Comparison of DDI-predictor to SimCYP for prediction of metabolic drug-drug interactions.

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Background and Objectives

- Quantitative prediction of the magnitude of a drug-drug interaction (DDI) is useful to identify the clinical interaction studies to be performed during drug development, and the dosing adaptation to be made.
- Two approaches for quantitative prediction of DDIs mediated by cytochromes are the Mechanistic Dynamic interaction Model (MDM) based on in vitro data plugged into a physiologically-based pharmacokinetic (PBPK) model [1], and the Mechanistic Static interaction Model based on in vivo data (IMSM) [2]. The aim of this study was to evaluate the performance of IMSM and to compare IMSM with the MDM approach.

Methods

- The magnitude of a PK interaction is expressed as the ratio of the victim drug AUC given in combination with an interacting drug (inducer or inhibitor) to the victim drug AUC given alone: AUC*/AUC
- The predictive performances of IMSM (implemented in https://www.ddi-predictor.org/) were evaluated on a panel of 628 clinical sudies of DDIs.
- The predictive performances of IMSM and MDM (implemented in Simcyp software) were compared on a set of 104 clinical sudies of DDIs.
- The metrics is the fold prediction error, i.e. the predicted AUC ratio / observed AUC ratio.

How works DD-predictor (simplest case)

$$\frac{AUC^*}{AUC} = \frac{1}{1 - CR.IR} \qquad \frac{AUC^*}{AUC} = \frac{1}{1 + CR.IC}$$

CR: in vivo fraction of substrate CL metabolized by a CYP

IR / IC: in vivo potency of the inhibitor / inducer

Results

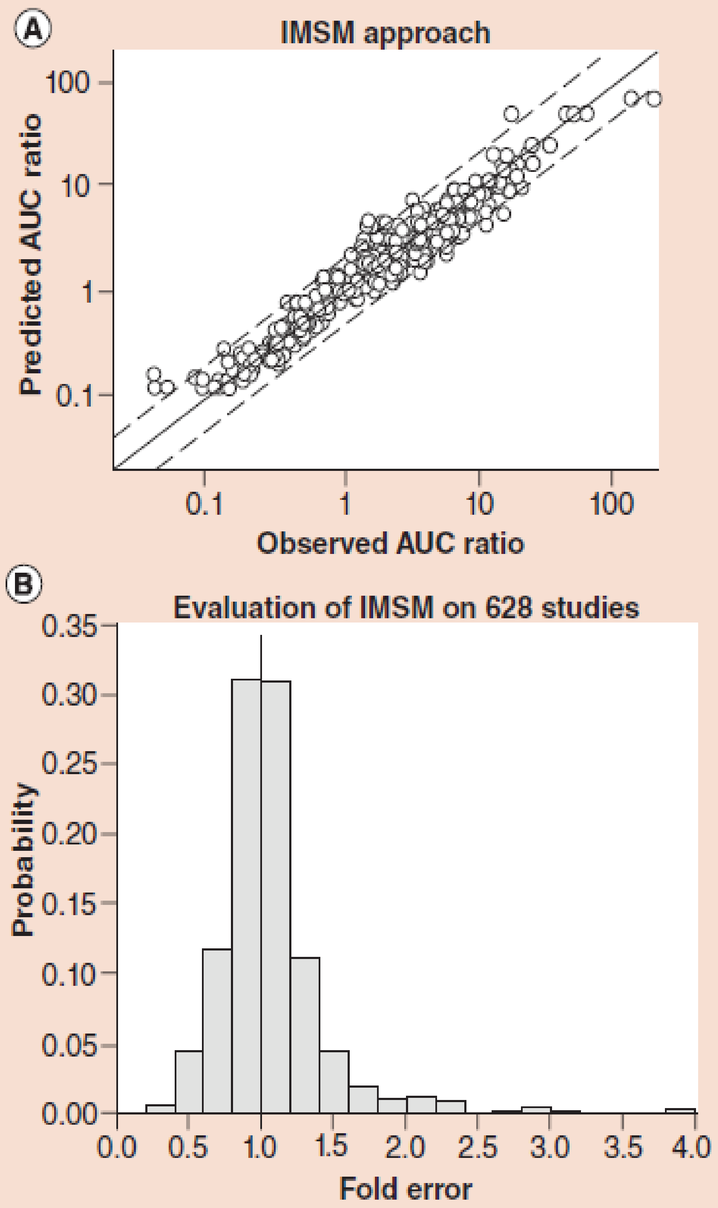

Fig 1. Evaluation of the IMSM approach (DDI-predictor) based on 628 published interaction studies. (A) The line is the y = x line. The dashed lines represent the 50–200% interval. Values above x = 1 represent DDIs by inhibition. Values below x = 1 represent DDIs by induction. (B) Histogram of the fold errors (= pred/obs AUC ratio). The vertical line at x = 1 represents the ideal value (no prediction bias).

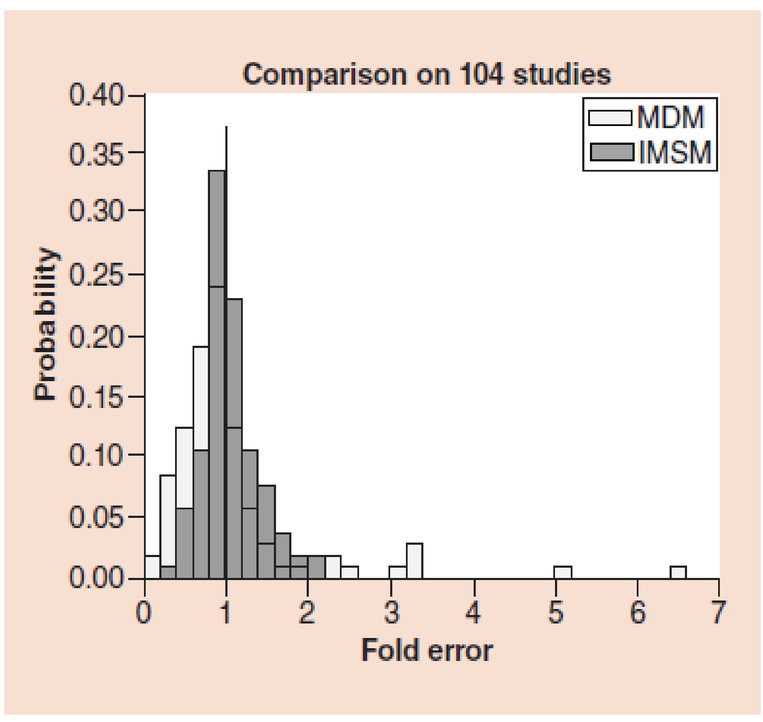

Fig 2. Histogram of the fold errors (= pred/ obs AUC ratio) for the comparison of Simcyp (MDM) and DDI-predictor (IMSM) on 104 studies. The vertical line at x = 1 represents the ideal value (no prediction bias).

See all results in

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	Number and percentage of predictions within twofold of observed AUC ratio	
All DDIs (n = 104)		
IMSM	90 (87%)	DD-predictor
MDM	82 (79%)*	Simcyp

Conclusion and perspectives

- The IMSM approach is a quick, inexpensive and simple alternative for the prediction of metabolic DDIs mediated by CYPs. It may be of interest for both drug development and management of DDIs in clinical practice. The IMSM approach works correctly if cytochromes are the main interaction mechanism, and the kinetics of the substrate is (at least approximately) linear. The MDM approach remains the best approach for the prediction of DDIs involving transporters, provided that the PBPK model is correctly specified.

See also https://www.ddpred.com/ to apply the IMSM approach to drug development

References

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