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Editorial—What is the point of pharmacokinetics?

Any major disaster—such as a train or plane crash, sinking of a ferry, or collapse of a bank—seems to be inevitably followed by the clamour of politicians calling for a public enquiry. More personal misfortunes—and here I should try and be less cynical—such as surgical operations that are not successful may also be the subject of calls for investigation. Perhaps there is some deep-seated need in man to justify his actions even when nothing can be done to repair the damage. Would it be too provocative to suggest that the science of pharmacokinetics is a symptom of the same need?

Typically, registration dossiers for investigational drugs and for new drugs to be marketed will include pharmacokinetics of the new chemical entity in rats. Why?

It could be that it helps to understand the pharmacology, or that it helps explain long-lasting effects. But knowledge of these things will not alter the clinical pharmacology that will need to be established in man. What is more, the dose needed to be able to assess pharmacokinetics in individual small animals is often much larger than any dose projected for the clinic; if the dose is kept low and several animals need to be used to obtain sufficiently large biological samples for the analyst, then the resulting profile could well be so vague as to be meaningless.

Interestingly enough, with extremely powerful new drugs which are administered in microgram quantities, the requirement for an analytical method capable of detecting such vanishingly small quantities in the blood may often be waived. If it can be waived in this instance, then can the need really be justified in the simpler cases?

Pharmacokinetics (including drug metabolism studies) is often pointed out as being useful in validating particular animal species as toxicological models for man. This is a viewpoint that has been aired for at least a quarter of a century, but is actually highly unlikely to be justified in practice. Toxicity studies are conducted in animals long before any meaningful dose is administered to man; if found toxic in animals, the development will be terminated. There may be an argument that termination is premature and that the particular animal species may metabolize the drug differently compared with man, who may consequently tolerate the drug with perfect safety. However, once toxicity has been identified, which pharmaceutical company executive will authorize funds to carry out research on the comparative metabolism? And even if the case is proved, it is inconceivable that any company will market a drug which has been shown to be toxic in any animal species?

The use of radiolabelled studies in animals also seems to be a necessary part of drug registration documents, with heavy emphasis on accounting for all the administered radioactivity. It is instructive to consider how these studies came about. Initially, radiolabelled studies were considered as a useful and rapid method for determining the metabolic pathways in man as well as in experimental animals. However, it was appreciated that large doses of radioactivity would be unwise in human subjects; even the trace amounts usual in metabolic studies could be dangerous if radioactivity (whether in the form of the parent drug or even a minor metabolite) accumulated in a particular tissue. Hence the need for elaborate pharmacokinetic studies to assess the distribution and accumulation of radioactivity in animals and the subsequent risk assessment to humans before the radiolabelled drug is administered to man. Obviously there is a need to account for the all the label in the animal studies to make sure the data is complete for the predictions, but once the labelled drug has been administered to the volunteer, accounting for all the radioactivity is not a safety issue. To put it crudely, the damage will have been done and no amount of measurement will change that. If the experiment has been designed thoughtfully and maximum use of the radiolabelled material is made, then this ought to be the only occasion on which this particular drug is administered in a radiolabelled form to human subjects. But pharmaceutical scientists have become considerably more sophisticated in separation and identification techniques since radiolabelled compounds were hailed as the last word in carrying out metabolism studies. NMR, for example, is increasingly used to characterize metabolites, sometimes with little prior treatment of the biological sample. Hence metabolism studies can be carried out in volunteer studies without the use of radiolabelled drug, and consequently the preliminary work in animals which is designed only to assess the safety of a radiolabelled dose is unnecessary. Additionally, once a compound has been used in man and shown to be safe and effective, then all animal-metabolism studies become irrelevant.

Perhaps I should rephrase my original question as 'What is the use of pharmacokinetics in animals?' If the arguments I have used above are valid, then the answer could be 'not very much'. We would then need to turn to the use of pharmacokinetics in man. It is argued that a knowledge of single dose kinetics can be used to predict the accumulation or steady state levels of test drugs on multiple application. However, even this relatively straightforward exercise needs to be confirmed by experiment and if the analytical method is not sufficiently sensitive, a long half-life may be missed and accumulation will occur even when not predicted. (Although once the unlooked-for accumulation is found, there will be no shortage of pharmacokinetic explanations!)

I would conclude from these arguments that pharmacokinetics has only proved useful in its role as a public enquiry—that is, it can be used to satisfy the needs of providing an explanation when an explanation is needed, but does not actually help in decision-making in drug development. However, this need not remain the case and there are now an increasing number of laboratories which are actively developing the predictive powers of pharmacokinetics and with the use of computers this can only increase in the not-too-distant future.

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