Editors' view

Prediction and Reverse Prediction in Therapeutics and Toxicology

J. M. Ritter, Editor-in-Chief British Journal of Clinical Pharmacology

Department of Clinical Pharmacology, School of Medicine at Guy's, King's College & St Thomas' Hospitals, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH UK

Clinical pharmacologists, in common with other basic and clinical scientists, are in the business of generating and testing predictions, often using drugs as tools to investigate physiological and pathological mechanisms (see 1–6 for some recent examples). The models they have developed in the course of such investigations have, furthermore, proved crucial in translational medicine [7]. Without formal pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) modelling, where would we be when it comes to selecting a biologically appropriate dosage regimen (as opposed to one based on commercially motivated wishful thinking) for definitive phase III trials? Here we address two different problems of practical clinical importance: predicting trouble from drug interactions before they occur (so as to avoid or minimise harm in patients) and attempting to identify a toxicological cause of death in forensic medicine.

Predicting drug interactions

Many pharmacodynamic (PD) interactions are highly predictable, both qualitatively and quantitatively (think of an organ bath experiment involving an agonist and a reversible competitive antagonist). PK interactions are less direct and more variable, including variations in individual susceptibility which have been somewhat neglected- see [8] for a discussion. Despite these complexities, some drug-drug interactions should also be predictable if we know enough about the absorption, distribution, metabolism, and excretion (ADME) of each member of a pair of drug suspects. It became apparent from the pioneering work of Brodie and his group at the NIH that interference with drug metabolism involving cytochrome P 450 (CYP) isoenzymes is a rich source of clinically important interactions [9]. The importance of induction of drug metabolising enzymes in addition to enzyme inhibition complicated the early

picture, but not impossibly so. However, the early observation that the spectral properties of CYP450 differ subtly in liver microsomes from rats pre-treated with an inducing agent (a shift in absorption maximum from 450 to 448nm), which may initially have seemed a small matter, proved to be the cloud on the horizon that presaged a whirlwind: it was the first hint that CYP enzymes exist in multiple isoforms. This has introduced huge complexity, blowing away naive hopes that interactions related to drug metabolism would be easily predicted (and hence avoided). Indeed, the multiplicity of CYP isoenzymes underlies some of the considerable risks that drug interactions pose to individual patients and to pharmaceutical companies. The withdrawal of mibefradil [10] after it had been licensed by regulatory agencies in both the USA and Europe, and shortly after its commercial launch, is a salutary reminder that investment in investigating the potential for interactions is a crucial part of both pre-clinical and early phase clinical drug development. Powerful methods have been devised to support such investigations, including *in vitro* studies with pooled human liver microsomes (HLM), with selective inhibitors of different CYP isoenzymes, with individually expressed CYPs, and with computational ADME simulation models [11–14].

In this issue of the *Journal* [15] we publish a paper by Ruth Hyland and her associates from Pfizer Global Research and Development that elegantly combines these methods in an assessment of the drug-drug interaction (DDI) potential of maraviroc, a chemokine (C-C motif) receptor 5 (CCR5) antagonist developed for the treatment of HIV infection. Combined therapy with three or more drugs (known as highly active anti-retroviral therapy –HAART) is well established, and patients with HIV often need other medications for co-morbidities. It is a therapeutic area in which clinically important interactions are legion. The investigators characterised maraviroc N-dealkylation in HLM, demonstrated selective inhibition

of metabolism by ketoconazole (a CYP3A4 inhibitor), characterised maraviroc metabolism by expressed recombinant CYP3A4 (rCYP3A4), showed that there was only minor production of its N-dealkylated product by rCYP2B6, demonstrated only weak effects of maraviroc on the metabolism of other drugs by CYP isoenzymes, and compared estimates of intrinsic clearance from HLM and from rCYP. They obtained clinical oral clearance values for maraviroc and compared these with *in vitro* simulations, demonstrating remarkably good agreement. Finally, they measured maraviroc C_{max} and AUC *in vivo* with and without a panel of inhibitors (ketoconazole, ritonavir, atazanavir, saquinavir) at licensed doses, and compared these measures of DDI with *in vitro* simulations (both time-based and steady-state), with generally good agreement. This *tour de force* not only establishes that maraviroc is a substrate for CYP3A4, but confirms the value of computational simulation based on *in vitro* data in predicting CYP-based DDIs, paving the way to future applications of this approach. Prevention is better than cure, and these kinds of meticulous studies should prevent much future harm.

Beware drawing inferences from drug analyses in post-mortem samples

Given a post-mortem drug concentration, is it possible to decide whether the deceased died from the action of the drug, whether the drug contributed to the death, or whether it was present incidentally? Here the problem is to extrapolate back to the time just before death- reverse prediction. It has been said that 'it's tough to make predictions, especially about the future' – a saying that has variously been attributed to Niels Bohr, Yogi Berra, Albert Einstein, and Mark Twain (<http://letterfromhere.blogspot.com/2006/12/bohr-leads-berra-but-yogi-closing-gap.html>). It seems that it may be just as difficult to make predictions about the past. Historical predictions are nevertheless crucial in several branches of physical science (notably in cosmology). Biologists have also made major discoveries based on secure historical inferences, for example in evolutionary theory, often drawing on detailed observations of what are now regarded as quite humble phenomena. (Darwin wrote books on orchids, coral reefs, and earthworms that are masterpieces of such historical scientific reasoning). For a distinct, and less problematic, example of 'historical' clinical pharmacology see [16]. So it is superficially not unreasonable to hypothesise that post-mortem drug concentrations can be usefully interpreted, and indeed compilations of 'fatal' concentrations based on post-mortem measurements have been published.

In the current issue of the *Journal* [17], Robin Ferner (author of 'Forensic Pharmacology: Medicines, Mayhem and Malpractice', Oxford University Press, 1996), systematically analyses the general problems of interpreting post-

mortem drug data with forensic rigour. He argues convincingly that death 'renders the assumptions of clinical pharmacology largely invalid'. His relentless deconstruction should give pause to any clinical pharmacologist unversed in forensic science who is tempted to offer an 'expert' opinion in this context: qualitative tests can be positive for substances that were not present during life, and be negative for substances that caused death; quantitative tests can be highly misleading for diverse reasons. In life the circulation provides a highly efficient bulk distribution system, and for many drugs the circulation really is a 'well mixed compartment', but once the heart has stopped, redistribution can result in large differences in concentrations measured in samples obtained from different parts of the circulation (e.g. femoral vein versus heart blood). Samples from other regions can also prove highly misleading. Ferner convincingly demonstrates that compilations of 'lethal concentrations' are unreliable. Altogether rather depressing, but appreciating one's ignorance is after all the first step on the path to enlightenment, and one can only applaud his call for studies on the true relation between fatal events and drug concentrations that can be measured subsequently: we can hope that post-mortem measurements of drug concentrations in appropriate tissues and at defined intervals will in the future become useful in establishing the cause of death, but they are clearly not at present.

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