Leading articles

Animal models in antibacterial drug research

Animal pharmacology is considered indispensable for the development of new drugs as well as for elucidation of the mode of action of drugs, and this is certainly the case if not only intact animals but also organ systems, cell cultures, and the like are taken into account. However, in antibacterial drug research there is a unique situation in that the target is not a part of the animal and can therefore be studied in complete isolation.

The advantages of this situation are evident, especially because it permits the screening of a large number of substances to determine whether they have antibacterial properties against a large number of pathogens, but they also have a negative effect, since they have led to neglect of the scientific potential of animal studies for a better understanding of the therapeutic efficacy of antibacterial drugs. Notwithstanding repeated admonitions in the literature (O'Grady, 1976; Zak, 1980), the relative share taken by animal studies in antibiotic research seems to be still declining in favour of large-scale in-vitro studies and early clinical trials. This change is regrettable, because the predictive value of in-vitro studies in the development of new antibacterial drugs is often poor (Zak & Sande, 1982).

Historically, it is of interest that Domagk (1935) showed the efficacy of prontosil in an animal infection, although this compound is ineffective in-vitro. Since then, however, very few compounds have been developed that are effective in-vivo but not in-vitro (Zak & Sande, 1982). It is true that the therapeutic efficacy of some prototypes of antibacterial drugs, e.g. benzylpenicillin and streptomycin, was convincingly shown in clinical therapeutic experiments, against historical controls of untreated patients. At present, however, new drugs are often thought to be better than their immediate predecessors, mainly on the basis of in-vitro evidence. For almost any other class of drugs where the importance of patient factors is as great as in antibacterial drugs, double-blind controlled studies would be demanded for the assessment of the therapeutic effect. But for antibacterial drugs, the authorities seem to accept claims of effectiveness on the basis of open, non-controlled clinical trials, together with human pharmacokinetic data and crude estimates of in-vitro efficacy based on such measurements as the MIC.

There are, however, sound reasons why animal studies should be regarded as an indispensable step in the development of antibacterial drugs. For example in-vitro studies fail to take into account the important interactions between host and micro-organism as well as between host and drug, and in clinical studies these interactions are largely uncontrolled. The objection that animal studies do not have much value because man differs so much from the mouse or rat may have some validity, especially because authors sometimes draw such far-reaching conclusions from their experiments, but it disregards the wealth of information that can be gained by well-designed and properly interpreted animal experiments.

Although different problems call for different animal models, most of these models can be placed in a few categories whose limitations must be kept clearly in mind. To begin with, toxicological models in animals, although not the subject of this article, should be mentioned briefly here because antibacterial drugs are assumed to be selectively toxic only for bacteria. Therefore animal studies dealing with the toxicity of drugs, e.g. the ototoxicity of aminoglycosides, should be interpreted in the light of antibacterial efficacy. Both aspects should by preference be studied in the same kind of animal, since pharmacokinetic properties are important for both.

Furthermore, fundamental aspects of pharmacokinetics can be studied very well in animals, e.g. β-lactams or aminoglycosides in relation to active transport mechanisms. Results of this kind of experiment of course cannot be extrapolated quantitatively to the clinical situation.

Two categories of animal models used to elucidate the pharmacodynamic properties of
antibacterial drugs, can be recognized. The first comprises animal models used to assess antibacterial efficacy in vivo in relation to activity in vitro. The second comprises animal models of human disease that are employed to predict therapeutic efficacy in man. The fundamental difference between the two kinds of model is often forgotten. The first of these categories has been used to study the way in which pharmacokinetics modulate the intrinsic antibacterial efficacy (Mattie, 1981). An example of this type is the thigh infection model in mice, where a known number of bacteria is injected into a thigh muscle, and some time later the bacteria are counted in the homogenized muscle tissue. These bacterial counts can serve to establish an accurate dose–effect relationship, for instance as a basis for the comparison of different antibiotics in vivo, or, if pharmacokinetics are taken into account, with the activity in vitro (Kunst & Mattie, 1978; Mattie & Van der Voet, 1981). The cited experiments showed that there is as yet no scientific basis for reliable prediction of clinical efficacy, solely in terms of human pharmacokinetics and arbitrary in–vitro parameters such as the MIC. In the same model the contribution of host resistance factors, such as granulocytes, proved to be quantitatively related to the contribution of the antibacterial drugs. It was shown, for instance, that in granulocytopenia the dose of aminoglycosides must be doubled to achieve the same effect as in normal animals (Van der Voet, Mattie & Van Furth, in press).

Lastly, animal models of human disease suffer from a fundamental limitation of interpretability. If it may be assumed that the intrinsic antibacterial effect is identical in animals and in man, and even that bacterial growth kinetics are similar in both species, it is nevertheless certain that the pharmacokinetics differ widely and probably host resistance factors as well. This means that the time course of an infection under treatment will always be different in animals and in man. A good example is the endocarditis model in rabbits (Petersdorf, Pelletier & Durack, 1977). This model has proved to be very useful for qualitative predictions concerning the antibacterial treatment of endocarditis. If, however, the results are interpreted in terms of dosage regimens, the above mentioned objections should be kept in mind.

In conclusion, it may be said that the difficulty associated with animal models lies less in the performance of the experiments than in the interpretation of the results in a clinically relevant way. If, however, the limitations of interpretation, which always hold for animal experiments are properly respected, there is good reason to extend and improve the use of animal models in the field of antibacterial drugs, as a basis for carefully planned clinical research.

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References

Outpatient intravenous antibiotic therapy
Over the past five years, a number of publications (Antoniskis et al., 1978; Stiver et al., 1978; Poretz et al., 1982; Rehm & Weinstein, 1983; Kund et al., 1979; Williams et al., 1982) have demonstrated the efficacy, safety, and cost savings of outpatient intravenous antibiotics in a number of centres in the United States. Although differing in detail, in