Blood-milk barrier exploration in lactating species using a Physiologically Based PharmacoKinetic (PBPK) model
Case study with oxytetracycline

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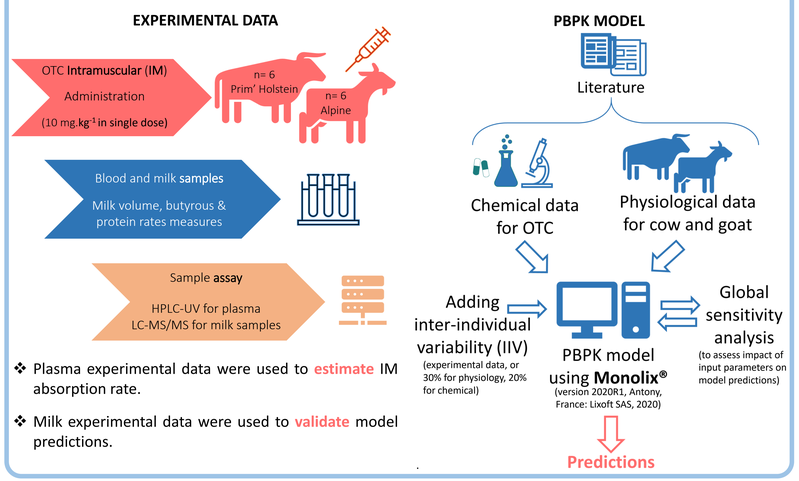
PURPOSE

- Antibiotic used in farm animals may be found as residues in milk that could promote the emergence or selection of **resistant bacteria** in consumer's intestines.
- The excretion of antibiotic towards milk depends on several factors[1] as :
  - **physicochemical properties of the drug** (ionization, lipophilicity, protein binding),
  - **organism** (species, race, lactation period, milking interval),
  - **milk composition** (fat, casein, whey proteins, ions).
- The aim of this study was to develop a **Physiologically Based PharmacoKinetic** (PBPK) model, considering the aforementioned factors and the animal's physiology, and use it to predict **oxytetracycline** (OTC) residues in milk of cow and goat.

MATERIAL & METHODS



- Plasma experimental data were used to **estimate** IM absorption rate.
- Milk experimental data were used to **validate** model predictions.

RESULTS

- The observed data in milk of both species were **well predicted** by the model (**Figure 3**), thus validating the model. The prediction intervals resulted from the addition of IIV on several parameters and the residual error equal to the intermediate precision of the analytical method.
- OTC was quantified in milk up to **4 days** after administration at **0.8%** and **0.5%** of the administered dose for cows and goats, respectively.
- The milk to plasma ratio (**MP**) was **1.50** for cow, comparable to previous published value[2], and **1.35** for goat.
- Milk and plasma pH and OTC acid pKa had a significant impact on the model predictions (**Figure 4**). The ionization difference between plasma (60% ionized) and milk (29% ionized) explained these impacts.
- The PBPK model is able to predict OTC **ionization** (**Figure 5**), **distribution** between milk fractions and **fixation** to milk components (**Figure 6**) for each species.

HIGHLIGHTS

- **OTC excretion in cow and goat milk was described by a PBPK model (Figure 1).**
- **A mechanistic udder model (Figure 2) was used to describe OTC partition[3] within:**
  - **vascular space (plasma), binding to proteins,**
  - **extracellular water (EW), binding to albumin,**
  - **intracellular water (IW), binding to lipids (NL), phospholipids (NP,AP) and milk components,**
  - **alveoli and cisternal milk[4], binding to whey proteins, fat, casein, free calcium (Ca^{2+}) and free magnesium (Mg^{2+}).**
- **Milk volume varied with milking intervals and a residual volume of alveolar milk remained after each milking[5].**
- **Only passive diffusion was considered between sub-compartments, based on *in vitro* studies. Only unionized and unbound OTC form could diffuse.**
- **OTC systemic clearance was found in the literature for each species.**

Figure 1. Whole PBPK model

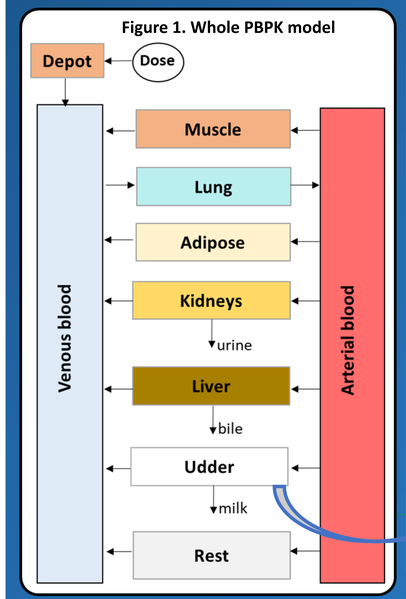
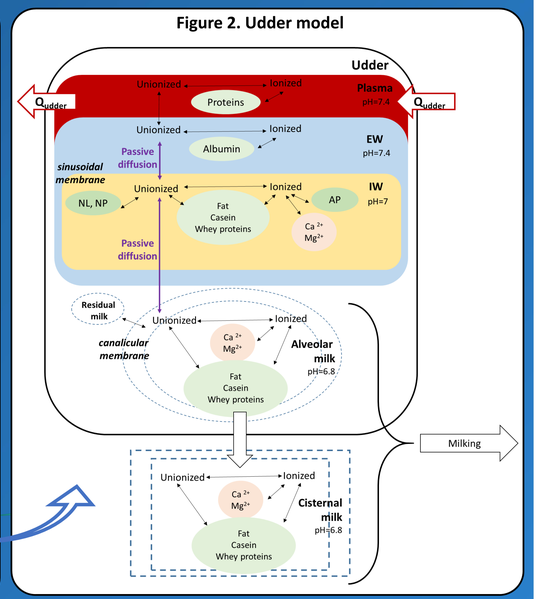


Figure 2. Udder model



RESULTS

Figure 3. Visual Predictive Check (VPC) in milk of cow and goat after a single dose of 10 mg.kg^{-1} OTC

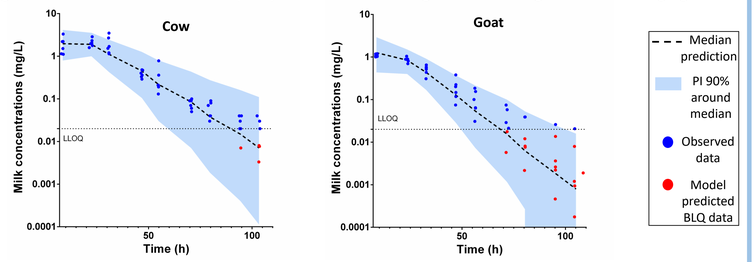


Figure 4. Global sensitivity analysis on predicted cow and goat milk concentrations ($AUC_{0\text{-}96h}$)

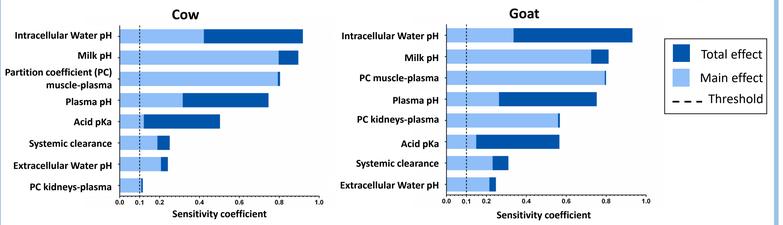


Figure 5. OTC ionization in milk

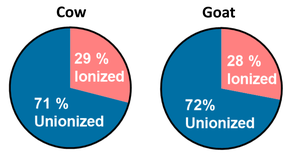
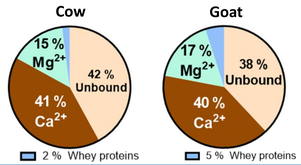
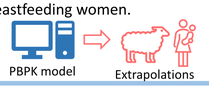


Figure 6. OTC binding to milk components



CONCLUSION

- The developed PBPK model succeeded in characterizing the OTC excretion into the milk of two lactating species.
- Further work is ongoing to assess the predictive ability of the PBPK model with **other antibiotics** having different chemical properties and potential **active transporters**.
- It will then be used to **extrapolate** the excretion of drugs or chemical into the milk of other animal species, such as ewe, and eventually to breastfeeding women.



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