The importance of clinical pharmacology in drug development

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Introduction
The development of new medicines is both time-consuming and expensive (George, 1974; Cromie, 1980). It is estimated that 10 years or longer may elapse from the taking out of a patent on a 'new product candidate' to its marketing, at an overall cost of between £16 and £40 million. Much of this expenditure is due to the requirements of regulatory authorities, which attempt to legislate for all possible eventualities. But, for several years, it has been recognized that the existing regulations may inhibit the introduction of new medicines to clinical practice (European Workshop, 1977; Breckenridge, 1980). An analysis from Imperial Chemical Industries (Cromie, 1980) suggests that only 3% of their research work is productive. Much of the remainder comprises extensive tests that have to be conducted on compounds that are abandoned during early clinical testing.

The time and work required before clinical testing can commence in the United Kingdom is on average four times that needed in other western countries, including Germany, Holland, Sweden and the U.S.A. These delays are further compounded in the process leading up to approval for clinical testing (estimated to be ten times as long in the U.K. as in the above countries). Continued pressure from both representatives of the pharmaceutical industry and university departments of clinical pharmacology has led to recognition by the Department of Health and Social Security that existing requirements may be disadvantageous. In a speech given at the Jubilee Dinner of the Association of the British Pharmaceutical Industry on 16th April 1980, the Secretary of State announced that arrangements are being made to revise the procedure for approval of clinical trials under the Medicines Act. Under the revised legislation it is proposed to introduce an Order [under Section 35(a) of the Medicines Act] to allow the licensing authority to permit exemption from the requirement for a company to obtain a clinical trials certificate. Unless further information or discussion is thought to be necessary, the processing of this exemption will be completed within 35 days of notification and delivery of a summary of the existing data. If these proposals are adopted some of the existing delays will be reduced. However, this is only part of a larger problem and it is important that a further look should be taken at the nature and amount of data required before clinical testing is permitted.

Existing situation
Before a new drug can be tested in man it must undergo extensive preclinical investigation. This preclinical testing in animals, tissue culture, bacteria etc. is intended to identify an action that may be of potential benefit to man and to prevent use of drugs that are likely to be hazardous. Although it cannot be denied that toxicity testing is necessary and that, on occasions, it can identify a potential problem (George, 1974; George, 1980a) it can have no absolute predictive value for unwanted effects in man. For example, it has been impossible to reproduce the oculomucocutaneous syndrome associated with practolol use in any animal species. The only way to find out whether a new drug is safe and efficacious in man is to give it to him. Some risk is unavoidable if new drugs are to become available for treating diseases that either do not respond at all or in which existing therapy is unsatisfactory. The major issue is what information is it reasonable to require for human testing? Clearly, representatives of the pharmaceutical industry believe that the existing require-
ments are excessive (Brimblecombe, 1978). Since this problem is being investigated currently by a Working Party of the Committee on Safety of Medicines, I shall not discuss it further. Instead, what I shall attempt in this paper is to demonstrate that decisions on the likely value of a new product could be based upon studies conducted on a small number of human subjects (normal volunteers or patients). Furthermore most of the evidence available suggests that the risks involved in performing such studies with limited pre-clinical toxicity data are small. In marshalling my arguments I shall draw heavily upon my own experience and quote only selected examples from the work of others. I shall confine myself to a discussion of drugs that have an effect on man himself, rather than organisms, such as bacteria, which may invade him.

**Potential advantages of making it easier to study drugs in patients**

The precise conduct of the first few administrations of a new drug to man depends on whether the investigator is based in the pharmaceutical industry or academic medicine (Blackwell & Martz, 1972), but is influenced greatly by current legislation. Thus most phase I studies in the U.K. are done without Government permission on volunteers who are often recruited from within industry (Breckenridge, 1980). The information that can be obtained from such studies relates to the effects of a drug and an assessment of its disposition and elimination in health. The alternative approach, which is difficult in the U.K. at present, is to conduct many of these initial evaluations in patients who are suffering from the disease in which it is intended to use the new drug. A strong case for this has been argued both by Azarnoff (1972) and Oates (1972). Potential advantages include a greater likelihood that evidence of efficacy will be forthcoming at this early stage of assessment. For example, although drugs may lower the blood pressure of normal subjects, an effect is more likely to be seen the higher the initial blood pressure (Cranston, Juel-Jensen, Semmence, Handfield-Jones, Forbes & Mutch, 1963). Similarly, evidence of dopamine-agonist activity could be obtained by studying the effect on plasma prolactin concentrations, but therapeutic effects will be more easily demonstrated in patients with Parkinson's disease. However, there are situations in which therapeutic effects can only be demonstrated in patients. Examples include the beneficial effects of prophylactic sodium cromoglycate in asthma (Altounyan, 1967) and the suppressant actions of anti-arrhythmic agents.

The precise number of patients needed for the initial studies will vary according to the disease in question and the confidence limits of the method(s) of assessment used. However, they are unlikely to be large and rarely exceed a dozen subjects. For example, in the case of the antihypertensive agent, indoramin, presumptive evidence of this action was seen in the first five patients studied and this was confirmed later in a double-blind evaluation in eight patients (Lewis, George & Dollery, 1973).

Alternatively, the 'new product candidate' might be abandoned at an early stage either because of failure to demonstrate any useful effect in patients or because of the occurrence of unwanted effects. Not only should this minimize the number of people who are exposed to potential harm, but also expenditure will be comparatively low since the short-term testing of new drugs in patients should not require more than 14–28 days toxicity testing in animals. For example, evidence of a positive inotropic action of a new imidazoline drug was obtained in only five studies performed on two individuals (C. F. George, unpublished work). Despite the fact that increased cardiac contractility occurred, it was decided to abandon the investigations at this early stage because of the occurrence of an unwanted effect, xanthopsia, during the infusion. No amount of animal toxicity testing would have allowed the prediction of this effect since you cannot talk to a rat!

There is now abundant evidence that drug disposition and elimination may differ significantly between normal subjects and patients with a variety of disease states. The latter may lead to alterations in protein binding (Piafsky, 1980) and hence distribution and efficacy as well as to change in the rates of metabolism (George & Watt, 1979) and renal elimination (Dettli, 1974). In addition, because many patients will be either middle-aged or over 65 years, data obtained from them may be more representative and relevant than those obtained from subjects in their second or third decades. In my view early studies of drug disposition and their main routes of elimination are essential to rational development (although not always possible). Many animal species differ from man in their specific rates of drug metabolism as well as in their preferred pathways of elimination. For example, rodents usually metabolize drugs very much more rapidly and in addition, biliary excretion is quantitatively more important because of the species variation in molecular threshold for biliary excretion (Hirom,
Millburn, Smith & Williams, 1972). Because of this the selection of two appropriate animal species for long-term toxicity testing should be influenced by the pattern of disposition and metabolism seen in man.

Secondly, it is important that clinicians who are likely to be undertaking studies of the new drug know as early as possible in which groups of patients special care needs to be taken. Amiloride, a potassium-conserving diuretic, represents an example of this. Soon after it was tried in man, severe hyperkalaemia occurred in a small number of patients (Bull & Laragh, 1968; McNay & Oran, 1970). The demonstration that this drug (or others) is excreted unchanged in urine (Weiss, Hersey, Dujovne & Bianchine, 1969) should alert physicians to the possibility that its elimination will be reduced and half-life prolonged as renal function deteriorates (George, 1980b). The logical corollary of this is that the drug should be avoided or used in smaller than normal doses in patients with renal failure. Similarly, the demonstration in four to six subjects that there is extensive metabolism at the first pass across the liver should lead to appropriate precautions in patients with chronic liver disease (George & Watt, 1979).

Potential disadvantages of early studies in patients

One of the chief disadvantages of using patients for the early evaluation of drugs relates to ethical considerations. At present, most Area Health Authority Ethical Committees have to deal with submissions relating to drugs that have already been subject to detailed scrutiny by the Committee on Safety of Medicines and have been studied in a limited number of normal volunteers. Reducing the amount of scrutiny by ‘outside’ organizations will shift the responsibility to the pharmaceutical company concerned and will place a greater onus on the investigator than is currently the case. He will have to balance the need for a new drug in a particular disease against the likelihood of the new compound being an advantage over existing treatments and the risks involved. The final decision that a study is justified can only be taken by the physician (Laurence, 1961) and he cannot make this until satisfied that the preclinical data are adequate. Any doubts that he may have must be resolved in personal discussion with the pharmacologist concerned and/or an independent expert(s).

However, because the investigator may be clinically responsible for the patient, the obtaining of informed consent is an area of potential difficulty. It is important to remember that patients with great trust in their doctors may accede to any request they may make and that this trust should not be abused when consent is requested. It follows that Local Ethical Committees will need to play a greater role in ‘policing’ projects that they approve than they currently do (Pappworth, 1978). In addition, there will be a greater need for pharmaceutical companies to seek the views of independent ethical review committees on protocols relating to new drugs (Ramsay, Tidd, Butler & Venning, 1977). Although these independent committees in no way replace the need for review by Area Health Authority Ethical Committees (indeed their activities are complementary) they have the advantage of greater expertise than can be found in most Area Health Authority Committees.

A second potential disadvantage of studies done on a limited number of patients is that a drug might be abandoned prematurely after the failure to demonstrate its efficiency. Although possible if the drug is given in an inadequate dose or it does not reach the target organ because of poor absorption of presystemic metabolism, it should not be a problem if its blood concentration is monitored. Alternatively, greater use could be made of intravenous administration than has been the case to-date (provided that the drug is given by slow infusion).

Finally, there is always the potential for unexpected effects to occur. Because of this possibility, it is essential that the initial studies of new drugs are undertaken by people who are trained physicians and performed in well equipped surroundings where resuscitative facilities exist. In this context, it is worthwhile remembering that in the 1940s a sulphonamide known as RP 22504 was studied as an antityphoid drug in France (Louhatières, 1957). This substance produced death in a small number of individuals and hypoglycaemic coma in others. This product was introduced during the Second World War and did not undergo formal testing in animals. It is highly unlikely that an occurrence such as this will be possible even with as little as 14 days’ preclinical toxicity testing. Nevertheless, close supervision and observation are essential not only to protect the individual patient but also because serendipity has led to important therapeutic advances. One of the best examples of recent years was the discovery during the early evaluation of clonidine as a nasal decongestant of its profound hypotensive properties (J. H. Shelley, personal communication). However, equally surprising were the occurrence of a hypertensive crisis on withdrawal of this drug (Conolly,
Briant, George & Dollery, 1972) and its interaction with the tricyclic antidepressants (Briant, Reid & Dollery, 1973), both of which were encountered in studies on a small number of patients. Neither of them were predicted from a knowledge of its preclinical pharmacology but their management, as well as subsequent investigation, required a sound knowledge of pharmacology.

Conclusions

New drugs are essential for treating diseases that either do not respond at all or in which the existing therapy is unsatisfactory. Pharmaceutical companies based in the U.K. have an impressive past record of innovative research. However, it is clear that existing regulations make it difficult to test new medicines in patients until very extensive preclinical toxicity tests have been done. Although some of these are essential, clearly they have no absolute predictive value for man. Furthermore much effort and expense will have been wasted if the new product candidate is without efficacy or produces unwanted effects during its initial evaluation in patients. Experience suggests that the risks of the latter occurring are small and that the effects can be minimized if the studies are carried out in well equipped surroundings by those trained in human pharmacology.

References


