MEETING REPORT

Highlights of the Society for Medicines Research Symposium held in London, United Kingdom

New Horizons in Drug Metabolism, Pharmacokinetics and Drug Discovery

by Alan M. Palmer

Summary

Along with minimal toxicity, good drug metabolism and pharmacokinetic (DMPK) properties are essential for the clinical success of a drug candidate. A major cause of failure of orally administered drugs during their development is the discovery that in humans they have low intestinal absorption and/or high clearance causing low and variable bioavailability. In addition, drug interactions and the presence of active metabolites can prevent or complicate their successful development. With poor pharmacokinetics it can be difficult to achieve a suitable dosage regimen for the required pharmacodynamic action. The main role of DMPK in discovery is, therefore, the prediction of human pharmacokinetics and metabolism. Reducing the rate of attrition during drug discovery and development is now considered essential, particularly as it is now possible to screen an ever-greater number of compounds.

Rapid changes in both technology and market dynamics are currently coming into confluence and are exerting a major influence within the pharmaceutical industry. These changes have induced a revolution in drug discovery, with developments such as genomics, combinatorial chemistry and high throughput screening now driving a radically new process for the discovery of novel drugs. There is also increased focus on cost-benefit in drug development. Thus, there has been a major increase in available chemistry and potential targets.

Introduction

The successful introduction of a new drug on to the market is not only an extremely costly and complicated process, but also fraught with a substantial risk of failure. At present, 10,000 compounds are required to get a single drug to market. A major contributor to this high rate of attrition is the drug metabolism and pharmacokinetic profile of drug candidates. The Society for Medicines Research symposium, held at the National Heart and Lung Institute of Imperial College of Science, Technology and Medicine June 27, 2002, focused on new horizons in drug metabolism and pharmacokinetics (DMPK) and drug discovery. The meeting was organized by Alan M. Palmer (Pharmidex, London, UK), who chaired the proceedings together with Sandy Pullar (Lilly, Windlesham, UK) and Malcolm Duckworth (GSK, Harlow, UK).

The science of DMPK applied to the process of drug discovery has undergone a revolution in recent years. In response to the need to assess DMPK-related parameters earlier in the drug discovery process, a fresh approach has arisen, with the introduction of new instrumentation and techniques. This conference considered the contribution of DMPK to drug discovery, with an overview of current progress and challenges *in silico, in vitro* and *in vivo* (in both animals and humans), together with consideration of the increasing contribution of bioanalysis and pharmacogenomics.

Simon Roberts (Celltech R&D, Cambridge, UK) described how

  CCC: 0214–0934/2003

knowledge of the fate of a drug, its disposition (absorption, distribution, metabolism and excretion - ADME) and pharmacokinetics (the mathematical description of the rates of these processes and of concentration-time relationships) play a central role throughout pharmaceutical research and development. DMPK departments were originally set up in the 1960s and 70s to investigate the metabolism of new drug candidates in animals used for toxicology testing and to compare these findings with humans. During development, DMPK has the important role of supporting the safety and efficacy assessment of new drugs. But little attention has been given to drug delivery, pharmacokinetics, duration of action, metabolism, solubility and formulation. This has meant that many pharmacologically active compounds, never become drugs because of development problems, *e.g.,* poor bioavailability, high clearance, low solubility and formulation difficulties. This is supported by an analysis of the causes of failure of drugs selected for development in the 1980s. Prentis and collegues[1], showed that inappropriate kinetics in humans accounted for 39% of the failures (Fig. 1).

A new role for DMPK has emerged in the discovery process, allowing unsuitable compounds to be filtered out earlier in the process. This change began in the mid 1990s and was enabled by major improvements in sample analysis utilising mass spectrometry and facilitated by the introduction of higher throughput *in vitro* and *in vivo* DMPK methodologies, together with (more recently) *in silico* modeling techniques to help predict what effect structural changes will have on individual pharmacokinetic parameters.

Examples of some of the DMPK issues that arise in the drug discovery process include low and/or variable bioavailability, high elimination rates and drug-drug interactions. Some of the consequences of a poor DMPK profile include difficulty in defining a dosage regimen sufficient to achieve required efficacy in target population, unacceptable drug interaction profile (*e.g.,* the nonsedating antihistamine terfenedine had to be withdrawn when coadministration with the antifungal ketoconazole resulted in cardiotoxicity).

Although animal techniques are still important in understanding the whole body kinetics of drugs, there is an increasing reliance on *in vitro* approaches, particularly on those using human material. New *in vitro* systems, such as expressed enzyme preparations and cell cultures, are now considered essential for the successful identification and optimization of leads. New analytical techniques such as those utilising LC/MS/MS instrumentation have led to large increases in sample throughput and sensitivity, while improved data management systems have sped up the information output. With improvements in analytical technologies and the increasing numbers of compounds produced during discovery, many *in vitro* screening methods have been adapted for higher throughput with multiwell plates and robotics. The evaluation of whole animal pharmacokinetics is generally low throughput, but the dosing of mixtures and modifications to sampling protocols have led to improvements. Another important development in recent years has been the adoption of *in silico* (computer) methods to help design libraries of compounds more likely to have appropriate DMPK characteristics.

A clinical perspective of the importance of DMPK in drug discovery was presented by Atholl Johnston (Barts and The London, London, UK). The classical description of the drug development process as a series of phases (discovery, pre-clinical [phase 0] and phase I through to phase IV) gives the impression that the development of a new drug is a smooth linear process with one stage finishing before another starts. However, in practice, the development process is seldom smooth and rarely (if ever) linear. The clinical phase of development starts with the first administration of the drug to humans, and pharmacokinetics play a critical role[1]. Thus, in a study of 49 marketed drugs from seven companies, the former being derived from 319 new chemical entities (NCEs) from the period between 1964 and 1985, Prentis and collegues[1] observed that 62% of the clinical candidates were withdrawn: 72% at phase I (143 candidates) and 28% in patient studies (55 candidates). The reasons for withdrawal are summarized in Figure 1.

In addition, development time has increased from 2 to 8 years. Thus, dur-

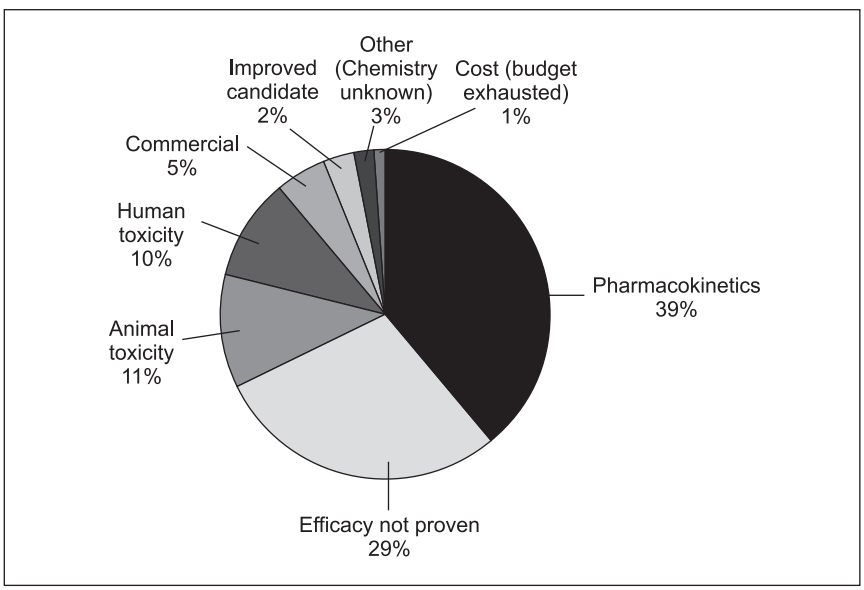

Fig. 1. Reasons for marketed drugs to be withdrawn (Ref. 1)

TABLE I. THE ROLE OF DMPK IN THE DEVELOPMENT OF A NEW DRUG

PHASE	STAGE	PURPOSE
Preclinical PK	Discovery	To chose the optimum candidate
	Development	To understand the pharmacology in experimental animals
	Toxicity testing	To determine exposure in two nonhuman species
Phase I	Dose ranging	Tolerability over a range of doses
	Dose linearity	Establishing whether plasma concentration increases in proportion to the dose administered in humans
	Definitive kinetics -Single dose -Multiple doses	Measurement of half-life, C_{max} and AUC using single and multiple doses
Phase II	Sex differences	Assessment of the influence of gender on PK profile
	Food interactions	Assessment of the influence of food on PK profile
	Absolute bioavailability	Quantitative determination of the distribution of a compound in bodily fluids and tissues
	PK-PD relationships	Establishing clear dose-response relationship avoids drugs being marketed at excessive doses
	Genetic polymorphisms	Assessment of the influence of genetic differences in drug metabolizing enzymes on PK profile
Phase III	Effect of disease	Determination of the PK profile in the target population
	Subgroup analysis	Determination of the PK profile in subgroup of the target population
	"Final" dosage form PK	Determination of the PK profile of the final formulation of the drug candidate
	Dose-response	Determination of a clear dose-response relationship in the target population. Response can be determined on the basis of a biochemical, imaging or clinical surrogate or the explicit demonstration of therapeutic efficacy
Phase IV	Dosage form improvements Change of formulation Modified release preparations	Determination of the PK profile of new formulations
	Line extensions	Determination of the PK profile of modified drugs designed to extend patent life
	Drug interactions	Determination of the possible influence of other drugs on the PK profile
	Pharmacovigilence	Continual assessment of competitor and potential competitor compounds

ing the early phases of clinical development of a drug, the DMPK findings clearly influence the direction and speed of the future development of that drug[2]. Table I shows the role of DMPK in the development of a new drug[2].

The importance of DMPK to drug development was starkly illustrated by a catalogue of compounds that initially were used with an incorrect dose, including: chlorthalidone (Hygroton), perhexilene, propranolol (Inderal), atenolol (Tenormin), captopril (Capoten), benoxaprofen, cimetidine (Tagamet), ranitidine (Zantac), zidovudine (Retrovir) and sumatriptan (Imigran). Getting the dose wrong can cause a number of unwanted consequences, such as toxicity to patients, impaired scientific credibility, progressive dose reduction, loss of revenue, and last–but not least–legal liability.

Surrogate markers of the action of a drug are extremely helpful in clinical trials. Such markers can be defined by a pharmacodynamic measure that predicts therapeutic or adverse effects of a drug in the target population of patients, including a direct measure of receptor or enzyme activity (*e.g.,* ACE inhibition, H1 antagonism) and a consequent pharmacological effect (*e.g.,* vasodilatation, sedation). Such surrogate markers can be used to establish relationship between dose or concentration and response. Examples are shown in Table II.

Mike Tarbit (ArQule, Cambridge, UK) considered the contribution *in silico* methods are making to the DMPK field, and how this approach is likely to change the face of DMPK in the future. A good medicine is a compound that exhibits the right balance of potency, pharmacokinetics and safety. Typically, these elements are approached serially, and the usual focus on potency as a first principle can make the subsequent optimisation process long and complex.

The wealth of data that is now emerging from relatively high throughput screening of ADME and toxicology parameters is enabling the production and validation of predictive *in silico* models of ADME properties. This is providing opportunities to filter

TABLE II: EXAMPLES OF CLINICAL SURROGATES

DRUG CLASS	CLINICAL SURROGATE
Alpha blocker	Standing blood pressure
	Retrograde ejaculation
Beta blocker	Exercise tachycardia
	Isoprenaline tachycardia
Vasodilator	Blood pressure
	Forearm blood flow
Cardiac inotrope	Non-invasive measures of cardiac function
Class Ic anti-arrhythmic	QRS interval of electrocardiogram
Class III anti-arrhythmic	QT interval of electrocardiogram
Gastric anti-secretory agent	Stimulated acid secretion
24-hour ambulatory pH	
Histamine H_1-antagonist	Skin wheal and flare

or design libraries and chemical arrays with the correct balance of ADME properties, in some cases even prior to synthesis. It is also enabling project teams to explore chemistry ideas with some indications of ADME advantages or liabilities.

The current systems for using ADME in drug design are low throughput and require re-synthesis. They are time consuming and expensive, yet only marginally predictive. Neither are they appropriate for screening large compound libraries. Therefore, there is a clear need to increase the effectiveness of research and development by exploiting technology that drives the optimisation of multiple ADME/toxicological (ADME/tox) properties simultaneously in a virtual environment. ArQule is developing an integrated suite of computational models of ADME/tox with predictions based upon chemical structure alone, using approaches that combine information technology with mechanistic understanding at a quantum mechanical level.

Thus, the capacity to assess ADME/Tox is markedly increasing. A traditional *in vivo* pharmacokinetic study is able to assess 1–5 compound a week. Using cassette dosing, this could increase to 20 compounds a week. A modern *in vitro* ADME screen would be able to process 500 compounds a week, whereas *in silico* ADME models can process 1000–100,000 compounds a day. Features that can be assessed include: human intestinal absorption, bioavailability, blood-brain barrier penetration, P450 affinity, 2D6 and 2C9, P450 regioselectivity/site liability and 3A4.

Such measures can be used to calculate pADME scores, which allow compounds to be prioritized for synthesis. The intention of pADME scoring is to indicate the degree of ADME "risk" associated with a compound. A score between 0 and 1.0 is assigned to each compound, reflecting both the probability that the compound satisfies the criteria for a particular ADME property and the relative importance of that property. An overall pADME consensus score for all predicted properties can be derived, which can be used in conjunction with potency, chemical diversity and tractability ratings to optimize library production. With virtual libraries, modifications can be made to try and eliminate the liabilities and the modified libraries re-submitted for assessment. Thus project profiles can thus be addressed from the pre-synthesis stage. It is also possible to use pADME scores to profile virtual libraries.

Alan P. Watt (Merck Sharp & Dohme Research Laboratories, Harlow, UK), examined the role of DMPK in the screening cascade. In today's drug discovery environment, the ability to generate several viable lead series and rapidly develop these into potent, selective molecules through a directed medicinal chemistry effort is often no longer rate-limiting. Instead, the emphasis has shifted towards designing molecules possessing not only high affinity at a biological target, but also suitable pharmacokinetic (low clearance, high oral bioavailability) and metabolic characteristics in both preclinical species and humans. This has lead to a paradigm shift in the integration of DMPK functions into increasingly earlier stages of drug discovery. In response to this, the throughput capabilities of both pharmacokinetics and *in vitro* metabolism assays have increased dramatically.

But where is the best place for a drug metabolism capability to intervene? From early on in the process, where minimal biological evaluation has occurred, newer high-throughput methodologies for assessing citochrome P450 inhibition potential and metabolic stability are now routinely employed. In addition, modern analytical technology allows more detailed pharmacokinetics and pharmacodynamics to be supplemented with structural elucidation of metabolites, with this information being rapidly fed back into the drug design process. Such features of the screening cascade will be illustrated with in-house examples demonstrating the growing importance of an integrated drug metabolism capability within a drug discovery setting.

Ken Page (AstraZeneca, Macclesfield, UK), considered the contribution of *in vitro* DMPK. Over the last 10–15 years, it has become evident that poor DMPK properties are a major cause of failure of NCEs prior to market. Consequently, DMPK is now considered integral to the drug discovery process (*i.e.*, the optimisation of structures prior to development). Furthermore, advances in medicinal chemistry (*e.g.*, combinatorial chemistry, multiple parallel synthesis, *etc.*) alongside complementary advances in biological screening technology (HTS, uHTS) have resulted in the necessity of screening many more compounds, more quickly, for DMPK properties. As a consequence, DMPK as a discipline has had to change rapidly to meet this challenge.

For most drug discovery projects, the oral route is their preferred means of dosing clinically and, for a drug to reach its target (generally in tissues or the central or peripheral blood supply), a number of barriers must be overcome to ensure activity. Clearly, *in vivo* pharmacokinetics (preferably in human) give the most reliable information, but human studies are not available preclinically, while compound quantities and practical and ethical issues preclude *in vivo* studies in animals to be undertaken in the numbers necessary to investigate the expanding numbers of molecules sufficiently quickly. To meet this need, *in vitro* tests have been developed that can profile NCEs in a model for each of the major barriers to good bioavailability post-oral dose, and are often able to screen hundreds of compounds per week. These models typically include: use of liver tissue preps (microsomes, S9 fraction, hepatocytes, slices) to determine the likelihood of metabolic stability, solubility, epithelial membrane permeability (*e.g.*, CACO2 or MDCK cells) and protein binding, one or all of which will have a major impact on the exposure of individuals to orally administered drugs and to their efficacy. Importantly, confidence in the 'predictiveness' of these models is building, so that predictions of human pharmacokintic properties are now undertaken from animal and human *in vitro* testing, although it remains to be seen how successful this approach will be.

Another major cause of DMPK-related failure in the clinic is the area of drug-drug interactions, causing undue toxicity and/or therapeutic failure. It is now possible to clone and express the five major human P450 isoforms (phase I metabolism), along with human uridinediphosphoglucuronyl transferase (phase II) allowing structural series to be screened for their potential to inhibit the metabolism of co-administered drugs that are eliminated by these routes. Transporter proteins can now also be investigated in a similar way.

Finally, as DMPK becomes involved at an ever-earlier stage in the drug discovery process, there is a clear need for the discipline to be able to screen thousands of 'hits' from an HTS campaign (whole company compound collections may need to be screened rapidly at some time in the future). The only practical means of doing this will be a form of 'virtual', (or *in silico*) screening for metabolic stability, permeability or enzyme inhibition.

Mohammad S. Alavijeh (Pharmidex, London, UK), described the assessment of DMPK *in viv*o. In addition to an optimal DMPK profile, CNS drugs require appropriate physicochemical properties to permit access through the permeability barrier between blood and brain (the blood-brain barrier). There is, therefore, a clear need for assay systems to increase both the speed and efficiency of assessment of systemic and CNS DMPK profiles. Rational DMPK screening requires a careful balance of *in silico* to *in vitro* and *in vivo* screens. Desirable properties include: good solubility, permeability and appropriate lipophilicity; available parental formulation; complete/consistent bioavailability; appropriate concentration at target site; adequate half-life; linear acute and chronic elimination kinetics; small first-pass effect; polyzymic metabolism; no(auto) induction; minimal cytochrome P450 inhibition; no interaction with P-glycoprotein (PGP); no PK interactions with potential comedications (drug-drug interactions); moderate (< 90%) plasma protein binding; and a wide therapeutic index.

Dr Alavijeh outlined current approaches to improve and accelerate DMPK profiling and (for compounds targeting CNS disorders) identify compounds with an optimal CNS DMPK profile. This included a parallel administration of compounds (cassette dosing) coupled with tissue (*e.g.*, brain and liver) and fluid (*e.g.* CSF and plasma) microdialysis. These techniques not only significantly reduce the number of animals used, but they also permit different dosing routes to be assessed in the same study and deliver high-quality data.

Steve Little (DxS Ltd, Manchester, UK) ended the meeting with a reminder of the impact pharmacogenomics has made, and will continue to make, in the future. The international efforts associated with the human genome project have generated sequence information, databases and technology tools that are having a significant impact on drug discovery, development and marketing. Within the pharmaceutical industry, the biggest impact is currently at the level of target identification and validation. Genomic analysis can generate targets from candidate genes or via a hypothesis-free genome scan. Expression databases give insights into genes turned on during disease processes and SNP analysis can indicate whether a drug's target or its metabolism is likely to be polymorphic within the general population.

Although most current applications of pharmacogenomics are targeted on identifying better drugs, there is also a growing level of interest in the concept of better drug usage. Clinical trials can be designed to generate genotype data to identify subsets of patients who are likely to respond well to a particular therapy. The same genotyping tests can then be used to select patients suitable for the drug. This concept of personalized medicine is generating significant debate within the pharmaceutical industry as to if, when and how it should be introduced. This presentation will examine some of the changes likely to occur as a result of our increased understanding of the relationship between genotype and drug response.

Conclusion

The successful introduction of a new drug to the market is not only an extremely costly and complicated process, but also fraught with a substantial risk of failure. The statistics for new introductions over the period 1990

to 2000 show a relatively constant number of between 30 and 50 per year, while the cost of pharmaceutical research and development has risen almost 2.5-fold, from $20 billion to $47 billion over the same period. What is not revealed by these figures, is that the chance of success for a drug candidate passing through the various hurdles in pharmaceutical development is at best 1 in 10, and this statistic has barely changed despite advancing technology in other research and development areas. While we expect high failure rates in drug discovery, it is of substantial concern that most candidates in development, on which large investments have already been made, are probably not going to make any return. A major stumbling block is the DMPK profile of drug candidates.

The science of DMPK applied to the process of drug discovery has undergone a revolution in recent years. In response to the need to assess DMPK-related parameters earlier in the drug discovery process, a fresh approach has arisen, with the introduction of new instrumentation and techniques. This meeting considered the contribution of DMPK to drug discovery and thus provided an overview of current progress and challenges *in silico*, *in vitro* and *in vivo* (in both experimental animals and humans), together with consideration of the increasing contribution of bioanalysis and pharmacogenomics. It is clear that the science of DMPK has changed and evolved, and this process is set to continue in the years ahead. We can therefore expect further significant contributions to the discovery and development of new safe and effective medicines.

References

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2. Lesko, L.J., Rowland, M., Peck, C.C. and Blaschke, T.F. *Optimizing the science of drug development: Opportunities for better candidate selection and accelerated evaluation in humans.* Pharm Res 2000, 17: 1335–44

Dr. Alan M. Palmer is a committee member of the Society for Medicines Research (SMR). The SMR Committee organizes conferences on behalf of the Society for Medicines Research four times a year. These one-day conferences are of a multidisciplinary natue, therapeutically focused and normally held in or around London. Details about forthcoming meetings can be obtained from the SMR Secretariat, Triangle House, Broomhill Road, London SW18 4HX, U.K. Tel: +44 (0)20 8875-2431; Fax: +44 (0)20 8875-2424;
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INFLAZYME MAKES STRIDES IN Q3 FY2002

In its quarterly letter to shareholders dated February 25, 2003, Inflazyme Pharmaceuticals Ltd. reported on progress made in the quarter ended December 31, 2002.

Inflazyme's collaboration with Aventis Pharma was expanded, with Aventis agreeing to increase its investment in **IPL-512602**, one of the company's oral LSAIDs (leukocyte-selective antiinflammatory drugs) by assuming responsibility for all costs and supplying clinical resources for the program. Aventis is now exploring IPL-512602's potential in allergic rhinitis, in addition to the asthma indication already covered. During the quarter, a phase Ib study was successfully completed and an Investigational New Drug application (IND) was filed with the FDA for IPL-512602. Following IND approval in January, a short food-effect study to confirm the dosing regimen was commenced. Phase II programs in asthma and allergic rhinitis are scheduled to commence in the second quarter of 2003.

Inflazyme also agreed to work with Aventis on the development of another respiratory compound, this time from the new **IPL-12 series** of compounds that are chemically distinct from IPL-512602 and which have demonstrated activity in preclinical models. If Aventis selects a lead compound for development from this series, Aventis will take over development and commercialization costs for respiratory disease. A successful project would result in USD 45 million in milestones plus royalties payable to Inflazyme.

IPL-550260, another oral LSAID, was found to be safe and well tolerated at doses studied in the completed phase Ib trials. Inflazyme continues to study the compound in various models of inflammatory disease in order to select a suitable indication for further development.

IPL-576092 continues to be reviewed by potential collaborators for inflammatory conditions of the eye.

Compounds from the new **IPL-99 series** of LSAIDs are being researched for nonrespiratory inflammatory diseases with the intent of identifying a number of molecules for different disease indications.

Inflazyme's phosphodiesterase type 4 (PDE4) research activities resulted in the identification of **IPL-455903** with potential in the treatment of disorders of cognitive function related to memory. This new molecule is being developed with Helicon Therapeutics, Inc., which in January took up an option on the compound. Inflazyme has an option to participate on an equal basis with Helicon in future development costs and profits. The option can be exercised any time up until 90 days after the completion of phase IIa by paying Helicon half of the development costs incurred to date.