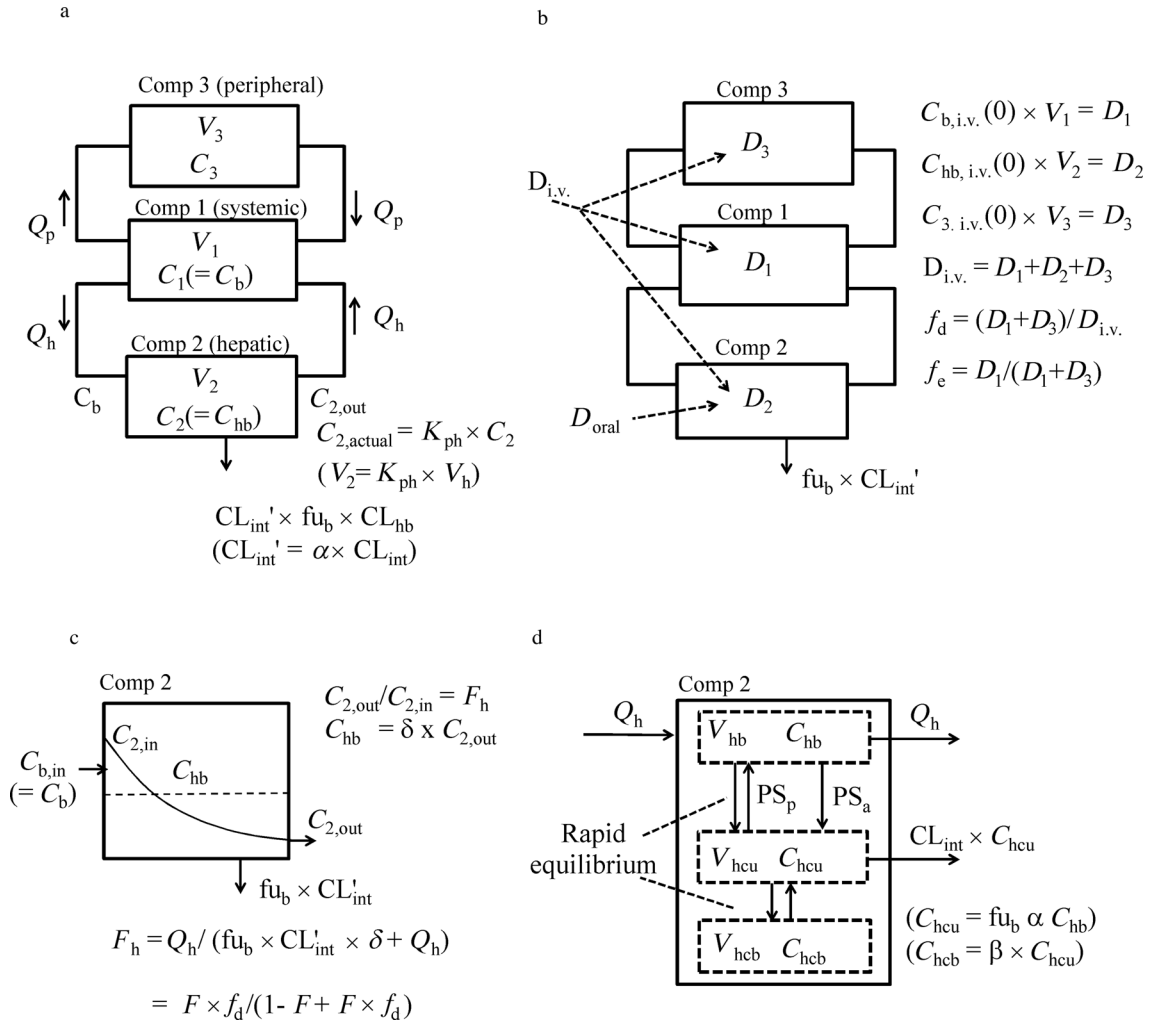

Figure 1. Three-compartment PBPK model for a drug elimination from the liver.