Clinical Pharmacology in the pharmaceutical industry*

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Background

The objective of pharmaceutical research and development is to discover, develop and achieve marketing authorisation for new medicines. This process begins with an idea or concept which leads to synthesis of a new chemical entity showing the required activity in a specifically designed test in animals or biological models. At the end of the process is the granting of marketing authorisations for the new medicine by governments around the world. In between is a period which is lengthening all the time, from an average of less than 3 years some 2 decades ago to some 10–15 years at present. This period is associated with costs of the order of £100M to £200M which also reflect that for each new medicine reaching the market around 5,000–10,000 compounds have to be synthesised and screened. Of the total research and development costs, around one third is attributable to discovery and two thirds to development. Within this two thirds the greatest proportion of costs are associated with clinical work and clinical trials. Similarly, of the total development time, clinical studies occupy the longest phase.

It is not always easy for those without direct experience to understand why it should take 10–15 years to produce a new drug: indeed this difficulty is often shared by those within the industry! The implications of lengthening research and development times are sizeable both in terms of how long it takes before valuable new medicines are generally available to patients and in terms of commercial return and hence research and development viability, given finite patent life. For a major new drug annual world-wide sales may be as high as £1 billion, so it is easy to calculate the potential adverse financial consequences of a delay of even a week, let alone a year, in the development process. To some extent, of course, these disappointing trends result from the increasing amounts of information on the safety and efficacy of a compound that are rightly expected before it can be registered for sale. There is, however, a need, long perceived by the basic scientists, to conduct the early evaluation of drugs in man more effectively and more rapidly. Some would look back enviously to, for example, the development of penicillin where all the work needed between isolation and first testing in man was achieved in less than 6 months.

Expectations

What are the research scientists working in industry, those who synthesise, discover and test new drugs, looking for from their colleagues in clinical pharmacology? As a new compound develops through animal tests there comes a time when it is necessary to examine its pharmacokinetics and pharmacodynamics in man. It is the task of the clinical pharmacologist to do this and also to produce feasible and realistic plans for clinical development of the compound. Early studies in healthy volunteers often provide the opportunity for important pharmacological observations. With a new anti-histamine, for example, the effects of oral dosage against histamine wheal and flare reaction in the skin can be assessed, together with rigorous measures of sedation. Similarly, for a new analgesic, there are simple ways by which the clinical pharmacologist can demonstrate activity of the compound in man.

The clinical pharmacologist should be able to ensure that the best methods are applied to provide information of maximum predictive value for drug safety and efficacy from both healthy volunteer and early patient studies. This work should then, together with the pre-clinical data, provide the indications of efficacy and relative safety such that a decision to go ahead with extended phase III clinical development can be made. The innovative clinical pharmacologist can make an important contribution by devising or adapting methods by which the desired activity is demonstrated and ineffective or harmful compounds are discarded at an early stage in their development. Millions of pounds can be saved, and spent more fruitfully elsewhere, by stopping the development of a compound early in its life rather than several years later.

The clinical pharmacologist has an important part to play in decisions regarding human dosage. In the initial human testing efficient dose ranging studies are needed and with good judgement these will not start with an infinite dilution working up to an active dose over a period of many months. Prediction and demonstration of optimum dose in early studies in patients are of vital importance as a foundation for the future successful development and registration of the compound. Often it is appreciated only too late in development that an optimum dose or dose regime has not been selected.

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It is important that the role of the clinical pharmacologist in industry is not hindered by lack of back-up facilities such as access to resuscitation and intensive care units which are appropriate to some studies. Several pharmaceutical companies have overcome this by providing clinical pharmacology facilities in an academic and hospital setting, to enable their own industrial clinical pharmacologists to work in a proper environment.

The role of the clinical pharmacologist in industry, however, is distinct from that of his academic counterpart and it is not the function of the discipline in industry to test new concepts. For instance, Wellcome Research Laboratories and the academic Department of Pharmacology and Clinical Pharmacology, St George's Hospital Medical School reported the effects of monomethyl-L-arginine on forearm blood flow in man (Vallance *et al.*, 1989). This inhibitor of endothelium-derived nitric oxide synthesis was shown to reduce basal blood flow and attenuate the dilator response to infused acetylcholine but not that to glyceryl trinitrate. This allowed the conclusion that nitric oxide is likely to be a key determinant of regional blood flow and of arterial blood pressure in man. This was an important observation and it might be asked why the study was not done within the Clinical Pharmacology Unit of Wellcome. In our view that would have been less appropriate. This was a sound piece of academic research, carried out in the right environment. Monomethyl-L-arginine might be followed by a specific inhibitor of nitric oxide formation with a potential in, for example, shock. In that case the testing in man of the properties of such a potential medicine should be carried out by the industrial clinical pharmacologists. These scientists can be expected to recognise the distinction between such academic and industrial roles.

Organisation

There is a much greater difference than often appreciated between the expertise and aptitudes needed for the investigative testing of a new chemical entity in man and that needed to organise the large scale phase III clinical development programmes. Clinical pharmacologists need to be in an environment where they can discuss the kind of techniques, the best methods to be applied and the range of indications which may be available for a new drug. They should constantly be involved in attempting to translate animal experiments, methods and results into human application. The information they generate may well be the foundation on which the later comprehensive phases of clinical development are based but such later activities are not within the remit of the clinical pharmacologist though his input may be usefully sought on, for example, methodology and dose selection.

It is not generally realised that in the highly structured organisation of a pharmaceutical company personality

characteristics, together with personal predispositions, may greatly interfere with what should be the smooth progression of a compound through different directorates. These are best exemplified by the contrast between the personalities needed for a marketing career (extrovert, assertive, good talker etc) and a research career (thoughtful, introvert, good writer etc). Such differences are relevant to where clinical pharmacology fits in the overall research and development structure because, given the wrong structure, the smooth progression of the drug's development is hindered. Certainly the transition from pre-clinical development to early human studies must be a smooth and continuous process. Artificial distinctions between pre-clinical and early phase clinical development are not necessarily sufficient reason to separate these aspects into completely different teams of scientists and different divisions within the company. To do so creates obstacles at a crucial stage of drug development and rapid and effective development is about removing, not creating, such barriers. Some companies have adopted systems whereby clinical pharmacologists, toxicologists, chemists, etc., are all organised into multi-disciplinary teams grouped around therapeutic areas. This has the disadvantage of separating people, like pharmacologists, who should be speaking the same language. In other companies scientists are organised, more rationally, by discipline. In yet others there is a matrix system with departments organised by disciplines but with multi-disciplinary teams assigned to each therapeutic agent and its development and led by one person who can adequately champion the drug as project leader.

The traditional organisation of a research and development directorate has been to create separate research, development and medical divisions. As far as the clinical pharmacologist is concerned this has the disadvantage of isolating him from research. Clearly, from the discipline point of view, having a medical degree is no more reason to band people together than is having a Ph.D. In our view a better organisation has the clinical pharmacologist as part of the research division, for their objectives are similar in demonstrating the activity of a substance both in animals and in man. A clinical pharmacology department which is part of the research directorate rather than the traditional medical department will be stimulated by day to day contact with research colleagues and will be well placed to respond to the opportunity to progress new compounds as quickly as possible. The remainder of the clinical division, together with capabilities for later phase clinical trials and all their associated organisational and logistic support properly belong in development. Given such an organisation the artificial obstacles to transition from pre-clinical to human evaluation should disappear and overall development time be reduced.

Hence we may conclude that just as the Clinical Pharmacology Section has remained an integral part of the British Pharmacological Society, so should clinical pharmacologists in industry be part of the overall pharmacological and research climate.

Reference and suggested reading

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