Clinical trials

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Summary

The choice of standard drugs to be used in clinical trials must be based on consideration of human absorption data, *in vitro* characteristics, possible interactions, comparative efficacy and safety, previous data regarding the standard in relation to the syndrome to be studied, and correlation of blood levels, effectiveness and safety.

ONE major objective of any clinical trial programme with a drug must be to evaluate that particular drug's clinical usefulness. This means it is highly desirable to have as much knowledge as possible of its efficacy and safety in relation to the leading compounds in its field.

I propose to limit my remarks to the discussion of some of the factors influencing the choice of the comparative or standard drug for a clinical trial.

Despite all that has been written, and the even greater amount that has been spoken on the subject of correlation of blood levels with effectiveness and/or toxicity, I believe that few would argue with the statement that there is a relationship between the amount of an active drug absorbed into the internal milieu of the human body and its effects, beneficial or toxic. Several good examples where a significant change in the formulation of certain drugs has caused changes in effect, come quickly to mind—the episodes of phenytoin toxicity in Australia (Tyrer *et al.*, 1970), digoxin toxicity in Britain (British Medical Journal, 1972) and lack of effectiveness as reported by Whittet (1971) with steroids, stand out among these.

Now, more than ever before, when we prescribe a drug we are really prescribing a formulation which should be fairly expected to behave in a reasonably predictable manner as regards absorption. If modern, it is a formulation which has been characterized by experiment and clinical usage with regard to safety and effectiveness. When we want to compare our trial drug with the standard drug (we should really say—the standard dosage form), controlled double-blind studies is the method 'par excellence' for doing this. For such a study, one must either use the 'double dummy' approach which has certain snags

(Freestone, 1969) or provide identically appearing placebo, trial drug and standard drug, dosage forms. To do this, we must either match in size, colour, shape, etc., our placebo and trial drug to the standard, or make a new dosage form of the standard drug. If we choose the latter, we must then make sure that our new dosage form and the standard dosage form do not give markedly different absorption in man. This means comparing them in a cross-over study and measuring blood or plasma levels with an appropriate assay. At this point, I would like firmly to lay a red herring which frequently crops up. We are not trying to work out the exact pharmacokinetics of the two formulations, or the exact percentage of the drug absorbed from the two formulations. We want to know if there is a marked difference in the blood level profiles, for example lag time of appearance of the drug in the blood, or in the rate of absorption, or peak level, or rate of initial elimination between the two formulations in the same subjects, under standardized conditions.

In other words, we are looking to see if there is a marked difference, say more than $\pm 25\%$, in amount absorbed if the two blood level curves are the same profile, or secondly, if there is a difference in the shape of the curve. As Wagner (1972) points out time to peak blood level, and the peak blood level, may be good indicators of bio-availability, provided the ratio between the first order absorption and elimination rate constants of the two dosage forms do not vary too widely. Although he is referring here to a simple pharmacokinetic model, provided the same amount of the drug of the same chemical composition is included in each dosage form, and possible complexing agents are excluded, and provided steady state levels are measured in patients in the clinical study, a simplified 'bio-availability' study will be adequate to avoid major over- or under-dosing with the standard. During the actual trial, steady state levels of the standard drug are monitored and should be correlated with effectiveness and safety. Similarly, of course, the blood levels of the trial drug should be estimated during the clinical study.

Now let us look at some examples with both 'old' and 'new' drugs. Perhaps I might recall that average

FIG. 1. Graphical representation of one possible result of a simulated blood level study.

FIG. 2. Effect of taking mean levels of simulated data shown in Fig. 1.

FIG. 3. Composite of Figs. 1 and 2 to show the misleading effect of taking mean blood levels.

curves can, if used wrongly, convey misinformation. For Fig. 1, it is wrong to project Fig. 2. If, with such data, one must project the average, some method such as Fig. 3 should be used. Standard errors or deviations marked in the appropriate places are perhaps not quite so clear to the general audience. However, to save time (but with the above in mind!), I am going to show 'average' blood levels for some examples.

Figure 4 shows plasma salicylate level curves from two dosage forms of aspirin (Garnham *et al.*, 1973a). If one were considering these dosage forms for a trial in the rapid relief of headache, they would not in my opinion be equivalent. However, for rheumatoid arthritis, where long term total salicylate levels are important, they almost certainly would be. Incidentally, although the peaks look to be different, the information in Fig. 5 shows what happens when the peaks are moved to a common point on an adjusted time scale—they are virtually identical.

Figure 6 shows indomethacin plasma levels in ten subjects from two different dosage forms (Garnham *et al.*, 1973b). A superficial examination of the data suggesting there are no marked differences is confirmed by statistical analysis. However, another consideration emerges here; what other drugs are

FIG. 4. Mean plasma salicylate levels from aspirin tablets (○ — — ○) and capsules (△ — — △).

FIG. 5. Adjusted time scale graph for peak levels and elimination phase of aspirin in tablets (△ — — △) and capsules (● — — ●). Maximum level = zero time. When 'time' = 0.0, capsule mean = $66.2 \mu\text{g ml}^{-1}$, s.d. = 10.8; tablet mean = $64.1 \mu\text{g ml}^{-1}$, s.d. = 10.3.

commonly taken with indomethacin? Aspirin and antacids. Please note particularly that at half an hour all ten subjects had low or unmeasurable indomethacin levels. After pre-treatment with, and simultaneous administration of, buffered aspirin, Fig. 7 shows what happened to the plasma levels in four of the subjects. You may note that at half an hour there is a significant difference between the two curves previously obtained and the third, although the peaks are not markedly different. The side effects seen were much greater on the third occasion than on the previous two occasions, which is why we stopped the study after the first four subjects. This illustrates the importance of considering different therapy which might be given in relation to the trial drug. Other medicaments which might also be used to treat patients in the trial should be carefully vetted.

It is sometimes said that *in vitro* testing of dosage forms is sufficient to make a prognosis of blood levels in man. Whereas this can be true for some drugs, provided the formulation and make-up of the dosage form are not markedly altered, for others, an apparently small change in formulation which may not

FIG. 6. Plasma indomethacin levels after a single oral dose of 100 mg in two formulations, E (solid line) and C (broken line).

FIG. 7. Plasma indomethacin levels after a single oral dose of 100 mg in two formulations after pretreatment and concurrent administration of Bufferin. E (solid line) and C (broken line); C after pretreatment and concurrent administration of Bufferin (broken and dotted line).

FIG. 8. Mean plasma sulphadiazine levels after three formulations AP (solid line), AS (broken line) and SS (hyphen line). Dose 1000 mg.

affect the *in vitro* characteristics can markedly alter the blood level picture. Figure 8 shows blood levels obtained with different dosage forms of sulphadiazine in a group of volunteers (Garnham *et al.*, 1973c). The *in vitro* characteristics of the dosage forms of AP and AS were not different, whereas they were different between AS and SS. Yet you can see the blood levels show exactly the reverse. Whether AP is better or more toxic than AS or SS is immaterial in this instance—it is different! So if, say, AS were the 'standard' in common use, it would be wrong to use AP for the standard in the clinical trial.

Now, this situation is fine provided the standard comparative drug and its dosage form chosen is one well studied such as branded indomethacin, Indocid, or methyldopa, Aldomet, but it gets much more difficult when there are a lot of different preparations on the market as for example with quinine. The Merck Index (1968) lists twenty-seven different chemical quinine compounds which are or have been used in man. I can find no reports in the literature comparing human blood levels obtained with any of these quinine compounds with any other. Our own work would suggest quinine dihydrochloride as the appropriate salt, but I do not think one could

call any of the currently available preparations 'the standard'.

With some of the more modern drugs, when there is a choice of several different chemical preparations of the same base such as erythromycin, one must be very careful. To most physicians erythromycin is erythromycin, is erythromycin.

However, there are four commonly used different chemical forms of erythromycin available to the physician today; the estolate, the stearate, the ethyl succinate and the coated erythromycin base. How would one choose 'the standard'? The main reason for these different forms is that erythromycin base is acid labile, and the absorption of all these erythromycins mentioned, with the exception of the estolate, is significantly affected by food.

Advantages, therefore, based on blood level data, are claimed for the estolate, but it is the only preparation of erythromycin where serious toxicity is a relatively common feature (Goodman and Gillman, 1968; A.M.A. Drug Evaluation, 1971; Federal Register, 1973; Robinson, 1961a; Brown, 1963; Herskovic *et al.*, 1965; Johnson and Hall, 1961; Robinson, 1961b; Tolman, Sannella and Freston, 1973).

I refer of course to the liver toxicity sometimes labelled as cholestatic hepatitis, but which can also present as acute abdominal pain, which may be confused with biliary colic, pancreatitis or viral hepatitis.

Originally, justification for the estolate was based on 'very much higher blood levels than other erythromycins'. However, since it was found that 60–80% of these 'very much higher blood levels' are in an inactive form in the blood (Tardrew, Mao and Kenney, 1969; Eli Lilly and Company, 1972), emphasis has shifted to the fact that food interferes less with its absorption than with the other erythromycin preparations. However, if the other erythromycin preparations are given well before or after meals, absorption is perfectly adequate.

Since the vast majority of erythromycin used is for the treatment of mild to moderate infections, often without benefit of bacteriological examination, it would seem there would have to be overwhelming advantages to justify the use of the estolate as a standard, to treat mildly to moderately ill patients. I use this example to illustrate that not only must the blood levels of a drug be considered when choosing a standard for clinical trial, but the innate toxicity of the chemical form of the compound to be used must also be carefully considered.

There are of course many other points which could be mentioned but to summarize, the following must be considered among the most important.

- (1) Compare study dosage form and standard in man;
- (2) *in vitro* equivalence alone is not sufficient;
- (3) evaluate possible interactions before the study;
- (4) careful evaluation of the literature regarding effectiveness and safety is essential when more than one 'standard' is available;
- (5) relate all information obtained to the clinical syndrome to be studied;
- (6) obtain where possible blood level/effectiveness/safety correlations.

Figures 4–8 show data resulting from part of a co-operative programme between Professor E. Shotton and Mr K. Raymond of the School of Pharmacy, London, and Professor P. Turner and Dr J. C. Garnham of the Department of Clinical Pharmacology, St Bartholomew's Hospital, London.

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Discussion

Professor Sir Derrick Dunlop wondered if anyone from Eli Lilly would stand up for erythromycin estolate. Dr. W. H. Lyle found himself doing so on behalf of Dista Products. He thought that one had to

decide which was more important, good blood levels or occasional toxicity. He accepted that as reported by the Committee of Safety of Medicines, 1973, there had been forty cases of reversible jaundice in 8 years,

though about half a million prescriptions were written yearly for erythromycin estolate (Ilosone), excluding hospital use. Professor L. P. Garrod, not speaking for Eli Lilly, said that he had held the view for some years that if erythromycin was to be used at all it should be in the form of the estolate; he did not believe that even on a fasting stomach the base or the stearate were always adequately absorbed. Nor was he convinced by the work which suggested that when the estolate was given the antibiotic existed in the blood to the extent of 60–80% in an inactive form.

Dr J. C. Garnham stressed the frequency of abdominal pain in patients receiving erythromycin estolate and mentioned that he had recently seen a case in which laparotomy had been considered; he was disturbed by the prospect of laparotomy for sore throat. Dr Lyle thought that a knowledge of the toxicity of any compound was essential to the prescriber if he was to use it sensibly.

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