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Investigating the role of altered systemic albumin concentration on the disposition of theophylline in adult and pediatric asthma patients by using the physiologically based pharmacokinetic approach

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List of abbreviations:

HSA, Human serum albumin; PK, pharmacokinetics; PBPK, physiologically based pharmacokinetics; ADME, absorption, distribution, metabolism and eliminition; iv, intravenous; ADAM, advanced, dissolution, absorption and metabolism; $P_{eff,man}$, human jejunum permeability; CYP, cytochrome P-450; NCA, non-compartmental analysis; AUC, area under the systemic drug

concentration-time curve; C_{max}, maximal systemic drug concentration; iv, intravenous; CL_{iv}, clearance after iv application; CL/F, clearance after the oral application; $R_{(Obs/Pre)}$, ratio of observed/predicted pharmacokinetic parameter; V_{max}, maximum rate of reaction; K_m, Michaelis-Menten constant; VPC, visual predictive checks; NCA, non-compartmental analysis; AFE, average fold error; RMSE, root mean square error.

Abstract

Theophylline is commonly used for the treatment of asthma and has a low hepatic clearance. The changes in plasma albumin concentration occurring in asthma may affect the exposure of theophylline. The aim of the presented work was to predict theophylline pharmacokinetics (PK) after incorporating the changes in plasma albumin concentration occurring in asthma patients into a physiologically based pharmacokinetic (PBPK) model to see whether these changes can affect the systemic theophylline concentrations in asthma or not. The PBPK model was developed following a systematic model building approach using Simcyp®. The predictions were performed initially in healthy adults after intravenous and oral drug administration. Only when the developed adult PBPK model has adequately predicted theophylline PK in healthy adults, the changes in plasma albumin concentrations were incorporated into the model for predicting drug exposure in asthma patients. After evaluation of the developed model in the adult population, it was scaled to children on physiological basis. The model evaluation was performed by using visual predictive checks and comparison of ratio observed/predicted ($R_{obs/Pre}$) for PK parameters along with their 2-fold error range. The developed PBPK model has effectively described theophylline PK in both healthy and disease populations as $R_{obs/Pre}$ for all the PK parameters were within the 2-fold error limit. The predictions in asthma patients showed that there were no significant changes in PK parameters after incorporating the changes in serum albumin concentration. The mechanistic nature of the developed asthma-PBPK model can facilitate its extension to other drugs.

Significance Statement

Exposure of a low hepatic clearance drug like theophylline may be susceptible to plasma albumin concentration changes that occur in asthma. These changes in systemic albumin concentrations can be incorporated into a physiologically based pharmacokinetic model to predict theophylline pharmacokinetics in adult and pediatric asthma populations. The presented work is focused on predicting theophylline ADME in adult and pediatric asthma populations after incorporating reported changes in serum albumin concentrations to see their impact on the systemic theophylline concentrations.

Introduction

Asthma is a chronic disorder that affects people from all age groups in the whole world (G.P. CURRIE, 9 April, 2015; Asthma, 2018). Asthma is characterized by variable symptoms that can be managed by initiating appropriate drug therapy (Ferraro et al., 2018). Since, asthma is a disease that requires long term management, therefore the selection of drug and its dose has to made very carefully after taking into account all the possible drug-drug and drug-disease interactions (Taburet and Schmit, 1994). Asthma is reported to be associated with changes in serum albumin concentrations, these pathophysiological changes in serum albumin levels can potentially affect the absorption, distribution, metabolism and elimination (ADME) of administered drugs (Mitenko and Ogilvie, 1973). The changes in serum albumin concentration occurring in asthma can potentially affect the unbound drug concentrations, particularly for the drugs with low hepatic clearance. Therefore, the changes in serum albumin levels should be considered while describing the pharmacokinetics (PK) of drugs being administered in asthma (Blanchard et al., 1992; Shima and Adachi, 1996; Picado et al., 1999; Vural and Uzun, 2000; Misso et al., 2005; Ejaz et al., 2017).

The physiologically based pharmacokinetic (PBPK) approach provides novel opportunities to incorporate the relevant pathophysiological changes occurring in various diseases for the construction of disease models. (Li et al., 2012; Park et al., 2017). There are some published examples of drug-disease PBPK models that incorporate pathophysiological modifications occurring in different chronic conditions (Edginton and Willmann, 2008; Johnson et al., 2010; Rowland Yeo et al., 2011; Li et al., 2012; Schaller et al., 2013; Sayama et al., 2014; Vogt, 2014; Chadha and Morris, 2015; Li et al., 2015; Rasool et al., 2016; Shah et al., 2019). Although there are few published reports of PBPK models for theophylline in adults and children (Ginsberg et al., 2004; Björkman, 2005) but till now there is no published report of a theophylline-asthma PBPK

model that has been utilized to predict drug exposure in adult and pediatric asthma patients after incorporation of changes in human serum albumin concentrations. Therefore, if such a PBPK drug-disease model is developed it may have many clinical implications.

Theophylline is a low hepatic extraction drug that is commonly used for the treatment of asthma (Mazza, 1982). It has a narrow therapeutic index and is usually reserved for those asthma patients who cannot be treated with conventional combination drug therapies (Kim and Mazza, 2011). Theophylline belongs to biopharmaceutical classification system (BCS) Class I having high solubility and permeability, this is why it is rapidly absorbed after oral administration and has a bioavailability range of 80–100% (Griffin; Taburet and Schmit, 1994). It undergoes hepatic metabolism through different cytochrome P-450 (CYP) enzymes (CYP1A2, CYP2E1 and CYP3A4) (Kim and Mazza, 2011). The availability of clinical PK data for theophylline in the published literature makes it an ideal candidate for development and evaluation of its PBPK model in adult and pediatric asthma patients (Mitenko and Ogilvie, 1973; Ellis et al., 1976; Richer et al., 1982; Hendeles and Weinberger, 1985; Björkman, 2005). It is already known that plasma protein binding may have a significant impact on the exposure of low hepatic extraction drugs like theophylline (Colli et al., 1988; DiPiro, 2010). Therefore, if a theophylline-asthma PBPK model is developed that incorporates the plasma albumin changes, it can be utilized to predict the systemic theophylline concentrations in asthma patients. Furthermore, after evaluation of the developed theophylline-asthma PBPK model in adults, it can be scaled to pediatric asthma patients on physiological basis by using a PBPK simulator.

The aim of the presented work was to predict theophylline PK in adults and children with asthma after incorporating the changes in plasma albumin concentration into a physiologically based

pharmacokinetic (PBPK) model to see whether these changes can affect the systemic theophylline concentrations in asthma or not.

Methods

Modelling Software

The PBPK model was developed using Simcyp ® population-based simulator, version 16 release 1 (Certara UK Limited, Simcyp Division, Sheffield, UK).

Strategy for Model Building

A total of 24 PK profiles from 16 clinical studies were selected for model development and evaluation, which includes 17 in healthy adults (iv: 06 and oral: 11), four in adult asthma patients (iv: 01 and oral: 03) and three (iv: 1 and oral: 02) in pediatric asthma patients. The details of the population data used for model development and evaluation can be seen under heading "Clinical/Pharmacokinetic Data". The development and verification of the PBPK model was based on previously reported systematic model building and verification approaches (Khalil and Läer, 2014; Rasool et al., 2015; Sager et al., 2015). The systematic model building approach is focused on the selection and optimization of drug-specific model input parameters that are responsible for predicting drug disposition in healthy adults after intravenous (iv) administration. After evaluating the developed model with the iv clinical PK data, the parameters that govern the oral drug absorption process are selected and optimized for predicting the drug PK after oral application. This was done by using 33 % of clinical PK data sets (n=6, three iv and 3 oral) in adults for model parameterization and remaining 66 % (n = 11) for subsequent model verification. All these clinical PK data sets were included in final model evaluation. After model evaluation in healthy adults, the disease-specific parameters were incorporated into the developed model to constitute the disease

model. Thereafter, the developed PBPK disease model was used to predict ADME of administered drug in the disease population. After the evaluation of the developed PBPK models in adult healthy and disease populations, it was scaled to children on physiological basis by using Simcyp® pediatric module. The implemented model building strategy can be seen in **Supplemental Figure 1**.

Model Structure and Parameterization

In order to identify and select various model input parameters, a detailed literature review was conducted. The input parameters were selected from the Simcyp® theophylline compound library and from the published literature. The final model input parameters can be seen in **Supplemental Table 1**. A detailed explanation of model parameterization is given below.

Absorption

The advance dissolution, absorption and metabolism (ADAM) model was used for prediction of oral drug absorption process. This model incorporates information on various physiological factors that can influence drug absorption process, such as gastric emptying time, small intestine transit time, gastrointestinal pH, fluid dynamics, abundance of gut wall enzymes, transporters and segregated segmental blood flows (Jamei et al., 2009). The reported theophylline human jejunum permeability ($P_{eff,man}$) of 4.2×10^{-4} cm/s was used for prediction of oral drug absorption process (Simcyp® compound library, version 16 release 1). The predicted value of absorbed drug fraction (f_a) was 0.93, that is in line with the reported literature as theophylline belongs to Biopharmaceutical Classification System (BCS) class I and has a high permeability and a high solubility (Chavda et al., 2010). It is known that the gastric emptying time varies with the type of administered drug formulation. The oral drug formulations like pellets are reported to be absorbed

in a different manner when compared with the conventional oral dosage formulations (Davis et al., 1986). In order to predict the absorption of oral theophylline pellets, their dissolution profile was incorporated into the ADAM model (Gonzalez and Golub, 1983).

Distribution

Minimal PBPK model was used for the prediction of drug distribution. The steady state volume of distribution (V_{ss}) and tissue-plasma partition coefficient (K_p) were predicted by using Poulin and Theil method (Poulin and Theil, 2002). The predicted and reported values for V_{ss} were 0.45 L/kg and 0.51 L/kg (Obach et al., 2008).

Elimination

Theophylline is metabolized in liver via CYP1A2, CYP2D6, CYP2E1 and CYP3A4 enzymes (Ha et al., 1995). The individual values of maximum rate of reaction (V_{max}) and Michaelis-Menten constant (K_m) for each CYP-enzyme were used for predicting theophylline metabolism (Simcyp® compound library, version 16 release 1). A renal clearance (CL_R) value of 0.31 L/kg was also used for predicting theophylline elimination (Simcyp® compound library, version 16 release 1).

Disease Model

It is known that the systemic concentrations of drugs with low hepatic clearance may susceptible to changes in their serum albumin concentration. Therefore, any pathophysiological condition that can potentially affect the serum albumin concentration of low clearance drugs will affect their systemic concentrations (both unbound and bound) and pharmacodynamic effect. Moreover, these serum albumin concentration changes may cause serious therapeutic problems (adverse drug reactions and toxicity) if a low clearance drug with a narrow therapeutic index is administered (Funk et al., 2012).

It has been seen reported that human serum albumin (HSA) concentrations are altered in asthma patients (Blanchard et al., 1992; Shima and Adachi, 1996; Picado et al., 1999; Vural and Uzun, 2000; Misso et al., 2005; Ejaz et al., 2017). The serum albumin concentration is reduced to 41 g/L in patients with asthma (Blanchard et al., 1992). In order to predict systemic drug concentrations in asthma patients, the model input value of serum albumin concentration was reduced from 50.34 g/L in males and 49.38 g/L in females to 41 g/L (similar in both males & females) within the Simcyp® population library. These reductions in serum albumin concentrations were incorporated into the developed PBPK model to predict theophylline exposure in adult asthma population.

Model Scaling to Children

When the adult model has adequately predicted theophylline ADME in adult healthy and disease populations, it was scaled to children by using Simcyp® pediatric module. The Simcyp® pediatric population incorporates the age specific anatomical and physiological changes that form the basis for PK differences between adult and pediatric populations (Johnson and Rostami-Hodjegan, 2011; Johnson et al., 2018). All the pediatric patients included in model evaluation were having asthma. The main enzymes involved in the metabolism of theophylline are CYP3A4, CYP2E1, CYP2D6 and CYP1A2. The differences in ontogeny profiles of these cyp-enzymes may lead to age related changes in theophylline clearance (Salem et al., 2013). Due to the absence of information on serum albumin changes in pediatric asthma patients, the incorporated changes in serum albumin concentrations in the developed pediatric model were based on adult values.

Clinical/Pharmacokinetic Data

In Adults

In order to search, screen and extract the clinical PK data on theophylline in healthy and disease populations, a comprehensive literature review was performed using online search engines: Google Scholar and PubMed. Initial screening of PK studies was based on the presence of systemic concentration vs. time profiles of theophylline in the published literature. The final selection of clinical PK data was based on the presence of clear information on: age, weight, administered dose (oral & iv), disease condition, the proportion of females and the fasting/fed state. Finally, 09 pharmacokinetic studies were selected for model development and evaluation in healthy adults. These studies include 17 systemic concentration vs. time profiles (iv: 06 and oral: 11) in 114 healthy individuals (Chrzanowski et al., 1977; Ishizaki et al., 1979; Antal et al., 1981; Rovei et al., 1982; Gonzalez and Golub, 1983; Gundert-Remy et al., 1983; Lagas and Jonkman, 1983; St-Pierre et al., 1985; Lelo et al., 1986). Characteristics of healthy population data used for theophylline model development are given in **Supplemental Table 2**. The clinical PK data used for model evaluation was based on reported mean systemic concentration vs. time profiles (Chrzanowski et al., 1977; Ishizaki et al., 1979; Antal et al., 1981; Rovei et al., 1982; Gonzalez and Golub, 1983; Gundert-Remy et al., 1983; St-Pierre et al., 1985; Lelo et al., 1986) except in one study where individual systemic concentration vs. time profile was used for comparison (Lagas and Jonkman, 1983). Four studies were selected in asthma patients with 04 mean PK profiles (iv: 02 and oral: 02) in 134 adults with asthma (Mitenko and Ogilvie, 1973; Richer et al., 1982; Steinijans et al., 1982; Weinberger and Hendeles, 1986). Characteristics of data used for theophylline model development in adult asthma population are given in **Supplemental Table 3**. The observed data was extracted by scanning the drug concentration vs. time graphs from literature using Get Data Graph Digitizer software (version 2.26) (Digitizer, 2013).

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In Children

Three clinical PK studies of theophylline (iv: 02 and oral: 01) with 62 children having asthma were included for model evaluation in the pediatric population (Ellis et al., 1976; Loughnan et al., 1976; Hendeles and Weinberger, 1985). Characteristics of clinical PK data used for theophylline model development in asthma pediatric population are given in **Supplemental Table 3**.

Model Evaluation

Simulations were performed by creating a virtual population of 100 individuals (10 trials of 10 individuals) with similar demographic characteristics (age range, proportion of females, fasting/fed state) as in reported clinical studies. The visual predictive checks (VPC) were used for initial model evaluation. In VPC, the mean observed and predicted systemic drug concentration vs. time plots were overlaid for direct visual comparison. Additionally, the 5^{th}–95^{th} percentiles and maximum, minimum predictions were also used for model evaluation.

A non-compartmental analysis (NCA) was performed for the comparison of observed and predicted PK parameters, such as the area under the curve from time zero to last measured systemic drug concentration ($AUC_{0\text{-last}}$), the maximum concentration of drug (C_{max}), clearance of drug (CL; in case of iv application: CL/F; in case of oral application) by using excel add-in program pK solver® (Zhang et al., 2010). Furthermore, the observed/predicted ratio ($R_{obs/Pre}$), for the PK parameters like C_{max}, $AUC_{0\text{-last}}$ and CL were also calculated along with their 95% confidence intervals for model evaluation **(Equation 1)**. A 2-fold error range was used as a reference for all the evaluations (De Buck et al., 2007; Li et al., 2012; Khalil and Läer, 2014). Additionally, fold-error, average fold error (AFE) and root mean square error (RMSE) are also used for assessing model accuracy and precision **(Equation 2,3, 4)**.

Ratio ($R_{obs/pre}$)

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$$R = \frac{\text{Observed values of CL}}{\text{Predicted values of CL}} \quad \textbf{(1)}$$

Fold-error

$$\text{Fold} - \text{error} = \frac{\text{Observed values of parameter}}{\text{Predicted values of parameter}} \quad \textbf{(2)}$$

Average fold error (AFE)

$$AFE = 10^{\frac{\sum \log(fold-error)}{N}} \quad \textbf{(3)}$$

Root mean square error (RMSE)

$$RMSE = \sqrt{\frac{\sum_1^N (observed\ PK\ parameter\ value - predicted\ PK\ parameter\ value)^2}{N}} \quad \textbf{(4)}$$

Results

Healthy adult population

Intravenous Doses

The observed and predicted systemic theophylline concentration vs time profiles after administering different intravenous doses (4–6 mg/kg and 193.2–386.4 mg) in the healthy population are shown in **Figure 1 (a-f)** (Chrzanowski et al., 1977; Ishizaki et al., 1979; Gundert-Remy et al., 1983; St-Pierre et al., 1985). It is apparent from the VPC that the model has successfully apprehended the observed PK data after iv application. The mean $R_{Obs/Pre}$ for AUC_{0-}

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$_{last}$ was 0.89 (95 % CI 0.82–0.97), and the mean $R_{Obs/Pre}$ values for C_{max} and CL were also within the acceptable 2 –fold error range **(Table 1, Figure 3)**. Additionally residual plots demonstrated that there was no systematic error in model prediction **(Supplemental Figure 2a-c)**. Furthermore, the AFE and RMSE values showed that the developed model has adequately described theophylline PK after iv application **(Supplemental Table 4)**.

Oral Doses

The observed and predicted systemic theophylline concentration vs time profiles after application of different oral doses of theophylline i.e. 125–600 mg in the healthy population are shown in **Figure 1 (g-p)** (Antal et al., 1981; Rovei et al., 1982; Gonzalez and Golub, 1983; Lagas and Jonkman, 1983; Lelo et al., 1986). It can be seen from the comparison of observed and predicted systemic concentrations through VPC that the model has successfully predicted theophylline PK after oral application. The mean $AUC_{0\text{-last}}$ $R_{Obs/Pre}$ values after oral application was 1.05 (95 % CI 0.92–1.18) and the mean $R_{Obs/Pre}$ values for C_{max} and CL were also within the acceptable 2–fold error range **(Table 1, Figure 3).** Moreover, the residual plots showed that all the predicted concentrations were in harmony with the observed data and there was no systematic error in model predictions **(Supplemental Figure 2d-f)**. Additionally, the AFE and RMSE values for all the PK parameters showed that the model has successfully predicted these parameters **(Supplemental Table 4)**.

Adult Asthma Patients

The developed asthma model has efficiently predicted systemic theophylline concentrations after administration of both iv (5.6 mg/kg and 351 mg) and oral (7.5 mg/kg and 600 mg) doses in asthma patients **(Figure 2a-d)**. (Mitenko and Ogilvie, 1973; Richer et al., 1982; Steinijans et al., 1982; Weinberger and Hendeles, 1986). The VPC **(Figure 2a-d**) and residual plots **(Supplemental**

Figure 2g-l) showed that the model predictions were in agreement with the observed clinical PK data. However, after analyzing the predictions closely, it was seen that the incorporation of the reported decrease in HSA resulted in no significant changes, as the mean CL $R_{Obs/Pre}$ after iv and oral application with HSA changes were 0.93 and 1.04 compared to the mean CL $R_{Obs/Pre}$ of 1.02 and 1.08 without incorporation of changes in HSA. The mean $R_{Obs/Pre}$ values for $AUC_{0\text{-last}}$ and C_{max} were within the 2–fold error range **(Table 2, Figure 3a,c,e)**. Furthermore, the AFE and RMSE values showed that the model has adequately predicted theophylline PK in asthma patients **(Supplemental Table 4)**.

Pediatric Asthma Patients

The predicted systemic theophylline concentrations after iv (3.2–4 mg/kg) and oral (8.2 mg/kg) administration in children with asthma were in agreement with the observed data **(Figure 2e-g)** (Ellis et al., 1976; Loughnan et al., 1976; Hendeles and Weinberger, 1985), this was further confirmed by looking into residual plots **(Supplemental Figure 3a–f)**. Moreover, the mean CL $R_{Obs/Pre}$ with and without considering changes in HSA after iv and oral theophylline administration were 1.5 and 1.0 respectively. The mean $R_{Obs/Pre}$ for $AUC_{0\text{-last}}$ and C_{max} were within the 2–fold error range **(Table 2, Figure 3b,d,f)**. Additionally, the AFE and RMSE values in children with asthma showed that the model has predicted theophylline PK adequately **(Supplemental Table 4)**.

Discussion

In this study, the PBPK approach was used for the prediction of theophylline PK in healthy and disease populations (adult and pediatric). The PBPK model development process was initiated by selecting drug specific parameters that govern theophylline disposition in healthy adults after iv administration. When the developed PBPK model was successfully evaluated with the reported

clinical PK data, the parameters that control the oral drug absorption process were incorporated into the model for predicting ADME of theophylline in healthy individuals after oral application. Once the developed PBPK model has successfully predicted theophylline PK in healthy adults, the reported pathophysiological changes in HSA that occur in asthma patients were incorporated into the model for predicting theophylline ADME. Only when the developed adult PBPK model has adequately predicted theophylline ADME in healthy and disease populations, it was scaled to children by using Simcyp® pediatric module. The model predictions in asthma patients showed that there were no significant changes in PK parameters after incorporating the reported pathophysiological changes in HSA. The developed PBPK model has effectively described theophylline PK in both healthy and disease populations.

The developed model has successfully predicted systemic theophylline concentrations in healthy population after iv drug administration, which is evident from the agreement between the mean observed and predicted CL values of 0.05 L/hr/kg (95 % CI 0.03–0.06) and 0.04 L/hr/kg (Chrzanowski et al., 1977; Ishizaki et al., 1979; Gundert-Remy et al., 1983; St-Pierre et al., 1985). Similarly, the mean observed and predicted CL/F values after oral administration of theophylline were 2.73 L/hr (95 % CI 2.10–3.35) and 2.72 L/hr (95 % CI 2.38–3.06) (Antal et al., 1981; Rovei et al., 1982; Gonzalez and Golub, 1983; Lagas and Jonkman, 1983; Lelo et al., 1986). The predicted oral bioavailability of 93% (62–99%) was within the reported range of 80–100% (Griffin; Taburet and Schmit, 1994). Moreover, the mean observed and predicted $AUC_{0\text{-last}}$ and C_{max} after iv and oral application were also within the 2–fold error range. The values of AFE and RMSE after iv and oral application suggested that the developed model has effectively described the PK of theophylline .

Theophylline is a drug with low hepatic clearance and a narrow therapeutic index. It is already known that exposure of drugs with low hepatic clearance is susceptible to changes in plasma protein binding (Zhivkova, 2018). Since, theophylline is a low hepatic clearance drug that is bound to albumin, therefore any change in serum albumin concentration can potentially affect its ADME and systemic concentrations (Fleetham et al., 1981; Blanchard et al., 1992). Moreover, it is reported that asthma is associated with pathophysiological reduction in serum albumin concentration and these reductions in HSA levels may affect serum concentration of theophylline in asthma patients (Blanchard et al., 1992). Keeping this in view the reported pathophysiological reductions in HSA, its input value was reduced to 41 g/L in the developed model for predicting theophylline ADME in asthma patients (Blanchard et al., 1992). The developed model has successfully predicted theophylline CL in adult asthma patients after administering iv doses of 5.6 mg/kg and 351 mg, as the observed theophylline CL was 0.04 L/h/kg and 2.41 L/h; whereas the predicted CL was 0.05 L/h/kg and 3.21 L/h respectively (Mitenko and Ogilvie, 1973; Steinijans et al., 1982). Similarly, the predicted theophylline CL/F after administering oral doses of 600 mg and 7.5 mg/kg was 2.70 L/h and 0.04 L/h/kg that was comparable to the observed values of 2.93 L/h and 0.04 L/h/kg (Richer et al., 1982; Weinberger and Hendeles, 1986).

To see the impact of plasma protein binding changes on ADME of theophylline in asthma patients, the simulations were performed with and without incorporation of changes in HSA. There were no significant differences seen in predicted PK parameters after comparing the simulations with and without the incorporation of changes in HSA. Moreover, the unbound theophylline concentration was also predicted to see whether the changes in HSA has any significant effect on the unbound $AUC_{0\text{-last}}$ or not in adults with asthma. There were minor differences seen in the predicted unbound $AUC_{0\text{-last}}$ after iv and oral administration in adult asthma patients with and

without incorporation of changes in HSA. The unbound $AUC_{0\text{-last}}$ in adults with asthma after administering 5.6 mg/kg iv theophylline with and without changing HSA was 46.1 mg/L.h and 44.5 mg/L.h. Similarly, after administering 600 mg oral theophylline the unbound $AUC_{0\text{-last}}$ with and without changing HSA was 102.8 mg/L.h and 100 mg/L.h. The probable reason behind not seeing any significant change in predictions after incorporating changes in HSA in the asthma patients may be supported by the fact that changes in plasma protein binding have minimal effect on the exposure of low clearance drugs (Rowland, 1984; Benet and Hoener, 2002; Heuberger et al., 2013).

The developed adult PBPK model after the evaluation was scaled to children on physiological basis by using the pediatric module of Simcyp®. Since, there was no information available in the published literature regarding the changes in HSA in pediatric asthma patients, therefore the pathophysiological reductions in HSA that were used in the adult disease model were adopted in the pediatric model. The developed pediatric PBPK model has successfully predicted theophylline CL in pediatric patients with asthma after administering iv doses of 3.2 mg/kg and 4 mg/kg, as the observed theophylline CL was 0.11 L/h/kg; whereas the predicted CL was 0.07 L/h/kg (Ellis et al., 1976; Loughnan et al., 1976). Similarly, the observed and predicted theophylline CL/F after administering oral doses of 8.2 mg/kg in children with asthma was 0.07 L/h/Kg (Hendeles L, 1985). In comparison with adults, the observed theophylline CL is higher in children with asthma (5.6 mg/kg iv: adults 0.04 L/h/kg vs. 4 mg/kg iv children: 0.11 L/h/kg; after oral: 7.5 mg/kg adults 0.04 L/h/kg vs. 8.2 mg/kg children 0.07 L/h/kg), the developed model has successfully predicted this increase in CL after iv and oral administration of theophylline **(Table 2)** (Ellis et al., 1976; Loughnan et al., 1976; O'Hara, 2016). This increase in pediatric theophylline CL is associated with the age-related physiological changes occurring in this population (from 1-10 years). The

increase in pediatric CL supported by the fact that children have a higher liver weight to body weight (LW/BW) ratio than adults which increases their capacity to clear administered drugs (Kanamori et al., 2002). Moreover, the major metabolic enzymes involved in the metabolism of theophylline (CYP1A2 and CYP3A4) reach adult equivalent values within the first few years after birth (Ginsberg et al., 2002; Salem et al., 2014).

To see impact of HSA changes on theophylline PK in children with asthma, the unbound theophylline concentration was also predicted. There were no changes seen in the predicted unbound $AUC_{0\text{-last}}$ after iv and oral administration with and without incorporating HSA changes in children with asthma. The unbound $AUC_{0\text{-last}}$ in children with asthma after administering 3.2 mg/kg and 4 mg/kg iv theophylline with and without changing HSA was 18.80 mg/L.h and 24.67 mg/L.h. Similarly, after administering 8.2 mg/kg oral theophylline the unbound $AUC_{0\text{-last}}$ with and without changing HSA was 57.50 mg/L.h.

Here, it is worth mentioning that children are not young adults and the developmental changes occurring in children can potentially affect the ADME of administered drugs (Verscheijden et al., 2020). Several factors can influence the disposition of administered drugs in the pediatric population. Some of these factors, such as the age-dependent changes in tissue composition (Fernandez et al., 2011), the ontogeny of different metabolic enzymes and the decreased protein binding are already known (Johnson et al., 2006; Abduljalil et al., 2014; Salem et al., 2014; Jones, May 2018). However, the other disease-related factors that may affect the ADME of administered drugs in children that are not very well known are, variability in organ blood flow, the abundance of various drug transporters and changes in protein binding. The presence of limited information on disease pathology and developmental biology in children are the two major challenges being faced during the development of pediatric PBPK models (Cheung et al., 2019; Verscheijden et al.,

2020). Therefore, the predictive performance of the developed pediatric PBPK model should be assessed on the above-stated argument.

There are few published reports of PBPK models for theophylline in children and adults (Ginsberg et al., 2004; Björkman, 2005). One of the published models was focused on predicting theophylline disposition in infants and children after administration of iv theophylline only (Björkman, 2005) and the other was used for risk assessment from environmental agents (Ginsberg et al., 2004). On the other hand, the presented work is focused on developing and evaluating the PBPK model for theophylline in adult (healthy and asthma) and pediatric (asthma) populations after incorporating changes in HSA. Moreover, by allowing the incorporation of in-vitro dissolution profile of theophylline pellets in the ADAM model **(Figure 1n)**, the presented theophylline PBPK model can provide additional advantage in predicting ADME of novel theophylline dosage forms. Furthermore, by using a systematic model building approach, the presented model may help in understanding theophylline ADME after iv and oral application in different healthy and disease populations.

The developed drug-disease PBPK model for theophylline has efficiently predicted theophylline PK in asthma adult and pediatric population. The incorporation of HSA changes in the asthma population did not result in the improvement of predictions. The $R_{obs/Pre}$ for all the PK parameters i.e. $AUC_{0\text{-}last}$, C_{max}, CL, CL/F were within a 2-fold error range. Moreover, the AFE and RMSE values show that the developed model has predicted theophylline PK accurately and precisely **(Supplemental Table 4)**.

The mechanistic nature of the developed PBPK model can help in its extension to other drugs (high and low clearance) being used in the management of asthma. Moreover, it can also assist in the optimization of novel theophylline dosage forms.

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Authorship Contributions

Participated in research design: Rasool, Khalid, Imran, Majeed, Saeed, Alasmari, Alanazi and Alqahtani

Conducted simulations: Rasool, Khalid and Alqahtani

Performed data analysis: Rasool, Khalid, Imran, Majeed, Saeed, Alasmari, Alanazi and Alqahtani

Wrote or contributed to the writing of the manuscript: Rasool, Khalid, Imran, Majeed, Saeed, Alasmari, Alanazi and Alqahtani

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Footnotes

(Unnumbered footnote)

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FIGURE LEGENDS

Figure 1.

Comparison of observed and predicted systemic theophylline concentration versus time profile in healthy subjects after intravenous and oral dosing.

Healthy population after intravenous application: (a) 4 mg/kg (Ishizaki et al., 1979), (b) 2.78 mg/kg (Ishizaki et al., 1979), (c) 3.84 mg/kg (Chrzanowski et al., 1977), (d) 193.2 mg (Gundert-Remy et al., 1983), (e) 386.4 mg (Gundert-Remy et al., 1983), (f) 6 mg/kg (St-Pierre et al., 1985) and after oral application: (g-j) 125-500 mg (Rovei et al., 1982), : (k-l) 200 mg geriatric & adult (Antal et al., 1981), (m) 250 mg (Lelo et al., 1986), (n-o) 600 mg sprinkle (n) & tablet (o) (Gonzalez and Golub, 1983) and (p) 250 mg (Lagas and Jonkman, 1983). The observed data is shown as solid red circles. Predicted results are shown as mean values (solid lines),5th and 95th percentile (dotted lines) and minimum/ maximum values (dashed lines).

Figure 2.

Comparison of observed and predicted systemic theophylline concentration versus time profile in asthma population after iv and oral dosing.

Adults with asthma after intravenous and oral application: (a) 5.6 mg/kg iv (Mitenko and Ogilvie, 1973), (b) 351 mg iv (Steinijans et al., 1982) (c) 600 mg oral (Richer et al., 1982), (d) 7.5mg/kg oral (Weinberger and Hendeles, 1986). Children with asthma after intravenous and oral dosing: (e) 3.2 mg/kg iv (Loughnan et al., 1976), (f) 4 mg/kg iv (Ellis et al., 1976), (g) 8.2 mg/kg oral (Hendeles and Weinberger, 1985) . The observed data is shown as solid red circles. Predicted result are shown as mean values (solid lines), 5th and 95th percentile (dotted lines) and minimum/ maximum values (dashed lines).

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Figure 3.

Comparison between observed and predicted values of pharmacokinetic parameters in healthy and asthma populations (adults and children).

Area under systemic concentration versus time curve from time zero to last measured concentration $AUC_{0\text{-last}}$, the maximum systemic concentration (C_{max}) and drug clearance (CL). Results are shown as mean observed/predicted ratio $R_{(Obs/Pre)}$ with 95 % confidence interval (95 % CI) or range (range is used instead of 95 % CI when there are two or fewer data sets available). **(a, c, e)** adults (healthy and asthma populations) and **(b, d, f)** pediatric asthma population. The shaded area shows 2-fold error range. Iv intravenous, n number of sets. * Range is used instead of 95 % CI when there are two or fewer data sets available.

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TABLES

Table 1: The observed/predicted ratio ($R_{obs/Pre}$) for pharmacokinetic parameters in healthy adults after administration of intravenous and oral theophylline.

PK parameters		observed	predicted	$R_{obs/pre}$	Reference
intravenous administration					
AUC_{0-t} (mg/L.h)	4 mg/kg	84.8	93.7	0.90	(Ishizaki et al., 1979)
	2.78 mg/kg	57.8	64.8	0.89	(Ishizaki et al., 1979)
	3.84 mg/kg	92.7	90.1	1.03	(Chrzanowski et al., 1977)
	6 mg/kg	112.7	125	0.90	(St-Pierre et al., 1985)
	193.2 mg	36.9	44.4	0.83	(Gundert-Remy et al., 1983)
	386.4 mg	76.8	88.4	0.87	(Gundert-Remy et al., 1983)
CL (L/h/kg)	4 mg/kg	0.04	0.04	1.00	(Ishizaki et al., 1979)
	2.78 mg/kg	0.04	0.04	1.00	(Ishizaki et al., 1979)

	3.84 mg/kg	0.03	0.04	0.75	(Chrzanowski et al., 1977)
	6 mg/kg	0.05	0.04	1.25	(St-Pierre et al., 1985)
	193.2 mg	0.07	0.04	1.75	(Gundert-Remy et al., 1983)
	386.4 mg	0.06	0.04	1.50	(Gundert-Remy et al., 1983)
C_{max} (mg/L)	4 mg/kg	16.7	9.27	1.80	(Ishizaki et al., 1979)
	2.78 mg/kg	13.5	6.36	2.13	(Ishizaki et al., 1979)
	3.84 mg/kg	14.1	8.25	1.71	(Chrzanowski et al., 1977)
	6 mg/kg	18.1	13.3	1.36	(St-Pierre et al., 1985)
	193.2 mg	9.88	6.96	1.42	(Gundert-Remy et al., 1983)
	386.4 mg	19.6	13.9	1.41	(Gundert-Remy et al., 1983)
	Oral administration				
AUC_{0-t} (mg/L.h)	125 mg	50.5	44.60	1.13	(Rovei et al., 1982)

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	250 mg	96.3	89.90	1.07	(Rovei et al., 1982)
	375 mg	150.4	136.39	1.10	(Rovei et al., 1982)
	500 mg	234.8	184.05	1.28	(Rovei et al., 1982)
	250 mg	86.4	80.85	1.00	(Lagas and Jonkman, 1983)
	600 mg	146.4	183.89	0.80	(Gonzalez and Golub, 1983)
	600 mg[a]	134.3	153.97	0.87	(Gonzalez and Golub, 1983)
	200 mg[b]	116.7	112.27	1.04	(Antal et al., 1981)
	200 mg[c]	93.7	68.68	1.36	(Antal et al., 1981)
	250 mg	59.5	69.43	0.86	(Lelo et al., 1986)
CL (L/h)	125 mg	2.43	2.72	0.89	(Rovei et al., 1982)
	250 mg	2.55	2.69	0.95	(Rovei et al., 1982)

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	375 mg	2.42	2.66	0.91	(Rovei et al., 1982)
	500 mg	1.95	2.63	0.74	(Rovei et al., 1982)
	250 mg	2.56	2.88	1.01	(Lagas and Jonkman, 1983)
	600 mg	3.86	2.84	1.36	(Gonzalez and Golub, 1983)
	600 mg[a]	3.82	3.28	1.16	(Gonzalez and Golub, 1983)
	200 mg[b]	1.59	1.51	1.05	(Antal et al., 1981)
	200 mg[c]	2.03	2.77	0.73	(Antal et al., 1981)
	250 mg	4.05	3.21	1.26	(Lelo et al., 1986)
C_{max} (mg/L)	125 mg	3.90	3.34	1.17	(Rovei et al., 1982)
	250 mg	7.44	6.70	1.11	(Rovei et al., 1982)
	375 mg	10.1	10.1	1.00	(Rovei et al., 1982)

	500 mg	13.7	13.5	1.02	(Rovei et al., 1982)
	250 mg	6.88	7.00	0.98	(Lagas and Jonkman, 1983)
	600 mg	12.3	13.5	0.91	(Gonzalez and Golub, 1983)
	600 mg[a]	8.04	9.69	0.83	(Gonzalez and Golub, 1983)
	200 mg[b]	8.72	6.59	1.32	(Antal et al., 1981)
	200 mg[c]	7.38	5.83	1.26	(Antal et al., 1981)
	250 mg	5.66	5.50	1.03	(Lelo et al., 1986)

[a] Given as Sprinkle pellets

[b] Dose administered to geriatric population

[c] Dose administered to adult population

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Table 2: The observed/predicted ratio ($R_{obs/Pre}$) for pharmacokinetic parameters in adults and children after administration of intravenous and oral theophylline.

PK parameters	Dose	observed	predicted	$Ratio_{obs/pred}$	Reference
intravenous administration in adults with asthma					
AUC_{0-t} (mg/L.h)	5.6 mg/kg	90.4	69.9	1.29	(Mitenko and Ogilvie, 1973)
	351 mg	59.9	47.2	1.27	(Steinijans et al., 1982)
CL (L/h/kg)	5.6 mg/kg	0.04	0.05	0.93	(Mitenko and Ogilvie, 1973)
CL (L/h)	351 mg	2.41	3.21	0.75	(Steinijans et al., 1982)
C_{max} (mg/L)	5.6 mg/kg	29.4	13.4	2.19	(Mitenko and Ogilvie, 1973)
	351 mg	15.6	10.8	1.44	(Steinijans et al., 1982)
Oral administration in adults with asthma					
AUC_{0-t} (mg/L.h)	600 mg	163.7	156.1	1.05	(Richer et al., 1982)
		155.7	125	1.25	(Weinberger and Hendeles, 1986)

	7.5 mg/kg				
CL (L/h)	600 mg	2.93	2.70	1.09	(Richer et al., 1982)
CL (L/h/kg)	7.5 mg/kg	0.04	0.04	1.00	(Weinberger and Hendeles, 1986)
C_{max} (mg/L)	600 mg	16.0	15.5	1.03	(Richer et al., 1982)
	7.5 mg/kg	16.11	12.74	1.26	(Weinberger and Hendeles, 1986)
intravenous administration in children with asthma					
AUC_{0-t} (mg/L.h)	3.2 mg/kg	23.5	29.8	0.79	(Loughnan et al., 1976)
	4 mg/kg	36.5	40.2	0.91	(Ellis et al., 1976)
CL (L/h/kg)	3.2 mg/kg	0.11	0.07	1.58	(Loughnan et al., 1976)
	4 mg/kg	0.11	0.07	1.51	(Ellis et al., 1976)

C_{max} (mg/L)	3.2 mg/kg	9.28	7.39	1.26	(Loughnan et al., 1976)
	4 mg/kg	9.33	8.93	1.04	(Ellis et al., 1976)
Oral administration in children with asthma					
AUC_{0-t} (mg/L.h)	8.2 mg/kg	97.8	91.3	1.07	(Hendeles L, 1985)
CL (L/h)	8.2 mg/kg	0.07	0.07	1.08	(Hendeles L, 1985)
C_{max} (mg/L)	8.2 mg/kg	14.8	12.5	1.19	(Hendeles L, 1985)

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FIGURE 1

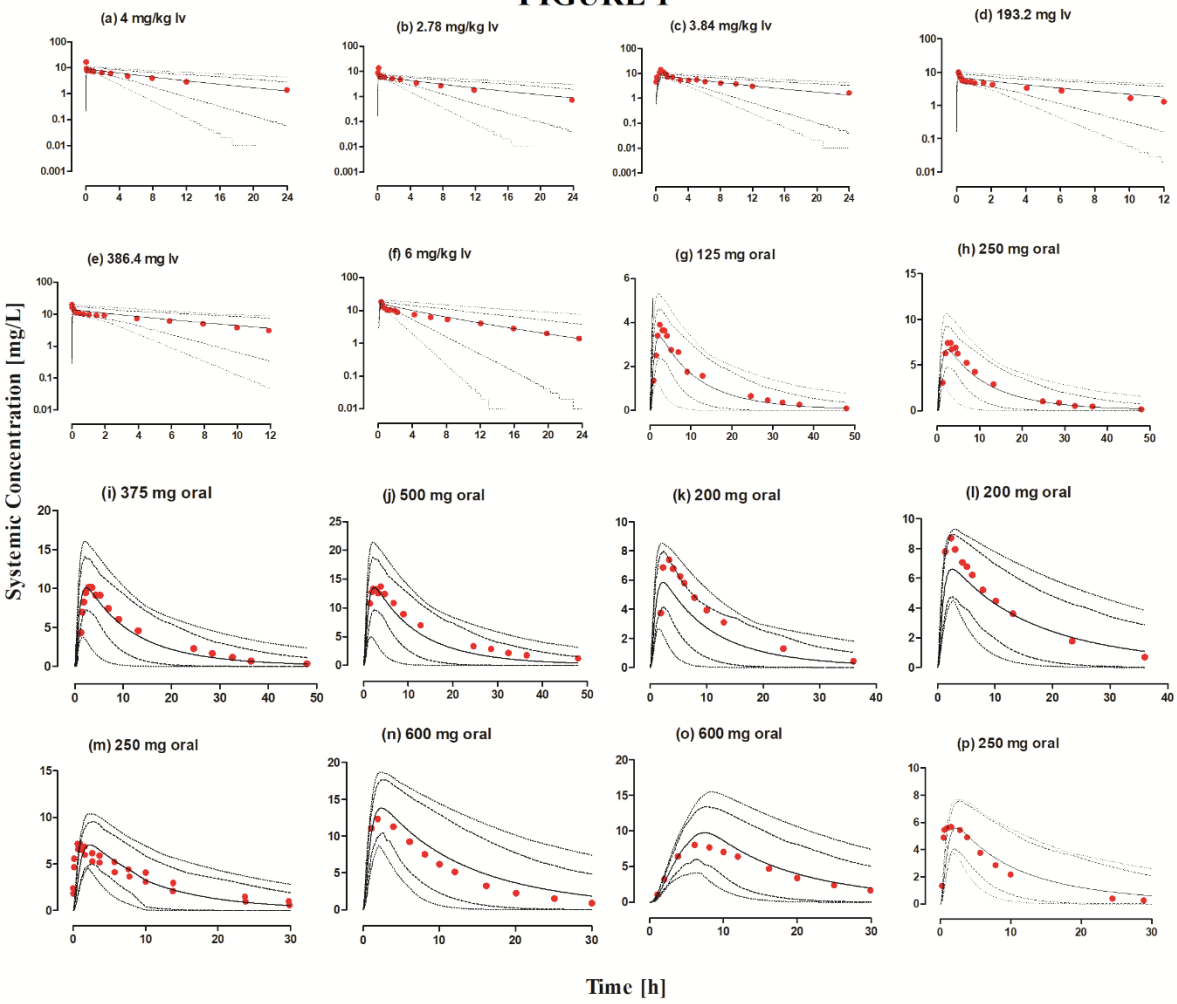

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FIGURE 2

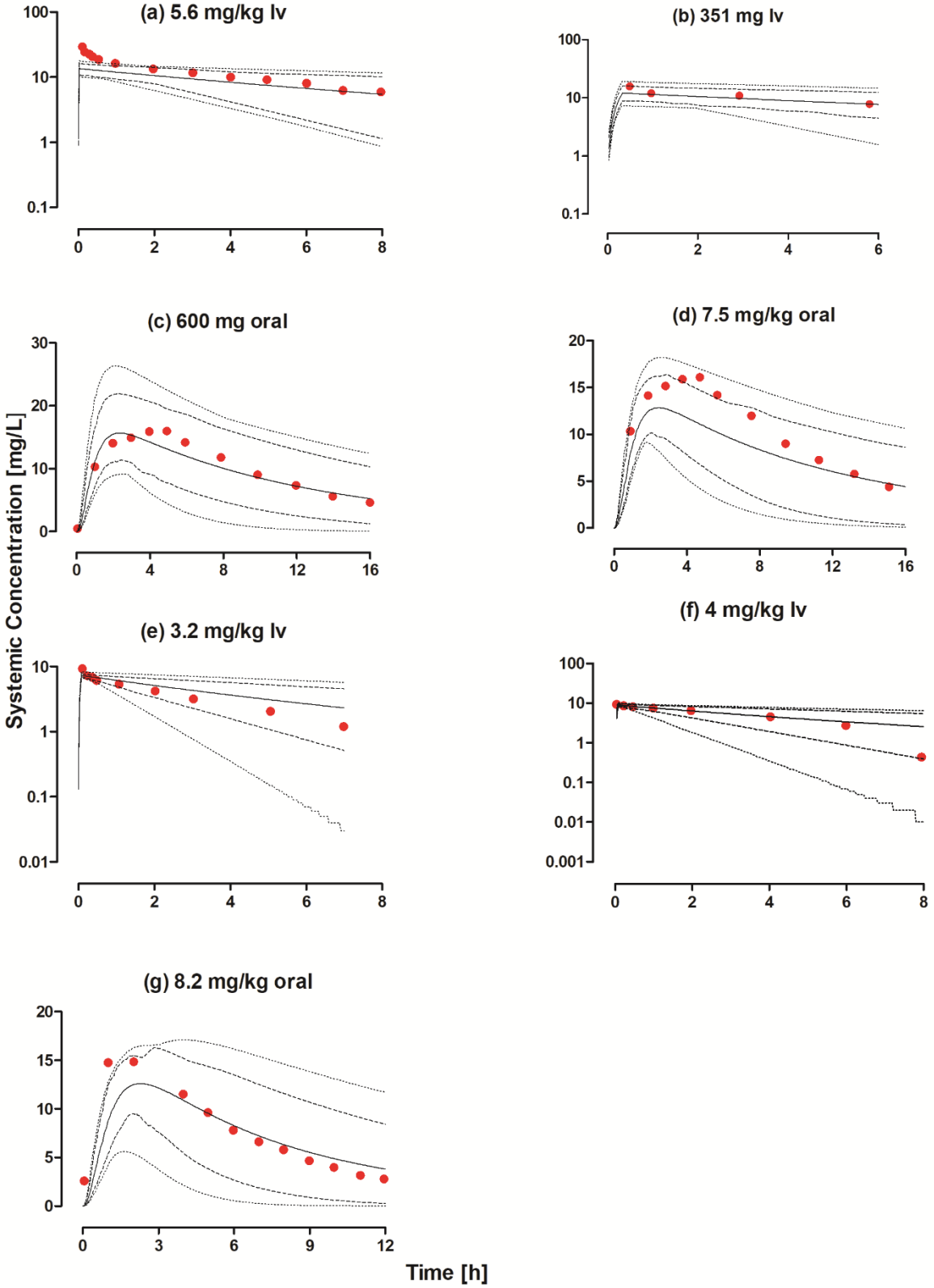

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FIGURE 3