Clinical Trials of New Drugs

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Every new drug passes through a number of stages of investigation before it becomes generally available on prescription. It is usual to distinguish four phases of clinical investigation, the first three before marketing, the fourth being monitoring after release. This article deals with the first three phases from the standpoint of the clinical investigator and the patient.

Before a new drug is given to man there must be some rational justification for doing so. This may be a pharmacological action demonstrated in animals, or it may be arguments from clinical observations or theory. An example of the latter was the decision to use large doses of l-dopa to treat Parkinson’s disease. This decision was based upon the observation that the amount of l-dopa was reduced in the brains of those who suffered from the disease. This is the positive aspect; on the negative side the drug must have an acceptably low degree of toxicity in animal tests. It cannot be stated that the drug should be harmless, for any active substance will be toxic if the dose is raised high enough; for example, penicillin has a toxic effect upon the brain when given in very high doses, although in most respects it is a remarkably non-toxic compound.

In the United Kingdom a new drug may not be given to a patient without the matter being considered by the Committee on Safety of Medicines (CSM) which reviews the animal studies, the proposed use in man, and the clinical investigators who have been named to do the work. The existence of the CSM is a powerful safeguard against drugs being given to patients with inadequate study of their toxicity in animals, or too great a degree of toxicity in relation to the proposed use.

PHASE ONE

The question asked at this stage is: ‘Has the new drug a pharmacological action that may be useful in therapy?’ Typical studies might involve 10 to 30 individuals who are meticulously screened beforehand to eliminate conditions that might increase the experimental risk. Often, the studies are done on normal volunteers, who may be members of the scientific staff of a pharmaceutical company or a university department. Everything is done to ensure that as much information as possible is obtained and as few risks as possible are run.

If normal volunteers are used, they are usually people able to understand the implications of the experiment and the risk. They may be paid for the discomfort
they suffer. They are protected by an ethical committee which will have reviewed
the protocol in advance, and they may be insured through a commercial insurance
company or by the pharmaceutical company sponsoring the new drug. The
volunteers themselves have little to motivate them except altruism and,
sometimes, a small money payment.

From the standpoint of the investigator, the responsibility for giving the first
doses of a new chemical entity to man is considerable. It is usual to start at a small
fraction of the dose predicted to be active on the basis of animal experiments and
work up by doubling the dose until some effect emerges; for example, if the first
dose is 1/32nd of the predicted dose, a doubling regime would reach an active
dose in six experiments. The experiments must be carried out in a well-equipped
and well-staffed laboratory with facilities for resuscitation at hand. Known
antidotes must also be ready, but few drugs have effective antidotes. It is usual to
test the function of the kidney, liver, and blood-forming organs before each dose
and 48 hours after it. Several different types of risk may arise at this stage or later
in a new drug investigation.

Overdose
The greatest hazard is an excessive amount of the main pharmacological action of
the drug; hence the need for caution in increasing the dose. This may be a
particular problem with drugs that are incompletely and irregularly absorbed from
the gut, or when a variable amount is inactivated during absorption. A drug such
as phenytoin can saturate the drug-metabolising enzymes of the liver within the
clinical dose range and this could present a difficult problem. For this reason and
others it is helpful to be able to measure concentrations of the drug in blood
plasma during Phase One studies and to know something about how it is handled
in the body. There are very large interspecies differences in the rate at which drugs
are metabolised, but much smaller differences in the concentration in the blood at
which an effect is observed. The risk of toxicity can also be diminished by
keeping the concentrations achieved in man near those that were harmless in
animals, and avoiding levels shown to be toxic in other species.

Predictable Toxicity
Animal experiments may indicate that a particular type of toxicity is likely, or
previous experience with other molecules of the same general structure may
suggest a possible hazard. Specific monitoring will then be done in the course of
the study to detect this if it occurs; for example, monitoring vision in a drug that
has been shown to be associated with retinal degeneration in animals. Review by
the CSM before the issue of the Clinical Trial Certificate ensures that proper
consideration is given to problems of this sort, and the CSM often specifies the
minimum monitoring of a particular type of toxic reaction that it deems to be
necessary.
Unexpected and Unpredictable Toxicity

Some humans lack certain enzymes required to destroy foreign compounds and these compounds may prove highly toxic to them although safe in other people. An example is the lack of the enzyme pseudocholinesterase, which may lead to prolonged paralysis after an anaesthetic in which succinylcholine has been used to produce muscle relaxation so that an endotracheal tube can be passed into the airways to ventilate the lungs. Some people readily become allergic to foreign compounds and may develop a life-threatening anaphylactic reaction when exposed to them. This is most likely to be a problem with structures related to existing drugs that are known to provoke allergic reactions, such as penicillins or sulphonamides. Species differences may also lead to hazard when a drug is safe in an animal but unsafe in man who happens to metabolise it by a different route or react to it in a different way. Species differences impose an important limitation on the usefulness of animal tests in predicting toxicity in man. Furthermore, it is almost impossible to predict subjective symptoms caused by drugs on the basis of animal tests. For example, a number of drugs cause unpleasant vivid dreams or even daytime visual hallucinations and there is no reliable way of detecting such phenomena in animals.

Risks of Procedures

Medical techniques such as puncturing blood vessels, infusing supposedly sterile solutions and the like contribute a very small but nonetheless real component to the risk of a new drug investigation.

Risks of Circumstances

The training of the staff, the availability of first-rate equipment for measurement and resuscitation will help to minimise these risks. Deputing such procedures to inexperienced and poorly trained staff will increase them.

Despite this chronicle of risks, the reality is that Phase One studies are extremely safe. Dr Varley reported on 1,300 studies over a ten-year period run by Upjohn and Parke-Davis and carried out in a prison unit at Jackson State prison. During this time, only eight people had to be put in hospital and in only three was the illness thought to be drug-related. There were no deaths. Some years ago, Dr Frances Kelsey of the Food and Drug Administration testified that drugs under investigation were very safe. She added that she was unaware of any deaths during a Phase One study (Abrams, personal communication).

PHASE TWO

The question now asked is: 'Is the pharmacological action likely to be useful in therapy?' The subjects of the study will be patients who suffer from the disease
the drug is designed to treat. They will have been asked to participate because they happen to be under the care of the institution or group of doctors where the work is being done. Patients entering the study will be given an explanation and be invited to signify their consent, usually in writing. Few patients refuse if they get on well with their doctor, though it is doubtful how many have a complete understanding of the possible risks. In hospital, although not always in general practice, they will be protected by an ethical committee review of the protocol. No commerical insurance is available. The sponsoring pharmaceutical company may give an indemnity to the investigators or the institution but the value of this in the case of non-negligent mishaps is not clear. The number of patients in Phase Two studies will build up slowly but, ultimately, might be between 100 and 200. The Clinical Trial Certificate often limits the numbers, duration and upper dosage level that may be used in the trial. The patients will be attending regularly for supervision by the doctors running the trial and various safety tests such as blood counts, urine tests and liver function tests will be carried out periodically. It is likely that only some of the patients will receive the new drug; others will either have the current standard treatment or an inert placebo if ethical considerations allow.

From the standpoint of the investigator, this part of the trial is harder and duller work than Phase One. If the study is double-blind he does not know which patients are getting which treatment, and he must concentrate his attention on maintaining a high standard of observation and record-keeping. Often, one member of the team will have the responsibility of monitoring symptoms and possible toxicity and he may break the treatment code if something adverse seems to be happening. It is worrying if patients fall ill from some quite independent process or fail to keep appointments or simply want to go away on holiday. They ought to remain under strict supervision throughout, but this is harder to achieve than one might imagine when dealing with independent human beings.

If there are adverse effects it is important to try to eliminate the possible causes such as intercurrent disease; for example, it is worrying if a patient on a new drug develops manifestations of liver damage such as jaundice. But the jaundice might be due to a viral infection or gall-stones and if this can be established a valuable therapeutic agent might avoid being unjustly condemned. All potential toxic effects must be reported to the manufacturer and to the CSM.

Unfortunately, follow-up is often far from perfect and by no means all adverse effects are reported. Doctors who do this type of work often fail to appreciate the need for meticulous record-keeping and may resent it, for it can be very time-consuming.

Phase Two studies are usually of limited duration. If the drug behaves as expected in lowering the blood pressure, relieving inflamed joints, lowering blood sugar, relieving depression, or whatever it may be, the numbers will be expanded and the duration of treatment lengthened into Phase Three.
PHASE THREE
Two questions dominate this phase: ‘Is the beneficial effect still evident in larger numbers and over a longer time?’ and ‘What is the frequency of side-effects and toxicity?’ The number of patients involved in the study may now expand to over a thousand, but the conditions of their recruitment and protection will be similar to those in Phase Two. However, to get the number of patients required the clinical investigators are likely to be drawn from less well-equipped centres and to have less experience of clinical pharmacology and clinical trials. It is more difficult to maintain a uniform standard of record-keeping and reporting in Phase Three and there may be long delays before single reports of isolated adverse effects reach the notice of the pharmaceutical company or the CSM. Eventually, all this experience will be collected on reporting forms, which will be compiled by a computer and used to form the basis of an application to market the drug.

LIMITATIONS OF THE EVIDENCE
It is important to realise the strengths and weaknesses of the evidence gathered with such labour and at such cost in Phase One, Two and Three studies. There should be reasonable evidence that the drug has a pharmacological effect which looks as though it will be beneficial in therapy. That evidence will probably not include evidence of outcome. The drug may lower blood pressure or blood sugar but does it improve the life expectancy of hypertensives or diabetics as much, more, or less than alternatives? This evidence will certainly not be available at this stage and if it is obtained at all it will not be until years later. Similarly, the evidence of safety will be modest. If there are 1,000 patients treated there may be no more than 300 patient years of drug exposure. If the drug causes a serious toxic effect once in every 100 patient years of exposure it might be noticed but probably will not be. Yet drugs in general use have been drastically limited in their indications because they caused a deadly toxic effect, perhaps only once in 100,000 patients treated, as in the case of chloramphenicol. To multiply the number of individuals in Phase Three trials would not be the solution to this problem, for no readily attainable size of trial could detect events of such low frequency. In relation to the practolol problem, if one per 1,000 patients had a really serious toxic effect and the mean induction time was two years, it is probable that even with perfect reporting something like 15,000 patient years of exposure would be needed to detect the effect. It is most important that the general public should understand that there is no way of proving complete safety of a new drug before it comes into widespread use. Past experience and improvement in scientific knowledge have improved the likelihood of predicting certain types of severe toxicity, such as injury to the liver, but our ability to make such predictions is still at a very early stage of development. The only possible way of limiting the toxicity of new drugs is to have a highly effective system of monitoring them after their release (Dolley and Rawlins, 1977).
WHAT DO THE PARTICIPANTS GET OUT OF IT

Once it could be said that the patients who participated in a clinical trial were privileged because they were the first to receive the benefit of a new wonder drug. Nowadays it is probably true to say that individuals taking part in a trial receive a higher quality of care and much more personal attention, but the chances that the drug they are helping to test will be a breakthrough are much less because the yardsticks of comparison are so much more severe. Finding a better penicillin is by no means easy.

The situation with respect to insurance protection of patient volunteers in pre-marketing trials is unsatisfactory. There is a need for some nationally agreed type of no-fault insurance cover for these individuals who are the pathfinders for the community. This is bound to bring with it closer supervision of what is done, but that need not be a disadvantage. The main problem will be to distinguish adverse effects due to drugs from those caused by the diseases from which the patient suffered. This appears to be the reason why commercial insurance companies are unwilling to quote terms for insuring patients taking part in clinical trials.

The doctors who carry out Phase One studies get a lot of excitement and intellectual reward because they are probing the unknown. Phase Two and Phase Three studies are another matter. Trainees in clinical pharmacology and their supervisors can regard this as part of their normal training and work, but most doctors find the randomised controlled trial a time-consuming chore, interesting when the results finally come to hand two or three years later, but tedious in the meantime. As a result such work is often deputed to the most junior members of teams and this may in part account for the rather unsatisfactory standards that often prevail. Specially trained nurses undoubtedly have an important role to play as participants and co-ordinators in such studies.

THE NEEDS OF THE COMMUNITY

The community is the potential beneficiary of all new developments in treatment, which are still badly needed in many fields. It would be a tragedy if an excessive degree of caution prevented or curtailed research designed to discover new drugs. It is in the interests of the community that such work should continue. It is also in the national interest, for this is a field in which British companies have had a remarkably successful record. But there are aspects that need attention to maintain a high ethical standard and prevent avoidable catastrophes due to drug toxicity. In my opinion, three matters are particularly important —

1. A scheme on a no-fault basis to protect the financial interests of patients who suffer harm in ethical and well-conducted studies of new drugs.
2. Better facilities and training for those who conduct clinical trials, including doctors, nurses, pharmacists, and so on.
3. Improved methods for positive monitoring of marketed drugs to detect toxicity as early as possible.

DISCUSSION
Dr O. L. Wade emphasised the very close collaboration necessary between the pharmaceutical company and those doing the work in man. Early work in man could guide the development of animal work. Those in the Health Service did not appreciate sufficiently the importance of developing new drugs for the future treatment of their patients. Much closer collaboration between the Health Service and the drug industry was needed. He was also concerned with the indemnification and insurance of volunteers taking part in drug investigations. Volunteers should be paid for their trouble but not enough to constitute a bribe. The limits of indemnification were not clear. Every precaution was taken to prevent harm to the volunteers; for instance, they were taken home after the experiment. But it might be that a volunteer, still high on amphetamine, would cross the road at home and be knocked down by a car. Indemnification was a very serious subject now under discussion by a group of professors of clinical pharmacology and the pharmaceutical industry.

Dr P. Turner was interested in the form of consent signed by volunteers. Initial trials of a drug were conducted because their outcome could not be predicted. To what extent should the hazards of a new drug be laboured? Dr Dollery replied that, at Hammersmith, the ethical committee vetted the form of consent so that the wording was not entirely at the discretion of the investigator. It was not his habit to refer to all possible hazards. With any drug a possible hazard was death. Perhaps this should always be mentioned but he had not done so. In the case of beta-blocking drugs it was right to state that there should be no hazard if the volunteer did not suffer from asthma and had a normal ECG. Even with intelligent volunteers, trained in science, the understanding of hazards was often faulty. Here the opinion of the ethical committee was a correcting force. The consent of a volunteer must be sought because he was a free-thinking independent human and must be treated as such. His consent did not absolve the investigators or the ethical committee from their responsibilities.

Dr J. Crooks raised the question of national differences in drug testing procedures. He suspected that the number of new drugs created in the U.S.A. had fallen in comparison with Europe because of the rigid rules in the U.S.A. He understood that it was very difficult to do any drug trials with volunteers in France. This must lead to a tendency for drug companies to conduct trials in countries with less rigid criteria. Dr Dollery said that the French legal system, under the Code Napoleon, made it impossible for anyone to volunteer to do something that might injure his body. The original idea was to stop anything that might decrease the number of soldiers available for the Emperor. This was a special case and the situation in the U.S.A. was different. There the Food and
Drug Administration took a very restricted view of marketing but not of investigation. However, hospitals and universities had restricted or stopped investigation in man because of the issues of legal liability. But Dr Kelsey of the Food and Drug Administration had stated that, in the initial trials of a new drug, no volunteer had died as a result of the drug. At this early stage of investigation the risk was small and undue restrictions would hold up the development of new drugs.

Dr D. Jack (Research Director, Allen and Hanbury) said that the pharmaceutical industry was keen to get quick results and would go to countries where these could be obtained. This was not accepting second best, as the quality of investigators, say in Scandinavia, was first class. Dr Dollery thought that delays in issuing clinical trial certificates were administrative and not scientific. He would like to make it easier to get man into limited investigations at an earlier stage to check the species most appropriate for long-term toxicity studies. The main long-term safety precaution should come from monitoring large numbers of people. Sir Eric Scowen assured the meeting that at the moment no submissions for Clinical Trial Certificates were awaiting decision.

Reference
Dollery, C. T. and Rawlins, M. D. (1977) British Medical Journal, 1, 96.

DOCTOR’S DILEMMA
Before a surgeon engage professionally to attend a duellist to the field of combat, it behoves him to consider well, not only how far he is about to countenance a deliberate violation of the duties of morality and religion, but whether, in the construction of law, he may not be deemed an aider and abettor of a crime, which involves in it such turpitude, that death is alike denounced against the principal and the accessory. . . . But whatever be the objections against the attendance of a surgeon in the field of combat, they cannot be construed to extend to the affording of all possible assistance, to any unfortunate sufferer, in an affair of honour; provided such assistance be not preconcerted, but required as in ordinary accidents or emergencies. For in the offices of the healing art, no discrimination can be made, either of occasions or of characters. . . . A physician has no special interest in an acquaintance with the statutes relative to duelling. But as he possesses the rank of a gentleman, both by his liberal education and profession, the law of honour, if that may be termed a law which is indefinite and arbitrary, has a claim to his serious study and attention.

(Extracted from the writings of Dr Thomas Percival (1740-1804).)