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LETTER TO THE EDITOR

Reproducing prolonged time to peak bisoprolol concentration by PBPK modeling with lysosomal trapping in enterocytes

Bisoprolol, a Biopharmaceutics Classification System (BCS) class 1 drug, exhibits a prolonged time to maximum concentration (T_{max}) after an oral solution administration, challenging mechanistic bisoprolol pharmacokinetic simulations. As noted by Dr. Macwan,[1] there are three bisoprolol physiologically-based pharmacokinetic (PBPK) models attempted to simulate the delayed T_{max} in dissimilar manners,[1–3] the first one with a modified gastric emptying time of 0.6 h by us,[2] the second one with a "worst-case" scenario intestinal permeability for BCS class 1 drugs of 1.1×10^{-4} cm/s[3], and the third one by Macwan et al.[1] with a fitted fraction unbound in enterocytes (fu_{ent}) of 5% to account for lysosomal trapping in enterocytes. Dr. Macwan et al.[1] believe strongly that their model with lysosomal trapping is the most probable.

At that point, the first bisoprolol PBPK model[2] was developed a decade ago, little information concerning the impact of lysosomal trapping on oral drug absorption was available. To our knowledge, lysosomal trapping in enterocytes was incorporated into PBPK modeling for the first time in 2017.[4] Hence, we had to consider any alternative mechanisms probably causing prolonged T_{max} when we developed the first bisoprolol PBPK model.[2] Given large variability in gastric emptying time (0.25 h and 0.4 h implemented in Gastroplus and Simcyp, respectively) and a phenomenon of drug-induced gastric emptying prolongation,[5] we decided to modify the Gastroplus default value of stomach transit time to reproduce the delayed T_{max}, without compromising maximum plasma concentration (C_{max}). Indeed, we were aware of a couple of shortcomings by modifying the value. First, it might be difficult to translate bisoprolol pharmacokinetics from healthy subjects to a specific population when the intended population shows an impaired or accelerated gastric emptying. Second, drug-induced gastric emptying prolongation for bisoprolol has neither been determined nor excluded.

Regarding lysosomal trapping on distribution, we have to clarify that we had already considered by fitting in silico blood-to-plasma ratio of ~0.85 to 1.1 to simulate elevated volume of distribution at steady state (V_{ss}) owing to lysosomal trapping in tissues.[2]

Overall, although we are persuaded by Macwan[1] that their model is, thus far, the most mechanistic one by accounting for lysosomal trapping in enterocytes, we believe PBPK models should be viewed as knowledge-driven models, which could evolve when new knowledge/information of either systems physiology or drug-specific mechanisms becomes increasingly available. Based upon current knowledge, we agree, for highly permeable, lipophilic, week base compounds showing an unexpectedly long T_{max}, who are similar structurally to those demonstrated to undergo lysosomal sequestration, lysosomal trapping in enterocytes should be considered in mechanistic absorption modeling.

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CONFLICT OF INTEREST

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Dan-Na Wu[1]
Guo Yu[2,3]
Guo-Fu Li[2,3]

[1]*Department of Pharmacy, Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University), Hainan, China*
[2]*Clinical Medical College, Yangzhou University, Yangzhou, China*

[3]*Subei People's Hospital, Yangzhou University, Yangzhou, China*

Correspondence
Guo-Fu Li, Subei People's Hospital, Yangzhou 225009, China.
Email: guofu.g.li@gmail.com

ORCID

Guo Yu https://orcid.org/0000-0001-6685-2167
Guo-Fu Li https://orcid.org/0000-0002-4628-9941

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