Commentary

An agenda for UK clinical pharmacology

Research priorities in pharmacokinetics

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An opinion is expressed on the past, present and future roles of pharmacokinetic–pharmacodynamic research in the context of UK clinical pharmacology. On the basis of its current constitution, it seems unlikely that this area of research will be driven from within academic clinical pharmacology in the UK. Therefore, in order to bring its expertise and experience to bear effectively on the evolving emphasis on translational medicine and modelling and simulation, this community would need to reach out beyond its current preoccupations to increase interactions with the next generation of pharmacokineticists and pharmacometricians.

Introduction

In a survey conducted by the International Pharmaceutical Federation (FIP), the five conceptual developments in pharmacokinetics that have had the greatest impact on drug discovery, development and use over the last 50 years were identified as bioavailability/bioequivalence, whole body physiologically-based pharmacokinetic modelling (PBPK), pharmacokinetic–pharmacodynamic link models (PK–PD), the clearance concept and population pharmacokinetics. Clinical pharmacologists (with and without medical qualifications) have been at the forefront of these developments. Indeed, in the UK several senior clinical pharmacologists established much of their early careers around the subject, at least with regard to the component processes of drug absorption, distribution, metabolism and excretion (ADME), including Sir Michael Rawlins [1], Sir Alasdair Breckenridge, Sir Charles George and Sir Colin Dollery, although the last did express some concern as to whether pharmacokinetics was ‘master or servant’ of clinical pharmacology [2]. The questions now are what went wrong/right with the subject in the context of clinical pharmacology, where the international centres are that produce well-trained pharmacokineticists, where these centres are in the UK, where pharmacokinetics is going and what the future of the subject is in the context of UK clinical pharmacology.

What went wrong?

Monitoring drug therapy

With regard to the practical application of pharmacokinetics to drug therapy, the concept of measuring blood drug concentrations in individual patients (referred to as ‘therapeutic drug monitoring’), and associated pharmacokinetic forecasting as a guide to dosing, was never widely accepted in the UK. One recalls several lively debates in the late 1980s in the correspondence columns of the *British Journal of Clinical Pharmacology* (BJCP) between ‘the practising physician’ and ‘practising pharmacists/chemical pathologists’ [3–5].

Pharmacogenetics

In the 1990s the rapid rise of genetics/genomics exactly paralleled the decline of clinical pharmacology in UK medical schools. Unless you were collecting DNA, nobody wanted to know you. Some of us thought that studying molecular biology at the expense of understanding function was not going to work and we are still waiting for many of the hyped promises from sequencing the genome to materialize. As a member of one of the first groups to study functional aspects of polymorphisms in CYP2D6 in the 1970s [6], I find it disappointing (although understandable) that after 35 years the evidence base for genotyping

drug metabolizing enzymes and transporters in clinical practice is still largely lacking [7].

Early clinical drug development

The unfortunate circumstances surrounding the first-in-human studies of TGN1412 [8] have had significant repercussions with regard to the ease with which competent clinical investigators can pursue PK–PD studies in the UK [9].

As a crude measure of the decline in UK clinical pharmacology in general and in pharmacokinetics as a part of the discipline over the last 10 years, I compared both the sources (by country) of all papers published in the BJCP and the numbers of PK/ADME studies in 1990 vs. 2010. Of the 124 published by UK groups in 1990, 38 (31%) were PK/PD/ADME related against 4/38 (11%) in 2010. In 1990, 115 papers relating to PK/ADME were published, of which 38 (33%) were from the UK. In 2010 only four out of 73 (5%) were from the UK. It is perhaps reflective of the change in the complexion of UK clinical pharmacology that nearly half (16/38) of the UK papers published in 2010 were related to pharmacovigilance and pharmacoeconomics.

What went right?

In contrast to events with regard to the role of pharmacokinetics in academic departments of clinical pharmacology, pharmaceutical companies have found increasing applications of the subject in drug discovery and development and pharmacokineticists and pharmacometricians are in high demand. It has taken some time for the realization to emerge that good drugs require good pharmacokinetic properties, not just potency and selectivity. However, now that developing successful candidate compounds has become more difficult and increasingly expensive, many companies are taking seriously the prospect that modelling and simulation, from molecular and quantitative structure–activity relationships (QSAR) modelling [10, 11], PB–PK modelling [12], PK–PD modelling [13] and clinical trials simulation [14] to pharmacoeconomic modelling [15], may produce significant cost savings, not the least by breaking down silos along the development chain.

Where are the academic centres?

Good pharmacokineticists are born, but they also need training. Currently, the global centres with the highest profiles for providing in-depth training include Departments of Pharmaceutical Science in the Universities of Buffalo, Florida, Gothenburg, Leiden, Otago, San Francisco, Tokyo, Uppsala and Washington. In the UK, the Universities of Manchester (Pharmaceutical Sciences) and Sheffield (Clinical Pharmacology) in particular have been recognized internationally as centres of pharmacokinetic excellence. However, retirements and impending retirements and, in

the case of Sheffield, the disappearance of any systematic pharmacology presence in the Medical School, may dilute the capacity for the UK to produce people with the necessary PK–PD skills, at least within universities.

Where is PK–PD going?

The importance of quantitative and systems pharmacology/toxicology is receiving increasing recognition, and, as part of this, it is an exciting time for PK/PD. Now that systems biology is at the forefront of the research agenda, and there is increasing interest in the development of biomarkers of disease severity and drug response and in predictive toxicology, the capability of PK–PD modelling is set to reach even higher levels of sophistication and utility [16]. A particular development over the last 10 years has been the increasing acceptance and utilization by pharmaceutical companies of whole-body PB–PK modelling as a basis for ‘bottom up’ prediction and simulation of pharmacokinetic behaviour with respect to age, genetics, diseases, formulations and drug–drug interactions [12]. Using concepts from *in vitro*–*in vivo* extrapolation of data obtained from human cells and tissues, this approach has been instrumental in helping to break down the divide between pre-clinical and clinical drug development. Further developments will see the merging of ‘bottom-up’ and ‘top-down’ approaches to PK–PD, the latter exemplified by the so-called population approach (POPPK) based on sparse sampling. Thus, models will become increasingly mechanistic rather than being driven purely by the observed data.

Now that PBPK modelling is coming of age in drug development and is being recognized as a useful tool in regulatory assessment, particularly for asking ‘what if’ questions [17], its potential use in the health care arena as an educational tool and for the direct provision of advice on individualized drug dosing at the point of care will begin to emerge. One day, when sufficient information is available for a patient, clinicians will be able to link that person to his or her virtual twin in a model system, providing rapid, safe and effective individualized dosages and avoiding undesired drug–drug interactions. The challenges in providing such guidance at the point of prescribing are its validation and the avoidance of significant information overload and fatigue by removing irrelevancies. Collaboration and consultation with clinical pharmacists will also be a key element, since their basic training in the principles of pharmacology and therapeutics is increasingly more extensive than that of medical practitioners.

Is there a future for PK–PD in UK clinical pharmacology?

It seems unlikely that pharmacokinetics and pharmacodynamics will be driven from within academic clinical phar-

macology, at least on the basis of its current constitution. The challenge will be for clinical pharmacologists to reach out beyond their current preoccupations to interact with the pharmaceutical scientists, control engineers and systems biologists who will form the next generation of pharmacokineticists and who should inject new life into the training of UK pharmacokineticists and modellers. While the major UK grant-giving bodies, such as the MRC and the Wellcome Trust, have never invested very much in PK–PD studies, this might change now that systems biology has supplanted genomics as ‘flavour of the month’ for funding. The realization that there is value in using PK–PD for studying the whole human body as a system may then also emerge.

Competing Interests

There are no competing interests to declare.

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