The Importance of Drug Metabolism Studies for Efficient Drug Discovery and Development

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Summary: Drug action is the result of interaction with target sites, for both desired (pharmacological) and undesired (toxic) actions, modulated by the transfer processes, the pharmacokinetic variables of absorption, distribution, metabolism and elimination, by which the drug enters and leaves the body. There exist in general better relationships between effect and internal exposure, i.e. target concentrations, most frequently related to plasma concentration, than with the external dose offered. Drug metabolism and pharmacokinetic studies have essential roles to play in all stages of the research and development process, ideally being involved from the pre-nomination phase in drug discovery through to post-marketing surveillance. There occurs far more inter- and intraspecies variation, in animals and humans, in the factors influencing the nature and extent of internal exposure, than in the sensitivity of drug targets and this pharmacokinetic variability is the cause of major problems in drug development. The origins of this may be termed “pharmacokinetic defects” and include, inter alia, poor absorption, very short or very long half-life, enzyme induction and high first pass effect. Failure to take these into consideration can cause expensive delay and/or failure during development and make an approved drug vulnerable in the marketplace. It will be argued that the thoughtful inclusion of new feedback loops will improve decision making at various stages during drug development. These should be based on quality metabolic and pharmacokinetic data and exploit the opportunities which the new biology offers for predicting metabolic pathways, anticipating kinetic variability and understanding mechanisms of toxicity. Such improved decision making should contribute to enhanced time- and cost-efficiency of development and ultimately lead to safer, more easily used, drugs.

Key words: Drug metabolism, Pharmacokinetics, Drug discovery, Safety evaluation, Toxicokinetics, Drug delivery, Clinical pharmacology, Drug development, “Pharmacokinetic defects”

Introduction

The actions of drugs on the human body are the consequence of their interactions with the specific target sites responsible for both desired (pharmacological/therapeutic) and undesired (adverse/toxic) actions, which are modulated by transfer processes, the pharmacokinetic variables of absorption, distribution, metabolism and elimination, by which the drug enters the body, reaches its site of action and is eliminated. Successful drug therapy requires there to be reliable relationships existing between dose and response and an understanding of factors which influence these relationships. In general, there exist better relationships between effect and internal exposure, i.e. concentration at the relevant target sites, most frequently related to plasma concentration, than with the external dose presented to the patient.

After a candidate molecule has been shown to possess activity of potential therapeutic value, the development programme which is necessary to transform a candidate new chemical entity to a therapeutically useful medicinal product is intended to provide information on a variety of topics relevant to its safe and effective use. Thus the headings on what in the United Kingdom is known as the product data sheet and in the United States as the package insert comprise:

1. The action of the compound
2. Indications for its use in therapy
3. Contraindications
4. The dosage to be administered, the dose form and the dose regime
5. The consequences of overdosage
6. Precautions which the prescriber must take
7. Side effects and adverse reactions
8. Drug-drug interactions of relevance

It has been estimated that between 1 in 1000 and 1 in 10,000 of all the new chemicals synthesized in pharmaceutical companies are taken into further development after the initial discovery phase. Within the discovery phase, the success rate is between 1 in 5 and 1 in 10 of those molecules nominated into development reaching the market place as a therapeutically useful and governmentally approved new drug. Of these, only one third will be genuinely profitable and generate more income than simply to recover the costs of development, which in the U.S.A. in 1992 averaged $231 million. The
time from first synthesis to registration is, on average, between 11 and 12 years. There is thus pressure for the drug development process to become more time- and cost-efficient: indeed, it is arguable that time efficiency is more important than cost efficiency in this particular context. It is therefore relevant to analyze the causes of failure of new compounds entering the development phase. The most significant reasons for the failure of candidate drugs during development are matters to do with pharmacokinetics. The second and third most important causes of failure are animal toxicity and human adverse reactions, both of which are at least in part related to pharmacokinetic problems.

The Pharmacological and Toxicological Significance of Drug Metabolism

The pharmacokinetic sphere has immense significance in drug development because the ADME (absorption, distribution, metabolism and elimination) studies which it involves generate information on:

1. The chemical natures of molecules produced within the target organism to which specific target sites will be exposed, and
2. The quantities and concentration-time courses of these various compounds (parent and metabolites) within the target organism and at specific target sites within it.

The vast majority of drugs and other foreign chemicals which enter the animal body undergo enzymic metabolism before elimination, principally in the urine or the faeces, subsequent to biliary excretion. Although accepting a profusion of substrates, the metabolic pathways have a common feature in that they involve first a functionalization reaction of oxidation, reduction or hydrolysis, which serves to introduce or unveil a functional group to which an endogenous moiety can be attached in a second reaction of conjugation. This sequence generally results in a readily excreted and inactive product, more water soluble and more polar than the parent compound, but there are some remarkable exceptions. The functionalization reactions result in relatively minor changes to the structure of a molecule e.g. loss of N- and O-methyl groups, aliphatic hydroxylation etc. but may introduce reactive functionalities such as epoxides and hydroxylamines. The products thus may retain, or even have enhanced pharmacological activity and may be involved in toxic responses as a result of their enhanced reactivity, resulting in covalent binding to critical macromolecular targets in the cell.

The processes of metabolism are thus critical determinants of biological responses by determining (a) the chemical nature and reactivity of metabolites formed within the body and at specific targets within it, (b) the concentration-time courses of the parent compound and its various metabolites within the body and at specific targets within it. Both inter- and intra-species variation, in animals and humans, in the nature and extent of internal exposure and in the sensitivity of drug targets are the cause of major problems in drug development and use and pharmacokinetic variables are most commonly determinants of variability in response.

The Purpose of Drug Metabolism Studies in Drug Development

The objectives of the various pharmacokinetic studies which are performed during the course of drug development may be summarised briefly as follows:

1. Assessment of drug levels and kinetics in blood, body fluids and tissues.
2. The rate and extent of absorption at different dose levels.
3. The distribution of the drug and its metabolites in tissues, organs and body fluids at different dose levels and after single and multiple doses.
4. The pattern and rate of metabolism and excretion at different dose levels.
5. Plasma protein and tissue binding of drug and metabolites at different dose levels.
6. Accumulation and/or retention of drug and metabolites upon chronic dosing.
7. Enzyme induction and inhibition potential of the compound.

From the foregoing, it will be apparent that the drug metabolism scientist is the person who should have the longest contact with a drug molecule during its development phase. As will be seen later, drug metabolism and disposition studies have critical roles to play in the process of nominating new compounds into development. Through the development phase, the work of metabolism and kinetic scientists is absolutely critical to the successful development programme and even in post-marketing support, drug metabolism workers have a great deal to contribute. The stages of drug development where drug metabolism and pharmacokinetic studies have inputs to make may therefore be summarised:

1. Discovery
2. Toxicology and safety evaluation
3. Biopharmacy and drug delivery
4. Clinical pharmacology

and these will be discussed in turn.

Drug Discovery

Although drug discovery cannot have as a primary aim the production of compounds on the basis of their metabolism but produces compounds as ligands for receptors, inhibitors of enzymes etc., it is important that the drug metabolism and pharmacokinetic scientist contributes to the selection of compounds with favourable disposition properties. Thus, it is frequently important to establish the relative extent of absorption, rate of metabolism etc., within a series of compounds,
with the intention of identifying candidates with favourable disposition properties for further development. This is increasingly possible with the aid of a variety of in vitro strategies rather than the classical metabolic studies in whole animals. In this context, it is important to appreciate that we have an increasing ability to make predictions of metabolism through computer modelling of various enzymes and pharmacokinetics, notably with physiological pharmacokinetic models, which in the future may enable the design of drugs to take disposition properties into account as well as primary activity of the molecule in question.

**Toxicology and Safety Evaluation**

Once a compound has been nominated into further development, the pivotal preclinical studies are intended to give confidence that the compound is safe. Most toxicological testing is inevitably done in animals, followed by a judgemental extrapolation of animal data to the human situation. Since “man is not a big rat”, it becomes important to understand factors influencing the validity of extrapolation of animal data to humans. A plethora of variables impinges on such issues, but experience tells us that of these metabolism and kinetic criteria emerge as having prime importance in general terms. During preclinical safety evaluation studies, metabolic and kinetic studies are thus essential to ensure the exposure of test animals to the range of metabolites seen in humans and to assess comparative exposure levels in animals and man to allow the calculation of safety margins on a rational basis.

It is nowadays a matter of common experience that metabolism and kinetic studies are used for the interpretation of the human significance of animal studies in a retrospective manner. However, the application of the same principles presents opportunities for their prospective use in the design of toxicity tests of greater relevance to the human situation. In this context, they can help particularly by:

1. Guiding the choice of animals species appropriate for testing, although it must be admitted that the range of species realistically available is extremely limited to rodents (e.g. rat, mouse, hamster), dogs and certain non-human primates.
2. Providing a sound basis for the design of dose regimes, in particular presenting opportunities to avoid guideline-drive Maximum Tolerated Dose concepts in the execution of pivotal toxicity studies.

In recent years, there has been immense emphasis on the new activity of toxicokinetics and it is particularly significant to consider this in the present context. Toxicokinetics is a term used to refer to the determination of the pharmacokinetic behaviour of drugs at the doses used and in animals used in safety evaluation procedures. Toxicokinetic studies should ideally be model studies, at least in rodents, intended to support formal toxicology studies; it can be frequently very difficult to use the same animals for toxicokinetic and toxicological studies, although in primates and dogs it may well be necessary to combine the two. Properly performed toxicokinetic studies provide an essential bridge between classical toxicology on the one hand and pharmacokinetics and drug metabolism on the other. Such studies are nowadays obligatory in safety evaluation since they provide a basis for the assessment of the relevance of animals safety studies for the human situation.

It is important to distinguish between toxicokinetics and biomonitoring, a term used to describe the limited sampling carried out during subchronic and chronic animal toxicity studies, either on the test animals themselves or on satellite groups, to assure exposure. Biomonitoring is separate from but complementary to formal toxicokinetic studies. A toxicokinetic study of say, thirty days duration may well provide support for studies up to two years duration in rodents provided there has been a rationally-designed monitoring programme during these lengthy studies.

The support of toxicity studies with appropriate toxicokinetics is obligatory in the assessment of safety multiples on a rational basis. The discrepancies between dose offered and concentration in body fluids with so many compounds means that comparisons on a mg/kg basis are inappropriate and it is highly desirable, indeed necessary to design and carry out toxicity studies knowing that animals are exposed to adequate multiples of the anticipated human situation.

**Biopharmacy and Drug Delivery**

Drug metabolism and pharmacokinetic data are essential in the various processes required to convert the new chemical entity which is a drug into a medicinal product suitable for widespread patient use. Included in this process are matters like the selection of route of administration, dose form and frequency of administration which are most convenient for the patient receiving the product.

For many drugs, it is the case that a window of plasma levels may be defined, with a lower threshold concentration, below which little therapeutic benefit may be derived and a higher concentration, above which signs of toxicity may be expected. It is the aim of the formulator to create a dose form and dose regime which keeps the plasma levels of a drug within this therapeutic window for as long as possible.

Drug metabolism and pharmacokinetic information is essential to determine:

1. Optimal route of administration
2. The type of delivery system most appropriate for the drug and disease in question
3. The design of the delivery system to have the required input characteristics

Unfortunately, it is the case that many drugs have been taken into the development process despite their
Clinical Pharmacology

The xanthine alkaloid theophylline was widely used for the treatment of bronchial asthma in the 1950's and 1960's but fell from favour due to an unacceptably high incidence of adverse reactions. This was due to its relatively short plasma half life and wide intersubject variability in its disposition\(^3\). After 15 years of therapeutic disfavour, it became the drug of choice for the treatment of mild bronchial asthma after the introduction in the late 1970's of a number of sustained release formulations, which overcame in different ways the pharmacokinetic difficulties presented by this drug\(^3\).

Nifedipine was the first 1,4-dihydropyridine calcium channel blocker in widespread clinical use. Although valuable for the treatment of cardiac arrhythmias, its acceptability to patients was limited by quite severe headaches seen soon after dosing in a number of patients\(^3\). Pharmacokinetic studies revealed that this was due to transient peak plasma levels being achieved early after administration of conventional tablets. This problem was subsequently overcome by the use of a properly designed controlled release preparation which avoided early peaks in the plasma levels whilst sustaining them for a prolonged period.

Clinical Pharmacology

The programme of clinical studies carried out during drug development has five main aims, each requiring comprehensive input from drug metabolism and pharmacokinetics. These are the:

1. Definition of dose-effect relationships
2. Construction of therapeutic dose regimes
3. Assessment of the magnitude and origin of interindividual variation in response
4. Assessment of possible drug interactions
5. Description of adverse reactions

It is the case that the concentration of a drug in a body fluid such as plasma is generally far better related to its biological effect than the dose administered\(^4\). This means that clinical studies require appropriate pharmacokinetic monitoring and in this regard it is important to ensure that the correct material is being analysed, giving appropriate data for the construction of correlations. Particular problems in this regard may be caused by:

(a) Active metabolites, where it is important to assay the active material in the blood rather than simply the parent drug\(^5\) and
(b) Stereoisomerism, where the analysis of the active stereoisomer is required if a racemate is being given. If non-chiral methods of analysis are used, the results will, at best, have limited value and may be highly misleading\(^6,7\).

A major area of investigation in drug metabolism has been the delineation of factors responsible for interindividual variation in humans\(^2\). It is now understood that there are at least four major sets of factors responsible for such variation:

1. Genetic
2. Physiological e.g. diet, haemodynamics, age etc.
3. Pathological, notably diseases affecting the organs responsible for metabolism and elimination, the liver and the kidney.
4. Environmental e.g. drug interactions, enzyme inducers, enzyme inhibitors etc. which may be encountered deliberately, coincidentally or accidentally.

There are three well defined genetic polymorphisms of drug metabolism in humans, each of which is an autosomal single gene effect which follows simple Mendelian inheritance\(^2\). These are:

(a) The hydroxylation of debrisoquine, sparteine and some thirty other drugs mediated by variant CYP2D6. Some 7% of Caucasian populations are deficient in this enzyme\(^12\).
(b) CYP2C19 mediates the hydroxylation of S-mephenytoin, and this enzyme is defective in some 5% of Caucasian populations and up to 25% in Asiatic populations\(^3\).
(c) The genetic polymorphism of the N-acetylation of aromatic amines and hydrazides, including a number of therapeutically useful drugs, has been known for the past forty years\(^2\). The incidence of this defect is approximately 50:50 in Caucasian populations.

The consequences of these genetic polymorphisms of human drug metabolism are essentially identical\(^2\). In each case, the failure to metabolise\(^16\) a drug along its normal pathway will lead to unexpectedly high exposure of affected subjects with consequently enhanced, generally toxic, effects. Alternatively, failure of a primary pathway of metabolism may throw emphasis on a secondary, normally minor pathway, a phenomenon called "metabolic switching". This may lead to the appearance of toxicity mediated by metabolites in the genetically determined poor metaboliser (PM) phenotype. In this context it is important to appreciate that some 80–90% of all adverse drug reactions are extensions of the known pharmacology of the drug and are dose related\(^5,23\). These arise in general from pharmacokinetic abnormalities leading to unexpectedly high exposure. The genetic polymorphisms represent a major cause of this: other causes include; drug-drug interactions and drug-diet interactions. The remaining 10–20% of drug toxicity emerges from reactions that are in general not dose related\(^4\), are not anticipated on the basis of a knowledge of the pharmacology of the drug and represent new actions, generally mediated by metabolites and which are much harder to anticipate.

The dispositional basis of drug-drug interactions is important to assess. In particular, an appreciation of their
mechanistic basis can often help in the design of rapid and efficient studies which investigate interactions of major consequence while minimising the number of studies performed simply to fulfil guideline requirements. In particular, human drug interactions originating at the level of plasma protein binding displacement, enzyme induction and enzyme inhibition have major consequences, since they can be frequently difficult to predict on the basis of animal studies\(^\text{18,20}\). In particular, insufficient attention is paid to interactions based on enzyme inhibition since these are rapid in onset and lead to exaggerated drug responses.

**The Concept of the “Pharmacokinetic Defect” in a New Drug**

It is arguable that attitudes in drug discovery have suffered from an obsession with potency to the exclusion of all other criteria. Medicinal chemists have typically synthesized compounds, examined their specificity and potency in test systems of relevance and optimized structure-activity relationships on this basis. This approach has ignored those processes involved in the transfer of a drug from its application site to its site of action in the whole animal and the time course of the concentration of active molecular species at these target sites. The consequence of this is that numerous drugs have been advanced through development and even reached the market carrying what can be considered as “pharmacokinetic defects” which have been detrimental to their effective use and profitability. These have been defined\(^\text{8}\) as:

“Pharmacokinetic and metabolic behaviour which makes a drug harder to develop and/or use”

They are generally not absolute barriers to drug development but add significantly to the complexity of development and require a drug to be very carefully prescribed. **Table I** presents a list of “pharmacokinetic defects” and the problems they can give rise to in drug development and use.

Each of these pharmacokinetic defects results in the need for additional work during development and require a drug to be very carefully prescribed. **Table I** presents a list of “pharmacokinetic defects” and the problems they can give rise to in drug development and use.

<table>
<thead>
<tr>
<th>Table I Some “Pharmacokinetic Defects” in drugs and their consequences</th>
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<tbody>
<tr>
<td><strong>Low solubility</strong></td>
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<tr>
<td>Poor absorption; formulation difficulties</td>
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<td><strong>High plasma protein binding</strong></td>
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<td>Variable response in disease states; drug interactions</td>
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<tr>
<td><strong>High First Pass Effect</strong></td>
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<td>Variable bioavailability; variable response; extra clinical studies</td>
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<td><strong>Short half-life</strong></td>
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<td>Dose interval too short; once-a-day dosing not possible</td>
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<tr>
<td><strong>Long half-life</strong></td>
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<td>Accumulation upon repeated dosage</td>
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<td><strong>Active metabolites</strong></td>
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<td>Variable response; extra clinical studies</td>
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<td><strong>Racemate, not defined stereoisomer</strong></td>
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<td>Numerous extra studies required for racemates</td>
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<tr>
<td><strong>Dose-dependent (non-linear) metabolism</strong></td>
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<tr>
<td>Difficulty in setting dose regimes; need for Therapeutic Drug Monitoring</td>
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<tr>
<td><strong>Enzyme induction</strong></td>
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<tr>
<td>Rodents: association with liver and thyroid tumours</td>
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<tr>
<td>Humans: origin of drug interactions</td>
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<tr>
<td><strong>Auto-induction</strong></td>
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<tr>
<td>Difficulty in setting dose regimes for animal toxicity tests or human use</td>
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<tr>
<td><strong>Enzyme inhibition</strong></td>
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<tr>
<td>Origin of major drug interactions</td>
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<tr>
<td><strong>Genetic polymorphism</strong></td>
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<tr>
<td>Population variability in pharmacokinetics and response; difficulty in identifying susceptible patients</td>
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The Concept of the “Pharmacokinetic Defect” in a New Drug...

Integration of Drug Metabolism and Pharmacokinetic Studies within Drug Discovery and Development

Drug metabolism scientists are thus challenged to make hard considerations of exactly what metabolic and kinetic information is necessary and relevant at each stage of drug development. In particular, there is a need to create hierarchies for the acquisition of data. Thus, for a drug intended for oral administration, the early assessment of its extent of absorption is immediately seen to be extremely important. In comparison, while phar-
macrogenetic defects in drug oxidation are academically fascinating, there is no need to investigate phenomena of this type until we have demonstrated that the drug is (a) absorbed, (b) metabolised by oxidation by one of the P450 isozymes known to exhibit the genetic polymorphism, (c) shows a high metabolic clearance through that pathway, and (d) has a steep enough dose-response curve for a change in its pharmacokinetic behaviour to have a real therapeutic or toxicological relevance.

Consideration of the literature shows that in many cases, the drugs of choice in a particular therapeutic area are those with few pharmacokinetic defects. These agents are often not the first drugs of a class to be introduced and many market leaders were introduced second or third in sequence. They have reached their position of commercial dominance as a consequence of their relative absence of pharmacokinetic defects over therapeutically novel drugs which may have been rushed into the market place with little consideration being given to pharmacokinetic defects. Table II provides a list of examples of such drugs.

The quality of the comparisons made is obviously variable. One of the best examples is that of cimetidine with ranitidine. Cimetidine was the first histamine H2 blocker whose introduction revolutionised therapy of gastric ulceration and other related diseases. However, cimetidine has a short half life, requiring administration four time a day and widespread human experience has revealed it to be an inhibitor of cytochrome P450-mediated oxidations of a variety of drugs, leading to drug interactions purported to be of therapeutic significance. Ranitidine, although requiring the same frequent administration as cimetidine, does not possess the imidazole ring of cimetidine responsible for its interactions with cytochrome P450 and the absence of therapeutically relevant drug interactions in this case has been a major contributor to its reaching its current dominance in the marketplace. This, together with other examples to be found in Table II, represents a case where, rather than producing "me too" drugs, pharmaceutical companies who are second or third in the development sequence in a new therapeutic area can produce new compounds which are "me better" as a consequence of reducing the significance of pharmacokinetic defects in the first drug to reach the marketplace.

**Conclusion**

This short review has emphasized a critical role which metabolic and kinetic studies have to play throughout the pharmaceutical research and development process. Illustrating this with reference to pharmacokinetic defects in new drugs has shown the need for the contribution which metabolic and kinetic studies have to make to be enhanced yet further. The need for four innovative developments requires emphasis here:

1. New "feedback loops" in the drug discovery process are required, based on past experience and new experimental data and including pharmacokinetic and metabolic criteria.
2. Very rational decisions must be made about exactly what pharmacokinetic and metabolic information is required to inform decision making at each stage of drug development.
3. Both existing and novel technologies must be exploited so as to obtain the desired metabolic and kinetic data faster than is the case at present.
4. The research management system within pharmaceutical companies must be expanded so as to be able to co-ordinate these new aspects of the discovery and development process, to enable the full benefit of the enhanced contribution of metabolism and pharmacokinetics to be realised.

<table>
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<th>&quot;Defective&quot; drug</th>
<th>&quot;Advantageous&quot; drug</th>
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<tr>
<td>Procaine (rapid ester hydrolysis)</td>
<td>Lignocaine (stable amide bond)</td>
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<tr>
<td>Penicillin G (penicillinase-sensitive)</td>
<td>Cloxacillin (penicillinase-resistant)</td>
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<tr>
<td>Propranolol (lipid-soluble; high first pass effect)</td>
<td>Atenolol (water-soluble; low first pass effect)</td>
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<tr>
<td>Nifedipine (short half-life; variable plasma levels)</td>
<td>Amlodipine (longer half-life)</td>
</tr>
<tr>
<td>Amiodarone (25 day half-life)</td>
<td>Verapamil (5 hour half-life)</td>
</tr>
<tr>
<td>Cimetidine (P-450 inhibitor; numerous interactions)</td>
<td>Ranitidine (no inhibition or interaction problems)</td>
</tr>
<tr>
<td>Ketoconazole (mechanism-based CYP3A inhibitor; numerous interactions)</td>
<td>Fluconazole (minimal inhibition or interaction problems)</td>
</tr>
<tr>
<td>Terfenadine (CYP3A metabolism readily inhibited; unchanged drug is cardiotoxic)</td>
<td>Loratadine (metabolism not easily inhibited; minimal inhibition or interaction problems)</td>
</tr>
<tr>
<td>Ofloxacin (racemate poor solubility; species differences in fate)</td>
<td>Levofloxacin (single enantiomer enhanced solubility and activity; less species variation in metabolism)</td>
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The increasing recognition of the value of drug metabolism studies in drug discovery is one of the pressures to modify the traditional two-phase research and development approach in the pharmaceutical industry. A number of companies have adopted a three-phase approach, inserting a pre-development step between the research or discovery phase and full-scale clinical development. In this, initial candidates are tested in human subjects together with selected relevant formal metabolism and toxicology studies. These latter are chosen on a case-by-case basis to provide the maximum indication of problems later in full development.

In addition to the intensive physiological monitoring on human subjects in Phase I studies, these should also be designed to provide the maximum amount of metabolomic and pharmacokinetic information. It has been claimed that the inclusion of this third phase can enhance the success rate through formal development to 50% or more. Whether or not the third, predevelopment phase is introduced formally, it is ever more true that there is no alternative to the early evaluation of candidate new drugs in human subjects. Data of direct human relevance, obtained both in vivo with traditional approaches and in vitro with human-derived samples, are increasingly used in decision making. The enlightened regulatory attitudes to early human investigation in the United Kingdom have greatly facilitated the use of this approach, leading to discussion of the issue within the ICH process.

The sequence for decision making in drug development in Japan generally differs from that commonly seen in Europe and North America, with a much stricter division between "preclinical" and "clinical" phases\(^{26}\). The preclinical work done in Japan before first human exposures is far more extensive, notably in terms of formal toxicology studies and human data are generally not part of the decision making process. Project planning in Japan is thus more rigid than is generally the case in Europe or North America, with early decision making still based on the classical criteria of specificity and potency of action.

Drug metabolism and pharmacokinetic studies have essential roles to play in all stages of the pharmaceutical research and development process, ideally being involved from the pre-nomination phase in drug discovery right through to post-marketing surveillance. Failure to take metabolic and kinetic variables into consideration results in the progression of drugs with "pharmacokinetic defects" which cause expensive delay and/or failure during development and make an approved drug vulnerable in the marketplace. It is argued that the thoughtful inclusion of new feedback loops, based on relevant metabolic and pharmacokinetic data, into decision making at the various stages during drug development will contribute to enhanced time- and cost-efficiency of development and ultimately lead to safer, more easily used, drugs.

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