Editors' view

Drug–drug interactions: is there an optimal way to study them?

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Newly approved drugs expand our therapeutic armamentarium, but augment the potential for drug–drug interactions. These can be broadly categorized into pharmaceutical (physicochemical, usually occurring *ex vivo*), pharmacokinetic (PK) or pharmacodynamic (PD). Importantly a drug–drug interaction that primarily causes a change in PK will consequently cause a secondary alteration in its pharmacodynamics. The literature has a plethora of human drug–drug interaction studies with widely differing designs, addressing the existence and possible clinical importance of specific potential drug–drug interactions.

Study designs used to determine drug–drug interactions

Most drug–drug interaction studies in humans compare drug substrate (D) concentrations with and without the interacting drug (I), thus focusing on the pharmacokinetic type of interaction. There are many study designs used for this purpose, which include: (i) a parallel group design (D in one group of subjects and D + I in another), (ii) a randomized crossover with a washout period (e.g. D followed by D + I, or D + I followed by D) and (iii) a one-sequence crossover (e.g. D always followed by D + I or the reverse). Several drug dosing regimen combinations for a drug substrate and interacting drug can be used: single dose/single dose, single dose/multiple dose, multiple dose/single dose and multiple dose/multiple dose. The selection of which one of these to use, or an alternative study design, depends on factors which relate specifically to the drug substrate and the interacting drug. These should include (i) acute or chronic use of D and/or I, (ii) safety aspects, including whether a drug is likely to have a narrow therapeutic concentration range, (iii) the pharmacokinetic and pharmacodynamic properties of both the drug substrate and the interacting drug and (iv) assessment of drug metabolizing

enzyme inhibition (which in the case of reversible inhibitors typically equilibrates rapidly) as well as induction (which typically occurs over several days). The inhibiting/inducing drugs and the drug substrates should be dosed so that the exposures to both drugs are appropriate to their clinical use, including the highest doses likely to be used clinically [1]. In this issue of the *Journal* we publish several papers describing drug–drug interaction studies, and a cadre of papers that highlight the value of careful clinical observation and investigation in a single clinical case, which draws attention to potential, but previously undefined or poorly defined, drug–drug interactions.

Drug–drug interaction studies, designs, and outcomes

Derks *et al.* [2] studied the potential interaction between the cholesteryl ester transfer protein inhibitor dalcetrapib (900 mg) and the cholesterol absorption inhibitor ezetimibe (10 mg) in a randomized, open-label, three-period, three-treatment crossover study in 27 healthy men who took dalcetrapib, dalcetrapib plus ezetimibe or ezetimibe alone, each for 7 days with a 7–14 day washout period between treatments. The pharmacokinetic profiles of each drug were determined on day 7 of each treatment. Based on the least mean squares ratios for AUC and $C_{\max}$ ezetimibe had no significant effect on dalcetrapib pharmacokinetics, while dalcetrapib slightly reduced the AUC and $C_{\max}$ of ezetimibe. The plasma lipid profile effects were similar for all treatments, except that dalcetrapib plus ezetimibe produced a greater reduction in LDL-C. While this study did not reveal a clinically significant pharmacokinetic interaction between the agents, it was a relatively short-term study and was not performed in patients taking these agents, where the findings could be different.

A number of reports to agencies in Canada and Europe of increased warfarin anticoagulant effects in patients

concomitantly taking oseltamivir prompted Davies *et al.* [3] to undertake a randomized, non-placebo controlled, two-way crossover study of 22 patients with chronic cardiac or vascular conditions who were taking stable doses of warfarin (INR 2.0–3.5 for 2 weeks). They were randomized to concomitant oseltamivir 75 mg twice daily for 4.5 days or warfarin alone, with a 4–8 day washout between treatments. The pharmacokinetics of R (+) and S (–) warfarin and oseltamivir were studied. Anticoagulant effects were studied by calculating the area under the effect concentration curve (AUEC(0,96 h)), the observed maximum increase in INR from baseline, the decrease from baseline in Factor VIIa, and the change in vitamin K₁ concentrations. Oseltamivir caused minor or no significant changes in R (+) or S (–) warfarin pharmacokinetics and no changes in pharmacodynamics. The duration of oseltamivir treatment in the study, while appropriate for influenza treatment, may not be long enough for patients with severe H1N1 infection. The authors also point out that the influenza virus infection can produce cytokines (e.g. interferons) which could have altered warfarin CYP450 mediated metabolism in the reported cases.

Egerer *et al.* [4] undertook a randomized, two-cohort, placebo-controlled study and investigated the effect of the NK₁ antagonist aprepitant (an antiemetic) on the pharmacokinetics of high-dose melphalan in 30 patients with multiple myeloma. Aprepitant is a moderate inhibitor of CYP450 and may inhibit drug transporter proteins. It was given orally (125 mg) 1 h before intravenous melphalan (100 mg m⁻²). Melphalan concentrations were measured by LC-MS-MS. Melphalan C_{max}, AUC and plasma clearance were the same with aprepitant and placebo. Thus, 125 mg of aprepitant given orally 1 h before the melphalan infusion did not alter the disposition of melphalan.

The contribution of clinical cases as a signal for potential drug–drug interactions

Monte *et al.* [5] describe a 19-year-old man who took an overdose of an antitussive agent containing dextromethorphan (estimated dose ingested 1440 mg) and the H₁-receptor antagonist chlorphenamine (estimated dose ingested 192 mg). He developed the serotonin syndrome (as diagnosed on clinical Hunter criteria) [6] and made a good recovery. A literature review revealed three cases of overdoses in which solely dextromethorphan and chlorphenamine (including that reported in this paper) had been ingested and in which serotonin syndrome developed. Chlorphenamine has been reported to be a serotonin re-uptake inhibitor (at least as potent as dextromethorphan) [7] and a weak inhibitor of the CYP2D6 (K_i approximately 11 µM) [8] the major metabolizing enzyme for dextromethorphan.

The authors sensibly suggest that in patients who take a combined overdose of dextromethorphan and chlorphenamine, the development of serotonin syndrome should be considered a potential complication.

Heine *et al.* [9] describe a patient with non-small cell lung cancer who, while taking erlotinib, developed gastrointestinal symptoms, culminating in haemorrhage from a gastric ulcer. Initially the gastrointestinal symptoms were treated with antacids and then with the proton pump inhibitor pantoprazole intravenously for 2 days and then orally for 5 days. Erlotinib plasma C_{min} (trough) concentrations were reduced during high dose intravenous pantoprazole therapy compared with baseline, but rose into the putative therapeutic range when pantoprazole was used orally in a lower dose. The proposed mechanism for this observation is reduced absorption of erlotinib (pK_a 5.4) when stomach pH is increased. Clearly, further studies are needed to confirm the potential interaction between pantoprazole and erlotinib and to define its dose-dependency.

The role of *in vitro* studies in understanding drug–drug interactions

There is a controversy in an evolving literature concerning the putative effect of proton pump inhibitors (e.g. omeprazole) in impairing the metabolic activation of clopidogrel and compromising its antiplatelet effects [10, 11]. A recent paper in our sister Journal by Zahno *et al.* [12] described the effects of different CYP450 inhibitors on the two-step bioactivation of clopidogrel to its active metabolite R-130964 in human liver microsomes and the antiplatelet effects of clopidogrel. The conversion of clopidogrel to its active metabolite (R-130964) is a two-step CYP450-dependent process. At clopidogrel concentrations over 10 µM, CYP3A4 is mainly responsible for clopidogrel metabolic activation, whereas CYP2C19 contributes mainly at clopidogrel concentrations of 10 µM and below. Clopidogrel itself inhibited CYP2C19 at concentrations greater than 10 µM. The CYP2C19 inhibitor lansoprazole inhibited clopidogrel biotransformation at clopidogrel concentrations of 10 µM and below. It is difficult to interpret these data from a clinical perspective, because the C_{max} of clopidogrel after 75 to 150 mg oral doses is only 0.1–0.15 µM (3–5 ng ml⁻¹) [13] posing the question of what the corresponding range of clopidogrel concentrations in hepatocyte cytoplasm is in the environment of the CYP enzymes. It appears that only a prospective randomized placebo controlled trial will settle this debate.

The panoply of study designs outlined above may be used to generate definitive data on *in vivo* drug–drug interactions, but, not surprisingly, there is no one single optimal study design. The suggested study designs using healthy volunteers may not be optimal for investigational or approved drugs, particularly when small numbers of

subjects are studied where the drug–drug interaction only occurs in a few susceptible individuals [14]. Moreover, drug–drug interaction studies in appropriate patient populations have higher relevance and accuracy, providing they are feasible and can be conducted safely. Well documented case reports play a definite role in informing and guiding well-controlled further studies. *In vitro* studies, particularly for CYP450-mediated interactions, can be helpful in estimating the likely magnitude of any interaction and understanding its mechanism. The incidence of drug–drug interactions in clinical therapeutics will continue to increase and challenge prescribers; as well as drawing the interest of clinical pharmacologists.

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