A PHYSIOLOGICALLY BASED PHARMACOKINETICS MODEL FOR BONE-SEEKING AGENTS

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Abstract. *Bone seeking agents have as main characteristic the great affinity with the bone, in which they remain for prolonged periods of time maintaining a low systemic concentration. Drugs commonly used in the osteoporosis treatment such as bisphosphonates belong to this group. This work presents a physiologically based pharmacokinetic model (PBPK) for bone seeking agents. The proposed model describes the time course of drug concentration in bone and other organs using physiological parameters such as blood flow and organ volume. The bone tissue model distinguishes two compartments for each bone type (cortical and trabecular): one metabolically active, where remodeling develops, and other metabolically inactive, which does not undergo remodeling. Two dosing regimens for drug administration were simulated: 10 mg/day via intravenous infusion for 4 hours and 10 mg oral/day. A conceptual pharmacodynamic (PD) response based in a sigmoidal model were also simulated. Preliminary results indicate that the proposed model is able to reproduce the expected behavior of bone tissue exposed to bone-seeking agents. Further studies are needed to fit the model and simulate commercially available drugs.*

Palavras chave: *PBPK, bone-seeking agents, mathematical modeling, bone remodeling*

1. INTRODUCTION

1.1 Physiologically based pharmacokinetic model

A physiologically based pharmacokinetic model (PBPK) describes drug concentrations in blood and other organs using physiological parameters such as blood flow and organ volume as well as compartments representing different tissues and organs. A schematic of the PBPK model structure is given in Fig. (1). As can be seen in the model, the body is divided into a number of tissue compartments, each one characterized by appropriate volume and flow rates. For simplicity, we adopt the compartments blood, gut, liver, kidney, well perfused tissues, poorly perfused tissues and bone. The bone compartment consists of two subcompartments: a rapidly exchangeable vascularized surface bone and an extravascularized bone matrix, which will be more detailed at the next subsection. The temporal evolution of the drug concentration in the tissue is described with a mass balance equation wich accounts for tissue blood flow rate (Q_i) and the concentration difference between the arterial blood (c_A) and the venous blood (c_{V_i}). Each tissue bone flow rate is assumed to be proportional to the cardiac output (Q_c) and based on reference values for a 70 Kg man (Yokley et al., 2006). Mean cardiac output is assumed to be 276 liters per hour. Physiological values are adjusted to satisfy the requirement $Q_c = \Sigma Q_i$ where i correspond to the tissues: gut, kidney, liver, rapid perfused, slowly perfused and bone. Volumes of each organ are considered fractions of body weight(BW) in Kg as seen in Tab. (1).

Route of administration for a drug may be intravenous, usually as an injection or infusion, or oral, through the alimentary canal (gastrointestinal tract). In addition to these routes of administration, there are also pulmonary (inhalation), subcutaneous (adhesives), muscles (injection) and eyes (eye drops). Drugs administered orally may be absorbed in different parts of the gastrointestinal tract. Drugs absorbed through the oral cavity or rectum ignore the liver. All other parts of the alimentary canal (especially the stomach, duodenum, large and small intestine) carry blood (and drugs) in the liver through the portal vein. There are also transporters in the mucosal cells of the gut wall that pick up the drug from the gut and may excrete the drug back into the intestine. Relatively high drug concentrations are processed by the liver during the first passage of the drug. The liver can excrete the drug in the bile and then into the duodenum. Therefore, the drug can be resorbed resulting in a enterohepatic cycle (Gieschke and Serafin, 2013).

The main organs of drug elimination are the liver and the kidneys. The liver with its enzymatic equipment is the main metabolizing organ in the body. The kidneys help to filter wastes (including small drugs) from the blood and excrete them with urine. Absorption of the drug by tissue may be limited by blood perfusion or tissue permeability.

The mass balance equations for the PBPK model ilustrated in the Fig. (1) are listed in Eqs. (1). The variables V_i, c_i, Q_i are volume, concentration and blood flow in the tissue/organ i, respectively. The indices b, G, L, K, RP, SP, B

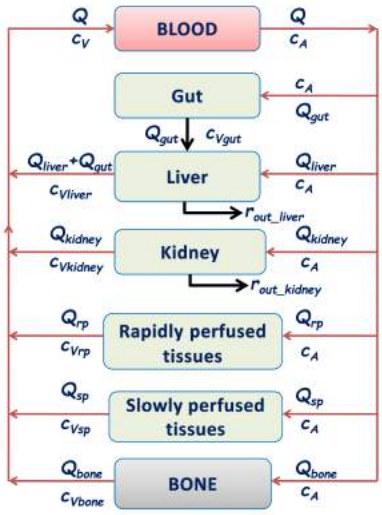

Figure 1. Physiologically based pharmacokinetic (PBPK) model. Q terms are blood flow rates, c terms are concentrations. Arterial input is on the right and venous effluent in on the left. Source: Prepared by the author.

refers to blood, gut, liver, kidney, rapidly perfused tissues, slowly perfused tissues and bone, respectively.

$$V_{blood}\frac{dc_{blood}}{dt} = Q\left(c_V - c_A\right) \tag{1a}$$

$$V_{gut}\frac{dc_{gut}}{dt} = Q_{gut}\left(c_A - c_{V_{gut}}\right) \tag{1b}$$

$$V_{liver}\frac{dc_{liver}}{dt} = Q_{liver}c_A + Q_{gut}c_{V_{gut}} - \left(Q_{liver} + Q_{gut}\right).c_{V_{liver}} - CL_{hepato-bilis}.c_{V_{liver}}.F_u \tag{1c}$$

$$V_{kidney}\frac{dc_{kidney}}{dt} = Q_{kidney}\left(c_A - c_{V_K}\right) - CL_{renal}.c_{V_{kidney}}.F_u \tag{1d}$$

$$V_{rp}\frac{dc_{rp}}{dt} = Q_{rp}\left(c_A - c_{V_{rp}}\right) \tag{1e}$$

$$V_{sp}\frac{dc_{sp}}{dt} = Q_{sp}\left(c_A - c_{V_{sp}}\right) \tag{1f}$$

$$V_{bone}\frac{dc_{bone}}{dt} = Q_{bone}\left(c_A - c_{V_{bone}}\right) \tag{1g}$$

where at $t = 0$ we have $c_{blood} = c_{gut} = c_{liver} = c_{kidney} = c_{rp} = c_{sp} = c_{bone} = 0$. Furthermore, $c_A = c_b$, $c_{VG} = c_G/R_G$, $c_{VL} = c_L/R_L$, $c_{V_K} = c_K/R_K$, $c_{V_{RP}} = c_{RP}/R_{RP}$, $c_{V_{SP}} = c_{SP}/R_{SP}$, e $c_{V_B} = c_B/R_B$. Indices A and V in each concentration expressions refers to arterial and venous effluent, respectively. Thus, the total venous concentrations is given by:

$$c_V = \frac{\left(Q_{liver} + Q_{gut}\right)c_{V_{liver}} + Q_{kidney}c_{V_{kidney}} + Q_{rp}c_{V_{rp}} + Q_{sp}c_{V_{sp}} + Q_{bone}c_{V_{bone}}}{Q} \tag{2}$$

Finally the total blood flow is expressed by:

$$Q = Q_{liver} + Q_{gut} + Q_{kidney} + Q_{rp} + Q_{sp} + Q_{bone} \tag{3}$$

The PBPK model was implemented in Matlab. Physiological parameters were taken or derived from O'Flaherty (1991); Pertinez et al. (2013) and are listed in Tab. (1). The drug concentration in bone define an input for the bone remodeling model based on cells activities.

1.1.1 Bone tissue modelling

The mineralized components of bone tissue are described by an adaptation of the permeability rate limited tissue compartment model (Nestorov, 2003; Pertinez et al., 2013). Thus, the bone compartment is composed by a vascular

Table 1. Physiological parameters used in the PBPK model.

Simbol	Unit	Value	Description	Source
Q_c	l/h	276	Cardiac output	Calculated
Q_{gut}	l/h	$0.19Q_c$	Blood flow to gut	Brown et al. (1997)
Q_{kidney}	l/h	$0.19Q_c$	Blood flow to kidney	Brown et al. (1997)
Q_{liver}	l/h	$0.06Q_c$	Blood flow to liver	Brown et al. (1997)
Q_{bone}	l/h	$0.19Q_c$	Blood flow to bone	Brown et al. (1997)
Q_{rp}	l/h	$0.36Q_c$	Blood flow to well perfused tissues	Brown et al. (1997)
Q_{sp}	l/h	$0.125Q_c$	Blood flow to slowly/poorly perfused tissues	Calculated
V_{gut}	l	$0.2895BW$	Gut volume	Adapted from Pertinez et al. (2013)
V_{kidney}	l	$0.004BW$	Liver volume	Yokley et al. (2006)
V_{liver}	l	$0.025BW$	Kidney volume	Yokley et al. (2006)
V_{rp}	l	$0.04BW$	Well perfused tissues volume	Yokley et al. (2006)
V_{bone}	l	$0.04BW$	Bone volume	O'Flaherty (1991)
V_{sp}	l	4	Poorly perfused tissues volume	Calculated
R_{gut}	n/a	0.9	Partition coefficient gut/plasma	Pertinez et al. (2013)
R_{liver}	n/a	0.47	Partition coefficient liver/plasma	Pertinez et al. (2013)
R_{kidney}	n/a	3	Partition coefficient kidney/plasma	Pertinez et al. (2013)
R_{rp}	n/a	0.9	Partition coefficient well perf. tissues/plasma	Pertinez et al. (2013)
R_{sp}	n/a	0.6	Partition coefficient poorly perf. tissues/plasma	Pertinez et al. (2013)
R_{bone}	n/a	2	Partition coefficient bone/plasma	Authors
CL_{renal}	n/a	0.03	Renal clearance	Pertinez et al. (2013)
CL_{hepato_bilis}	n/a	0.03	Hepato-biliary clearance	Pertinez et al. (2013)
F_u	n/a	0.73	Fraction unbound in blood	Pertinez et al. (2013)

compartment that is taken as the bone surface and a extravascular as the bone matrix. The bone remodelling process will govern the exchange between these two compartments. Expressing in mathematical terms, the concentration in vascularized bone surface A_{vas} and extravascular bone matrix A_{bm} can be modelled by:

$$\frac{dA_{vas}}{dt} = \left(\frac{Q_{bone}c_A}{V_{vas}} - \frac{Q_{bone}A_{vas}}{V_{vas}R_{bone}}\right) - k_{form}\frac{A_{vas}}{V_{vas}} + k_{res}\frac{A_{bm}}{V_{bm}} \tag{4}$$

$$\frac{dA_{bm}}{dt} = k_{form}\frac{A_{vas}}{V_{vas}} - k_{res}\frac{A_{bm}}{V_{bm}} \tag{5}$$

The terms k_{form} and k_{res} describes the bone formation and bone resorption rates, respectively, and are similarly defined to the bone remodeling models based on dynamics of cells populations like Lemaire et al. (2004); Pivonka et al. (2008), among others. Equations (4) and (5) are defined separately for trabecular and cortical bone, as ilustrated in Fig. (2).

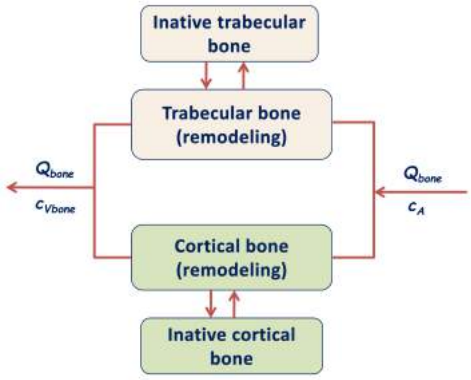

Figure 2. Bone tissue compartment model. Source: Prepared by the author.

2. PRELIMINARY RESULTS

The proposed PBPK model for bone seeking agents was solved by the $4th$ order Runge-Kutta method and implemented in Matlab. In order to test the procedure two dosing regimens were tested: one of 10 mg drug/day via intravenous infusion over a 4 hour periods and other of 10 mg oral/day. Figure (3) illustrates the time course of drug amount in each tissue or organ for the first regimen. Note that each dose (10 mg) is divided by the infusion time (4 h) and multiplied by the

bioavailability (0.006). The curve referring to the bone includes the vascular bone surface and extravascular bone matrix for both cortical and trabecular. A simulation with dosing regimen of 10 mg drug oral/day is presented in Fig. (5).

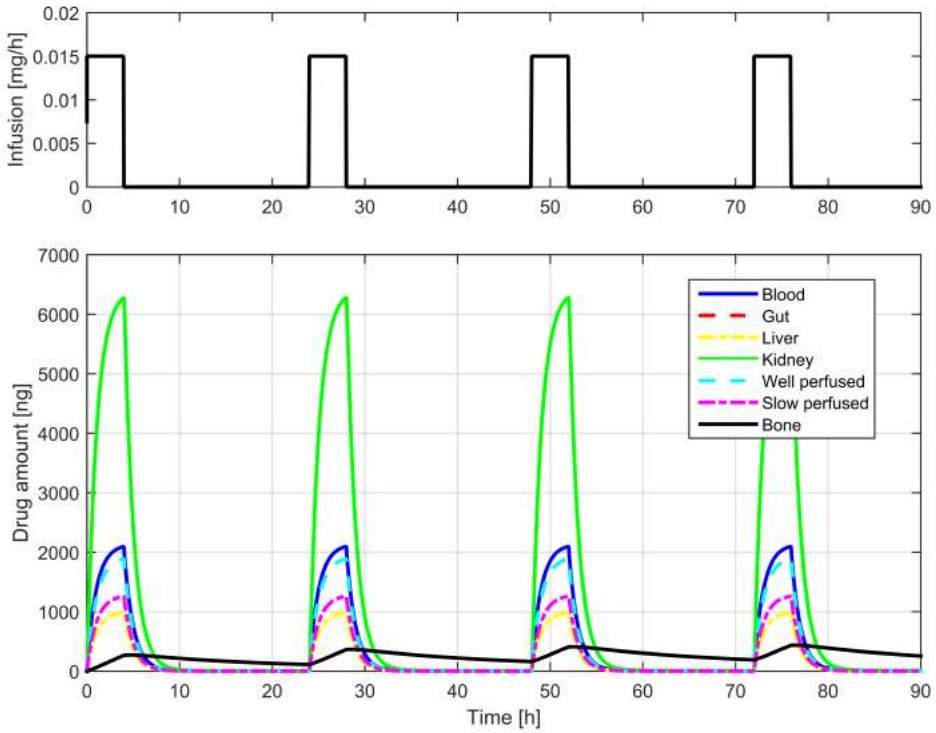

Figure 3. Implementation of proposed PBPK model. A dosing regimen of 10 mg drug/day via intravenous infusion over 4 hours period. The graph shows drug infusion rate and amounts in each organ/tissue. Source: Prepared by the author.

Figure (4) ilustrates the four compartments referred to the bone tissue as proposed in the model, which includes the vascular bone surface and the extravascular bone matrix for cortical and trabecular.

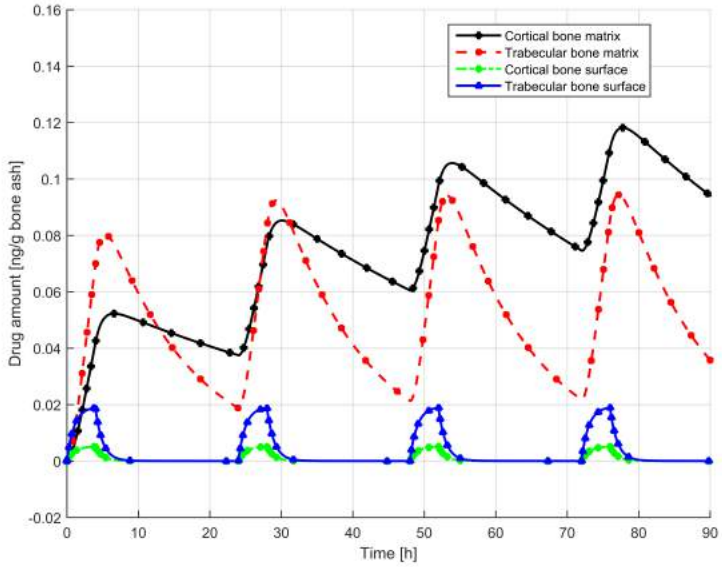

Figure 4. Predicted trabecular and cortical bone drug amounts for a dosing regimen of 10 mg drug/day via intravenous infusion over 4 hours period. Source: Prepared by the author.

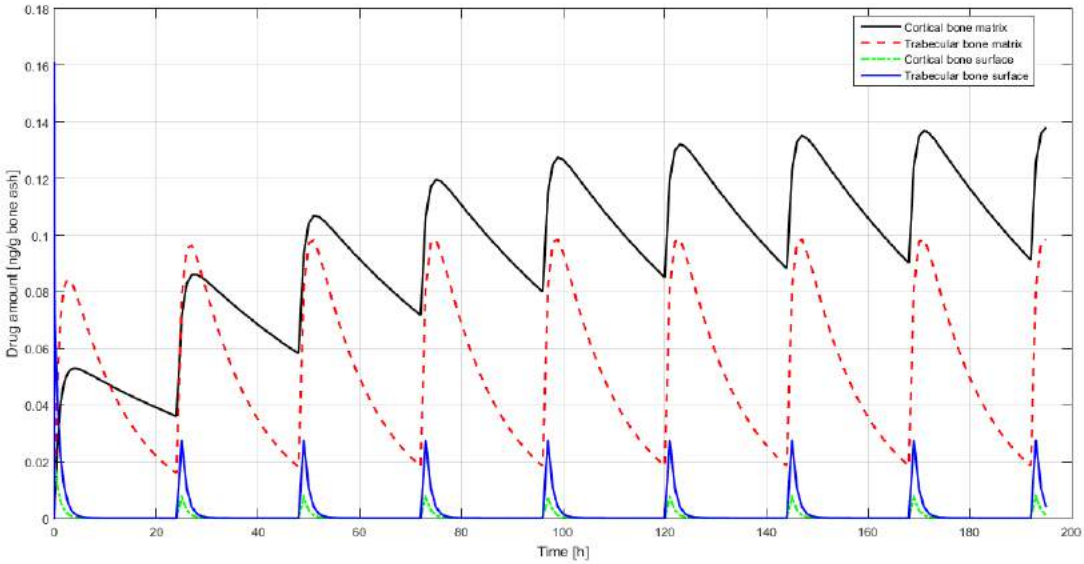

Figure 5. Predicted trabecular and cortical bone drug amounts for a dosing regimen of 10 mg drug oral/day. Source: Prepared by the author.

The pharmacodynamics (PD) response for this conceptual model is given in terms of changes in bone resorption. Those changes can be acessed using an indirect response model according to clinical routine. For instance, uCTX levels or OPH and Cr concentrations in urine samples, that are assumed to decreased as an effect of bisphosphonate treatment. Here we addopted an inhibitory sigmoidal E_{max} model to quantify our virtual PD response. A sigmoidal E_{max} model is summarized as:

$$E = E_0 + \frac{E_{max} C_{drug}^n}{EC_{50}^n + C_{drug}^n} \tag{6}$$

where E is the drug effect or response, E_0 the baseline value, E_{max} the maximum effect of the drug, C_{drug} is the drug concentration, EC_{50} the concentration that produces 50% maximum response, n is the Hill coefficients. Table (2) presents the model parameters used in this simulation. The PD response is ilustrated in Fig. (6).

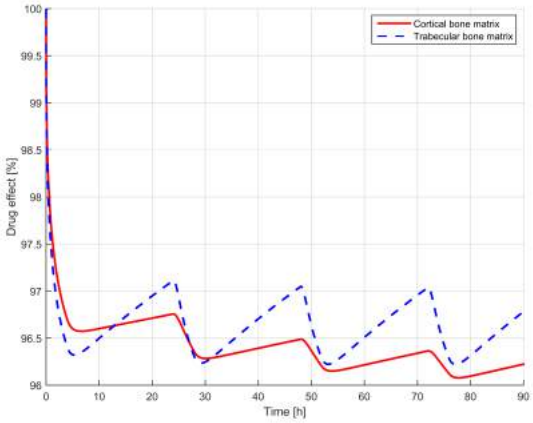

Figure 6. Predicted drug effect using a sigmoidal E_{max} model, considering trabecular and cortical bone amounts during treatment with 15 mg drug/day via intravenous infusion over 4 hours period. Source: Prepared by the author.

Table 2. Pharmacodynamic parameters for the PK-PD model describing bone-seeking agents pharmacokinetics and urinary data ratio in a virtual treatment.

Simbol	Unit	Value	Description
E_{max}	%	44.3	Maximum effect
E_0	%	100	Baseline value
EC_{50}	μm	0.05	Half-maximum effect
n	n/a	0.18	Hill coefficient

3. CONCLUSION

We described here a PBPK model for bone seeking agents that aims to predict the time course of drug concentrations in bone. The model has potential for future uses in PBPK modelling of drugs used in osteoporosis treatment, like alendronate, ziledronate, among others, providing a safely way to test different dosing regimens and find more effective therapeutic strategies. Additional efforts should be employed to calibrate model parameters for better replicate the behavior of commercially available antiresorptive medications.

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5. RESPONSIBILITY FOR INFORMATION

The authors are solely responsible for the information included in this work.