PK-PD INTEGRATION AND PK-PD MODELLING: ALTERNATIVES TO DOSE TITRATION STUDIES FOR SELECTING OPTIMAL DOSAGE SCHEDULES OF ANTIMICROBIAL DRUGS

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PROPOSITIONS UNDERLYING THIS REVIEW

1. Reliance on clinical cure alone in disease models and clinical trials is very unlikely to lead to optimal dosage selection for antimicrobial drugs (AMDs). The gold standard is bacteriological cure.

2. The so-called optimal dose will differ, depending on whether the outcome evaluated/required is clinical cure, bacteriological cure or prevention of emergence of resistance.

3. Graded dose titration/determination studies in disease models in target species can be virtually guaranteed to lead to selection of an effective but not an optimal dosage regimen for AMDs.

4. There are universally applicable formulae for systemically acting (including antimicrobial) drugs which: (a) define the relationship between the 3 pivotal pharmacokinetic (PK) parameters, clearance, volume of distribution and elimination half-life; (b) define drug action (pharmacodynamics, PD) quantitatively through the sigmoidal E_{max} equation, linking concentration to effect; (c) predict a potentially optimal dose. A PK-PD approach to predicting dosage (as an alternative to dose titration studies) is possible for most drugs and many diseases.

5. Distinction should be made between PK-PD integration and PK-PD modelling, but both can be used sequentially and both have value in predicting optimal dosages.

6. It cannot be assumed that AMD PK profiles in healthy animals of the target species will be the same as or even similar to profiles in the target clinical population. Therefore, the ideal will be to use population PK and PD data with Monte Carlo simulations to predict an optimal dosage regimen.

7. Greater utilisation of PK-PD approaches and population PK should not impose additional requirements for registration of AMDs. These approaches should generally be viewed as alternatives to dose titration studies in disease models and PK pre-clinical studies in healthy animals, respectively. There may be both animal welfare and cost benefits from utilising the approaches outlined in this review; they may reduce the overall regulatory burden.

EMA/CVMP GUIDELINES ON EFFICACY OF AND RESISTANCE TO AMDs

Document EMA/CVMP/287420/2010, entitled "CVMP strategy on antimicrobials 2011-2015" was adopted by CVMP on 14th July 2011.

It is both a vision and a strategy statement, and it rightly concentrates heavily on antimicrobial resistance. Resistance to AMDs is of concern not only for their continued effectiveness in treating animal diseases, but is now a public health issue, through the possibilities (some real, some possibly imagined) of transfer of resistance from animal pathogens and commensals to human pathogens and commensals and *vice versa*. In minimising opportunities for the emergence of resistance, everyone recognises the importance of *prudent* and *responsible* veterinary use. However, less attention has been paid to *rational* use and this encompasses the relatively little discussed subject (in veterinary circles) of predicting optimal (as opposed to merely partially effective) dosage schedules.

Document EMA/CVMP/287 refers to dosage selection very briefly. In discussing the strategy over the period 2006-2010, it refers to "possibilities to further use PK-PD modelling in the establishment of

the best dose and dosage regimen". However, on "CVMP actions taken", the annex to the report states "no guidance documents have been developed", because "the area needs to be covered on a product level rather than generally". This differs from the stance of the FDA/CVM in the U.S.A.

It is the purpose of this review to re-state the case for a more general application of PK-PD integration and PK-PD modelling in dose selection of AMDs for veterinary use, with a view to maximising bacterial kill and minimising the emergence of resistance.

CLINICAL CURE TO SELECT DOSAGE REGIMENS IN DOSE TITRATION STUDIES

There are several problems with reliance on dose titration studies for selecting a dosage regimen for subsequent evaluation in dose confirmation studies/clinical trials (as recommended in current EMA/CVMP Guidelines) as follows: (a) they are generally conducted using parallel study designs without generation of PK data, so that the body is a "black-box" – literally nothing is known of plasma/tissue concentrations required for efficacy, yet plasma concentration is superior to administered dose from the optimal dosage regimen prediction perspective; (b) statistically, data cannot be interpolated between or extrapolated beyond doses actually evaluated in parallel design studies; (c) if reliance is placed solely on indices of clinical cure (i.e. no data available on bacteriological cure), the judgement of efficacy may be influenced by the Pollyanna phenomenon, i.e. a weak bacteriological cure may be associated with a good clinical response, whilst complete bacteriological cure may not yield 100% clinical response; (d) generally, clinical indices of response/efficacy are indirect, relatively crude (e.g. semi-quantitative assessment of demeanour, posture etc.) and either not known or not shown to correlate with bacteriological outcome.

COMPARISON OF PK-PD AND DOSE TITRATION APPROACHES TO DOSAGE SELECTION

Feature	PK/PD integration and modelling	Dose titration or clinical trials
Subjects	Healthy	Infection models, clinical cases
End points	Surrogates: T>MIC, C_{max}/MIC and AUC/MIC, AUC/MPC	Clinical outcome (cure, failure) only or bacteriological outcome (eradication, resistance) also
Sensitivity to dose ranging	Yes	No (difficult to perform dose ranging in diseased animals)
Validity (clinical relevance)	Needs to be validated (prospectively or retrospectively)	Possible drawbacks (*vide supra*) and Pollyanna phenomenon
Reliability	High	Low
Extrapolation (from *in vitro* models or between species)	Easy	Difficult
Application to drug discovery and development	Early screening	Later confirmatory
Dosage individualization	Yes	No
Breakpoint setting	To be explored (promising)	Yes
Population studies: pharmacokinetic or pharmacodynamic origin of variability allowed for	Yes	No, if clinical outcomes only are measured

Feature	PK/PD integration and modelling	Dose titration or clinical trials
Cost	Low	High
Regulatory acceptance	In progress ?	Studies are pivotal; designed to satisfy authorities but not to optimise dosage

PK-PD INTEGRATION AND PK-PD MODELLING FOR AMD DOSE SELECTION

Dose selection guidelines for AMDs differ between regulatory authorities. However, all require the provision of pre-clinical PK data in the target species and the PD profile of the drug. The PD of AMDs is usually quantified using minimum inhibitory concentration (MIC) and/or minimum bactericidal concentration (MBC), whilst growth inhibition time curves are used to define both the type of killing action and steepness of the concentration-effect relationship. There are additional useful indices, such as mutant prevention concentration, for some drug classes but these are outside the scope of this brief review. From the median or geometric mean MIC_{50} and MIC_{90} values for the microbial species of interest is predicted a provisional dose by PK-PD integration, using one or more of the indices: $C_{max}:MIC_{90}$ (for concentration-dependent drug classes e.g. aminoglycosides); $AUC:MIC_{90}$ (also for most concentration and co-dependent drugs e.g. fluoroquinolones, tetracyclines and macrolides) and $T > MIC_{90}$ (for penicillins and cephalosporins). $T > MIC_{90}$ is the percentage of the inter-dose interval for which plasma concentration exceeds MIC_{90}.

There is an extensive literature proposing numerical values of these indices, for example $C_{max}:MIC_{90} \geq 10:1$ for aminoglycosides, $AUC:MIC_{90}$ ratio $\geq 125h$ for fluoroquinolones and $T > MIC_{90} \geq 50\text{-}80\%$ for beta-lactams. However, these values provide only a general guide to clinically effective dosage for the following reasons: (1) type of killing action (time or concentration dependency may vary between microbial species; (2) target numerical values are specific to both individual drugs *and* target microbial species (drug and bug specific) and even vary with strains of microorganisms of a given species; (3) an effective dose depends on factors such as bacterial load and level of immune competence of the host animal; and (4) the dose required varies with the assessment end-point, which may be clinical cure, bacteriological cure or avoidance of emergence of resistance.

PK-PD integration is a useful tool for initial prediction of an effective dose. Lees *et al.* (2004) Toutain *et al.* (2002) have recommended PK-PD modelling as the next stage in dosage prediction. PK-PD modelling, utilising computer programmes based on the sigmoidal E_{max} equation, generates data for the whole sweep of the plasma (or other biological fluid) concentration-effect relationship. This enables determination, using *in vitro*, *ex vivo* and *in vivo* techniques, of drug concentrations and dosages required to achieve specific levels of inhibition of bacterial growth, for example bacteriostatic, bactericidal and eradication of bacteria. Aliabadi and Lees (2003) used this approach to determine an effective dose of danofloxacin against a strain of *M. haemolytica*, a causative organism of calf pneumonia. This led to increase in the manufacturer's originally recommended dose for the drug from 1.25 mg/kg to 6.0 mg/kg.

DISEASE STATE AND POPULATION PHARMACOKINETICS

AMDs are used extensively in farm animal species for prophylaxis, metaphylaxis and therapy and in small animal practice for therapy. For regulatory purposes, authorities require generation of PK profiles in healthy animals of the target species; small numbers of animals, usually of a single breed, of similar age and possibly of the same gender are used, generally with an intense sampling schedule. However, in the three clinical circumstances outlined above, the PK profiles are likely to differ in terms of mean values of clearance, terminal half-life, etc. and also possibly in respect of greater inter-animal variability.

There are a few studies in the veterinary literature, conducted with large animal numbers and a sparse blood/plasma sampling schedule, which illustrate this variability in PK. Such data are described as population PK, as they are obtained from a sample of the clinical, usually diseased, population. Toutain and co-workers have presented data on the population PK of doxycycline administered orally (in feed) to a large group (n = 273) of pigs. Plasma concentrations exhibited marked inter-animal variability, such that plasma AUC for the drug ranged from 3 to 20 mg.h/mL. Nevertheless, using Monte Carlo simulations on the PK data, together with data on MICs for target pathogens causing respiratory disease in pigs, they were able to predict doses required to provide breakpoint AUC/MIC ratios for each target pathogen.

In summary, the objective of population PK is to determine both the variables which enable an optimal dose to be determined for the clinical population and also to explain inter- and intra-animal variability in terms of age, sex, breed and health/disease status, etc.

FURTHER READING

This brief review has focussed on general principles of dosage selection for AMDs. For more detailed accounts of PK-PD (including population PK) approaches to optimal dose determination (approaches now widely accepted for AMD dose optimisation for human use) the following articles may be consulted.

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