A physiologically based pharmacokinetic (PBPK) modeling of amlodipine: High enterocyte binding, not enterohepatic circulation, is responsible for the long $T_{\text{max}}$

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What is this? A page from a scientific paper discussing a model of amlodipine's pharmacokinetics.

**Backgrounds**

Amlodipine is a second generation calcium channel blocker that has been widely used in the therapy of hypertension and angina pectoris. As a BCS class I drug with high aqueous solubility and high passive permeability, amlodipine has an unusually long $T_{\text{max}}$ of 4–9 hours after oral administration. Raušl et al. explained this long $T_{\text{max}}$ with enterohepatic circulation [1]. This hypothesis has been adopted in a recently published PBPK model [2].

However, the possibility of enterohepatic circulation of amlodipine is low.

- There is no evidence of amlodipine biliary excretion in humans.
- While delayed $T_{\text{max}}$ (~4 h) of amlodipine was observed in rat after aqueous oral solution administration, studies in bile duct-cannulated rats (Ni et al. [3]) and Walker et al. [4] reported that no or less than 1% of the total dose was detected in the bile and that metabolism is the main clearance mechanism of amlodipine.

On the other hand, lysosomal trapping could be a more plausible explanation of the long $T_{\text{max}}$ of amlodipine. It has been proposed that lysosomal trapping could cause delayed absorption after oral administration of dextromethorphan [5] and pulmonary administration of Olopatader [6]. Given that amlodipine has the identified common properties of lysosomotropic agents, such as a $\log P > 2$ ($\log P = 3.0$) and a basic $pK_a$ between 6.5 and 11 (basic $pK_a = 9.1$), it could be sequestered in the lysosomes during the absorption and resulting in delayed $T_{\text{max}}$. In addition, its lysosomal trapping potential has been confirmed by several in vitro cell based assays [7].

Thus, we proposed that the high lysosomal trapping in the enterocytes rather than enterohepatic circulation, is responsible for the long $T_{\text{max}}$ of amlodipine.

**RESULTS AND DISCUSSIONS**

A cellular simulation of the Caco-2 transwell permeability assay assuming the lysosomal pH = 4.0 can be seen in Figure 2A. At a lysosomal pH = 4.0, the simulated lysosome concentration is ~3 orders of magnitude higher than the cytoplasm concentration. As seen in Figure 2B, with the lysosomal pH = 6.5, the concentration in the lysosomal compartment is reduced to similar to that in the cytoplasm.

As shown in Figure 3, the simulation with the adjusted $R_p$ of 2.8 accounting for lysosomal trapping matched with the observed plasma concentration time profile of amlodipine after intravenous administration better than the simulation with the experimental $R_p$ of 1.48.

The reason why we adjusted $R_p$ to scale Kps for taking into account of lysosomal trapping is: $R_p$ is commonly used as a substitute to account for the unknown interaction between drug molecules and acidic components of tissue cells when predicting Kps [8,9]. $R_p$ was changed back to the experimental value of 1.48 once Kps were scaled up since the experimental $R_p$ is good for the calculation of blood clearance.

**CONCLUSIONS**

- The long $T_{\text{max}}$ of amlodipine, considering its physicochemical properties, is more likely to be caused by its high lysosomal trapping in enterocytes rather than enterohepatic circulation.
- Ignoring lysosomal trapping when predicting Kps causes underprediction of volume of distribution for lysosomotropic agents.

**REFERENCES**