Dose-response relationships in clinical pharmacology.
L. Lasagna, S. Erill, C.A. Naranjo, editors

THE DOSE RESPONSE RELATIONSHIP AND CLINICAL TRIALS

DR. CYRIL MAXWELL
Clinical Research Services Limited, 36 Neeld Crescent, London NW4 3RR, U.K.

INTRODUCTION

The clinical trial is a scientific tool for the evaluation of therapies in sick man and is the key element in the development programme of new medicines lying between the ultimate use of the drug in clinical medicine on the one hand, and the pharmacology and toxicology from which its anticipated effects derive on the other [33]. The clinical trial is normally defined as a scientific experiment in sick man to evaluate a treatment, primarily for its beneficial effects. It is normally assumed that the trial is performed with therapeutic intent: to improve the patient's illness or to ameliorate his suffering. Because of the special interest in the dose response relationship, it is helpful to expand this definition to include patient volunteer studies and dose ranging studies.

In the context of physiology, pharmacology and toxicology, "dose" is usually a precise quantity of drug delivered to an isolated organ or whole animal model. "Response" consists usually of the changes seen in a specific variable or organ. It will be seen in due course why it is necessary to expand both these terms.

Clinical trials are performed to answer specific and precisely formulated questions and have several uses. They are thus used for exploratory purposes, for proving causality, for drawing comparisons and for optimising the efficiency of drug usage in a number of ways. These include the thorough identification of clinical indications and contra-indications, proper dosage regimens and the identification of, and judgment on, unwanted or unsafe occurences in relation to the benefits on offer. Clinical trials and the development of a new drug follow a generally logical chronology despite occasional need to revert back to earlier steps as the total knowledge of the drug in man unfolds.

The first task is to identify two critical dose levels, the dose at which patients appear to benefit and the dose beyond which either further benefit is negligible or unwanted effects become troublesome. Dose finding studies are often performed on healthy volunteers but often need to be repeated in patients. Sometimes they must be commenced only in patients.

Having identified the two apparently critical dose levels it is then necessary to identify the optimum working dose range of the treatment. Because many diseases also respond to placebos, one must then confirm that the observed clinical effects are indeed causally related to the treatment administered. This requires the controlled clinical trial: one from which valid comparisons can be drawn [33]. Later, comparisons of the treatment's benefits and unwanted effects will be made with those of

alternative therapies. Of all the possible outcomes in the early studies, perhaps the most important is the absence of any effect at all. The reality might well be that the so called medicine is without effect though a frequent explanation is that the drug is being given in inadequate dose or failing to reach the proper site of action.

Secondary objectives. These primary objectives are supplemented by secondary objectives no less important to the totality of the drug research programme. These include the study of unwanted effects of the drug in man generally and the patient under study in particular. The unwanted effects fall into two major categories: side effects, which may be common or relatively rare but probably acceptable considering the proposed application of the drug; and secondly, the toxicity in man that might be expected to occur with the treatment. The study of toxicity would never be a primary objective of a clinical trial for obvious reasons but the experimental model does offer a natural opportunity to study surrogates of toxicity. A surrogate measurement has been described as "something we measure place of the end-point we really want to measure" (Byron W. Brown). In human toxicity, surrogates are the accepted measurements (eg liver function tests rather than biopsy) and batteries of laboratory tests are frequent, especially in early clinical trials or when animal toxicology studies indicate possible and particular hazards in man.

The study of adverse reactions, defined as rare, idiosyncratic or life threatening, is not normally an objective for clinical trials though the methodology of clinical epidemiology often gives studies in this field the appearance of clinical trials when they are not. The apparent similarity between the case control study and the randomised matched pairs clinical trial is an example.

The need for patient volunteers. Under normal circumstances clinical trials concern patients in need of treatment. It is sometimes both ethical and permissable to invite a sick person, or a person known to be at hazard to the disease under study (eg asthma attacks) to take part in a scientific drug study relevant to their illness but from which they may not benefit during the experiment. To be ethical it should offer possible benefit to other patients if not to the patient volunteer though he might also benefit ultimately. With clinical trials, the moral and ethical constraints are ever present and exaggerated to compensate for the patient's dependence and trust towards his physician. The healthy volunteer has nothing to gain and potentially much to lose from participating in drug research. The patient volunteer might have much to gain but only afterwards. Patient volunteers are needed for cancer therapies where many therapies are so hazardous that it is impossible to study these drugs in healthy people: many cancer therapies are deliberately used at sub-toxic dose levels and dose finding studies can only be performed in patients suffering from a disease severe enough to justify the toxicity involved.

THE DOSE, THE RESPONSE AND THE RELATIONSHIP

The dose response relationship is characterised in physiology, pharmacology and toxicology by the familiar sigmoid curves of the log-dose response curve or the straight lines of the Lineweaver-Burk plots using the reciprocals of dose and effect.

The dose. In both of these plots, dose is a precise quantity of drug which may be delivered to an isolated organ or to a whole animal. In clinical trials a different set of problems arise: the dosage form may be a tablet, capsule, dragee, suppository or other prepackaged formulation of the drug. Here the quantity of drug is only one of many factors influencing how much of the drug will reach its effector organs and when. Time becomes a major consideration in the experimental methodology. The rates at which the formulation releases its active ingredients into the appropriate compartment, and the processes by which it is moved from one compartment to another on its route to the end-organ become critical to the validity of the experiment.

It is salutary to remember that when the British manufacturer of the most widely used tablet of digitalis merely made the particle size smaller than it used to be, there followed an epidemic of well stabilised cardiac patients suddenly developing digitalis poisoning. But from the clinical trial viewpoint, a major consequence of formulation and re-formulation is the need to support changes of formulation with clinical trials to demonstrate bio-equivalence. Another consequence of the formulation is that changes to clinical dosage tend to occur in multiples of the manufactured quantum. It is clearly desirable that the dose contained in the formulation should be such that increases or decreases in the number of units keeps the dosage levels in the optimum part of the dose response curve as it is perceived. Dosage steps in clinical practice are too often determined by the quantity of drug in the formulation: changes are often made in terms of dosage units (tablets etc) rather than the actual dose.

Clinical therapy rarely produces an immediate response: treatment is often necessary for a considerable time. The timing of repeat doses, the duration of therapy [1], whether the therapy is given continuously or intermittently [2 3 4], the number of treatment exposures [31], are important considerations of dosing requiring clinical trials. A three period crossover trial in children comparing the effects of high dose versus low dose required that identical tablets contain 15 different strengths of the drug to cope with differing body weights: plus placebo [32]. The concept of "dose" in clinical trials can be highly complex.

The response. Similarly, the "response" in clinical trials may differ considerably from those in physiology, pharmacology and toxicology. Therapeutic intent relates to the whole patient and one way or another, it is the total well-being of the patient that ultimately matters. None the less, it is frequent to perform clinical trials studying dosage measuring selected direct or indirect variables [5–15].

Diseases clearly relevant to a known physiology lend themselves to efficacy studies

using these variables as surrogates for clinical response. Diseases of the cardiovascular, respiratory and renal systems are particularly amenable, offering a wide variety of proven or accepted surrogates for the total disease. Plasma drug levels are often used as a surrogate measures in clinical trials though it is not always clear until much later how relevant these are to clinical outcome. For many years, measurements of reductions of lipid factions as surrogates for the risk of infarction and stroke were the only practical way of testing hypolipidaemics though they were not accepted as relevant to clinical response by many. The proof of their validity in preventing clinical sequelae of undesirable plasma levels has taken not only very many years but also long term time consuming and extremely expensive clinical trials to prove their relevance [16]. Similar surrogates have been shown to be relevant in cardiology [17].

Time. The classical dose response curve does not normally accommodate time. Yet time is frequently a vital consideration in clinical trials and includes the time taken for a drug to start exerting its effect, the duration of treatment, whether the treatment is continuous or intermittent, or studies on the best approach to terminating a treatment (eg by sudden withdrawal or by gradual decrease). With vaccines and immunisations it may be necessary to study when booster doses are required. Many trials study treatment given for a relatively short period of time but follow up patients for very long time periods awaiting the consequences of that treatment, perhaps years later: vaccination and immunisations come to mind. Dose may by a major objective of such studies.

Time to response may be almost nil, as occurs especially in intensive care and in anaesthetics and abortifacients[18]. Reaction is so quick and measurable that the classical dose response relationships and their various modes of demonstration are often feasible. Yet in psychiatric disease where therapy is of limited value and knowledge of the illnesses rather deficient, response may be not only complex but also slow to occur [1]. Even 30 years after their introduction, many antidepressants still take three weeks of steady state plasma levels to produce a response. The fact that many patients respond much sooner with the same treatment only complicates clinical trial design considerations.

Side effects and toxicity as a "response". Clinical trials frequently compare a trial treatment with an alternative therapy anticipating difference in efficacy but aiming to demonstrate that a new treatment is superior on account of a lower incidence of side effects or a more acceptable profile. In this case the "response" is the frequency and profile of side effects. Many trials are performed with all treatments given at the same fixed dose. This writer has repeatedly confirmed the wisdom of categorising patients at the end of such trials by the incidence or severity of side effects. This can be done in three or four broad categories such as "severe", "moderate", "mild" and "none" and then correlating these categories against a mg/Kg

dose[19] . This is done by dividing the fixed dose by each patient's body weight. It has frequently helped in determining the optimum dose to go into a tablet or capsule. Routine toxicology measures can also be treated this way at the end of a clinical trial with several dose levels.

DOSE FINDING STUDIES AND CLINICAL TRIALS IN PRACTICE

Most clinicians performing clinical trials assume that dosage regimens have already been moderately well worked out and the only outstanding question is to choose between just a couple or so dosage regimens. It is usually left to the clinical pharmacologist to explore dosage minima and maxima in early studies in healthy and patient volunteers even though healthy people may be irrelevant to the disease process. It is interesting to note that the classic sigmoid log-dose response curve in patients sometimes plots not dosage of drug against response but a fixed dose of drug with varying doses of a challenge[20] ; as in asthma. Here the objective is to to use the indirect dose response curve as an aid to estimating an optimum therapeutic dose level.

Initial dose finding studies. The first aim in dose finding in patients is to identify what is thought to be the straight line part of the sigmoid curve. Traditionally, an escalating dose regime is employed starting usually at a dose 100th (or sometimes one 20th) of the dose estimated by the pharmacologists and toxicologists to be effective in man[11–13 21 22] . Dosage is increased usually by doubling though also geometrically (especially with vaccines[23]) until a desirable of undesirable effect is observed. Such studies are rarely published and are frequently performed by the research scientists developing the drug and experimenting on themselves as healthy volunteers. In cancer studies, it has become fashionable to escalate doses (in patients only) in something less than doubling. The chosen method is to escalate according to a series of steps conforming to the Fibonacci series. These escalate about 62% of the previous dose though this is slightly variable within the series. The series starts 1, 1, and 2 and each subsequent number is the sum of the last two (3, 5, 8, 13 etc). Treatments are ultimately given therapeutically at just below toxic levels and the objective is to identify the maximum safe dose.

Escalating dosage regimens are often performed before a method of estimation of the drug has been developed in biological fluids. Escalating dosages without knowledge of the kinetics is morally undesirable and scientifically dubious unless either single patients are subjected to only a single dose or a satisfactory time lapse is allowed before repeat dosing in a given patient. Randomisation in dose finding studies appears to be unusual until critical levels have been established and these seem to be dependent on an escalating regime despite their weaknesses.

If the dose response curve follows the classical sigmoid shape it should indicate the threshold dose at which a noticeable proportion of patients will respond and the dose

at which very few more are able to. With luck, the straight part of the curve will be found. It is not unusual then to perform a randomised dose response study in volunteers using five or six doses one of which could be a placebo. Similar approaches can be taken with the earliest studies in patients though these often use ad hoc dosages. A better method has been described by Bolognese[24] which he calls the "up-and-down" design.

Non-randomised trial designs. Zelen[25], struggling against recruitment problems consequent to the ethical problems of informed consent to randomisation in patients eligible for cancer trials, devised a non-randomised clinical trial technique devised which he called "Play-The-Winner". It requires that the response be dichotomous: satisfactory or unsatisfactory, success or failure. Two treatments (though they could be two doses of a single treatment) are compared. The next patient's treatment is determined by the success or failure of the previous patient: the first patient is randomised to treatment. If the last patient did well, the same treatment is given to the next one. But if the last patient's response was unsatisfactory, the alternative treatment is given. Clearly, if one treatment suits more patients than the other a preference will become apparent merely with hindsight.

A similar approach was taken separately by Bolognese looking specifically at the problems of dose finding studies in general and aiming to identify with as much accuracy as possible the two critical points on the sigmoid dose response curve. This time the plot is log-dose against the proportion of patients showing a response at each dose level. He called it the "up-and-down" design. A range of doses is made available to patients in increments of double the last one. The dose given to the next patient is determined by the response of the previous patient. If the patient has a good response to a dose, the next patient has the next lower increment, if the previous patient's response was unsatisfactory then the next patient gets the increment higher than the last patient's. This way, the opportunity for a response rate at each dose is built up.

In his published description, Bolognese suggests that very early information about the location of both threshold and plateau is needed and describes a series of computer simulations to test the theoretical efficiency of three suggested experimental designs. Design 1 is a single dose exposure to 30 subjects. Design 2 is a three period exposure of three doses in 10 subjects: the second and third period being determined by the response to the former treatment. Design 3 is also a three period study in 10 subjects but the dosage in the third period is progressed in the same direction as the second (remorselessly increasing or decreasing).

His Monte Carlo simulation to test the device randomly allocated 30 "responses" in each design. Depending on the design, it was either one response to each of 30 hypothetical subjects or three responses to each of 10 subjects. The assumed dose response curve (the truth) consisted of 13 points simulating log doses. The lowest four

were given a 0% response rate. The highest four had a 100% rate and the middle five increased by doubling. For each of the three designs, and for each of the 13 doses, 1000 computer runs were made to test for how well they estimated the threshold and the plateau dose. All the designs worked quite well. Design 2 (the three period one with within-subject up-and-down dosing) was no better than the others. When the starting dose was within the effective range, design 3 worked best. When it was outside, design 1 was best. As a physician, this writer must point out that none of these computer games included a simulation of unwanted effects (as does his clinical trials simulator, "Instant Experience in Clinical Trials"). None the less, the plateau (and also the threshold) were predicted to within one dosage increment in more than 80% of the simulations.

Later, he opted for sets of four patients and proposed using, if necessary, four sets of four patients, each set of four patients using a different starting dose. With a doubling increment and a set starting at, say, 2.5 mg. the range theoretically available to the fourth patient would be anything from 1.25 to 20mg [27] . If the second set started at 5.0 mg., the fourth patient in that trial could lie in a range as wide as 1.25 to 40 mg (responses at 1.25 would continue at that dose). And so on.

In theory the system works and works well. For it to work well in practice the investigator must adjust dosage strictly according to the very simple dichotomous algorithm at each step. From the writer's own experience over 25 years designing, supervising, monitoring and reporting clinical trials, investigators have never seemed able to abide by even the simplest set of rules though others have had better luck [11] . Violations seem common particularly when either adjusting dosage or removing patients from a trial is concerned. Bolognese's method has at this time been used and reported in only two communications: in cardiology [5 6] . They were presented as a two period escalating dose trial. It is so far impossible to tell whether the invention works clinically.

DOSE STUDIES USING RANDOMISED CLINICAL TRIALS

When randomised controlled clinical trials are indicated the commonest methods are the parallel group trial and the crossover trial [10 12 14] . It is not infrequent to have as many as three different drug levels plus a placebo in double blind studies. Because of the inherent difficulties with treatment-by-period interactions in crossover trial it is relatively unusual to see more than three period crossover designs though the theoretical methodology is available for comparing many more.

Crossover trials restricted by number of treatment periods. The two period crossover can handle two doses and the minimum block size is two (two patients required for a complete block). With three doses and three periods, the permuted block requires six patients. With four doses and four treatment periods the number of patients to complete a block rises to 24 and with more than four the system fast

becomes impracticable. Incomplete block designs[29] offer some compromise if the need is imperative. Latin squares also become an adequate compromise but while these offer the assurance of balancing treatments within patients and in each time period, the actual change overs from one dose to another are not completely represented.

Incomplete Latin square designs. Incomplete Latin squares (or Youden squares [29]) offer a number of useful compromises in which, for example, six doses can be compared with each patient exposed to only three treatment periods using only 10 patients. Another three period crossover design can cope with seven doses using only seven patients.

Graeco-Latin square designs. With combinations of two therapies, a five sided Graeco-Latin square [29] could cope with 25 different treatment combinations using only five patients in a five period crossover trial. This could well be practicable in chronic diseases in which the crossover design has already been established as a standard method. The weaknesses of trying to work out optimum dose combination therapies from parallel groups can be seen in various studies.

EPILOGUE

When all is said and done, one must remember that dose response studies in the clinical trial end up as nothing more, in the hands of the practising physician, than history which is good to have but free to ignore. A recent study of plasma levels in epileptic patients [30] showed that between 22% and 46% of assays (depending on the drugs) were outside their target levels. This might not surprise but it is worrying that only half of those patients had their dosage changed by their doctors when they were given detailed information. Changes were more frequent with apparent underdosing than with overdosing. One must wonder about the setting of plasma level targets when the clinicians will still make their own value judgments. Perhaps they no something that we don't.

SUMMARY

This paper has considered the differences between the dose response curve of physiology, pharmacology, an toxicology and discussed how the the dose and the response are different in clinical trials. It introduces time as a complicating factor. It describes the procedures used for dose finding studies in patients and patient-volunteers and describes the "up-and-down" method of Bolognese which appears to work in computer simulation but is yet to be proven clinically. It mentions the choice of sophisticated crossover designs available for dose studies but notes that the commonest trials studying dose response are either uncontrolled, parallel group or two-period crossover randomised blind trials, usually selecting the better of two alternatives.

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Discussion - Dose-response relationships in clinical trials

L. Lasagna

I wonder whether people ever use techniques such as Zelen's "play the winner". Most of the papers I see use traditional techniques.

C. Maxwell

Unfortunately this seems to be the case. I think that Zelen's design is quite attractive and clearly solves a lot of problems, but I cannot mention any recent trial using it.

S. Erill

I can mention one. It is a trial about extracorporeal circulation in neonatal respiratory failure, published in Pediatrics (1985; 76 : 479-487).

C. Maxwell

As far as the Bolognese approach is concerned there are two citations of it in the literature (5, 6, 27). Unfortunately both are clearly part of multicenter trials in congestive cardiac failure. The two published papers are hemodynamic studies. As hemodynamic studies, they are important pieces of research, but from a methodological point of view there is not enough evidence there to decide whether it does or does not help in dose finding.

L. Lasagna

The up and down approach has been used for years quite successfully in analgesic trials by Houde & Wallenstein, who unfortunately don't publish most of their stuff. They use two doses of the standard drug and two doses of the new drug and then, depending on how the results come out, they move up and down, and it seems to work quite well.

A. Reinberg

What type of statistics do you recommend in the "play the winner" and "up and down" methods?

C. Maxwell

In dose finding studies, the brief answer to that is that it does not matter, because all that one is trying to do is to identify a threshold dose and a plateau dose. I do not think statistics are necessary is this situation, particularly with the numbers that have been used in the application of the "up and down" method.

L.F. Prescott

I am surprised that this method which seems to answer so many problems, has not been widely used. There must be uncertainty as to whether or not it is a valid alternative to existing traditional methods of clinical trial design. It seems to me that it would be entirely possible to put this to the test very nicely in animal studies.

C. Maxwell

In fact, Bolognese took it from animal studies. The toxicologists have used a method like this. It has the advantage that it works when results are expressed as the proportion of patients who show response.

R.J. Temple

It strikes me that those methods are useful principally in situations where one doesn't expect much of a placebo response, or much spontaneous improvement, because if there is a lot of that, some sub-effective doses will seem to work. That seems important to me, because where there isn't a lot of spontaneous improvement, almost any method will work out reasonable well. Haemodynamic studies, for example, are often done in relatively poorly designed ways, with the dose just going up willy nilly and, on the whole, the answer comes out more or less right, because variables are easily measured and pretty stable, if you avoid things like meals. I wonder if these methods help in the difficult cases. My intuition is that they will not.

C. Maxwell

My intuition also is that they will not. What you are ultimately looking for is the superiority over placebo. The trouble is

you are then into a controlled trial. I frankly have no objection to the escalating dose regimen which we know somehow or other will produce a ballpark threshold and usually a ballpark intolerance level, particularly if the drugs do produce noticeable side effects. If there is a high placebo response rate in the condition, I don't think I would want to know about the up-and-down method. In that I agree with you.

P. Simon

Could you comment on the usefulness of Bolognese's method regarding side effects?

C. Maxwell

Bolognese's design is not intended to identify the intolerance dose level. It is designed only to produce the threshold and the plateau level. As we know, the intolerance level theoretically could occur before that plateau is reached; there might be plenty of room for more patients to respond, but one can't give more of the drug because of the side effects. In that case, the plateau cannot be reached.