Development and Application of a Multiroute Physiologically Based Pharmacokinetic Model for Oxytetracycline in Dogs and Humans

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ABSTRACT: Oxytetracycline (OTC) is a commonly used tetracycline antibiotic in veterinary and human medicine. To establish a quantitative model for predicting OTC plasma and tissue exposure, a permeability-limited multiroute physiologically based pharmacokinetic model was developed in dogs. The model was calibrated with plasma pharmacokinetic data in beagle dogs following single intravenous (5 mg/kg), oral (100 mg/kg), and intramuscular (20 mg/kg) administrations. The model predicted other available dog data well, including drug concentrations in the liver, kidney, and muscle after repeated exposure, and data in the mixed-breed dog. The model was extrapolated to humans and the human model adequately simulated measured plasma OTC concentrations after intravenous (7.14 mg/kg) and oral exposures (6.67 mg/kg). The dog model was applied to predict 24-h OTC area-under-the-curve after three therapeutic treatments. Results were 27.75, 51.76, and 64.17 μg/mL*h in the plasma, and 120.93, 225.64, and 279.67 μg/mL*h in the kidney for oral (100 mg/kg), intravenous (10 mg/kg), and intramuscular (20 mg/kg) administrations, respectively. This model can be used to predict plasma and tissue concentrations to aid in designing optimal therapeutic regimens with OTC in veterinary, and potentially, human medicine; and as a foundation for scaling to other tetracycline antibiotics and to other animal species. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:233–243, 2015

Keywords: oxytetracycline; physiologically based pharmacokinetic (PBPK) modeling; dogs; tetracycline antibiotics; Food Animal Residue Avoidance Databank (FARAD); computational ADME; mathematical model; pharmacokinetics; *in silico* modeling; disposition

INTRODUCTION

Oxytetracycline (OTC) is a member of the tetracycline family of antibiotics that is currently used worldwide to treat infectious diseases in humans, dogs, and many other animals, and as an *in vivo* marker of new bone formation.[1,2] Tetracycline antibiotics are very effective in the prevention of protozoal infections and against tick-borne intracellular pathogens such as Rickettsiaceae and thus continue to be used in human and veterinary medicine.[2] The widespread use of OTC and the emergence of microbial resistance to OTC have led to common extralabel use of OTC.[3,4] As a result, there is an increasing concern about potential adverse health effects because of OTC overexposure.

Studies have shown that excessive exposure to OTC produces a range of toxic effects to multiple organ systems, especially the kidney and liver.[5–7] For example, accidental exposure to a high dose [130 mg/kg; intravenous (i.v.)] of OTC twice resulted in immediate clinical signs of renal toxicity, including oliguria and/or anuria in dogs.[8] Administration of a bone-labeling dose (25 mg/kg) of OTC to dogs also produced clinical signs consistent with renal toxicity, including azotemia.[6] In humans, a variety of adverse effects have been reported from the use of clinical doses of OTC, including liver injury and diarrhea.[9] In this regard, it is crucial to understand OTC's pharmacokinetic characteristics and to develop a quantitative tool that can be used to predict OTC target tissue concentration associated with the observed toxicity as a function of administered doses. In addition, accurate tissue exposure profiles would be a useful tool to calculate target tissue pharmacokinetic profiles used to treat bacterial infections in these tissues where experimental data on tissue concentration profiles are difficult to obtain (e.g., dogs and humans).

The pharmacokinetics of OTC has been studied in multiple veterinary species, including dogs, pigs, cattle, and sheep.[2,10] The oral bioavailability is 3%–5% in pigs and intramuscular (im) injection bioavailability is 79%–98% (depending on injection site) in cattle.[2] In the body, OTC is widely distributed throughout most tissues, metabolically inert, and excreted unchanged primarily via urine.[2,11,12]

Physiologically based pharmacokinetic (PBPK) modeling is a process that simulates the absorption, distribution, metabolism, and excretion of compounds in the body with mathematical equations.[13] Advantages of PBPK models are their ability to predict tissue concentrations of chemicals/drugs and their metabolites after complex exposures and their great power to extrapolate across species, doses, and exposure paradigms. PBPK models have been widely used in predictive risk assessment for a variety of environmental contaminants in laboratory animals and humans,[14] and in estimating tissue residues and withdrawal times for drugs in food animals.[15–17] In the case of OTC, PBPK models are available in several food animal species, that is, salmon,[18] cattle (this work has not been published in a peer-reviewed journal),[19] and sheep,[12] but not in

Abbreviations used: AUC, area under the curve; FARAD, Food Animal Residue Avoidance Databank; im, intramuscular; i.v., intravenous; OTC, oxytetracycline; PA, tissue permeability area cross product; PBPK, physiologically based pharmacokinetic; PC, tissue–plasma partition coefficient; WHO, World Health Organization.

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Table 1. Literature Used in the Model Calibration, Evaluation, and Species Extrapolation

Purpose/ Route	Species (Breed)	Sex	*n*	BW[a] (kg)	Dose (mg/kg)	Formulation[b]	Matrix	Assay[c]	References[d]
Calibration									
Intravenous	Dog (beagle)	NA	6	10.52	5	OTC hydrochloride	Serum	Bioassay	11
Intramuscular	Dog (beagle)	F	5	12	20	Conventional, Terramycin 100	Plasma	SFM	20
Intramuscular	Dog (beagle)	F	5	12	20	Long-acting, Terramycin LA	Plasma	SFM	20
Oral	Dog (beagle)	M/F	6	NA	100	250 mg/capsule, Liquamycin	Blood	SFM	21
Evaluation									
Intravenous	Dog (beagle)	NA	4	NA	10	Terramycin	Serum	Bioassay	22
Intramuscular	Dog (mixed breed)	M/F	5	19.1	20	Long-acting, Terramycin LA	Serum	Bioassay	23
Oral	Dog (beagle)	M/F	6	NA	50	250 mg/capsule, Liquamycin	Blood	SFM	21
Oral	Dog (beagle)	M/F	4	11.4	44	100 mg/tablet, Terramycin	Plasma	Bioassay	24
Oral	Dog (beagle)	M/F	6	NA	50 × 2 (12-h interval)	250 mg/capsule, Liquamycin	Blood	SFM	21
Oral	Dog (beagle)	NA	4	NA	25 × 5 (6-h interval)	Experimental solution	Serum, liver, kidney, and muscle	Bioassay	25
Species Extrapolation									
Intravenous	Human	M	4	67.8	7.14	484 mg OTC hydrochloride dissolved in 150 mL of 5% aqueous solution of dextrose	Serum	Bioassay	26
Oral	Human	M	5	75	6.67	OTC dihydrate sugar-coated tablets, swallowed with 250 mL water	Plasma	Bioassay	27

NA indicates information not available from the manuscript or not applicable.
M, male; F, female.
[a] Values represent the average body weights reported from each study.
[b] OTC hydrochloride and OTC dihydrate are two common pharmaceutical formulations of the active ingredient OTC.
[c] SFM, spectrofluorometric method. Detailed description of the bioassay and SFM is provided in Supporting Information.
[d] These references could be obtained from the Pubmed or upon request from the corresponding author.

humans nor dogs. The cattle and sheep models properly simulate the pharmacokinetics of OTC following single im injection with a long-acting formulation. However, the pharmacokinetics of OTC following other exposure routes (i.v. and oral), repeated exposure, and with different formulations has not been simulated with PBPK modeling.

To provide a quantitative tool to help design appropriate OTC therapeutic regimens in animals and humans, considering the data gaps about OTC PBPK models, the objective of this study was to develop and apply a multiroute PBPK model for OTC as a model drug in dogs, and extrapolate it to humans. We chose to develop a canine model because adequate OTC pharmacokinetic data in dogs are available in the literature (Table 1), allowing development of a confident model, whereas data in humans are very limited. As mentioned earlier, OTC has also been modeled using PBPK in other food animal species, making it the ideal choice for true interspecies extrapolations. The goal of this research program is to assess the utility of using PBPK models to extrapolate drug disposition from disparate studies across species.

METHODS

Data Source for Model Calibration

The Food Animal Residue Avoidance Databank (FARAD)[28,29] comparative pharmacokinetic database, a USDA supported initiative in veterinary medicine, was used as the source of data for dog model calibration and evaluation. Pharmacokinetic data in healthy dogs after i.v., oral, or im administration of commercial or experimental, solid (capsules and tablets) or aqueous formulations of OTC were selected. Key information of selected studies is given in Table 1 and a brief description of these studies can be found in Supporting Information. All data were extracted from selected studies using WebPlotDigitizer (version 2.6, http://arohatgi.info/WebPlotDigitizer/).

Model Structure

On the basis of the previous PBPK models for OTC in cattle[19] and sheep,[12] the present model consisted of seven compartments: blood, liver, kidney, muscle, fat, richly, and slowly