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# A physiologically based pharmacokinetic model linking plasma protein binding interactions with drug disposition

J.L. Buur *, R.E. Baynes, G.W. Smith, J.E. Riviere

*Food Animal Residue Avoidance Databank, Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University, College of Veterinary Medicine, 4700 Hillsborough St. Raleigh, NC 27606, USA*

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ABSTRACT

Combination drug therapy increases the chance for an adverse drug reactions due to drug–drug interactions. Altered disposition for sulfamethazine (SMZ) when concurrently administered with flunixin meglumine (FLU) in swine could lead to increased tissue residues. There is a need for a pharmacokinetic modeling technique that can predict the consequences of possible drug interactions. A physiologically based pharmacokinetic model was developed that links plasma protein binding interactions to drug disposition for SMZ and FLU in swine. The model predicted a sustained decrease in total drug and a temporary increase in free drug concentration. An *in vivo* study confirmed the presence of a drug interaction. Neither the model nor the *in vivo* study revealed clinically significant changes that alter tissue disposition. This novel linkage approach has use in the prediction of the clinical impact of plasma protein binding interactions. Ultimately it could be used in the design of dosing regimens and in the protection of the food supply through prediction and minimization of tissue residues.



## 1. Introduction

Physiologically based pharmacokinetic (PBPK) models predict drug disposition based on physiological mechanisms. These models use a series of mass balance equations to link together selected tissue and blood compartments. These models include physiological parameters (e.g. blood flow, tissue volume), physiochemical parameters (e.g. tissue:blood partition coefficients) as well as those obtained from *in vitro* studies (e.g. Michaelis–Menten enzyme kinetics and protein binding) (Reitz et al., 1988; Grass and Sinko, 2002; Teeguarden et al., 2005). PBPK models allow for the analysis of data from multiple study designs as well as predictions for a wide variety of dosing regimens, routes of administration, species and interindividual variability (Riviere, 1999; Young et al., 2001; Clewell et al., 2004, Gentry et al., 2003).

The flexibility of PBPK models lends itself to the testing of biological hypotheses, prediction of tissue dosimetry, and the refinement of pharmacokinetic mechanisms. Currently, PBPK models are used in toxicology to predict internal dose metrics, in human medicine to calculate individual dose regimens for drugs of low therapeutic indices such as cancer chemotherapeutic agents, and in veterinary medicine to estimate meat withdrawal times for drugs after extralabel use (Kawai et al., 1994; Tsukamoto et al., 2001; Craigmill, 2003; Gentry et al., 2003; Buur et al., 2005, 2006a,b). PBPK models have also been used to predict drug interactions due to enzyme inhibition and to explore mechanisms behind specific pharmacokinetic phenomenon such as time to reach equilibrium in protected spaces or transdermal absorption of chemicals (Simmons, 1996; Kanamitsu et al., 2000; Liu et al., 2005; van der Merwe et al., 2006).

Since combination drug therapy is quickly becoming the standard of practice in both human and veterinary medicine, there is an increased likelihood of adverse drug reactions occurring due to drug–drug interactions (Saltvedt et al., 2005). The safety and efficacy of chemotherapeutics is determined by the concentration of free drug in the system. The interplay between a drug's affinity for plasma proteins, defined by the dissociation constant *Kd*, and the maximum plasma protein binding capacity, defined by $B_{max}$, contribute to the amount of free drug available in the system. Ultimately, free drug concentration is determined by a variety of physiological mechanisms including systemic clearance as well as the binding properties defined above (Wilkinson, 2001). Alterations in either *Kd*, $B_{max}$, or both could cause an increase or decrease in free drug concentration. Many theoretic arguments have been presented to show that the alteration of free drug concentration within an open system, such as a patient, would be transient due to compensatory mechanisms in free drug clearance and thus plasma protein binding interactions would have no clinical effect (Benet and Hoener, 2002; Toutain and Bousquet-Melou, 2002). However,

* Corresponding author. Address: Western University of Health Sciences, College of Veterinary Medicine, 309 East Second Street, Pomona, CA 91766, USA. Tel.: +1 909 706 3518; fax: +1 909 469 5635.
*E-mail address:* jbuur@westernu.edu (J.L. Buur).

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there have been no attempts to model or experimentally validate these interactions.

We hypothesized that PBPK models could be used as a tool to elucidate the underlying mechanism of and to evaluate the clinical consequences of plasma protein binding interactions. To our knowledge, there are no published models that link plasma protein binding interactions to drug disposition using a PBPK modeling approach.

Sulfamethazine (SMZ), a sulfonamide antibiotic, is commonly used in swine medicine. It is labeled for use in the prevention and treatment of cervical abscesses, colibacillosis, swine dysentery, and bacterial pneumonia. Flunixin meglumine (FLU), a nonsteroidal anti-inflammatory agent, has recently been approved for use in swine for the control of pyrexia associated with respiratory disease (Anon., 2006). Alterations in the pharmacokinetics of SMZ due to FLU have been reported in horses and attributed to protein binding interactions (el-Banna, 1999). Similar interactions in swine could theoretically alter tissue disposition and lead to increased tissue residues in the meat supply.

The purpose of this study was to develop a theoretical PBPK model that links plasma protein interactions to the disposition of an individual drug. Given the likelihood of concurrent administration of SMZ and FLU in swine, these compounds were used as model drugs. Additionally, *in vivo* studies were conducted to assess the accuracy of the model prediction.

## 2. Materials and methods

### 2.1. SMZ PBPK model development

A flow-limited PBPK model was developed for predicting SMZ concentrations in swine. The model consisted of tissue compartments including quickly perfused tissues, slowly perfused tissues, liver, and blood. Additional compartments for the *N*-acetyl metabolite were included and consisted of the liver, blood, and remaining body. In total, the final model had seven compartments (Fig. 1), and intravenous inputs for SMZ and FLU.

Physiological parameters of organ volumes and blood flow rates were taken from the literature where available (Tranquilli et al., 1982; Lundeen et al., 1983; Pond, 2001; Buur et al., 2005). Slowly perfused tissue included muscle, gastrointestinal tract, bone, and fat. Quickly perfused tissue included kidney and other tissues. Where appropriate, parameters were calculated as the difference between unity and the remaining tissues. The density of plasma was assumed to be 1 g $ml^{-1}$. Hepatic blood flow was modeled as the combination of hepatic arterial and portal circulations. Renal clearance is mainly due to filtration and was modeled as a first order rate constant from the quickly perfused tissue block. Enterohepatic recycling of SMZ was considered insubstantial and not included in the model. The unique acetylation–deacetylation pathway of SMZ in swine was incorporated into the model as described previously (Buur et al., 2005). Final parameter values can be found in Table 1.

Differential equations were used to describe the rate of change in mass in each compartment (Table 2). Model simulations were solved using ACSLxtreme, Version 2.3.0.12 (Aegis Technologies Group Inc., Huntsville, AL, USA).

Protein binding was assumed to be linear in nature and free and bound drug concentrations were determined by the use of the following equations:

$$C_T = \frac{A}{V_{plasma}} \quad (1)$$

$$C_F = \frac{Kd \cdot C_T}{B_{max} + Kd} \quad (2)$$

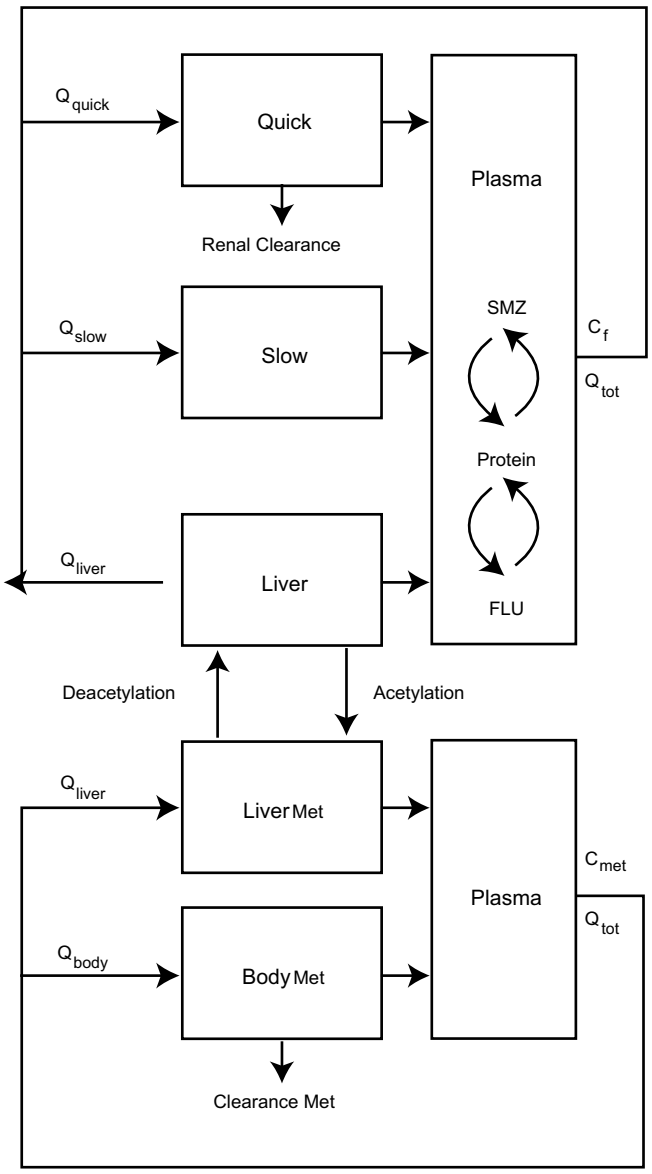


**Fig. 1.** Schematic diagram of the PBPK model for sulfamethazine in swine. Cf, free drug concentration; Cmet, concentration of metabolite; Q, tissue blood flow; Qtot, cardiac output; SMZ, sulfamethazine; FLU, flunixin meglumine; Straight arrows, blood flow; Curved arrows, protein binding equilibrium.

$$C_B = C_T - C_F \quad (3)$$

$C_T$, $C_F$, and $C_B$ are the total, free, and bound concentration of drug in the plasma compartment, respectively; $A$ is the amount of drug; $V_{plasma}$ is the volume of the plasma compartment; $Kd$ is the dissociation constant for the drug; and $B_{max}$ is the maximum binding occupancy for the drug. Mass transferred to tissue blocks was limited to free drug concentration.

Values for $Kd$ and $B_{max}$ were taken from *in vitro* data derived in our laboratory. Values for parameters not available in the literature were estimated using the parameter estimation module included in the simulation software. Model parameters were adjusted to "best fit" by use of a maximum-likelihood estimation algorithm. Limits were set to ensure biologically plausible values. The optimization data set was created using data collected from four published studies (Nouws et al., 1986; Nouws et al., 1989; Sweeney et al., 1993; Yuan et al., 1997) and consisted of mean total plasma concentrations calculated from 12, 6, 7, and 3 samples/data point