A prediction tool for the dose-proportionality of pharmacokinetics to guide decision making on microdosing studies

Sieto Bosgra, Joost Westerhout, Maria L. Vlaming and Wouter H.J. Vaes

TNO, Zeist, the Netherlands
sieto.bosgra@tno.nl

TNO innovation for life

INTRODUCTION

Microdosing studies allow investigation of clinical pharmacokinetics (PK) of drug candidates (first-in-man) earlier in development, at a stage where not all high dose safety concerns have yet been sorted out. Furthermore, they allow inclusion of patients or target groups that cannot be admitted in high dose phase 1 trials. A potential cause for concern when considering microdosing studies is that a drug candidate may display nonlinear PK. Guidance on the assessment of the likelihood of appreciable nonlinear PK based on preclinical data can be helpful in staging the clinical phase and the place of microdosing in it. Here, we investigate whether the concern of nonlinearities is justified by addressing two questions:

1. **How often do significant nonlinearities in PK occur in general?**
2. **Can they be foreseen based on preclinical information?**

OCCURRENCE OF NONLINEARITIES

We performed a systematic scan of abstracts of published ascending dose PK clinical studies in PubMed in the last 5 years, limited to systemically acting small molecules (see **Fig. 1**):

- 145 abstracts found;
- proportionality not conclusive in 44 abstracts;
- **79** studies reported **dose-proportional PK** in the dose range studied;
- **22** reported **nonlinearities**.

In those studies observing nonlinear PK, most occurred at the highest dose tested, and two to four orders of magnitude above microdose range.

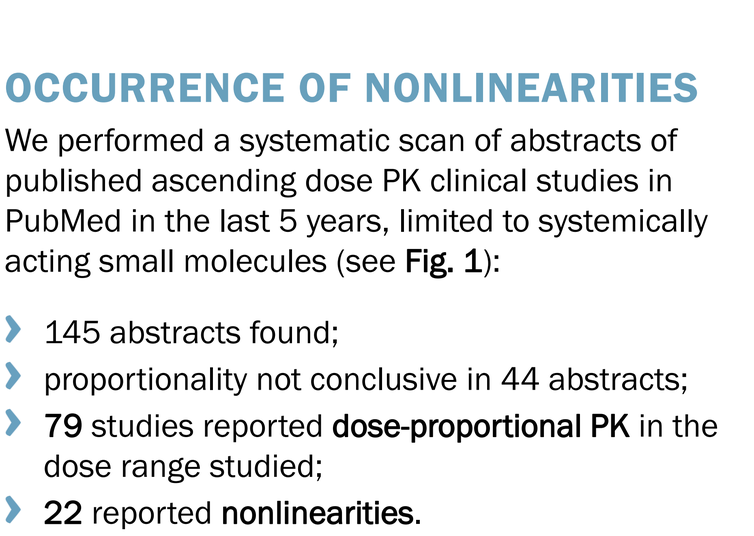

FIG. 1. Results of a literature scan of ascending dose studies (ADS). *Upper: frequency of dose-proportionality and nonlinearities reported. Lower: dose ranges (mg) displaying proportional PK and nonlinearities in intravenous (iv), oral (po) and subcutaneous (sc) ADS. The shaded area indicates the microdose range.*

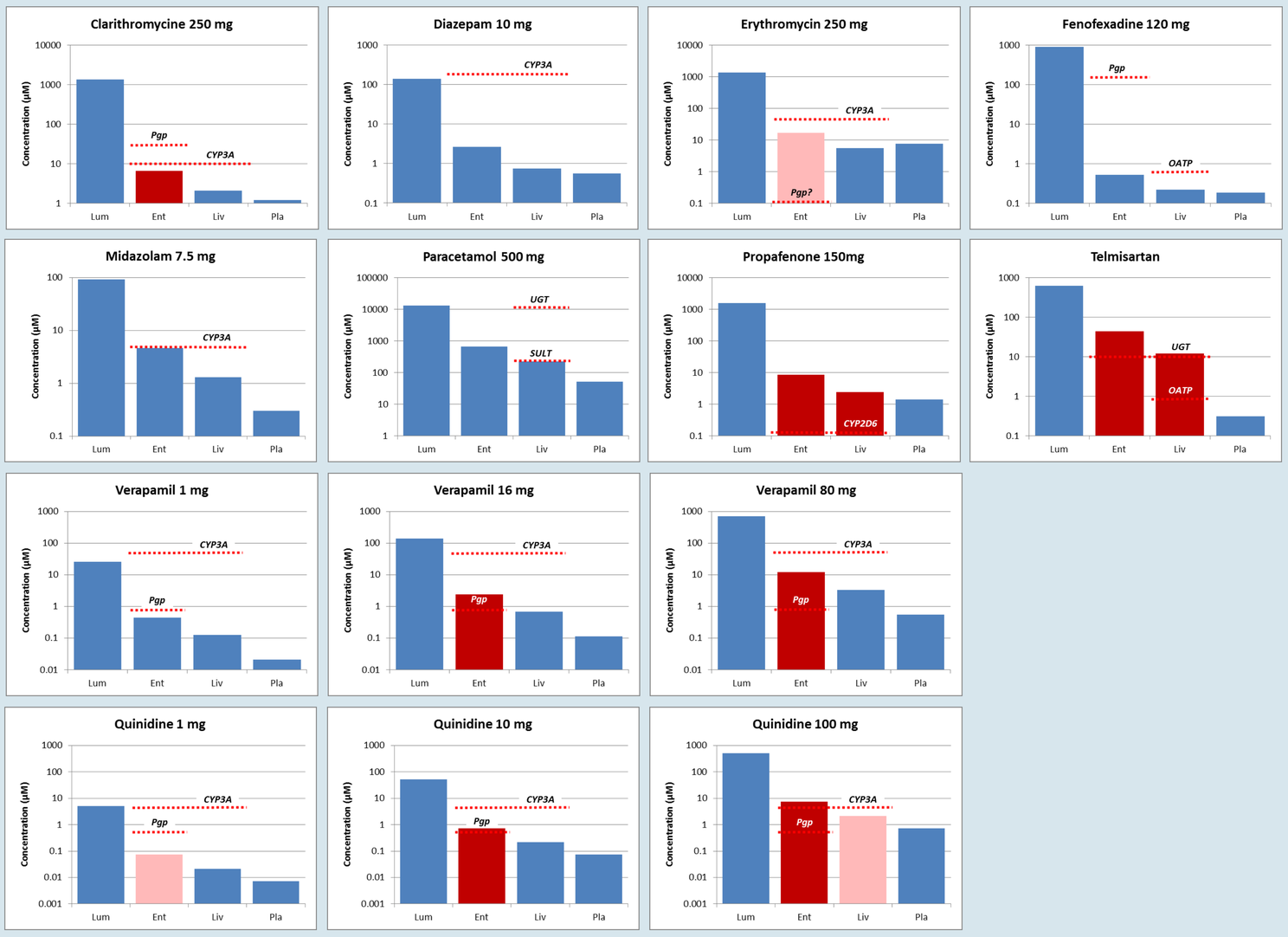

FIG. 3. Predicted maximum concentrations in gut lumen, enterocytes, liver and plasma for 10 compounds for which concerns about nonlinearities had been raised. Dotted lines show the Michaelis constants for processes of concern. Red bars indicate the observed nonlinearities between microdose and therapeutic dose and their proposed locations [1-5].

PREDICTING DOSE-PROPORTIONALITY

Our prediction tool considers possible non-linearities in GI dissolution; intestinal, hepatic and renal in- and efflux transport; intestinal and hepatic metabolism and plasma protein binding. The following principles are used:

- Maximum concentrations (C_{max}) in gut lumen, enterocytes, liver and plasma for the therapeutic dose range are estimated by non-compartmental methods (**Fig. 2**);
- enzymatic processes or transporter activity are of potential concern for C_{max} above K_m;
- GI dissolution is considered of concern for BDDCS class IV compounds;
- extensive plasma protein binding may cause nonlinearities if $C_{max} > 0.2*C_{protein}$.

The tool was applied to ten published cases comparing microdose and therapeutic dose PK [1-5]. The results in **Fig. 3** show that nearly all cases were correctly identified as showing dose-proportional or nonlinear PK.

1. $C_{lum} = D/0.25$
2. $C_{ent} = F_{abs}*k_a*Dose/Q_{gut}$
3. $C_{liv} = fu_b*C_{max} + F_{abs}*k_a*D/Q_{liv}$
4. $C_{pl} = F*Dose/V$

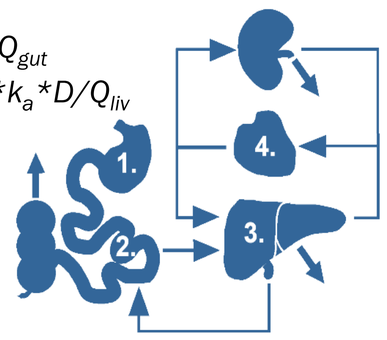

FIG. 2. The prediction tool calculates maximum concentrations for gut lumen, enterocytes, liver and plasma by non-compartmental methods.

CONCLUSIONS

- **Deviations from dose-proportional pharmaco-kinetics may be less common than often assumed, and are observed more frequently in the high than in the low dose range**
- **Based preclinical data, our decision tree correctly identified (deviations from) dose-proportionality between microdose and therapeutic dose for published cases**
- **This tool may help decide whether an early phase 0/1 clinical microdose trial is sensible**

References: 1. Lappin (2006) Clin Pharmacol Ther 80:203; 2. Lappin (2010) Eur J Pharm Sci 40:125; 3. Lappin (2011) Eur J Pharm Sci 43:141; 4. Maeda (2011) Clin Pharmacol Ther 90:263; Ieiri (2011) Pharmacogen Genom 21:495.