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The impact of formulation, delivery and dosing regimen on the risk of drug-drug interactions

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CONFLICT OF INTEREST

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Introduction

Pharmacokinetic(PK)-based drug-drug interaction (DDI) potential is assessed throughout drug development. Quantitative assays and translational methods have helped to reduce late phase failures due to unfavourable PK. It has been suggested that PK modelling can mitigate unwanted PK properties and variability, and in the process bring novel compounds to market. Here we highlight how formulation and dosing effects add uncertainty to metabolic DDI predictions and how PK modelling can be used to better manage DDIs.

Assessing the DDI potential in drug development

A compound's DDI potential is considered throughout drug development, from qualitative screening in early discovery to in-depth quantitative investigations closer to clinical development. This includes characterising a given compound's main route of elimination, enzymatic routes of elimination, transporter involvement, enzyme polymorphism, and activation/inactivation of metabolic enzymes and transporters. Drug metabolism and pharmacokinetic data are integrated with systems data to enable quantitative predictions of anticipated PK and interactions through *in vitro-in vivo* extrapolation (IVIVE), static and dynamic PK modelling. The outcome will inform further investigation and compound selection, where compounds with high DDI potential may be abandoned to eliminate those associated uncertainties and risks [1].

For metabolic DDIs, the predicted magnitude tends to be based on the maximum anticipated effect as the assessments do not account for all clinically relevant dosing regimens,

polypharmacy, or biopharmaceutics effects, or for the variety of clinically relevant routes of administration and formulations.

PK modelling, such as population pharmacokinetics, provides a useful tool for identifying the principal factors that govern drug disposition. Further, mechanistic modelling such as physiologically-based PK (PBPK) modelling and simulation (M&S) allows extrapolations from *in vitro* systems to *in vivo*, between patient populations, and across scenarios such as DDIs and biopharmaceutics effects. It has been argued that the current drug development process is too risk averse and that viable candidate drugs with unfavourable PK characteristics are abandoned, even though these PK properties might be manageable through model-informed precision dosing (MIPD) [2]. MIPD intends to integrate multiple patient characteristics to provide individualised dose optimisation, which is something that is not easily achieved through labelling and dose banding. Here we outline some of the formulation and dose specific factors that may influence the extent of clinical DDIs and how these may be considered through PBPK modelling and simulation in drug development.

Dose optimisation

Dose level optimisation is perhaps the most popular strategy for managing metabolic DDIs (Figure 1A). The approach is usually well-suited for drugs with a wide therapeutic window and where clinical DDIs may cause tolerable levels of toxicity. In clinical practice, polypharmacy results in a high possibility for DDIs. Here clinical trials can inform dose guidance for DDIs caused by specific perpetrator-victim drug combinations. PK modelling, informed by clinical and drug-specific data, allows predictions of DDIs of other drug combinations. This is usually an interpolation exercise, meaning that a PK model is

developed and validated against clinical data from a high-magnitude DDI and then used to predict low to moderate magnitude DDIs. PBPK M&S together with well-designed clinical trials and compound information may provide a powerful tool for investigating DDIs involving multiple drugs, transporter effects and patient comorbidities [3]. Here, further validation is warranted to build confidence in the approach.

Dose staggering

The conventional starting point for a clinical DDI investigation is to study the maximum interaction effect of the relevant perpetrator and victim drugs. This usually includes steady state dosing of perpetrator drug, timed concomitant intake of perpetrator and victim drug to maximise DDI effect, and studying the formulation most likely to exaggerate the DDI effect. Any deviation from this typically requires justification or supplemental studies. PBPK M&S can extend these investigations outside the scope of the clinical data.

Clinical evidence and simulation studies have shown that dose staggering, separating the time between perpetrator and victim drug administration, may provide a useful dosing strategy for minimising the effect of reversible inhibition, whereas it will be ineffective for time-dependent inhibition or induction (Figure 1B) [4]. The effect of dose staggering is likely to be highest for DDIs where the substrate exhibits substantial metabolic first-pass extraction in the liver and gut. This makes DDIs that affect Cytochrome P450 (CYP) 3A particularly good candidates for exploring staggered dosing regimens. For the interaction between ketoconazole (reversible inhibitor) and budesonide (CYP3A4 substrate), 12 h dose staggering led to a close to two-fold reduction in magnitude of the DDI. As the extent of reversible inhibition is driven by the local tissue concentration of the inhibitor, it is expected that the

effect of dose staggering on hepatic enzyme inhibition will be lower during steady state dosing of the perpetrator drug. Due to the short residence time of drug in the gut wall following oral administration, it is likely that the effect of dose staggering on intestinal first-pass metabolism may remain high during steady state dosing of the inhibitor. The absorption profile and elimination rate of the perpetrator drug are also of significance as these will determine the concentration-dependent fluctuation in inhibition over time.

The interaction between biopharmaceutics effects, first-pass effects and DDIs

As detailed above, the relative timing of perpetrator and victim dose can significantly affect the level of reversible inhibition. Similarly there may be a formulation-dependent effect on the level of a DDI following oral drug administration.

The release profile of an orally administered drug from its formulation may determine its first-pass extraction in the intestine, where up to a three-fold increase in drug exposure has been observed for the controlled versus immediate-release oral formulations of the CYP3A4 substrate, simvastatin. This is because some intestinal drug metabolising enzymes, such as CYP3A4, display regional abundance profiles where they are expressed to a higher extent in the proximal small intestine with reduced levels near the terminal ileum, and negligible levels in the colon. Active transporters expressed in the gut, such as the efflux transporter P-glycoprotein (P-gp), also display regional variation. Where P-gp is more abundant towards the distal gut. By delaying the release or dissolution of drug in the gut lumen it is therefore possible to bypass the regions that are highly abundant in CYP3A4. For P-gp substrates this can lead to reduced absorption [5]. If the oral release profile of a perpetrator drug is significantly different from that of a victim drug this can result in separate and possibly

overlapping absorption windows. During this area of overlap is when a DDI liability would exist (Figure 1C) [4].

Impact of route of delivery

The extent of a DDI can depend on the route of delivery. Altering one of the drugs in an oral-oral DDI to intravenous dosing may result in a reduction of the magnitude of DDI. Although systemic clearance may be altered to a similar extent the first-pass effects can be significantly altered, this is particularly true for drugs exhibiting high first-pass metabolism in the gut wall (Figure 1D).

Drug-disease interactions and their potential impact on metabolic DDIs in the gut

Clinical DDI studies are often carried out in healthy volunteers. This may not necessarily be representative of the relevant patient populations. Disease can indirectly or directly impact oral metabolic DDIs through modifying drug disposition, formulation effects, or gastrointestinal and overall physiology.

Liver cirrhosis is a notable example of a disease state modifying metabolic DDIs, where enzyme levels are downregulated therefore reducing the extent of metabolic DDIs. In untreated coeliac disease and gastrointestinal mucositis, the turnover of gastrointestinal epithelial cells is modulated which may result in reduced enzyme abundances and the turnover of intestinal CYP enzymes. This may alter both the extent of inhibition of gut wall metabolism but also the recovery rate in enzyme activity following induction or time-dependent inhibition. Enzymatic genetic polymorphisms can account for considerable

variability in DDI extent. As enzyme activity is reduced or overexpressed, the magnitude of a DDI can be attenuated or exaggerated. The effect will be systemic and therefore affect both first-pass effects and dispositional drug clearance.

Achlorhydria, more prevalent in elderly and Japanese populations, results in an increase in gastric pH due to reduced acid production. This can alter the *in vivo* dissolution profile of drugs exhibiting pH dependent solubility. The modulated dissolution profile may subsequently alter the extent of a metabolic DDI in the gut wall. Similarly, proton-pump inhibitors may alter the dissolution profile of pH-sensitive formulations leading to altered absorption. The anticipated effect of this is unclear.

Concluding remarks

Here we have highlighted some factors related to formulation, dosing schedule and patient characteristics that may lead to altered magnitudes of metabolic DDIs. The multifactorial nature of clinical DDIs is not easily manageable through label dosing recommendations alone. PK M&S may be a tool for quantitative assessments of DDI effects in the absence of clinical data. This approach requires considerable understanding about the drug, its formulation and human physiology. More progress is necessary for there to be sufficient confidence in PK M&S to predict more complex forms of DDIs, such as those involving multiple perpetrators or transporter interactions. It is anticipated that the application of PK M&S will expand beyond the interpolation of metabolic DDIs as confidence is built in the approach and novel systems and validation data become available. Future applications may include the use of modelling to manage complex DDIs in clinical care through a MIPD paradigm (such as companion tools for novel drugs and dashboard implementations in

healthcare to guide dose selection [2]), therefore enabling greater flexibility in compound selection in pharmaceutical development.

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Figure Legend

Figure 1. Dose and formulation effects on metabolic drug-drug interactions (DDIs). A: dose optimisation, B: dose staggering, C: per oral (PO) formulation effects, D: route of delivery. CR: controlled-release formulation; DDI: drug-drug interaction; F_G : fraction of dose escaping metabolism in the gut wall; F_G' : F_G following metabolic DDI; F_{oral} : oral bioavailability; F_{oral}' : F_{oral} following metabolic DDI; IR: immediate-release formulation; IV: intravenous dose administration. A reduction in F_{oral}'/F_{oral} refers to the reduced impact of a given DDI on the overall oral bioavailability. A reduction in F_G'/F_G refers to a reduced impact of a given DDI on gut wall metabolism.

Dose and formulation effects on metabolic drug-drug interactions

A | dose optimisation

B | dose staggering

C | PO formulation effects

IR inhibitor & IR substrate

CR inhibitor & IR substrate

D | route of delivery

CR: controlled-release formulation; DDI: drug-drug interaction; F_G : fraction of dose escaping metabolism in the gut wall; F_G' : F_G following metabolic DDI; F_{oral} : oral bioavailability; F_{oral}' : F_{oral} following metabolic DDI; IR: immediate-release formulation; IV: intravenous dose administration; PO: per oral dose administration.