Physiologically Based POP-PK modelling of Strontium in the ovariectomised rat disease model of post menopausal osteoporosis

Henry Pertinez [A], Marylore Chenel [B] Leon Aarons [A]

[A] Centre for applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical sciences, The University of Manchester, [B] Clinical PK department, Institut de Recherches Internationales Servier, Courbevoie Cedex

E-mail: henry.pertinez@manchester.ac.uk

1. Introduction and Objectives

- It was first observed in the 1950s that **moderate PO doses of Strontium can aid Calcium deposition in bone** and **clinical efficacy in this role has since been further demonstrated** i.e. increased BMD and reduced vertebral and non-vertebral fracture risk in post menopausal women with osteoporosis dosed PO 2g per day with Strontium as its ranelate salt[1], currently marketed by Servier as PROTELOS™ .
- Strontium is a **bone seeking agent**, one of a class of molecules sharing a high affinity for bone tissue. **PK and PD of bone seeking agents is made more complex by the heterogeneity of bone tissue**, i.e. the **physiologically distinct cortical and trabecular bone tissue sub-types** and the **distinct bone surface and bone matrix sub-compartments**. Distribution of Strontium into soft tissue is relatively low.
- The physiological influence and ADME of Strontium can be **readily considered in comparison to** that of **Calcium** (both group II metals in the periodic table with similar solution chemistry)
- Strontium is **absorbed** in the intestine via a saturable, active pathway, shared with Calcium and is **cleared principally by renal excretion** with **minor contributions from bile excretion and direct gut secretion in the rat**.
- The aim of the work described in this poster was to **develop a physiologically based pharmacokinetic (PBPK) model** that would be able to **describe bone exposure data for Strontium in the ovariectomised (OVX) rat** pre-clinical disease model for post menopausal osteoporosis, in a physiologically rationalised manner.

2. Model Design and Features

- A PBPK model for Strontium was developed incorporating elements from literature PBPK models for other bone seeking agents[2], allowing for a **description of the heterogeneity of bone tissue in the structure of the model** (i.e. cortical and trabecular bone compartments and bone surface and bone matrix sub-compartments) and also for a physiologically rationalized description of the processes of bone remodelling. (Schematic in ***Fig. 1***)
- Tissue compartments **other than bone are described with perfusion rate limited PBPK tissue models**, i.e where:

$$d C_{Tissue} / dt = (Q_{Tissue} * C_{arterial}) / (V_{Tissue}) - (Q_{Tissue} * C_{Tissue}) / (V_{Tissue} * Kp_{(Tissue)})$$

- Kp values for Lung, Liver and Kidney taken from a **satellite rat tissue distribution study**, where Strontium was dosed to steady state.
- Kp values for lumped well perfused and poorly perfused tissues were calculated using the formula of Nestorov et al.[3]
- 1st order elimination occurs from the Kidney and Liver (biliary excretion, no metabolic clearance) compartments.
- The **Cortical and Trabecular bone tissue** types are treated as **separate physiological compartments**, each using a **modified version of a permeability rate limited PBPK tissue model**.
- **Bone surface** in the cortical and trabecular tissue compartments is treated as the **vascular tissue sub-compartment** :

1). $$dA_{BONE-SURF-x} / dt = (Q_{BONE-x} * C_{arterial}) - (Q_{BONE-x} * A_{BONE-SURF-x} / (V_{BONE-SURF-x} * Kp_{-BONE-SURF-x})...$$
$$... - (STRONT * x\text{-}BFR * A_{BONE-SURF-x} / V_{BONE-SURF-x}) + (x\text{-}BRR * A_{BONE-MATRIX-x} / V_{BONE-MATRIX-x})$$

*(Where "x" is Cortical or Trabecular, and **STRONT** is a dimensionless scaling factor)*

- **Bone matrix** is treated as the **extravascular tissue sub-compartment**

2). $$dA_{BONE-MATRIX-x} / dt = (STRONT * x\text{-}BFR * A_{BONE-SURF-x} / V_{BONE-SURF-x}) - (x\text{-}BRR * A_{BONE-MATRIX-x} / V_{BONE-MATRIX-x})$$

*(Where "x" is Cortical or Trabecular, and **STRONT** is a dimensionless scaling factor)*

- **Exchange between surface and matrix** sub-compartments is **governed by the processes of bone remodelling** i.e. bone resorption rate (**BRR**) and bone (re)formation rate (**BFR**). Equations describing these processes are given below :

3). $$FBFR = (0.003 + 0.321 * \exp(-0.2 * AGE) + 0.081 * \exp(-0.021 * AGE)) / 24$$

Fractional bone formation rate (h^{-1}) in rat as a function of Age in years

4). $$BFR = FBFR * V_{bone} = BRR$$

*Bone formation rate (**BFR**) in (L/h), where V_{bone} = total bone volume...*
*...is equal to Bone resorption rate (**BRR**) in the mature rat where there is no (or negligible) net bone growth*

5).

T-BFR= BFR * PART	C-BFR= BFR * (1-PART)
T-BRR= BRR * PART	C-BRR= BRR * (1-PART)

*Where **T** = Trabecular , **C** = Cortical and **PART** = 0.7*
***PART** = fraction of total bone formation assigned to trabecular bone, based on its relative metabolic activity, blood flow and surface area. The factor **STRONT** in 1.) and 2.) scales bone formation rate into an intercompartmental clearance for Strontium.*

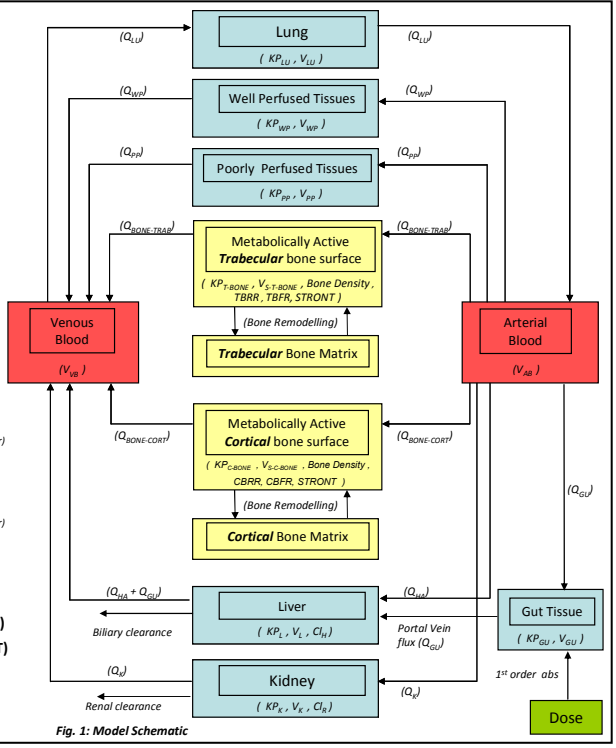

Fig. 1: Model Schematic

3. Modelling Dataset and Empirical POP-PK Plasma Forcing function

- PBPK model development focussed on a **plasma and bone exposure dataset from a study in the female ovariectomised (OVX) rat** model for post menopausal osteoporosis.
- Rats were dosed with **PO Strontium Ranelate at 250 mg/kg, QD for 6 months** followed by a **wash out period of a further 6 months**. 3 to 4 plasma samples were taken per rat over the timecourse, spread across the animals in the study design to allow a **composite plasma profile** to be constructed over the **12-month study period** with terminal sampling of **bone tissue from three sites** (vertebrae, femur and tibia). The study also included a **satellite IV PK study** with plasma sampling over a **2 day timecourse**.
- For **open loop PBPK modelling** of the OVX data, a **hierarchical, POP-PK, 3-compartment empirical model for use as a forcing function** was fitted to the plasma data using a **Bayesian approach in WinBUGS**[4] with **uninformative priors**. PO data was analysed simultaneously with satellite IV data.
- Diagnostic VPCs etc. (***Fig. 2a***, ***2b and 3.***) indicate an **acceptable modelled fit to the PLASMA data and description of interanimal variability**. Final population mean parameter estimates, %CVs of these estimates (%CV[param.est]), and parameter interindividual variabilities (expressed as %CV[IIV.est]) are given in ***Table 1***:

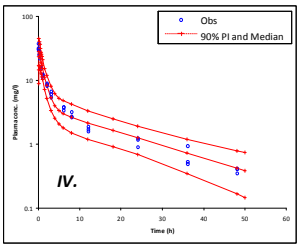

Fig. 2a.

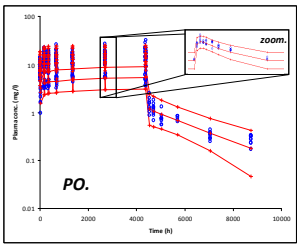

Fig. 2b.

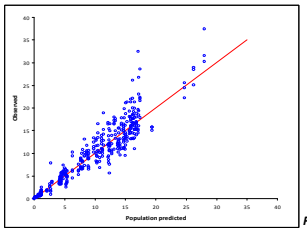

Fig. 3.

	CL (L/h/kg)	Q2 (L/h/kg)	Q3 (L/h/kg)	V1 (L/kg)
Est.	0.063	0.139	0.011	0.28
%CV [param.est]	6.3	11.5	9.1	9.3
%CV [IIV.est]	20.7	34.5	29.0	27.2

	V2 (L/kg)	V3-V2 (L/kg)	ka (h^{-1})	F
Est.	0.935	20.6	0.296	0.177
%CV [param.est]	9.9	11	10.5	14.1
%CV [IIV.est]	28.3	31.8	27.6	21.2

Table 1.

4. Open loop POP-PK implementation

- **Initial PBPK model development used a nonlinear regression approach**, treating the OVX rat data as a naïve pool. Adequate performance was demonstrated in both open and closed loop configurations.
- For a **POP-PK implementation of the model, the open loop configuration was used**, with each individual animal's predicted PK parameters (from the empirical POP-PK plasma fitting) used as the forcing function for each individual rat's bone exposure. **Only 1 bone tissue timepoint is available per animal** (due to the destructive nature of sampling). This removes the ability to partition interindividual and residual error in the hierarchical POP-PK model. The method of Hing et al.[5] (where the residual error component was fixed) was used to allow **estimation of a pseudo-interindividual variability** for the PBPK parameters being estimated.
- **Bone tissue samples do not differentiate cortical and trabecular bone sub-types**. Therefore the modelled **sum of the cortical and trabecular bone compartments was fitted to the average bone exposure** from the three sampling sites.
- Analysis was carried out in **WinBUGS using uninformative priors**.
- Diagnostic VPCs* etc. (***Fig. 4***. and ***5.***) indicate an **acceptable modelled fit to the BONE data and description of interanimal variability**.Final population mean parameter estimates etc. in ***Table 2.***

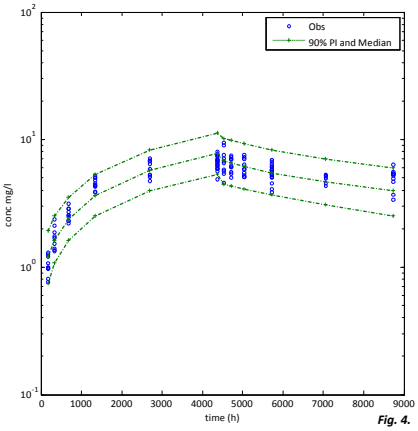

Fig. 4.

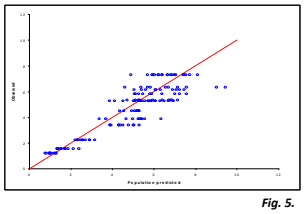

Fig. 5.

	STRONT	$K_{p\text{-}BONE\text{-}SURF\text{-}TRAB}$	$K_{p\text{-}BONE\text{-}SURF\text{-}CORT}$
Est.	0.073	34090	81870
%CV [param.est]	22.8	17.2	36.2
%CV [IIV.est]	39.8	41.1	43.6

Table 2.

**(Bone VPC created from 1000 simulations of the bone dataset, using the set of individual rat forcing function parameters, and PBPK parameters randomly generated from the estimates of the population mean PBPK parameters and their variabilities).*

5. Conclusions and future work/applications

- The PBPK model **successfully describes the bone exposure of Strontium** in the OVX rat in a physiologically rationalized manner, and in keeping with the Strontium's bone seeking nature.
- The model has the potential for **future use in modelling the PK-PD of Strontium** and/or other bone seeking agents and for **scaling to model human bone exposures for Strontium**.

6. References

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2. Stepensky, D., L. Kleinberg, and A. Hoffman, *Bone as an effect compartment : models for uptake and release of drugs.* Clin Pharmacokinet, 2003. **42**(10): p. 863-81.
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