HOW ANTIBIOTIC DOSAGE REGIMENS BASED ON PK-PD CONCEPTS
MAY BE AN IMPORTANT CONTRIBUTION TO THE RESISTANCE PROBLEM

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1. INTRODUCTION

The most important risk factor for emergence of resistance is repeated exposure of bacteria to suboptimal concentrations of antibiotics and thus, from an operational point of view, the most important risk factor for emergence of resistance is the selection of an inappropriate dosage regimen. There is therefore a need to design dosage schedules, not only to guarantee clinical efficacy, but also to minimize the emergence of such resistance. This is both a therapeutic issue (target pathogen) and a public health issue (non target bacteria) for veterinary antibiotherapy.

To achieve this goal, it is necessary to understand how an inappropriate dosage regimen may lead to the emergence of resistance. Although there are several possible scenarios, according to Drusano (2003) a counterselective dose design only offers an advantage when the total organism burden exceeds the mutational frequency to resistance and there is a high probability of a resistance clone being present at baseline.

In this review we examine why an optimal antibiotic therapy should aim to achieve clinical success through a total bacteriological cure. Indeed, if bacterial eradication does not occur and if the total organism burden consists of a mixture of populations, the less susceptible bacteria are likely to head the recolonization process during or after discontinuation of therapy and a more resistant mutated daughter population will become predominant. It is important as regards this situation, to realise that apparent clinical success is not a fully valid endpoint for determining the optimal dosage regimen (i.e. bacteriological cure) due to the so-called “Pollyanna phenomenon” (Toutain et al. 2002). This term refers to the fact that if the measurement of antibiotic efficacy is based on symptomatic responses, then drugs or dosing strategies with excellent antibacterial activity will not be as effective as anticipated, whereas the opposite will occur for antibiotics with poor antibacterial activity. These limits of clinical trials have led to the exploration of alternative approaches for determining an optimal dosing regimen. Currently, the most promising approach consists of linking the pharmacokinetic (PK) and pharmacodynamic (PD) properties of antibiotics within the framework of the so-called PK/PD approach because this serves as a bridge between in vitro and in vivo studies and also allows prediction of the emergence of resistance when designing a suitable dosage regimen (Lees et al. 2006; Lees & Shojaei Aliabadi, 2002; McKellar et al. 2004).
The aim of this review is to explain how the PK/PD approach can be used in this way for antibiotics with special emphasis on the potential contribution of PK/PD concepts in the minimization of drug resistance development.

2. WHAT IS THE PK/PD APPROACH?

The principle underlying the PK/PD approach is that two major factors may influence the outcome (expected or undesirable) of any antibiotherapy: exposure of the bacteria to the drug at the biophase level (a PK factor) and bacterial sensitivity (target pathogen, food-borne zoonotic or commensal bacteria) to the selected agent (a PD factor). The latter is normally characterized by an in vitro parameter such as the minimum inhibitory concentration (MIC). The combining of PK and PD information, to predict a dosage regimen, is termed the PK/PD approach. In practice this consists of building some hybrid PK and PD indices as surrogates of the clinical and bacteriological outcomes, then determining their optimal values (breakpoint values) based not only on drug efficacy but also on the risk of emergence of drug resistance, and finally using the optimal values of these indices to compute a dosage regimen.

Currently, three predictive indices of clinical and bacteriological outcomes are used namely:

- the AUC/MIC ratio (where AUC is the area under the plasma concentration vs. time curve, a measure of drug exposure), an index used for quinolones,
- Cmax/MIC ratio (where Cmax is the maximum plasma concentration), an index selected for aminoglycosides, and,
- T > MIC (the time during which plasma concentrations exceed the MIC, expressed as a percentage of the dosing interval), which is the index selected for the so-called time-dependent antibiotics such as β-lactams.

The advantage of having recourse to these PK/PD indices, rather than the conventional dose-titration, for determining a dosage regimen, results from the fact that all PK/PD indices incorporate the MIC of the pathogen. They therefore provide direct biological information about the susceptibility of the pathogen to be eradicated and can be used in PK/PD modelling to predict the dosing schedule which achieves a bacteriological cure.

All the selected PK/PD indices take into account the (free) plasma concentrations of antimicrobial drug as a measure of bacterial exposure. This is relevant when performing systemic antibiotherapy because most pathogens of clinical relevance in veterinary medicine are located outside the cells and there is direct proportionality between the plasma and biophase concentrations. In contrast, the plasma antibiotic concentration is not a meaningful surrogate of the antibiotic biophase concentration in local antibiotherapy (e.g. intramammary administration or an oral treatment of enteritis…) because in this case, the plasma exposure is not the driving force controlling the biophase concentration. Similarly the plasma antibiotic concentration may not be an appropriate surrogate when addressing the question of commensal digestive flora because the relationship between plasma concentration and the intraluminal antibiotic intestinal concentration is not straightforward as is the case for the extracellular fluid.

3. FROM THE BREAKPOINT VALUE OF A PKPD INDEX TO A DOSAGE REGIMEN

Some default breakpoint values are often proposed for clinical efficacy; these are 125 for AUC/MIC (quinolones); 10-12 for the Cmax/MIC ratio (aminoglycosides) and 40% or 80% of the dosing interval
A dosage regimen may easily be determined when the breakpoint value is known. The case of AUC/MIC will be used to show how a dosage regimen can be computed. AUC/MIC breakpoints are very frequently reported in the literature as dimensionless numbers (e.g. 125, 250…), but the AUC/MIC index actually has a time dimension and saying that the AUC/MIC should be 125 (actually 125 h) to optimize efficacy is equivalent to saying that the average plasma concentration over a 24 h dosing interval should be about 5 times the MIC (actually 125 h/24 h). If it is acknowledged that AUC is only determined by plasma clearance and bioavailability and that the free (not total) concentrations need to be considered, then the maintenance dose achieving a given AUC/MIC breakpoint value is easily estimated with the following equation:

\[
\text{Dose (per day)} = \frac{(AUC/MIC)_{\text{breakpoint}} \times MIC \times CI_{\text{(per day)}}}{fu \times F\% \times 24h}
\]

where \((AUC/MIC)_{\text{breakpoint}}\) is the targeted breakpoint (e.g. 125 h), MIC the MIC of the targeted pathogen, CI the plasma (total) clearance in days, \(fu\) the free fraction of the drug in plasma (from 0 to 1) and F\% the bioavailability factor (from 0 to 1). In Eq. 1, \([ (AUC/MIC)_{\text{breakpoint}}] /24h\), a dimensionless coefficient, may be viewed as the desired multiplicative factor by which the MIC of the targeted pathogen should be multiplied to estimate the optimal steady state plasma concentration required to obtain clinical efficacy (or any other endpoint) (Toutain, 2003).

The next step is then to select breakpoint values that minimise the risk of antibioresistance.

4. PK/PD INDICES AND THE RISK OF RESISTANCE FOR QUINOLONES

Forrest et al. (1993), examined retrospectively the relationship of ciprofloxacin exposure to clinical and microbiological response, as well as to time to bacterial eradication (mainly gram negative bacteria). It was observed that a total drug AUC/MIC of 125 was the relevant breakpoint predicting successful (> 80%) clinical and microbiological outcomes. In contrast the probability of a clinical response occurring at an AUC/MIC < 125, was 42% and even worse i.e., only 26% for a microbiological response thus confirming a possible discrepancy between clinical and bacteriological success. More importantly, two breakpoints were determined to predict the time to bacterial eradication. At an AUC/MIC < 125, the time to bacterial eradication exceeded 32 days whereas the time to eradication with an AUC/MIC >1 25 and 250 was significantly lower (6.6 and 1.9 days respectively).

As regards gram-positive bacteria, the breakpoint reported to achieve an appropriate efficacy with quinolones in man was initially reported as lower (e.g. 30-40 for \(S.\ pneumonia\)). Actually, it is now acknowledged that the appropriate dosage regimen for \(S.\ pneumonia\) should be designed to avoid the risk of emergence of highly resistant pathogens i.e. to prevent a second step mutation that will lead to a dramatic increase in MIC (see later) and require much higher breakpoints i.e. between 200 and 400 (DeRyke et al. 2006).

Several studies have been carried out recently to determine the temporal dynamics of a bacterial population exposed to different levels of antibiotics (especially quinolones) so as to preclinically predict the PK/PD breakpoints that prevent the development of resistance. With quinolones, resistance mechanisms can arise as the result of a single point mutation and the probability that a resistant subpopulation exists within a predominantly drug susceptible wild type population is dependent on the number of bacteria at the infection site (total population burden) and the mutational frequency. The spontaneous mutational frequency to resistance for mechanisms
attributable to a single point mutation is about $10^{-6}$ to $10^{-8}$ and a bacterial population is unlikely to be homogeneous when the inoculum size is high (e.g. $10^5$-$10^{10}$ CFU) i.e. when the total bacterial population burden exceeds the inverse of the mutational frequency to resistance by more than one order of magnitude (Jumbe et al. 2003). This kind of condition is encountered in severe infection where the inoculum is likely to behave as a mixture of distinct bacterial populations each with their own initial antibiotic susceptibility. In this situation, exposure to antibiotics selects rather than induces resistance. The emergence of resistance is due only to the predictable overgrowth of a pre-existing subpopulation with an initially lower level of susceptibility (Schentag, 2000). For quinolones, this phenomenon may be amplified if the antibiotic concentrations fall in the so-called mutant selection window (MSW), an undesirable drug concentration range within which exposure to antimicrobial concentrations confers a survival advantage to organisms with reduced susceptibility (Drlica, 2003). The MSW covers the concentration range between the MIC of a wild bacterial population and the so-called mutant prevention concentration (MPC), i.e. the MIC of the first mutant daughter subpopulation. The special relevance of the MPC concept to fluoroquinolones is due to the fact that two successive mutations (e.g. on gyrase and then on topoisomerase IV) result in mutant strains with a very high MIC and in order to grow above the MPC, a bacteria needs to acquire both resistance mutations at the same time, an event that will rarely occur without the selective pressure of an antibiotic. In this MSW, the first step mutant population has an advantage over fully susceptible bacteria and increasing the size of this population increases the probability of obtaining the second mutation i.e. fostering the generation of a new double mutant population. In contrast, for antibiotic concentrations above the MPC, the probability that a wild bacterium will directly undergo both resistance mutations is very low (only $10^{-16}$ i.e. $10^{-8} \times 10^{-8}$ if it is assumed that the 2 mutation probabilities are independent). A practical consequence is that a rational dosing regimen for a quinolone needs to be designed to imperatively avoid the concentration range falling within the MSW but instead ensure high enough concentrations (i.e. $>\text{MPC}$) to rapidly eradicate a possible less susceptible daughter subpopulation and thereby limit the risk of selecting a fully resistant bacterium. This can be achieved if the appropriate PK/PD breakpoints are determined to allow adjustment of the dosage regimen. Actually, it is now acknowledged that it is the overexpression of efflux pumps (probability of $10^{-5}$) that plays a central role in the rapid diminution of bacterial susceptibility rather than a single target (topoisomerase) mutation (probability of $10^{-9}$) when bacteria are exposed to a quinolone (Jumbe et al. 2003). In this case, the step size of change in the MIC of the mutant population is relatively small (2 to 8-fold) and, depending on the MIC of the parent population, it may be possible to counterselect the mutant with a high enough dosing regimen to suppress both the parent population and its daughter mutant subpopulation. This is not the case for resistance due to β-lactamases where the step change in MIC is too large to be counterselected with a high dosage regimen; in this instance, the solution consists of using a combination of antibiotics with independent resistance mechanisms (e.g. a β-lactam plus an aminoglycoside) (Drusano, 2003).

The MSW hypothesis was tested by Firsov et al. (2003) who demonstrated the abilities of different quinolones to selectively enrich resistant mutants of Staphylococcus aureus. The dynamics of antistaphylococcal effects were studied using an in vitro dynamic model reproducing the in vivo quinolone disposition in man over a course of 3-days. It was shown that most of the largest increases in MIC were observed only after a delay of 72 h (and not earlier) at those AUC/MIC values (from 24 to 62 h) that corresponded to the fluoroquinolone concentrations being within the MSW for most (i.e. 50 to 90%) of the dosing interval. In contrast no or less noticeable increases in MIC were observed with the lowest simulated AUC/MIC values (15 to 16 h), i.e. when less than 20% of the dosing interval was associated with a concentration within the MSW. Also, no changes in MICs were seen at the highest AUC/MIC values (201 to 244 h), when the fluoroquinolone concentrations exceeded the MPC over most (i.e. 80%) of the dosing interval. In other words, significant increases in MIC were observed when the duration of the MSW was more than 20% of the dosing interval (Firsov et al. 2003).
The selection window hypothesis was extended to gram-negative organisms in a study with *Escherichia coli* (Linde & Lehn, 2004). The MPC values for *E. coli* were 2 x MIC (trovafloxacin), 4 x MIC (ciprofloxacin, norfloxacin, ofloxacin), 8 x MIC (clinafl oxacin, levofloxacin), 16 x MIC (sparfloxacin) and 32 x MIC (nalidixic acid). To achieve a plasma concentration above these MPC the AUC/MIC ratio needs to be 24 times the numerical value of the MPC i.e. 48 for trovofloxacin, 100 for ciprofloxacin etc. It should be noted that general recommendations are difficult as the MPCs against different pathogens differ between the various quinolones. It can however be said that the new quinolones have lower MPCs than the old quinolones and this is probably due to the fact that new quinolones (such as gatifloxacin, moxifloxacin, gemifloxacin…) are able to bind to both topoisomerase II and topoisomerase IV, instead of just one of these targets, which was the case for the earlier quinolones (DeRyke et al. 2006).

5. PK/PD INDICES AND THE RISK OF RESISTANCE WITH BETA-LACTAMS, MACROLIDES AND AMINOGLYCOSIDES

Although very few data are available concerning the exposure required to prevent resistance to classes of antibiotic agents other than quinolones, there is no doubt that an inappropriate dosage regimen contributes to the spread of a drug-resistant pathogen. It was shown by Guillemot et al. (1998) in a human clinical setting that too low a dose combined with a long duration of treatment with an oral β-lactam helps to promote the pharyngeal carriage of penicillin-resistant *Streptococcus pneumoniae* (Odds ratio of 5.9) but unfortunately the corresponding numerical values of T > MIC, the pharmacodynamic variable most closely linked to bactericidal activity for β-lactam, were not measured in these patients.

The concept of MPC as developed for quinolones cannot be applied to β-lactams, macrolides and aminoglycosides because the primary mechanism of resistance is not a single point mutation. Thus the MPC might not be indicative of the organism’s ability to spontaneously mutate. What we do know is that all data converge to demonstrate the importance of bacterial eradication to avoid the selection of resistant clones and it is suspected that the PK/PD breakpoints recommended for efficacy (T > MIC for 40 to 80% of the dosing Interval) are not conservative enough to avoid the emergence of resistance and that a new PK/PD index (Cmin/MIC where Cmin is the minimum plasma concentration over the dosage interval) might be a better predictor of the emergence of resistance. Tam et al. 2005b examined the propensity of different β-lactam agents (piperacillin, ceftazidime and meropenem) to suppress spontaneous resistance within a dense population of *P. aeruginosa*. In vitro time-kill studies were performed at clinically achievable constant concentrations in relation to the MIC of the organism. Whatever the tested antibiotic concentrations (up to 4 x MIC), a resistant subpopulation grows after exposure to all three agents. More importantly, the amount of regrowth of the resistant subpopulation was proportional to the overall bactericidal efficacy against the dominant (i.e. more susceptible) bacterial population. For example meropenem was the most efficacious of the tested drugs and produced a ≥ 2 log reduction in the organisms at a concentration of 4 x MIC. However it also yielded the greatest regrowth of resistant subpopulations! These resistant clones were only suppressed once the meropenem concentrations had reached 16 x MIC i.e. a much higher concentration than the MIC. These investigations showed that the current recommendations in terms of breakpoints for T > MIC may offer inadequate protection against the emergence of resistance (at least in in vitro conditions where the immune system cannot participate in the overall antibiotic efficacy). The conditions required to optimize the bactericidal activity of meropenem and its ability to suppress *P. aeruginosa* resistance were investigated in an in vitro hollow-fiber infection model (Tam et al. 2005a). It was shown that the regrowth phenomenon was apparent after 3 days of meropenem exposure when the Cmin/MIC ratio was < 1.7 despite the fact that the time above the MIC was 100%. It was concluded that a high drug concentration with Cmin/MIC = 6 was required to suppress resistance emergence. This value is
consistent with those for which the bactericidal activities of β-lactams are maximized i.e. at 4 to 6x the MIC but greater than the widely accepted PK/PD breakpoint for the β-lactams offering optimal efficacy.

6. PK/PD INDICES AND THE MONTE CARLO APPROACH TO THE SELECTION OF OPTIMAL DOSAGE AT A POPULATION LEVEL

Any dosage schedules based on the PK/PD approach must take account for the variability of PK and PD (MIC) data. Indeed, although an “average” dosage regimen may be satisfactory in terms of clinical efficacy for many classes of drugs, it is unlikely to be the optimal regimen for an antimicrobial drug. An optimal dosage regimen needs also to prevent the selection and propagation of resistant pathogens at the population level. Inter-animal variability in the level of drug exposure is probably a major risk factor affecting the emergence of resistance. Indeed under-exposure of the target pathogen in only a few animals within a flock or herd may lead to the establishment in such animals of a less susceptible sub-population of the pathogen that subsequently may disseminate between animals or transmit resistance genes horizontally to the other members of the group. In other words, an optimal dosage regimen for an antibiotic drug must take the population dimension into account.

The question arises as to how this should be done to predict efficacy and avoid resistance. Lees et al. (2006) and Toutain et al. (2002), have proposed an integrated approach to population pharmacokinetics and microbiological susceptibility involving Monte Carlo simulations (Drusano, 2004). These take into account the variability in the input variables and therefore generate PK/PD indices not only for the population mean but for all individuals in the population. Monte Carlo is a term applied to a numerical method with a built-in random process. It involves combining the variability in antimicrobial drug exposure with the variability in pathogen susceptibility according to their respective distributions. With Monte Carlo simulations, a large hypothetical population of animals (or outcomes) may be generated to determine the probability of attaining a given PK/PD breakpoint in a given proportion of the population. This allows selection of a dosage regimen based on attaining the recommended PK/PD target breakpoint in a given quantile of animals. Thus, the goal of a Monte Carlo simulation is to ensure the clinical success of the treatment and increase the likelihood of bacterial eradication. It may also be used to define a range of drug concentrations favoring the emergence of resistance and amplification of the resistant clone, as recently illustrated in human medicine by Jumbe et al. (2003).

7. WHAT RECOMMENDATIONS FOR VETERINARY DRUGS

At present although no firm conclusions or recommendations (in either human or veterinary medicine) can be drawn from the limited existing experimental data, the following points nevertheless merit attention:

It is accepted that an optimal dosage regimen should not only ensure bacterial eradication but also achieve this goal as quickly as possible to minimise the risk of resistance; the so-called one-shot antibiotherapy currently promoted in veterinary medicine for several quinolones (marbofloxaxin, danofloxacin…) seems attractive in this respect and is supported by both human clinical data and in vitro results.

As the probability of resistance emergence is proportional to the burden of the total bacterial population, the effect of the bacterial inoculum at the beginning of a treatment on the final outcome seems critical and should be regarded as an essential factor in the prudent use of veterinary antibiotics. It is thus urgent to objectively assess the advantages and limits of the different strategies employed when using antibiotics in food-producing animals namely prophylaxis vs. metaphylaxis
vs curative antibiotherapy. These different modalities of antibiotic use correspond to very different situations in terms of bacterial population burden. This burden is probably non-existent or small in the case of prophylaxis (where treatment is initiated when only a risk of infection exists) and relatively limited for metaphylaxis (where the treatment is collectively initiated when only a fraction of the population exhibits symptoms of infection). In contrast the bacterial population burden is larger in the case of curative treatment when an antibiotic is only administered to animals that have fully developed an infection. The undesirable influence of a large initial population burden on the antibiotic effect was documented \textit{in vivo} using the mouse-thigh infection model (Jumbe \textit{et al.} 2003). A major difference was shown between the AUC/MIC exposures needed to attain similar \(\log_{10}\) killing for the two sizes of inocula tested. When increased by a factor of 10 from \(10^7\) to \(10^8\) CFUs/g, 2 to 6 times as much drug exposure (AUC/MIC) was required to obtain the same degree of antibacterial effect.

Regarding the best option for the collective treatment of food producing animals (prophylaxis, metaphylaxis or curative) it appears that the level of natural defence should be taken into account to decide the best option. The immunological status and nonspecific mechanisms of defence probably differ between the three options and it may be very important to consider the possible influence of fever (positive or negative?), associated viral infection, and the administration of other drugs such as antiinflammatory drugs etc. This is true especially in the case of bacteriostatic antibiotics and also for bactericidal \(\beta\)-lactams for which it has been shown \textit{in vitro} (i.e. in the absence of natural defence) that a concentration much higher than the MIC was required to prevent the emergence of resistance. In this instance, the best option is that in which the defence status is not depressed. This is also important for fluoroquinolones for which it was shown that in the absence of granulocytes, the AUC/MIC breakpoints should be doubled to suppress the emergence of resistance (Drusano, 2003).

Still regarding the best option for the collective treatment of food producing animals, the capacity of the oral route of administration to provide a reproducible drug exposure for all three options is crucial to assess in order to minimise the interanimal variability and the likelihood of some subjects being underexposed. This is because in a herd or a flock competing for access to medicated food, the least exposed animals will be the best candidates to foster the generation of a more resistant population with possible horizontal spreading. An empirical dosage regimen destined to collectively treated animals at the herd level should be determined within the framework of population PK/PD using Monte Carlo simulations to explore the consequence of PK and PD variability on the distribution of the PK/PD indices within the population.

The duration of treatment appears to be crucial for the emergence of resistance to both quinolones and \(\beta\)-lactams. It is unlikely that a single high quinolone administration would be able to promote resistance in the target flora. The practice with \(\beta\)-lactams and also with bacteriostatic antibiotics, which consists of “covering” animals (pigs) preventively over a relatively long period (weeks) seems debatable. Similarly the advantages and limits of very long acting formulations need to be carefully scrutinised from this point of view.

Traditionally, from a public health perspective, veterinarians are encouraged not to employ newer drugs, but rather to use the older antibiotics. This recommendation seems justified for macrolides and \(\beta\)-lactams. However, according to Jumbe \textit{et al.} (2003), this strategy is flawed in the case of quinolones, and may actually hasten the spread of resistant strains of pathogens such as \textit{Streptococcus pneumoniae} to newer members of the class. Indeed, it was shown in a mouse thigh infection model, that an initial exposure \textit{in vivo} to ciprofloxacin, allowed straightforward selection of clones resistant to levofloxacin in a subsequent experiment, ciprofloxacin exposure being prone to generate clones showing an overexpression of their efflux pump system. The reason underlying
the propensity of ciprofloxacin to select for pump-overexpressed clones is probably related to its hydrophilic nature.

Many generic versions of off-patented antibiotics are being marketed at present. The current requirements in terms of the demonstration of bioequivalence i.e. an average rather than a population bioequivalence, do not guarantee that the original and the generic version are equivalent in terms of propensity to foster resistance. Apart from this biological argument, there is also the possibility that the promotion of these generic formulations (because of price) will speed up the emergence of resistance.

Combinations of antimicrobials, especially the β-lactam antibiotics and an aminoglycoside are used extensively in veterinary medicine. Currently, no pharmacodynamic studies are available that describe the pharmacodynamic breakpoints for agents used in combination and the ability of these associations to be more valuable than a single monotherapy in preventing the emergence of resistance remains to be established. Contradictory results have been reported in human medicine: in a meta-analysis of eight randomized controlled trials, β-lactam monotherapy was not associated with a greater emergence of resistance than the combination of a β-lactam and an aminoglycoside (Bliziotis et al. 2005). In contrast Drusano et al. (2002) evaluated the emergence of P. aeruginosa resistance in neutropenic guinea pigs after the administration of suboptimal dosages of meropenem either alone or in combination with once-daily tobramycin. No resistant pseudomonal isolates developed in the animals that received combination therapy, while most animals receiving only meropenem developed resistance.

Finally but importantly, nothing guarantees that an optimal dosing regimen directed toward the target pathogen is an appropriate dosing regimen overall; this is because an appropriate dosing regimen may have a negative effect on the zoonotic bacteria and the commensal flora. Before paying attention to the target population to eradicate, it is essential to assess the effect of the antibiotic on the non-targeted flora. This is especially true when the oral route of administration is selected or when it is known that an antibiotic may be eliminated in its active form from the blood into the gut as is the case for fluoroquinolones that are extensively pumped out of the blood through the enterocytes. It is even possible to encounter situations for which no dosage regimen can be found that will both eradicate the pathogen population but have no or only a minimal effect on other flora.

8. CONCLUSION

PK/PD is a pre-clinical approach for screening possible dosage regimens, which subsequently must be confirmed by pivotal clinical trials. This approach will be truly powerful when used in conjunction with population PK/PD in clinical trials i.e. taking into account both PK (clearance, bioavailability) and PD (MIC) variability. This will circumvent the need to use clinical trials for exploratory searches for suitable dosage regimens, a strategy fraught with difficulties. The next step will be for veterinary pharmacologists to research these population PK/PD indices and propose optimal dosage regimens, not only to ensure efficacy but also to minimize the risk of development of resistance.

9. SUMMARY

The prevention of emergence of resistance is a priority goal in veterinary antibiotherapy. The most important risk factor for emergence of resistance is repeated exposure to suboptimal concentrations of antibiotics resulting from the selection of an inappropriate dosage regimen. The choice of optimal dosage regimen cannot be based solely on clinical endpoints but is facilitated by the so-called PK/PD approach. In the present review the mechanisms leading to emergence of resistance
are presented with special emphasis on the concept of the mutant selective window and of mutation preventive concentrations for quinolones. Although the results are still very limited, some new ideas for improving veterinary antibiotherapy may be considered.

10. KEY WORDS

Antibiotics, antimicrobial resistance, dosage regimen, PK/PD approach, Monte Carlo simulation.

11. RESUME

La prévention de l’émergence de résistance est un objectif prioritaire de l’antibiothérapie vétérinaire. Le principal facteur de risque est la mise en œuvre de schémas posologiques prolongés et/ou conduisant à des sous-expositions de la population bactérienne à éradiquer. Il a été montré que la seule prise en compte de critères cliniques ne garantissait pas l’optimalité d’un schéma posologique mais que l’approche PK/PD pouvait permettre d’atteindre cet objectif. Après avoir rappelé ce qu’est l’approche PK/PD, la présente revue explique les mécanismes conduisant à la sélection d’une population résistante et comment l’éviter en sélectionnant des valeurs adéquates pour les indices PK/PD ; une attention particulière a été portée à la classe des fluoroquinolones avec la présentation de la notion de fenêtre de sélection et de concentration préventive de mutation. A partir de résultats encore parcellaires, plusieurs pistes mériteraient d’être explorées en antibiothérapie vétérinaire parmi lesquelles l’intérêt potentiel des interventions dites métaphylactiques.

12. MOTS CLES

Antibiotiques, antibiorésistance, schéma posologique, approche PK/PD, simulation Monte Carlo.

13. REFERENCES


