Model-based precision dosing and remedial dosing recommendations for delayed or missed doses of isoniazid in Chinese patients with tuberculosis

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Abstract

Aim: Isoniazid (INH) has been used as a first-line drug to treat tuberculosis (TB) for more than 50 years. However, large inter-individual variability was found in its pharmacokinetics, and how to handle a delayed or missed dose of INH remains unclear. This study aimed to develop a population pharmacokinetics (PPK) model of INH in Chinese patients with TB to provide model-informed precision dosing and explore appropriate remedial dosing regimens for non-adherent patients. Methods: A nonlinear mixed-effects modeling was used to analyze the PPK of INH. Using Monte Carlo simulations to determine optimal dosage regimens and design remedial dosing regimens. A two-compartment model well described the PPK of INH. Results: N-acetyltransferase 2 (NAT2) genotype and body weight were identified as significant factors on INH PK. Monte Carlo simulations determined optimal dosage regimens for patients with different NAT2 genotype and body weight. For remedial dosing regimens, the missed dose should be taken as soon as possible when the delay does not exceed 12 h, and an additional dose is not needed. On delaying a INH dose exceed 12 h, only need to take the next single dose normally. Conclusion: PPK modeling and simulation provide valid evidence on the precision dosing and remedial dosing regimen of INH.

[09/04/2023]

Dear Editors,

I wish to submit an original article for publication in *British Journal of Clinical Pharmacology* titled "Model-based precision dosing and remedial dosing recommendations for delayed or missed doses of isoniazid in Chinese patients with tuberculosis".

This study aimed to develop a population pharmacokinetics (PPK) model of isoniazid (INH) in Chinese patients with TB to provide model-based precision dosing and explore appropriate remedial dosing regimens for non-adherent patients. Although INH has been used as a first-line drug to treat TB for decades years, large inter-individual variability was found in its pharmacokinetics, leading to the clinical treatment failure and drug resistance, and there is currently no uniform solution to this problem. In addition, owing to current TB therapy duration requiring up to 6 months, delayed or missed INH doses are common in clinical practice. Nonadherence has also been reported as one of the most important factors associated with the emergence of acquired drug resistance. However, there are no studies on the remedies dosing recommendations of INH for missed or delayed doing, the INH instructions provided by the CFDA and FDA also do not mention remedies for missed or delayed administration. Therefore, this study analyzed a total of 701 observations from 503 patients to establish a population pharmacokinetic model of INH; N-acetyltransferase 2 (NAT2) genotype

and body weight were identified as significant factors on INH CL/F and Vc/F. Monte Carlo simulations were used to determine optimal dosage regimens and design remedial dosing regimens. Optimal dosage regimens were recomended for patients with different NAT2 genotype and body weight. For remedial dosing regimens, the missed dose should be taken as soon as possible when the delay does not exceed 12 h, and an additional dose is not needed at the next scheduled time. On delaying a INH dose exceed 12 h, only need to take the next single dose normally. PPK modeling and simulation provide valid evidence on the precision dosing and remedial dosing regimen of INH.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for your consideration. We look forward to receiving comments from the reviewers. If you have any queries, please don't hesitate to contact me.

Sincerely,

Kan Xu

Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine.

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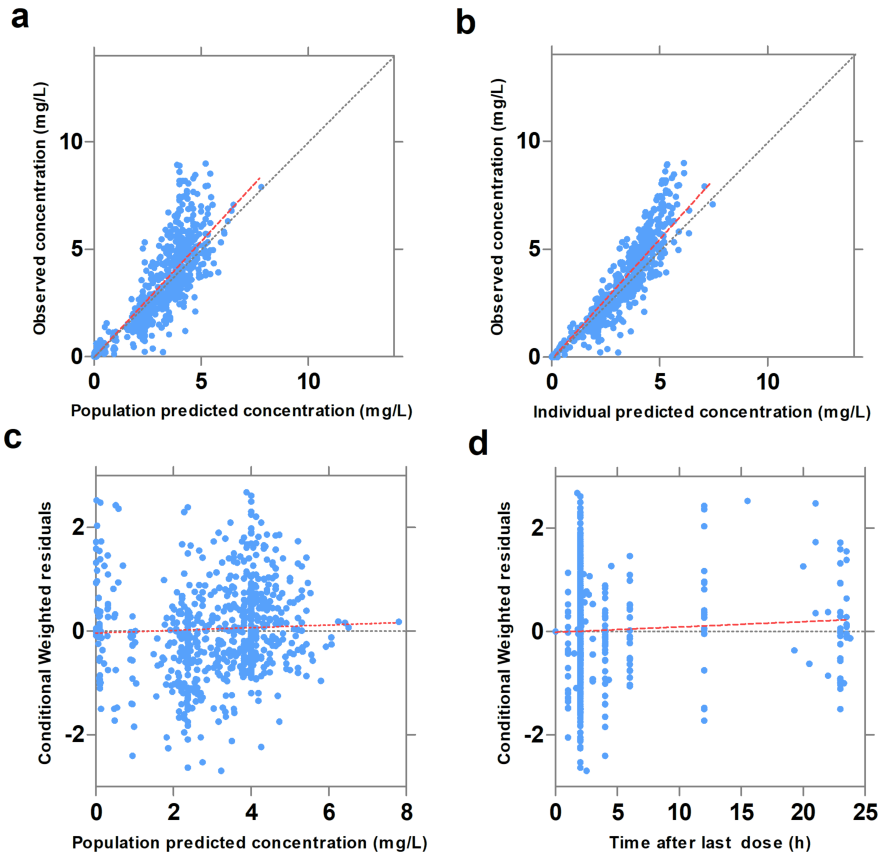

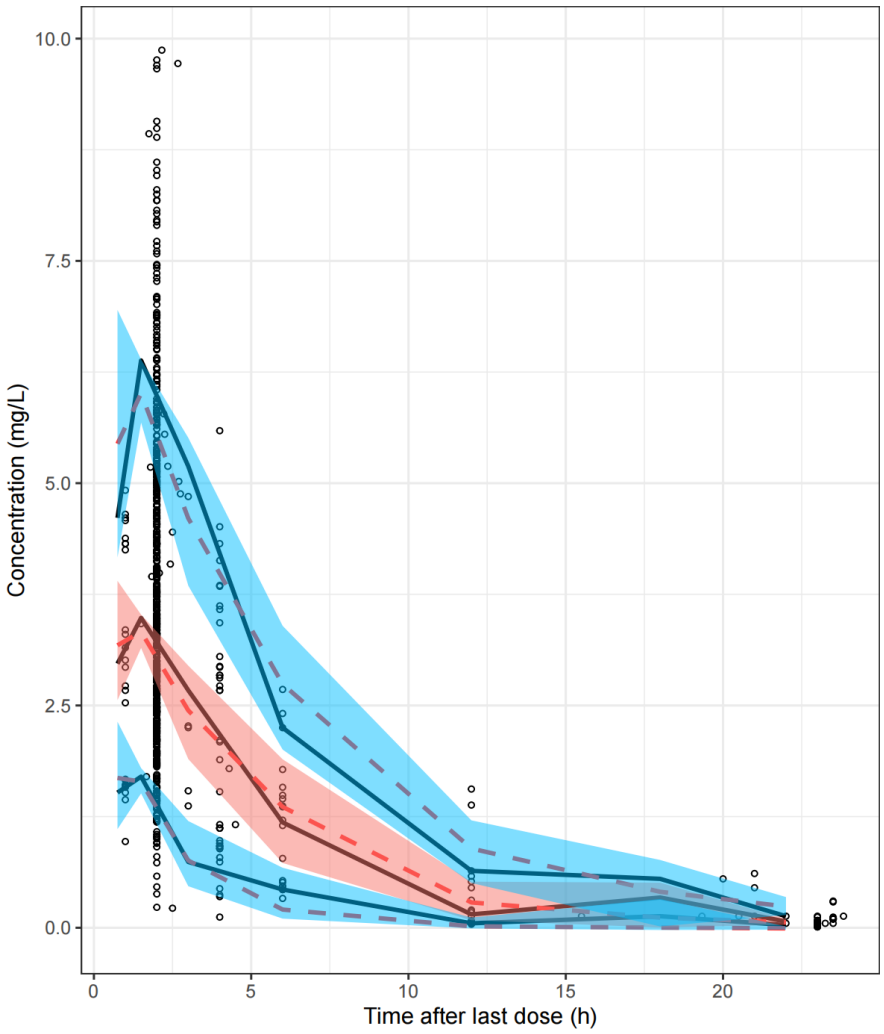

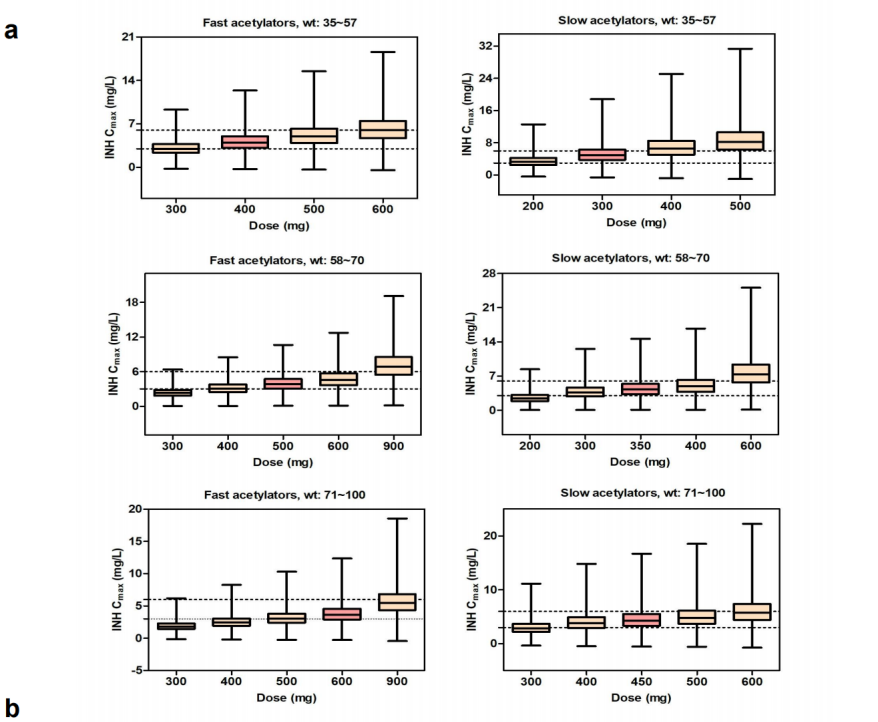

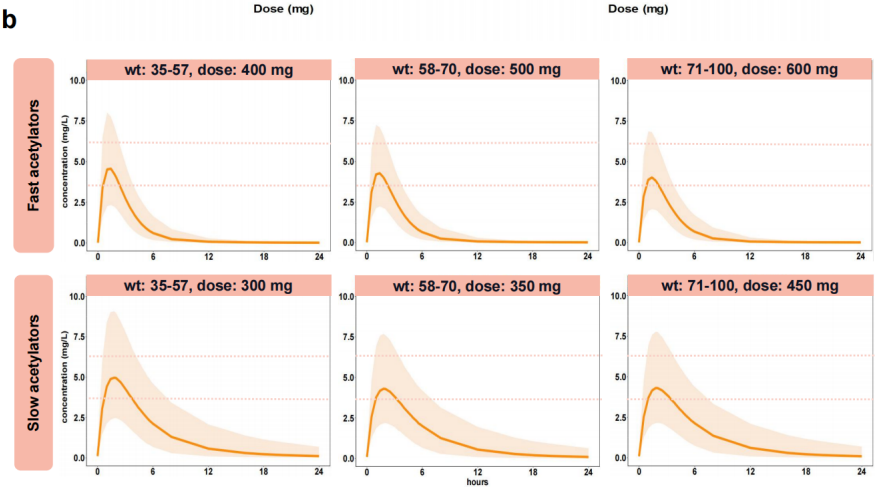

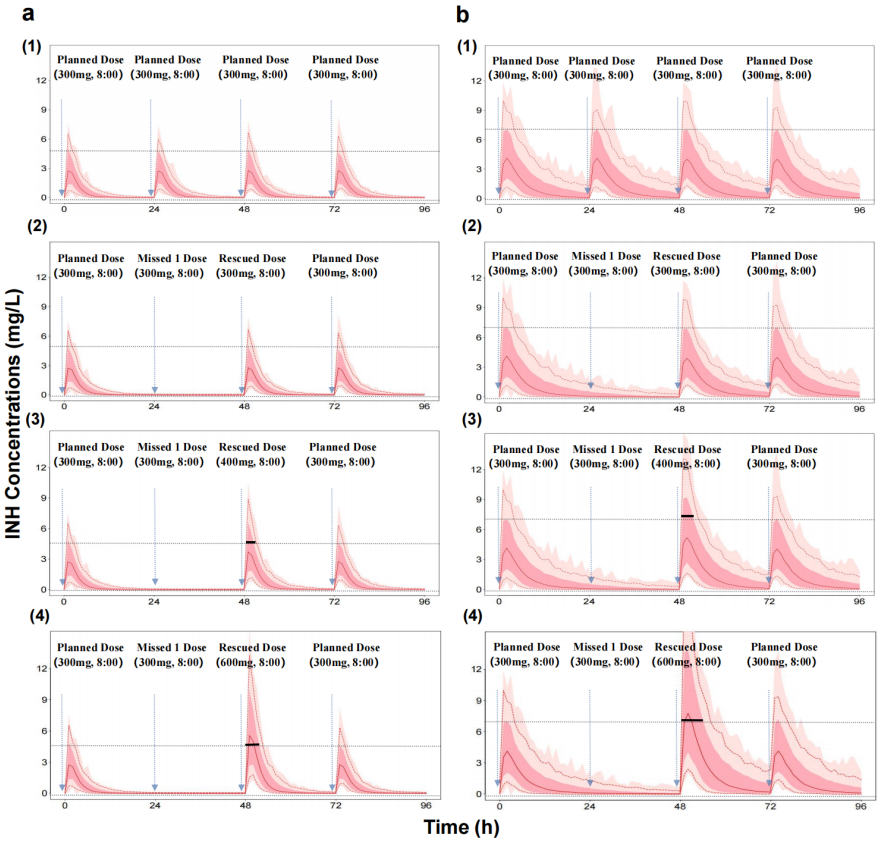

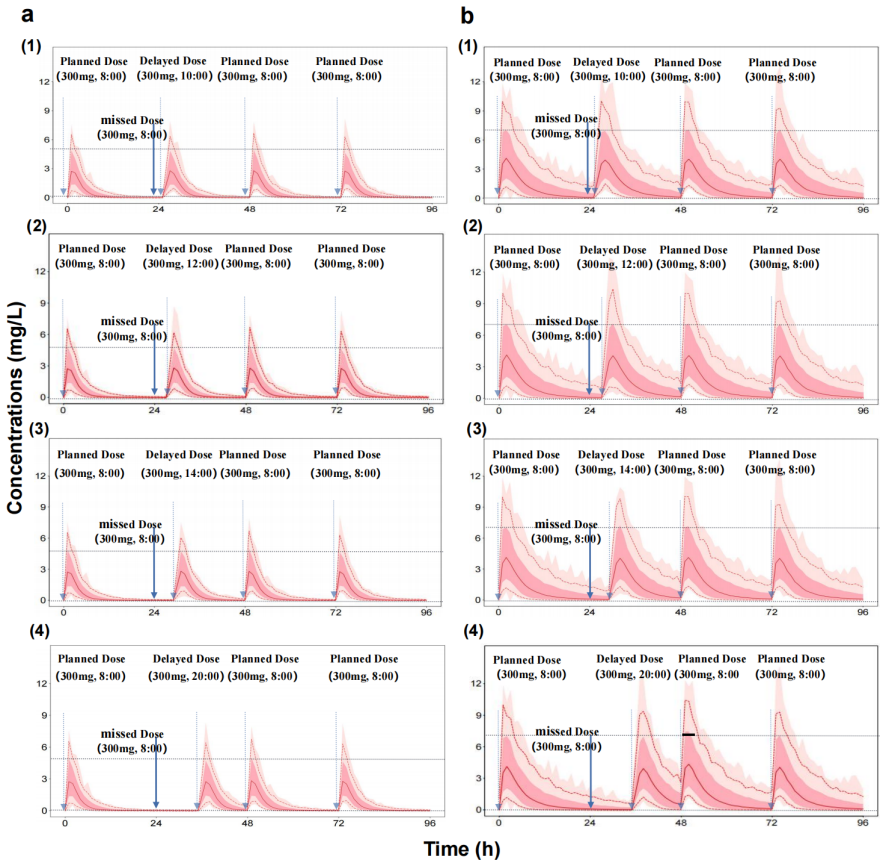

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