Animal models of respiratory infection


Antibiotic treatment of bacterial infections represents a dynamic interplay between the drug, the host, and the pathogen. Various factors may influence the activity of an antibiotic in vivo, some of which might not have been anticipated from in-vitro studies. Respiratory tract infections require special consideration because of the complex pharmacokinetics of antibiotic penetration into tissues and the lungs host defences. Acute bacterial infections such as pneumonia enhance the penetration of antibiotics into the lung, while the reverse is true in chronic infections such as bronchiectasis where pathological barriers are already in place (Cole & Wilson, 1989).

Animal models represent an essential step between in-vitro sensitivity testing and clinical studies. An animal model also has the advantage that it can be manipulated in ways that would not be possible in human studies. However, respiratory tract infections with human pathogens are not easy to produce in animals, and aerosol delivery frequently produces an insufficient inoculum (Pennington, 1985). Anaesthesia, skilled intubation and surgical procedures are often required, which make the model non-physiological at the outset. It is common practice to administer high inocula of infecting organisms in order to exaggerate therapeutic differences, but this is not usually the in-vivo situation and may disadvantage certain antibiotic classes or treatment regimens.

Broadly speaking animal models can be divided into screening models and discriminative (specialized) models (Zak & Sande, 1986). Screening models, such as the mouse protection test (Bergeron, 1978), are commonly used during the development of an antibiotic and the extra knowledge they impart is clear. Little emphasis is placed on the correlation of the infectious process to the clinical situation. The model has to be easy to use and reproducible, so that sufficient numbers of animals can be screened for statistical analysis. Small animals, such as the mouse, are commonly used because they are cheap and easy to handle. The outcome of the experiment is usually measured by survival or death of the animal. An inoculum is chosen which is several fold above the 50% lethal dose, and the antibiotic effect is measured as the dose that protects 50% of animals.

Discriminative models try to mimic as closely as possible a particular type of clinical infection. Many antibiotics have been studied in this type of model (Table) but the benefits are less clear. An ideal discriminative model would include a portal of entry similar to that in man, a bacterium that is pathogenic for both the animal and man so that artificial interventions are not required to lower the animals resistance, a predictable disease course which is similar to that in man and of sufficient length to assess therapeutic intervention, and the technique employed should be relatively easy so that it can be reproduced in different laboratories. These criteria are frequently not met, and the major weakness of discriminative animal models is that comparison of results from various investigators is difficult owing to numerous variations in experimental conditions.

The outcome of an experiment can be changed by an apparently minor alteration in the experimental protocol. The strain, age and sex of the animal; the strain, growth-phase and inoculum size of the bacterium; the dosage, timing and route of administration of the antibiotic can all influence the results obtained. For example, treatment of Gram-negative pneumonia in a guinea-pig model was influenced by the size of the challenge inoculum. When a higher challenge inoculum was used an aminoglycoside was found to be superior to a β-lactam, and an aminoglycoside plus a β-lactam were equivalent to an aminoglycoside alone. When a lower inoculum was used an aminoglycoside and a β-lactam were equivalent, and a combination was superior to an aminoglycoside alone (Pennington, 1985).

Attention to detail is therefore important when reporting the results from any animal model. The model should mimic human disease by clinical, histological and pathophysiological parameters (Pennington, 1985; Lapa e Silva et al. 1989; Woods et al., 1989), and there should be an understanding of the animal's natural defences against the pathogen (Winkelstein, 1984). To overcome difficulties...
Table. Antibiotic studies in discriminative animal models

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In interpretation caused by pharmacokinetic differences between species, the concentration of an antibiotic should be measured in the blood and lung to ensure that the levels are similar to those likely to be achieved in man. Bacterial viable counts in the blood and lung must be measured as well as animal survival, because death may be due to factors other than infection. For example, bacterial toxin production may cause death, so that whilst an antibiotic can be effective in decreasing bacterial numbers it might not influence mortality. Pneumolysin is an important intracellular toxin of the pneumococcus which is released during cell lysis induced by β-lactam antibiotics (Feldman et al., 1991). It follows that the more extensively a model has been studied, and the more widely it has been used in different laboratories, the more useful it becomes. Many animal models have been described, but few have been studied in sufficient detail to permit comparison of data between laboratories.

A new animal model should only be developed when there are problems with an existing model, or when new techniques become available, and clear benefits of the new model can be demonstrated. For example, most animal models used to study *Pneumocystis carinii* pneumonia rely on steroid-induced immunosuppression to activate latent *P. carinii* infections in rats. These models are often limited by the unknown baselines of *P. carinii* infection, the long time required for development of heavy infections, and the frequency of secondary infections that render many of the animals unusable. Recently, a new rat model has been described using subcutaneous methyl prednisolone and intratracheal instillation of *P. carinii*. This new model produces consistent heavy infections of a known *P. carinii* strain in a shorter time period, with minimal secondary infections (Boylan & Current, 1992). Transgenic animals may permit new infection models to be developed. These are animals in which deliberate human gene insertions and deletions create genetic lines of animals with important disabling human diseases such as cystic fibrosis (Ratcliffe et al., 1993). They open up exciting new possibilities for understanding the pathogenesis of some infections e.g. *Pseudomonas aeruginosa* in cystic fibrosis, and devising new therapies for such conditions.

Even the very best animal model is not free of limitations, and investigators need to pay at least equal attention to these, as to the merits of the model. Results should be interpreted with caution, and great care must be taken when extrapolating to the human condition. In order to facilitate the interpretation of data produced by studies of antibiotics in discriminative animal models, a smaller number of models which are better understood should be more widely used. Ethical considerations would support this approach (Zak & O'Reilly, 1993).

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References


### Endophthalmitis—problems, progress and prospects


Endophthalmitis is inflammation of the aqueous and vitreous chambers of the eye and adjacent structures within the sclera. When episcleral tissues are involved panophthalmitis is said to be present. This is a potentially devastating condition often ending in visual loss and commonly complicates intra-ocular surgery, such as cataract extraction, penetrating injury to the eye or septicemia (Rowsey et al., 1982; McDonnell & Green, 1990; Hassan, MacGowan & Cook, 1992). Symptoms include diminished vision, headache, and ocular pain. Examination reveals vitreous opacification and loss of the red reflex.

Several problems face those endeavouring to improve the management of endophthalmitis. Firstly, it is a rare condition; the exact incidence following surgery remains largely unknown, but is believed to be less than 0.5% (Allen & Mangiaracine, 1974; Fisch et al., 1991). In the largest series from the UK, we (Hassan et al., 1992) reported a total of 47 cases during an 11-year period. Secondly, the infrequency of the condition makes it difficult to compare treatment regimens in this potentially blinding disease. Thirdly, animal models used to evaluate new treatment modalities are beset with difficulties when extrapolating to man. Any progress in the management of this condition is likely to be guided more by personal experience or at best a consensus view.