

Clinical Drug Development—Practical Issues in Clinical Pharmacology Studies

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Abstract

Introduction: Clinical pharmacology refers to the study of the safety, pharmacodynamic activity, mechanism of action, pharmacokinetics, metabolism and excretion of a drug in man. **Methods:** Selected review of topics that provide guidance on practical issues for researchers conducting non-therapeutic investigational research in humans. **Results:** Close attention to the issues highlighted is needed to ensure successful research in this area of drug development. Resources dedicated to the discipline can logically optimise efficiency and outcome. **Conclusions:** There is increasing opportunity for clinical pharmacological research, offering an interesting career option to young physicians.

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Introduction

Clinical pharmacology (CP) as a discipline comes in many guises. The perception for a medical student, and for many doctors, may be that of a painful series of lists of drugs to learn, the drugs being traditionally classified by functionality and effects. For others, perhaps with a more investigational mindset, it is an integrative discipline at the interface of normal and pathological physiology and therapeutics. This is certainly the case in the context of drug discovery and development—the subject of this article. Here a reasonable working definition would be ‘the study of the safety, pharmacodynamic activity, mechanism of action, pharmacokinetics, metabolism and excretion of a drug in man’. This involves a deep understanding of (patho)physiology, the molecular basis of drug effects, as well as mechanisms of absorption, distribution, metabolism and elimination (ADME). In addition, the experimental nature of the discipline demands robust, practical techniques to investigate the effect of drugs in the human organism. The range of types of studies is broad (Tables I & II). Since this subject is so large, this article will seek to introduce the practical aspects of drug development studies, especially since this a rapidly developing area for Singapore’s involvement in health care research and delivery. For more comprehensive advice, the references in this paper may be usefully consulted.

Study Types

Other articles in this special issue discuss the drug development process, and the terminology. The term ‘phase 1’ is often misused; to encompass all the types of studies that can be performed in non-patient, ‘healthy volunteer’ subjects. This view comes from focussing on the substrate of the experiments rather than the scientific goals. Table I is a non-exhaustive listing of the types of studies that are commonly conducted in the CP arena of drug development. It is important to appreciate that this discipline is responsible for taking a new molecule into humans for the first time [true ‘phase 1’ (Table II)], as well as providing key supporting data for dosing in various populations and co-prescribing situations. In our experience, a typical new drug application supporting registration will contain around 25 clinical pharmacology studies. This total number involves exposures of about 200 subjects and provides critical information for decision making during the process of developing a drug, as well as key dosing information for prescribing. This is compared to 10 to 15 ‘clinical’ (phase 2 or 3) studies defining the efficacy and safety in upward of a thousand patients.

Prerequisites for Studies

Data

The overriding principle has to be to understand and

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TABLE I: EXAMPLES OF DIFFERENT STUDY OBJECTIVES

- Mass balance (e.g. radiolabelled to determine organs of elimination)
- Metabolic kinetics
- Effects of food
- Absolute bioavailability
- Relative bioavailability of oral formulations (e.g. solution/capsule/tablet)
- Bioequivalence of “market image” formulation (compared to clinical trial forms)
- Pharmacodynamic dose response
- Intra-subject variability in response
- Special populations, such as renal, hepatic, elderly, children, ethnic groups, etc
- Drug-drug interactions—pharmacokinetic, pharmacodynamic
- Effects on sleep
- Secretion in breast milk
- Chronobiology interaction (e.g. diurnal pattern of effect e.g. blood pressure)
- Receptor mechanistic (e.g. using positron emission tomography)
- Mechanistic studies using pharmacological agonist challenges
- Mechanistic—problem solving for adverse effects
- Mechanism of elimination (e.g. modification of metabolism or active transport in gut or kidney)

eliminate, as far as possible, risks to subjects in studies. This requirement is of particular importance for studies conducted in non-patient volunteers—after all, these people receive no medical benefit from the experience, and so the risk benefit ratio has an undefinable denominator. Whilst there is always the possibility of unforeseen effects, with good preparation, these situations should be infrequent. In addition, the conservative approach to phase 1 study design provides a step-wise exposure to doses of drug (see below), as well as intensive monitoring to identify and minimise the impact of any new effect.

Data needed to support studies fall into two broad categories:

- 1) preclinical or clinical data from exposure of the test drug in question, and
- 2) data (for example, published studies) from related drugs or mechanisms of action or different groups of subjects or patients.

As with all good science, it is inappropriate (and in this case, unethical) to proceed without basing the design on all the available evidence. For phase 1 studies, this involves specific preclinical experiments being conducted to provide the information. The exact nature of these studies will depend on the test molecule, but there are internationally recognised guidelines,¹ to which sponsoring pharmaceutical

TABLE II: PHASE 1 – FIRST HUMAN DOSE STUDY (FHD) OBJECTIVES

Phase 1 studies need to deliver a safe and workable dose regime to test the efficacy hypothesis in the target patient group.

Early Phase 1 Objectives

(generally performed in healthy volunteer subjects)

- Safety
 - to identify side effects: intensity, duration, relationship to dose/concentration
- Tolerability
 - generally at doses above those anticipated in efficacy studies
- Pharmacokinetics (PK)
 - C_{max}, T_{max}, T_{1/2}, dose proportionality and linearity, etc
 - ADME (absorption, distribution, metabolism, excretion)
- Pharmacodynamic (PD) activity
 - presence at effect site, dose/concentration-response relationship
- Relative or absolute bioavailability

Late Phase 1 Objectives

- Determine PK in patient population (population approach)
- Determine safety, tolerability, PK in special populations: concomitant diseases (e.g. hepatic, renal), drug-drug interactions, ethnicity, gender, etc
- Special PD studies e.g. PET, polysomnography

TABLE III: PRECLINICAL SUPPORT—SAFETY AND PHARMACOLOGY

Minimal Needs (ICH M3 Guideline)

- 14 days – rodent
- 14 days – non rodent
- Genetic toxicology – Ames, Chromosome aberration
(Supports single dose – 14 days dosing in adult human males and infertile females)

In addition, the following information is usually available:

- *In vitro* potency, efficacy, affinity and selectivity
- *In vitro* dose related effect on relevant activity
- Effect duration
- Relationship of parenteral and oral dose activity
- ADME data and activity of any metabolites
- Activity in animal disease model – preferably in more than one species with clinically relevant (human) surrogate markers

companies adhere. It is understood that these guidelines are also the basis for review and approval of early clinical studies in Singapore [in addition to the requirements of the Medicines Act,² International³ and Singapore Good Clinical Practice (GCP)⁴]. A simplified summary of information usually required prior to first dose in man is shown in Table III. Interpretation of this information by the investigator conducting the phase 1 studies is very important. There are two key elements:

- 1) the expected pharmacological effects, and the dosing threshold for these effects, and
- 2) observed organ or tissue toxicities.

For each element, the concept of systemic exposure to the test compound (and metabolites) is more important than dose level alone, even if expressed in a body size normalised format (e.g. mg/kg or mg/m²).⁵ This is because of the interspecies variation in absorption, distribution and metabolism of drugs, as well as in pharmacodynamic effect. For example, it is well known that dogs lack the ability to metabolise drugs via acetylation, and that rodents can tolerate doses of insulin 2 orders of magnitudes above humans without hypoglycaemia, due to the molecular specificity of the insulin molecule.

The general rule for ‘first in man’ studies (Table II) is to start at a dose level that the preclinical evidence would indicate is below the threshold for pharmacological effect and is at least 1 order of magnitude below the highest ‘no effect’ level in the most drug-sensitive animal species.

Workable, Approved Protocol

It is taken as a ‘given fact’ that the requirements of GCP will be complied with. This is a requirement for the necessary independent sanction of approval for a study by the hospital ethics committee and Medical Clinical Research Committee of the Ministry of Health (MCRC). However, this is not just a matter of ‘checking’ against a bureaucratic list. It is rather a matter of sensible study design—a mixture of science and pragmatism, but always considering the safety and convenience of the subject foremost. For example:

- Can the subject or patient reasonably be expected to spend 10 nights in the research unit or to come back late at night for blood samples daily or to spend 72 hours supine, hooked up to an intravenous infusion of the drug of interest?
- Is the total blood loss from pharmacokinetic and other samples during the experiment acceptable? (Commonly, the volume given during a single blood donation, i.e. about 450 mL, is used as a benchmark for the limit of total blood loss during a short-term experiment.)
- Does the study impose unreasonable restrictions on daily life outside the research context, e.g. diet, smoking and alcohol consumption, sexual activity, driving or operating heavy machinery, etc.?

Study Design

This is where science, experience and practicality come together, and is largely driven by statistical considerations and the relevance or measurability of the endpoints. The number of subjects and the intensity of measurements together determine the resources required for execution of the study. Whereas one may be able to get a clear view of the pharmacokinetic profile of a given drug with low variability in 6 subjects after a single dose, another drug

with more variable kinetics or metabolism may require 30-plus subjects and more prolonged dosing. Similarly, pharmacodynamic measures are often inherently more variable, and tend to increase the study size requirements. It is therefore imperative to reduce all sources of variability in the study. This is most commonly done by firstly restricting the study to healthy young subjects, perhaps all of the same gender. In the selection of subjects (see below), certain characteristics, known to impact study measurements, may need to be restricted. This may lead, for example, to a protocol with inclusion criteria which specify narrow ranges for age and body mass index, as well as restrictions on the diet, alcohol, other drugs, etc, during or between study periods.

The most commonly used study strategy in CP studies uses a ‘crossover’ design. Here the subject acts as his or her own ‘control’ between treatments or interventions. Such an approach relies on the *intrasubject* variability for most parameters being much less than the *intersubject* variability (even if subjects are well matched) in the alternative *parallel* group study design.

Phase 1 Studies

Whilst these studies comprise less than a quarter of the work of our CP organisation, the design issues deserve special mention. This part of a research programme is characterised by studies comparing doses over a range of perhaps 2 logarithm orders, and where endpoints are safety observations and pharmacokinetics. A typical phase 1, single rising dose, study may investigate 8 dose levels. The study needs to be a ‘rising dose’ study, for the obvious reasons of needing to understand the safety information at lower dose levels first (since toxic effects, like most pharmacodynamics, are most usually dose related). There is also a strong desire to have a placebo control at each dose level. Overall, this desire means that it is not feasible to have a crossover design, to allow comparison across all doses within the same subject. In addition, there are some disadvantages of the crossover approach related to the sequential administration of the same drug that need to be

TABLE IV: EXAMPLE OF PHASE 1 STUDY DESIGN, USING ALTERNATING GROUPS OF SUBJECTS TO COVER A DOSE RANGE OF 2 mg TO 400 mg

Dosing occasion	Dose escalations to be randomised	
	Group A	Group B
1	2 mg or placebo	*5 mg or placebo
2	*10 mg or placebo	*20 mg or placebo
3	*50 mg or placebo	*100 mg or placebo
4	*200 mg or placebo	*400 mg or placebo

* The subjects will not receive this dose until the previous dose has been given to subjects in the other group.

borne in mind, such as ‘first dose effect’, sensitisation, tolerance, and the carry-over of effect between study periods. All these facts mean that there is not an ideal, practical design for phase 1 studies. Such studies should therefore be designed carefully according to what is known about the drug and the class to which it belongs. Notwithstanding the previous statement, there are fairly common, pragmatic designs which have been frequently used. For example, a design that I have had success with uses 2 groups of subjects being exposed to 4 dosing periods, and the groups alternating in the dose escalation sequence. Each subject receives placebo on one occasion. As depicted in Table IV, this can provide a comparison of 6 active versus 2 placebo doses at each of 8 dose levels involving 16 subjects. The alternating sequence allows for efficiency of ‘washout’ and safety observation in between dosing periods for each subject, without slowing down the progression of the study unduly. The design allows a dose response across 3 doses within subjects, and 2 placebo exposures during each dosing period.

The above example would not, however, be suitable for a situation in which there is a prolonged biological effect resulting in impractical, or unknown, intervals between dosing exposures, or in which the first dose of drug may be expected to show different biological effects to subsequent doses (via pharmacodynamic or immunological mechanisms). In such situations, different groups of subjects would be needed for each dosing level, with the acceptance of loss of ‘power’ in interpreting the dose response relation.

Subjects

Facilities

The facilities used for clinical experiments must be able to provide the clinical care and procedures necessary for the conduct of the protocol as well as for coping with medical emergencies. These needs obviously require attention to staffing and training, in addition to the physical facilities. Whilst many CP studies will be conducted in a hospital environment, they may not be taking place in an area of the hospital where emergency care of acutely ill patients is routine. In this case, and in the case of research units not based within an acute hospital, particular care needs to be taken to ensure adequate training in life support and resuscitation facilities.

In addition, there will be equipment and laboratory needs that are specific to the investigations planned. One universal need is for a robust system to ensure the integrity of identity of blood samples and other specimens through the chain of laboratory processes that may be involved (such as centrifugation, separation, etc) and secure storage at the appropriate temperature to ensure stability of the analytes.

The Guidelines for Medical Experiments published by

the Association of British Pharmaceutical Industries (ABPI)⁶ is useful in discussing facilities for CP studies.

Selected Practical Issues in Conducting Studies

Volunteer Recruitment

The best-trained and experienced staff, and wonderful facilities, only go a small way towards attracting the most valuable asset—healthy volunteer subjects for studies. Recruiting volunteers is not an easy task, since by definition these people are not sick, or seeking medical care, and therefore they will not be already attending the clinic. A practice often used historically has been the recruitment of ‘volunteers’ from the staff of the research institution. Whilst this has the benefit of accessibility, and well-informed and motivated subjects, the practice is not uncontroversial. Difficulties arise because such subjects may have pressures from peers, supervisors, etc. that affect their ability to make an informed decision of their own free will. As a result, some institutions, including ours, have a policy against such practice, to completely protect staff.

For a busy CP unit, the recruitment of suitable subjects requires a dedicated infrastructure. With a continuing flow of studies, it is useful to have a ‘generic’ screening process that assesses subjects for entry to a ‘panel’ of volunteers that can be drawn upon for specific studies. Over a period of time, a database can be established that provides a range of subject characteristics for various studies. This may include panels of subjects with stable chronic conditions (e.g. diabetes, impaired renal or hepatic function, etc) and normal subsets (e.g. post-menopausal females). The screening process in our unit involves a medical assessment and battery of tests to ensure the health status of the subjects, as well as assessment of genotype or phenotype or both for certain drug metabolism processes. This is conducted according to a standard protocol, approved by the Ethics Committee.

Payment

Although many subjects believe their participation in CPs studies benefits medical science, it is unrealistic to rely completely on altruism to provide a supply of subjects. It is generally accepted practice to make payment for participation and travel, especially since subjects in CP studies derive no therapeutic benefit themselves. Payment for time, indexed at a low level (unskilled or minimum wage) rate is the most generally used method. Such an approach is compatible with the requirement in GCP for payments not to be ‘coercive’. This has been called the ‘Wage Payment Model’,⁷ and is the method we use.

Two important considerations for investigators and the reviewing ethics committee are the issues of risk versus payment, and the approach to payment for subjects who

discontinue a study prematurely. Whilst it is acceptable to modify payment for predictable discomfort or inconvenience, it is completely unacceptable to make (or be perceived to make) payment for risk. The onus here is on the investigator to protect the subject by a protocol design that seeks to eliminate risk of permanent injury or discomfort of more than a very short duration and to satisfy the ethics committee in this regard. Subjects who discontinue prematurely need to be reimbursed, but it is also reasonable to protect the investigator from the serious impact to the integrity of a study by the premature withdrawal for non-medical reasons by insincere subjects. The GCP guidelines are clear on the need to avoid payments being entirely contingent of completion of the study. A sensible approach is to differentiate between withdrawal 'for cause' (i.e. medical reasons such as adverse effects, etc.) and fully reimburse such situations, but to provide a financial disincentive for subjects to withdraw prematurely for trivial reasons (social engagements, etc.). Such a scheme, specifically endorsed by an ethics committee, and administered generously, should avoid legitimate criticism.

Whilst GCP guidelines and local law are not very specific on the subject of healthy volunteer studies, useful discussion is available from UK guidelines.^{8,9}

Ethnic Issues

This is an example of a special consideration in Singapore. This is not to say that other countries do not have multi-ethnic populations, but the transferability of trial-derived information across ethnic groups is currently an area of great interest. It is outside the scope of this article to review the scientific¹⁰ and regulatory backgrounds to this issue. It suffices to say that there is a guideline¹¹ addressing this subject for consideration of acceptance of data for registration of drugs. The scientific understanding of the impact of ethnicity on the behaviour of drugs is a particular interest of our unit. The available information is patchy, and whilst one can make reasonable scientific predictions based on an understanding of the class of drug, in particular the ADME characteristics, it is not possible to make definitive statements about effect in different groups of humans without generating the data. This fact, therefore, means that to extrapolate the results of a particular experiment with a specific drug across ethnic groups requires either a parallel study in alternative ethnic groups or a clear scientific justification as to why one believes there is not cause to expect differences. The latter requires a good description of the phenotype of your subjects, and may in some cases require genotype description. We are currently using the genotype results of our volunteer panel¹² to select subjects most appropriate to 'match' a Caucasian population for a drug that is metabolised by an enzyme

subject to genetic polymorphism, for which ethnic differences are known (cytochrome P450-2D6).

Special Pharmacodynamic Techniques (Biomarkers and 'Surrogate' Markers)

This area is one in which the specific interest, skill and experience of the investigator and staff are very specific. There are many clinical measurements, such as blood pressure, blood glucose concentration, etc. which are in general use and can be used as a marker of the biological effect of a drug. The next level is that of specialised tests, either readily available within a medical subspecialty, such as doppler flow echocardiography for cardiovascular dynamics or pulmonary function tests for anti-asthma drugs. However, often such measures lack the precision necessary for statistical power to detect differences in small studies. The third level of biomarkers are those that are specifically developed for CP studies. Examples in the metabolic and the cardiovascular domains, respectively of physiological pharmacodynamic measures are:

- 1) the glucose clamp technique, which measures the metabolic response to insulin,¹³ and
- 2) the forearm plethysmography model for limb blood flow.¹⁴

In addition to such clinical measurements, the advent of genomics gives us an ever increasing array of biochemical measures which might in time be validated as disease markers. These are obviously the areas where a CP unit can really establish a reputation and interest in the investigation of new drugs.

Surrogate outcome markers, on the other hand, are outcome measures that are believed to be a valid surrogate for a beneficial treatment effect. Such measures may be useful in CP studies, but are more relevant to phase 2 and 3 studies in patients. The acceptance of these measures will change with time. A recent example is that of changes in specific lymphocyte counts with anti-HIV treatment, subsequently replaced by measures of actual viral RNA 'burden'.¹⁵

Conclusion

Some of the practical issues in conducting CP research in the context of drug development have been highlighted. The nature of the studies and of the human subjects used, differentiate them from other clinical trials. This has been one of the historic reasons for the development and progression of the specific discipline of CP. Whilst in the past the opportunity has been small for contributions from Singapore in this area, the expanding area of drug development and the increasing focus on health care development in the region, both from government and pharmaceutical sponsors, provides excellent and stimulating

opportunities. This can translate into added interest for health care professionals, and additional career options in clinical research.

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