Editors' view

Pharmacology, basic & clinical: contrasts
& coherence

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Clinical and basic pharmacology share much common ground – unsurprisingly so, in view of the common ancestries of humans, other mammals, and more primitive life forms. There are also, however, important differences. Some of these relate to cultural differences between clinical and basic pharmacologists, and such barriers are best broken down: pharmacologists are much more influential if they speak with one voice. In this spirit, the clinical specialty in the UK is represented by the clinical section of the British Pharmacological Society (BPS – the owner of this journal as well as of the British Journal of Pharmacology (BJP) and of Pharmacology Matters) as its specialist society, and national meetings of the clinical section occur during a scientific meeting of the BPS (in recent years, the winter meeting). Clinical pharmacologists pull their weight in the Society and are recognised accordingly: for example, Jeff Aronson is currently President of the BPS and Colin Dollery was the 2007 winner of the Wellcome Gold Medal of the Society. There are, however, real (as well as cultural) differences between these branches of the discipline, and this editorial view comments on some of these. We plan to revisit the relationship between clinical and basic pharmacology more formally soon (see below).

Basic pharmacologists choose their experimental preparations with the greatest care and minimize potential sources of variation. Species, age, sex, conditions of anaesthesia for *in vivo* work, instrumentation, and so on are all standardized within tight limits. This applies even (or especially) when investigating the effect of a drug on an experimental model of a human disease that is the ultimate therapeutic target. Error bars are accordingly tight, even with only modest numbers of replicate experiments. Clinical pharmacologists by definition work with human preparations – indeed often with conscious subjects, who do not come in inbred lines but rather in a bewildering array of ages, sizes, and ethnicities, who suffer from diverse acute and chronic diseases that each encompass a wide spec-

trum of severity treated with different drugs, and each of whom has the right to decline to volunteer as a subject in research.

One might expect that only very large numbers of human subjects could yield reliable conclusions – and indeed that is the case when the endpoint of interest is a clinical outcome, such as stroke, death, or myocardial infarction, with tens of thousands of subjects enrolled into clinical trials such as the Heart Protection Study [1] and similar Phase III pivotal efficacy studies. Yet, paradoxically, clinical scientists have also become adept at capturing valid conclusions from careful observations made in very small numbers of subjects. Individual case reports or small case series have identified important idiosyncratic adverse drug effects, such as phocomelia following maternal exposure to thalidomide, and have identified adverse drug interactions, such as transplant rejection from enzyme induction by St John's wort and anticonvulsant drugs, causing loss of efficacy of the immunosuppressive drug regimen. In this issue we publish a paper describing an investigation into the transfer of amphetamines into breast milk in two nursing mothers who were occasional recreational users of intravenous methylamphetamine [2]. Drug was identified in urine by gas chromatography-mass spectrometry and quantified in breast milk by high performance liquid chromatography. The findings demonstrated, for the first time, that this very dangerous and increasingly used drug of abuse passes into breast milk. The authors estimated the drug exposure of such a breast-fed infant and recommend withholding breast feeding for 48 hours after recreational methylamphetamine use. Limited data for obvious reasons, but anecdotal reports have their uses, and these observations provide valuable evidence.

Vannacci *et al.* [3] also describe an elegant piece of pharmacological detective work with a curious outcome, triggered by reports from a small number of subjects. They were struck by the rapidity and extent of pain relief from

one to two tablets of a herbal remedy. The stated active ingredients made this seem too good to be true – and so it proved. High performance liquid chromatography-mass spectrometry revealed a peak compatible with the synthetic non-steroidal anti-inflammatory drug nimesulide. Identity was confirmed by electron impact mass fragmentation analysis. The preparation has been recalled by the manufacturer and the Italian Ministry of Health has ordered product withdrawal from the market.

Access to patients with the target disease (rather than having to make do with animals with a simulated version of it) is a particular strength of clinical pharmacology. Sometimes studies in such patients confirm expectations based on *in vitro* data. An example is provided by a study of efavirenz plasma concentrations in HIV-infected patients [4]. It is known from *in vitro* data that CYP2A6 is involved in the metabolism of efavirenz, in addition to CYP2B6. Polymorphisms of CYP2B6 strongly influence plasma efavirenz concentration, but this does not fully explain interindividual variation in plasma concentration following oral dosing. Kwara and colleagues have shown that CYP2A6 polymorphisms (*9B and/or *17) are independent predictors of efavirenz plasma concentrations in HIV-infected patients, suggesting that CYP2A6 genotyping, in addition to CYP2B6 genotyping, may be useful in tailoring individual dosage regimens in future. Debra Smith and her colleagues [5] studied the effects of ketoconazole (an enzyme inhibitor) and carbamazepine (an inducer) on lapatinib pharmacokinetics in healthy subjects and found that systemic exposure to this orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor was substantially influenced by altering the activity of CYP3A4 – indeed to an extent that altering the dosage regimen may be clinically indicated.

How important is it for pharmacokinetic or pharmacodynamic (as opposed to therapeutic) studies to be performed in patients with the target disease rather than in healthy volunteers? This varies from one clinical problem to another, but systematic differences that would be difficult to predict *a priori* do occur between healthy volunteers and patients, even when the patients have stable and chronic conditions. An example is provided by a study of the time course of the well known and clinically important interaction between sildenafil and sublingual glyceryl trinitrate (GTN) [6]. Subjects were challenged with GTN (400 micrograms) at various times after oral sildenafil (100 mg). In healthy men there was a greater reduction in BP with sildenafil/GTN than with placebo/GTN only at one hour, whereas in men with stable angina the interaction persisted ≥ 8 hours after sildenafil (as far as the data extended in this part of the study) – observations that may inform clinical decisions regarding the use of GTN in patients presenting with angina who have recently used sildenafil.

The use of general anaesthesia profoundly influences cardiovascular and respiratory reflexes, and the ability to

study subjects who are awake and relaxed provides a unique opportunity for cardiovascular and respiratory clinical pharmacologists. Cardiovascular reflexes can be studied in the absence of general anaesthesia. Leyla Cekici and colleagues [7] studied the effects of inhaled salbutamol (a β_2 -adrenoceptor agonist) on cardiac output, beat-to-beat heart rate, and arterial pressure. Cardiovascular autonomic tone was analysed from the beat-to-beat power spectrum. Salbutamol shifted sympathovagal balance towards increased sympathetic tone in the absence of baroreceptor activation, raising a question as to possible increased cardiac risk, an issue regarding the use of inhaled β_2 -adrenoceptor agonists in asthmatics that has long been debated.

One particularly powerful method of studying the effects of vasoactive drugs on resistance vessels in man is measurement of forearm blood flow during brachial artery infusion of doses sufficient to act locally in the forearm vasculature but too low to cause systemic effects, including effects on blood pressure or direct effects on the heart, brain, or kidneys. The method hence circumvents baroreflex changes that buffer changes initiated by intravenous administration of vasoactive drugs. The contralateral (non-infused) arm provides a perfect control. This method has been used by Afshavi *et al.* [8] to investigate actions of morphine on forearm resistance vasculature. Morphine has been known to liberate histamine from mast cells by a non-morphine receptor-mediated mechanism for many decades – indeed this is believed to be an explanation why morphine addicts often complain of itching. Histamine has vasodilator actions through H_1 receptors on endothelial cells, linked via an increase in cytoplasmic Ca^{2+} to activation of nitric oxide synthase (NOS) and endothelium-dependent vasodilatation, as well as direct actions on vascular smooth muscle in some vascular beds [9, 10]. Afshavi *et al.* have demonstrated a dose-dependent morphine-induced increase in forearm blood flow that persists during a 30-minute infusion, is not affected by naloxone, but is blocked by antihistamines or by inhibition of NOS. It will be interesting to find out the relative contributions of venodilatation (and pre-load reduction) versus resistance vessel dilatation (and after-load reduction) to the therapeutic effect of intravenous morphine in patients with acute pulmonary oedema.

Despite the fundamental coherence of basic and clinical pharmacology, many clinical pharmacologists are somewhat hazy as to what their basic colleagues actually get up to in their laboratories from day to day and *vice versa*. To lighten this darkness, Mike Curtis (reviews editor of the BJP) has commissioned a review from Jeff Aronson on 'What Is Clinical Pharmacology?' and Mike Schachter and I have invited Tom Blackburn to write a review to be published simultaneously in BJCP on 'What Is Pharmacology?' We hope that this pair of publications will help to define the complementary qualities of these two branches of our discipline more securely. Watch this space ...

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