MEDICAL PRACTICE

Today's Treatment

Clinical pharmacology**Drug development**

CHARLES F GEORGE

Currently between 15 and 20 new medicines (as opposed to new formulations of old drugs) are marketed in an average year. Before the introduction of any drug to man, many months and usually several years of research and development have taken place. The starting point for discovery of a new drug may be reached in several different ways. Firstly, chemical entities that have been synthesised by the same or another company are subjected to a battery of tests designed to detect different types of biological activity. These include studies of the effects on animal behaviour and work on isolated tissues. In addition animal models of disease states are sometimes used. In general this is not an efficient form of research since at best only one in every four to five thousand chemical entities screened is marketed as a medicine. Indeed, recent evidence suggests the ratio may be closer to one in ten thousand: it is for this reason that this "random" approach is losing favour.

A second approach entails the synthesis and testing of chemical analogues of existing medicines for biological activity. Although in general this leads to minor advantages such as better absorption, greater potency, and a more selective action, surprises may occur. On occasions these are disadvantageous and may limit the subsequent use of the drug. Additional properties, however, may become evident when the compound is tried in man. This serendipitous approach led to the introduction of the thiazide diuretics and oral hypoglycaemic agents (both of which represent slight modifications of the early antimicrobial sulphonamide) and of clonidine for hypertension.

The newest and most rational form of research and development has been to design a substance to fulfil a particular biological role. At its simplest this may entail the synthesis of a naturally occurring substance—for example, a hormone or

vitamin. A good example is the introduction of levodopa, a precursor of the neurotransmitter dopamine, which is deficient in patients with Parkinson's disease.

Alternatively, chemical analogues of naturally occurring substances have been developed with the intent of modifying the effects of the endogenous substances. Drugs of this type include the β -adrenoceptor antagonists (initially pronethalol and propranolol) to block the effects of circulating catecholamines and thereby reduce myocardial oxygen consumption to relieve angina pectoris. More recent examples include cimetidine to block the action of histamine on H_2 receptors, thus reducing acid output from the stomach to allow healing of peptic ulcers. Captopril is another substance introduced recently to inhibit the action of the converting enzyme responsible for generating angiotensin II, thereby lowering blood pressure.

Although this approach has been successful in recent years, the main problem limiting the rate of introduction of new drugs on a "logical" basis is the lack of understanding of basic physiological and biochemical processes (as well as the homeostatic mechanisms that will be brought into play when the "milieu intérieur" is disturbed).

A fourth approach, in which there is renewed interest, is the reinvestigation of traditional, usually herbal, remedies for their active ingredients. Although most remedies that have been in use for generations are pharmacologically useless, from them a few chemicals have been identified that may become useful either in synthetic or in semisynthetic form.

Preclinical testing

Before a "new product candidate" can be tried in man several months or years must be spent on toxicological studies, the development of analytical techniques, and metabolic studies. These are necessary to allow the prediction of what will be the effective dose in man and to minimise the risks. Countries

differ in their requirements for toxicity testing, but in general the following procedures will be necessary.

There are three main phases: firstly, acute studies in which the dose required to kill half of a group of animals from two or three species after a single administration is established: gross pathological changes are then noted. Secondly, subacute studies require the regular administration of the drug (by the same route as it is intended to use the product in man) in two or three animal species for up to 90 days. Organ function is measured, and not only is the gross pathology studied but also microscopic anatomy. Thirdly, chronic studies necessitate administering the drug to two or three animal species for at least six months. Similar measurements are made to those listed for subacute toxicity, but in addition studies of reproductive capacity and mutagenicity are usually required.

Examples in which animal toxicity data have been of good predictive value for man are the peripheral neuropathy associated with the use of isoniazid and both renal toxicity and ototoxicity associated with the aminoglycoside antibiotics. False predictions, however, may occur because of rapid excretion in animals, differences in their pathways of metabolism, receptor sensitivity, anatomy and physiology, and as a result of the lack of pre-existing pathology. Although toxicological testing is performed routinely, it has no absolute predictive value for adverse reactions in man. Examples of toxicity not seen in animals include the oculomucocutaneous syndrome seen with regular ingestion of practolol and the cutaneous and renal problems associated with the use of captopril. The only way to find out whether a new drug is safe 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 for which existing treatment is unsatisfactory.

Clinical studies

The purposes of clinical studies are, firstly, to establish that a drug has a useful action in man; secondly, to confirm that it is non-toxic; and, thirdly, to establish the nature of common side effects. It is conventional to subdivide the clinical testing into three phases, but the distinction between these is blurred and not everyone agrees on the classification that I shall use.

PHASE 1 STUDIES

Phase 1 studies is a term used to describe the first few administrations of a new drug to man. The precise conduct of these studies varies according to the type of drug being studied and whether the investigator is based in academic medicine or the pharmaceutical industry. The choice of subjects for phase 1 studies is normally "volunteers" recruited from within the pharmaceutical industry or by open advertisement.

The first few administrations are usually swallowed in a dose of 1/50th of the minimum required to produce some effect in animals.¹ In future, however, increasing use will probably be made of intravenous administration, since the disposition and fate of the drug as well as its actions may be studied more easily. Depending on findings obtained in animals, the dose may then be built up in man either by using small increments or doubling until either a pharmacological effect is seen or an unwanted effect occurs. One of the main objects of phase 1 studies is to screen for possible toxic effects; it is therefore usual to make routine haematological measurements and biochemical estimations of liver and renal function, as well as to perform routine urine analysis. Additional tests might be indicated if an analogue of the drug under study had produced a particular form of toxicity—for example, looking for DNA antibodies.

It is usual practice to study the disposition, metabolism, and main pathways of elimination of drugs at this early stage of

development.² Not only does this add precision to the choice of dose for subsequent study but also it may help to identify which animal species handles the drug in a manner similar to man. (This species might then be used during long-term toxicity studies.) Investigations on drug metabolism and pharmacokinetics often necessitate the use of beta-emitting compounds such as ¹⁴C or ³H or alternatively stable isotopes such as deuterium.

PHASE 2 STUDIES

In phase 2 the clinical pharmacology of the new drug is studied by a few designated investigators chosen for their training and skill. These doctors will have taken part in drawing up the protocol and should have submitted this to the local ethics committee. The design of the protocol to be followed will depend on the type of drug under study. In assessing a new antihypertensive, for example, patients might be given a placebo on the first day of study and recordings made of the pulse and blood pressure at 30-minute intervals both supine and erect for eight hours or so thereafter. Increasing doses of the new drug would then be given on succeeding days to establish whether it had an acute hypotensive effect and to gain some idea of the slope of its dose-response curve. Additional pharmacological studies could be undertaken to show that the hypotensive action was that predicted from animal studies—for example, methyl-dopa was introduced because of its ability to block dopa decarboxylase in animals, but it lowers blood pressure by a different action in man. If the blood pressure had been satisfactorily reduced during the initial studies the patient could then be started on a maintenance dose of the drug and any further adjustments made at regular outpatient attendances.

Often the initial assessment of drugs in phase 2 is done on an open basis. Although the results of such studies may suggest that a new drug has efficacy, this form of evaluation does not prove that it works. Some existing remedies (as well as many more that have since been discarded) were subjected to this empirical type of approach and the fact that diseases are dynamic (undergoing continuous change in their natural history) was not taken into account. Furthermore, the large subjective element in many illnesses means that more than one-third of patients respond favourably to any intervention. To prove that a drug has efficacy it is necessary to undertake formal clinical trials.

PHASE 3 STUDIES

Formal clinical trials seek, firstly, to establish whether a new drug works in comparison with a placebo that looks (and tastes) identical with the active compound. Secondly, they aim at establishing the advantages and disadvantages by comparison with the best available treatment. For example, with a new antihypertensive drug it would be appropriate to compare it with either methyl-dopa or a diuretic. Similarly, a new anti-inflammatory analgesic might be compared with aspirin or indomethacin. It is beyond the remit of this article to discuss clinical trials in detail. Suffice it to say that there are two main types: within patient "cross-over" studies or between patient comparisons.³ The latter may be performed on either a fixed number, chosen according to likely predictions,⁴ or using a sequential design.

The results of treatment with a new product are assessed by a combination of objective and subjective techniques. Pulse, blood pressure, size of finger joint, strength of grip, and the number of additional analgesic tablets, such as paracetamol, required to control pain represent objective measurements. Subjective measurements would include the duration of morning stiffness and the intensity of pain. Visual analogue rating scales have become a popular (and surprisingly accurate) way of assessing many subjective effects, such as pain relief, and may be used also to assess side effects, such as sedation.

MARKETING OF THE NEW DRUG

Once sufficient clinical and preclinical data have been collected on the safety and efficacy of a new chemical, submission is made to the Committee on Safety of Medicines. If the information provided is satisfactory a product licence can then be issued. By this time ten or more years may have elapsed since the taking out of a patent on the "new product candidate," and a total of £20m expended. Only a few hundred patients, however, will have been exposed to the drug. Thus the full benefits and problems associated with its use may not become apparent until months or years after it has been marketed. Because of the latter possibility I would suggest that practitioners should adopt a cautious attitude towards new medicines. In my view there is no justification for switching automatically to the 15th " β -blocker" from one that has been in use for ten years or more, since it is unlikely that the new compound will have a measurable advantage for most patients. Possibly, however, it may have advantages for some patients—for example, a cardioselective β -adrenoceptor antagonist would be preferable to propranolol if the patient had

coexistent airways obstruction or diabetes mellitus. Similarly, a tetracyclic antidepressant might be preferable for a patient with coexistent cardiac disease.

In addition my personal rule is to insist that there are at least two good clinical studies (with similar results) showing that the drug has therapeutic (rather than just statistically significant) advantages in a particular condition before prescribing it.

References

- ¹ Dollery CT, Davies DS. Conduct of initial drug studies in man. *Br Med Bull* 1970;26:233-6.
- ² Downie CC. Clinical pharmacology. In: Harris EL, Fitzgerald JD, eds. *The principles and practice of clinical trials*. Edinburgh and London: Livingstone, 1970;15-22.
- ³ George CF. The investigation of new drugs in man. *Br J Hosp Med* 1974;12:780-9.
- ⁴ Clark CJ, Downie CC. A method for the rapid determination of the number of patients to include in a controlled clinical trial. *Lancet* 1966;iii:1357-8.

Medicine and Mathematics

Statistics and ethics in medical research

Collecting and screening data

DOUGLAS G ALTMAN

Even with an impeccable design there are many ways in which a study can go wrong when the data are being collected. In general, the more complicated the design the more chance there is of the study not being carried out properly. As an example, consider this historic study. The story was related by "Student" (he of *t*-test fame):

"In the Spring of 1930 a nutritional experiment on a very large scale was carried out in the schools of Lanarkshire. For four months 10 000 schoolchildren received three-quarters of a pint of milk per day; 5000 of these got raw milk and 5000 pasteurised milk; another 10 000 children were selected as controls, and the whole 20 000 children were weighed and their height was measured at the beginning and end of the experiment."¹

There was no power problem here. The study found that children getting extra milk gained more weight in the period than did the controls. But did the extra milk cause the extra gain? The figure is a simplified chart showing the weight changes for girls during the study. Since the two milk groups are very similar, only one is shown here. There are two striking features of this graph. The first is that the controls were in all cases heavier than those getting extra milk (they were taller too). This can be easily explained by the discovery that some of the teachers who

allocated children to groups had juggled the randomisation to enable the poorer children to get the extra milk.

The second curious feature is that the observed growth rate in each group was much less than would be expected by looking at the next age group. The explanation for this is also very simple. The study began in February and ended in June, and the children were weighed on both occasions with their clothes on. The short-fall in weight increase is thus largely due to a different amount of clothing, and the smaller effect in the milk feeding group can be explained by the poorer children wearing relatively fewer clothes in winter.

It may be thought that errors such as these are really obvious, and nobody would make such mistakes nowadays. Two points may be made about the altruistic adjustment of the randomisation. Firstly, this procedure is not unknown in more recent times. Carleton *et al*² reported that strongly motivated doctors may upset trials by transilluminating envelopes containing the names of drugs in order to find the desired treatment. However well-intentioned, such underhand activities are by their nature likely to go undetected and can invalidate a whole study. Doctors should not agree to participate in a randomised controlled trial if they have a prior preference for one treatment. Equally, the study sample should not include subjects for which one treatment is clearly medically preferable. A trial where either of these conditions was broken would be unethical.³

The second point relating to the allocation of subjects to treatments is that a major reason for random allocation is to eliminate the effect of both deliberate and unconscious biases. If the groups are not selected randomly it will be impossible to know whether any observed treatment effect is genuine, as in the

Division of Computing and Statistics, Clinical Research Centre, Harrow, Middx HA1 3UJ

DOUGLAS G ALTMAN, BSc, medical statistician (member of scientific staff)