Introduction

Therapeutics is all about giving the appropriate drug in an appropriate dose to the appropriate patient. How to choose the appropriate dose is probably the most difficult of these. If one examines how thinking in the area of optimal dose identification has developed in modern times, it was probably concern for minimising risk that was initially considered most important.

Thalidomide in 1961 had focussed the attention of the world on drug toxicity and among the many consequences of this episode was the realisation of the importance of collecting all clinical adverse drug reactions and documenting their epidemiology. In the United Kingdom, a direct consequence of thalidomide was the establishment of the first spontaneous adverse reaction reporting scheme (the Yellow Card Scheme) in which medical practitioners would report all suspected adverse drug reactions to the Department of Health which was charged with their collection and analysis. At the same time, disease related databases were being established - for example the Blood Dyscrasia Registry run by the American Medical Association which had been started in 1955. Armed with such data, clinical scientists were in a position for the first time to analyse why some individuals seemed more susceptible to drug toxicity than others. Remember too, that it was around this time (1950–1960) that pioneering studies of drug metabolism in man were being carried out and giants like Bernard Brodie, Alan Conney and Herbert Remmer were around to interpret them and put them in a clinical context.

What emerged was that two main factors appeared to predispose patients to adverse drug reactions - firstly the inability to eliminate a drug (whether by metabolism or via the kidney for whatever reason) and secondly the number of drugs which the patient was taking. The concept of evaluating the pathway of drug elimination and calculating drug kinetics emerged as powerful tools to predict drug toxicity, as did understanding the basis of clinical drug interactions. Both of these were of relevance for selecting the appropriate dose of a drug.

From the standpoint of drug efficacy, the emergence of the controlled clinical trial in the 1950's put evaluation of drug efficacy on a scientific footing for the first time. In the U.K. the ground breaking studies were the trials of antituberculosis therapy designed by Austin Bradford Hill. Emerging from these and other such studies, pioneers such as Peter Armitage demonstrated how formal statistical analysis could be applied widely to clinical trials, including comparison of drug doses.

So these two arms – safety and efficacy - became better understood and, most importantly, measurable, and drug regulatory agencies now had means at their disposal to require industry to provide hard data on risk and benefit of a new drug and especially which dose should administered before a marketing authorisation could be given.

Since then, of course, many important scientific, commercial and ethical factors have influenced our thinking on how we identify optimal drug doses-influences as diverse as:

1. The understanding of genetically determined polymorphisms of drug metabolism, of drug transport and of receptor action.
2. New methodological tools for analysis of clinical trials such as meta-analysis.
3. Pharmaceutical innovation such as extended release and slow release drug formulations to improve compliance.
4. On the negative side, we have encountered ethical difficulties in conducting drug investigations in animals and in certain patient groups such as children.

So turning now to the composition of the programme for this meeting, we have chosen a series of problem scenarios relating to the underlying theme of predictability of drug response and how this relates to optimal dose identification, and we propose to review the current status of each of these areas.

We start by considering how optimal drug dosing is ascertained in drug development. This is the kernel of the problem. Much time and money is spent on ascertaining the appropriate dose, often fruitlessly. Traditionally, preclinical toxicology studies have predicted the size of the first clinical dose, but now drugs are being studied in man at ever earlier stages of drug development; are there other ways of predicting appropriate doses for phase 2 and phase 3 studies? Do we learn enough from late clinical studies - phase 4 studies - which might feedback to the next drug in a series? We are putting these questions to colleagues from industry, from academia and from drug regulation. One of the recurring themes of this symposium is what lessons can be learned from different diseases and different age groups; you will see that we have selected a diversity of important clinical conditions for consideration.

It was, I think, the early to mid 1990's that the idea of modelling not only pharmacokinetics but also pharmacodynamics and then PK/PD modelling arose. One of the main aims of PK/PD modelling was to select optimal doses early - very early - in drug development. We are extremely fortunate to have several of the real pioneers of this science with us, to reflect how their baby has matured and whether it is now a responsible contributing citizen or a wayward drop out.

Therapeutic drug monitoring was first advocated in the 1970's when its main goal was to prevent clinical toxicity. It has not had an although easy development since then; its role remains contentious and in these days when the importance of cost-effectiveness pervades all health care, it is relevant to re-examine its current status, and to see how it is being applied in new conditions such as HIV disease.

Drug development, of course, is now largely in the hands of molecular biologists and we thought it important to review how the new genomics were influencing considerations of drug efficacy and toxicity and hence optimal drug dosing. We ask the question whether drugs born of the new biology are likely to present a new series of problems in terms of their clinical usage, or will they be the same as drugs of the previous generation.

Finally we come full circle and we consider several common disease areas and ask what we have learned about dose optimisation in specific instances.

The Esteve Foundation Symposia have, over the years, assumed an important role in the world of Pharmacological and Pharmaceutical Science. We hope that the present one will live up to the reputation of its predecessors.

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