Evaluation of DDI-predictor for prediction of the impact of CYP polymorphism on drug exposure.

Lyon 1

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Background and Objectives

• Quantitative prediction of the impact of cytochrome (CYP) polymorphism on drug exposure is useful to identify the pharmacogenetic studies to be performed during clinical drug development.

• Static equations of a physiologically-based pharmacokinetic model based on in vivo data ("IMSM approach") have been developped to predict impact of CYP2D6, CYP2C9 and CYP2C19 polymorphism [1-3]. The aim of this study was to evaluate the predictive performances of this approach on a large panel of drugs.

Methods

• The impact of a CYP polymorphism is expressed as the ratio of the drug AUC in subjects with a genetic variant to the drug AUC in homozygous wild-type subjects: Rauc = AUC*/AUC

• The predictive performances of IMSM (implemented in https://www.ddi-predictor.org/) were evaluated on a panel of pharmacogenetic clinical studies involving polymorphism of CYP2D6, CYP2C9 and CYP2C19, found by a literature search.

• In the IMSM approach, the variant genotypes are characterized by their Fractional Activity (FA). The *1*1 genotype has FA = 1.

• The model is:

$$\frac{AUC^*}{AUC} = \frac{1}{\sum_{i=1}^{ncyp} CR_i.FA_i + (1 - \sum_{i=1}^{ncyp} CR_i)}$$

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

• The performance metrics is the fold prediction error, i.e. the predicted AUC ratio / observed AUC ratio.

Results

- A panel of 181 studies (65 drugs, 15 classes of genotypes) was available.
- The IMSM approach yielded 84% of predictions within 1.5 fold of the observed value.
- The median prediction error was 0.96 (a value of 1 means no bias), and the interquartile prediction error was 0.32.

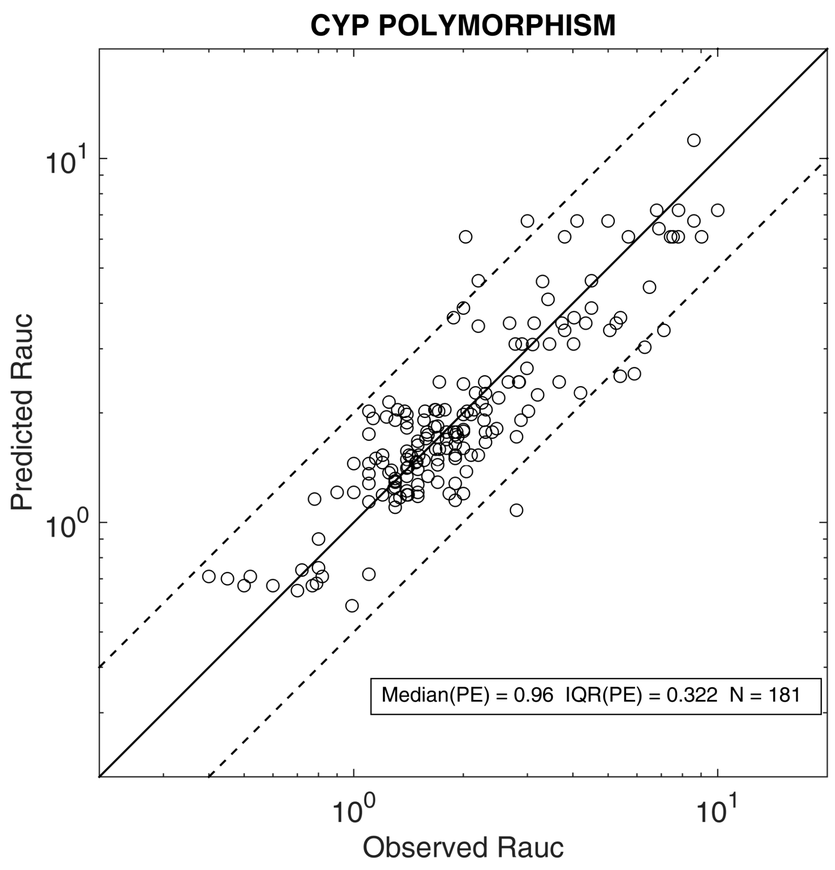

Fig 1. Evaluation of the IMSM approach (DDI-predictor) based on 181 published studies.

The line is the y = x line. The dashed lines represent the 50–200% interval.

Values above x = 1 represent Intermediate and Poor Metabolizers.

Values below x = 1 represent Ultra Metabolizers.

Conclusion and perspectives

• The IMSM approach is a quick, inexpensive and simple approach for the prediction of the impact of CYP polymorphism, that may be used after the first clinical studies in phase 1. The IMSM approach has also been extended to predict the impact of CYP polymorphisms and cirrhosis on drug-drug interactions. As such, it may be useful to identify the subpopulations of patients at risk and to define the prescribing informations for management of CYP polymorphism.

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

References

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