Forecasting drug-drug interactions for new drugs using the *in vivo* mechanistic static model: netupitant as a case study

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❖ Introduction

- ✓ Forecasting clinically relevant drug-drug interactions (DDI) is challenging for new drugs
  - ✓ Clinical data are limited
  - ✓ Extrapolation from *in vitro* data may be tricky

Objectives

- ✓ To illustrate ability of the *in vivo* mechanistic static model (IMSM) approach [1] to provide quantitative predictions of DDI for new drugs
- ✓ Case study with netupitant (NETU): a novel antiemetic, NK1 receptor antagonist

❖ Methods

- ✓ Literature review to identify DDI studies performed in humans with NETU
- ✓ Estimation of IMSM parameters : inhibition ratio (IR) and fraction metabolized by CYP3A4 (contribution ratio CR)
- ✓ Model for CYP inhibition

$$\frac{AUC^*}{AUC} = \frac{1}{1 - CR_{CYP3A4}.IR_{CYP3A4}}$$

- ✓ Model for CYP induction

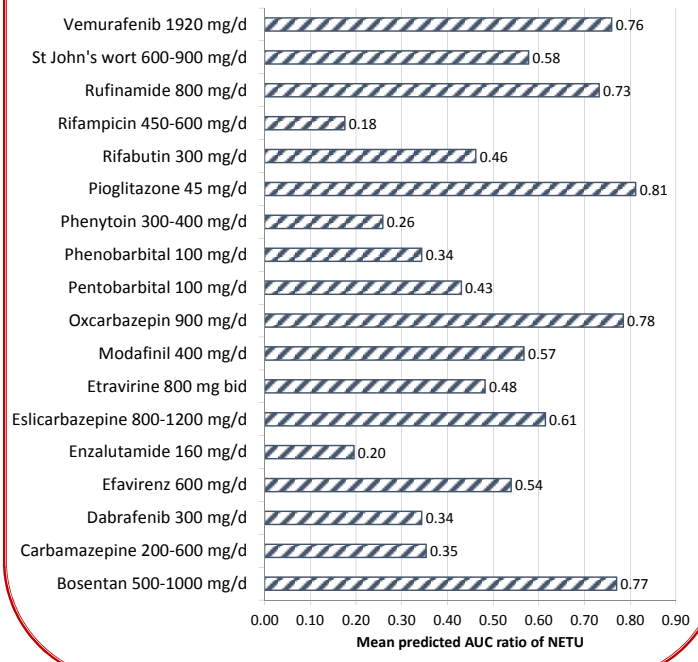
$$\frac{AUC^*}{AUC} = \frac{1}{1 + CR_{CYP3A4}.IC_{CYP3A4}}$$

- ✓ Calculation of AUC ratios for all potential DDI of NETU with known CYP3A4 substrates, inducers, and inhibitors listed in the DDI-Predictor database [2]

❖ Results

- ✓ NETU is a moderately sensitive substrate of CYP3A4: CR_{CYP3A4} = 0.61
- ✓ NETU is a moderate inhibitor of CYP3A4: IR_{CYP3A4} = 0.53
- ✓ DDI were predicted for NETU as a substrate with 18 inducers (Fig.1) and 50 CYP3A4 inhibitors (Fig.2)

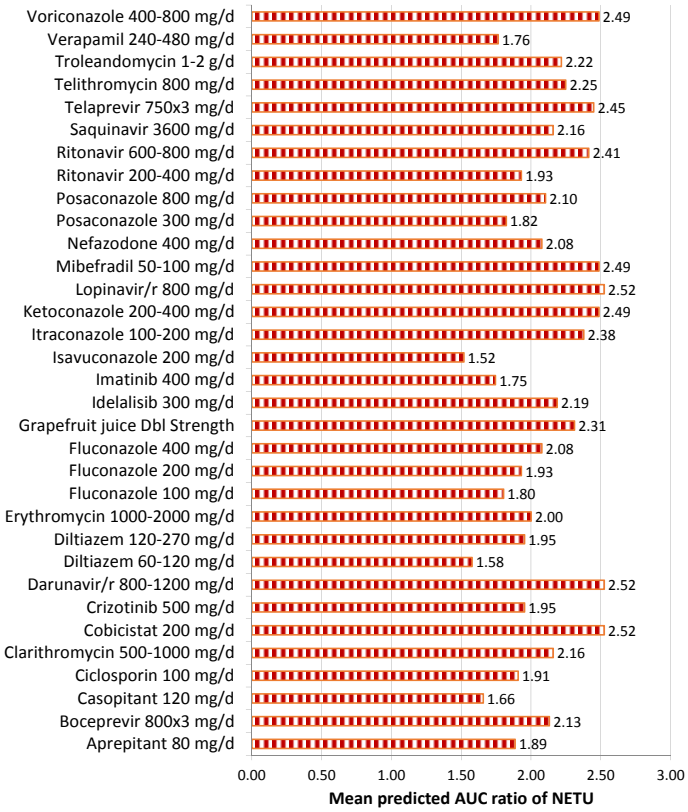
Figure 1: Effect of CYP3A4 inducers on NETU exposure



❖ Results (continued)

- ✓ Effect of CYP3A4 inhibitors on NETU exposure: non-significant (RAUC < 1.25, n = 6), weak (1.25 ≤ RAUC < 2, n = 24) and moderate (RAUC ≥ 2, n = 20)
- ✓ Effect of CYP3A4 inducers on NETU exposure: 8 moderate, 1 strong (rifampicin)

Figure 2: Effect of 33 CYP3A4 inhibitors on NETU exposure



- ✓ 119 DDI predicted with NETU as a CYP3A4 inhibitor:
  - ✓ 32 non-significant (AUC ratio < 1,25)
  - ✓ 77 weak (1.25 ≤ AUC ratio < 2)
  - ✓ 10 moderate (AUC ratio ≥ 2) including buspirone, évérolimus, ibrutinib, naloxegol, simvastatin

❖ Conclusions

- ✓ Netupitant may interact with many drugs
- ✓ Most DDI were predicted to be of limited magnitude
- ✓ A few interactions may require precaution / dose adjustment
- ✓ The IMSM approach can predict DDI *in vivo* for new drugs based on limited clinical data

References

1. Tod et al. Int J Pharmacokinet 2016 https://doi.org/10.4155/ipk.16.2
2. https://www.ddi-predictor.org/

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