Optimizing Antimicrobial Regimens

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Introduction

An antimicrobial regimen describes the dose, route, frequency, length of treatment, and milk and meat withdrawal times. As changes in antimicrobial susceptibility testing occur (see "Preparing for a Revolution in Antimicrobial Susceptibility Testing" in these proceedings), our understanding of how to design regimens grows, and antimicrobial therapy will become more complicated but also more effective. The purpose of this presentation is to discuss what we currently know about selecting a regimen based on the bacteria isolated (or presumed), the pharmacokinetics and pharmacodynamics of the antimicrobial selected for therapy, and clinical results.

Discussion

A starting point for this discussion is how doses are determined for drugs seeking approval by regulatory agencies. Generally speaking, dose titration studies are performed on animals with the bacterial infection: dose X mg/kg by a specific route resulted in a clinical cure in Y% of the animals, and the bacteria isolated from the animal had a Minimum Inhibitory Concentration$_{90}$ (MIC) of Z mg/ml. The result is a single dose or a range of doses on the drug label. Usually, the other parts of the regimen are iterated on the label, namely frequency, length of treatment and withdrawal times. The problem can occur when we attempt extra-label use, such that the organism targeted, the age or species of animal, or the location of the infection is different than on the label. What must be recognized is that all these variables may affect the pharmacokinetics of the drug and the efficacy of the therapy.

Once we have data that illustrates the pharmacokinetics of a drug, we need to put that together with the pharmacodynamics. Table 1 lists the parameters that appear to maximize efficacy for each group of drugs for which clinical data has been gathered. Note that concentrations refer to serum concentrations. The correlation of efficacy with tissue concentrations is less clear; clinical trials allowing this correlation have been performed only for specific diseases and specific drugs such as tilmicosin.[19] In addition, milk concentrations cannot necessarily be directly compared to pathogen MICs, since those relationships have not all been tested in vivo. The composition of milk does not allow it to be directly compared to serum, for which pharmacodynamics have been more clearly worked out. For example, *Staphylococcus aureus* cultured in milk and also in iso-sensitest broth required 4 times as much antibiotic in milk as in the broth, suggesting one reason for the difference between in-vitro testing methods for antimicrobial susceptibility and in-vivo clinical response.[18] Therefore, we must rely more on the results of clinical trials than simple pathogen susceptibilities to determine efficacy.

Questions to ask when examining the results of clinical trials of an antimicrobial regimen have been reviewed[14] and include: How were the animals selected for the trial? Were they assigned to treatment using acceptable randomization procedures? (Large discrepancies between numbers of animals in each group suggest unequal assignment.) Were control groups used? (Lack of control groups could result in attributing clinical success to treatment when in fact some cures occurred spontaneously.) What is the case definition? (Exemplified by the term "undifferentiated fever" by some investigators looking at presumed bovine respiratory disease.) How is success defined, and is this the same way you would define success? (For example, is a decreased body temperature at 3 days after treatment for respiratory disease a practical definition of success in a feedlot calf, or should we be looking at weight gain or return to full feed?)

Following are specific examples to illustrate the principles involved in regimen design and adjustment. This discussion will be limited to the drugs listed in Table 2; this table includes properties of the antimicrobial as well as indications for which it is labeled in the U.S.

Ceftiofur

Ceftiofur is a beta-lactam antimicrobial, so it is presumed that its efficacy will be maximized by keeping the serum concentration above the MIC of the pathogen for the majority of the dosing interval. The

Table 1.

	IMPORTANT PARAMETER	
Drug Group	**For efficacy**	**For reducing selection for resistance**
Beta Lactams	Serum concentration above MIC for at least 60%-70% of dosing interval (time may vary with gram positive vs. gram negative pathogens)	
Tetracyclines	Serum concentration above MIC for at least 60%-70% of dosing interval (time may vary with gram positive vs. gram negative pathogens)	
Aminoglycosides	C_{max} = 8-10x MIC	
Fluoroquinolones	AUC_{0-24}:MIC of at least 125	C_{max} = 8-10x MIC
Macrolides	Serum concentration above MIC for at least 60%-70% of dosing interval (time may vary with gram positive vs. gram negative pathogens)	

pharmacokinetics of 2.2 mg/kg ceftiofur sodium administered intravenously and intramuscularly to calves ranging from 1 month to 9 months of age are illustrated in Figure 1, with the serum concentrations reported as the mean of each group of animals minus 1 standard deviation.[7] It should be noted that the IV and IM routes result in very similar serum concentration profiles. The major age differences exemplified in this graph are that younger animals apparently exhibit a longer elimination half-life, resulting in the potential for an increased dosing interval.

For example, a survey of 42 isolates of *Pasteurella haemolytica* from diagnostic laboratories revealed a MIC_{90} of 0.015 µg/ml.[17] (It is important to realize that the MIC does not necessarily represent an absolute value. The actual MIC may be anywhere between the value reported and the next lowest dilution, and dilutions are typically two-fold.[12] So the MIC of an organism reported at 4 ug/ml may be as high as 4 and as low as 2 in the typical testing system. Practically speaking, when designing a regimen, the highest MIC should be assumed.) Looking at Figure 1, we can see that the serum concentration of ceftiofur sodium remains above 0.015 µg/ml for at least 48 hours, suggesting every-other-day therapy at 2.2 mg/kg IM would be effective.

Oxytetracycline / Tetracycline / Chlortetracycline.

The tetracyclines are commonly used antimicrobials that are presumed to be time-dependent in their pharmacodynamics, such that the time serum concentration remains above the MIC of the pathogen is important in maximizing efficacy. There are many products available and many dosing regimens suggested for these drugs, so a comparison of them is needed. It should become clear that the breakpoints currently utilized for the tetracyclines may not be appropriate for all the products available. One major difference among products is enteral vs. parenteral administration. Figures 2 and 3 show plasma concentrations of tetracycline[10] and chlortetracycline[5] after a single oral dose of 10 mg/lb in young calves. Although these products would typically be administered over a period of time in feed or water, these graphs represent a high estimate of plasma concentrations achievable with this dose. Even peak concentrations do not reach the susceptible breakpoint, which means that in order to best utilize these drugs *per os*, we must have the susceptibility information available with extended dilutions so we have the actual MIC of the organism.

The final piece of a regimen is establishing a withdrawal time if the regimen being used is extra-label. The best source of this information is the Food Animal Residue Avoidance Databank. However, some rules of thumb about withdrawal times have been suggested[16] For example, if the drug is labeled for the species in question, but a different dose is being used, such as doubling the dose, the withdrawal interval should be extended at least one half-life beyond the labeled withdrawal time. Since the elimination half-life is defined as the amount of time it takes for half of the drug to be removed from the body, it makes sense that if we double the dose, we add one half-life to the time it takes for the drug to reach the tolerance level. An important caveat here is that we must use the same route and the

Table 2.

DRUG	ACTION	VOLUMES OF DISTRIBUTION	MECHANISMS AND SITES OF ACTION	MILK: PLASMA RATIO	LABELED INDICATIONS[c2]
BETA-LACTAMS	**Bactericidal**		**Inhibit formation of cell walls**		
Ampicillin		0.16-0.50[11,21]		0.24-0.30[8]	Pneumonia caused by *Aerobacter* spp., *Klebsiella* spp., *Staphylococcus* spp., *Streptococcus* spp., *Pasteurella multocida*, and *E. coli*
Penicillin G		0.14-0.27[3,4]		0.13-0.26[8]	Pneumonia caused by *Pasteurella multocida*; pneumonia caused by *Streptococcus* spp., *Corynebacterium pyogenes*, *Staph. aureus*, upper respiratory infections caused by *A. pyogenes*, blackleg (*Clostridium chauvei*), in the treatment of disease organisms susceptible to penicillin, udder infections caused by *Strep. agalactiae*, *S. dysgalactiae*, and *Strep. uberis*, in combination with dihydrostreptomycin for *Staph. aureus* mastitis, in combination with novobiocin for *Strep. ag.*, *Strep. dysgalactiae*, *Strep. uberis*, *Staph. aureus*
CEPHALOSPORINS	**Bactericidal**		**Inhibit formation of cell walls**		
Ceftiofur		0.26-0.35[7]			Pneumonia associated with *P. haemolytica*, *P. multocida*, *H. somnus*, footrot associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*
Cephapirin				Intra-mammary product	Mastitis caused by *Strep. agalactiae* and *Staph. aureus*
'AMPHENICOLS			**Bind to 50S ribosomal subunit; interfere with protein synthesis**		
Florfenicol		0.62-0.77[6,9]			Respiratory disease caused by *P. haemolytica*, *P. multocida* and *H. somnus*
FLUORO-QUINOLONES	**Bactericidal**				
Enrofloxacin		1.46[1]			Respiratory disease caused by *P. haemolytica*, *P. multocida* and *H. somnus*
LINCOSAMIDES	**Bacteriostatic**		**Bind to 50S ribosomal subunit; interfere with protein synthesis**		
Lincomycin				2.50-6.25[8]	None
Pirlimycin				Intra-mammary product	Mastitis caused by *Staph.* spp., *Strep. agalactiae*, *Strep. dysgalactiae*, and *Strep. uberis*
MACROLIDES	**Bacteriostatic**		**Bind to 50S ribosomal subunit; interfere with protein synthesis**		
Erythromycin	Bactericidal against *P. haemolytica*[13]	0.789-1.596[20]		6.00-7.30[8]	Mastitis caused by *Staph.* spp., *Strep. agalactiae*, *Strep. dysgalactiae*, and *Strep. uberis*; treatment of pneumonia, shipping fever, mastitis, metritis, footrot

Table 2 Continued

Tilmicosin	Bactericidal against *P. haemolytica* and *P. multocida*[13]			Respiratory disease associated with *P. haemolytica*
Tylosin		0.95-2.32[20]	1.00-5.35[8]	Respiratory disease associated with *P. multocida* and *Arcanobacterium (Actinomyces) pyogenes*, footrot and diphtheria caused by *Fusobacterium necrophorum* and metritis caused by *Arcanobacterium (Actinomyces) pyogenes*; reduction in the incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes*
TETRACYCLINES	**Bacteriostatic**	**Bind to 30S ribosomal subunit; interfere with protein synthesis**		
Chlortetracycline		1.93[a5] 3.34[b5]		Pneumonia caused by *Pasteurella* spp., *Klebsiella* spp., and *Hemophilus* spp. control of active infection by *Anaplasma marginale*, enteritis caused by *E. coli* and *Salmonella* spp.,
Oxytetracycline		0.97-2.48[15]	0.75[22]	Pneumonia caused by *Pasteurella* spp. and *Hemophilus* spp., footrot and diphtheria caused by *Fusobacterium necrophorum*, enteritis caused by *E. coli*, wooden tongue caused by *Actinobacillus lignieresi*, acute metritis, wound infections caused by *Strep.* and *Staph.* organisms; infections caused by oxytetracycline-sensitive organisms; pinkeye caused by *Moraxella bovis*, *Leptospira pomona*
Tetracycline	Bactericidal against *P. haemolytica*[13] spp., *Hemophilus* spp., and *Klebsiella* spp.		1.22-1.91[8]	Enteritis caused by *E. coli*, pneumonia caused by *Pasteurella*

[a]conventionally-fed calves
[b]milk-fed calves
[c]At least one product labeled in the U.S. contains these indications; not all products are labeled for all indications. Only therapeutic indications are listed; feed additives used for weight gain or feed efficiency are not included.

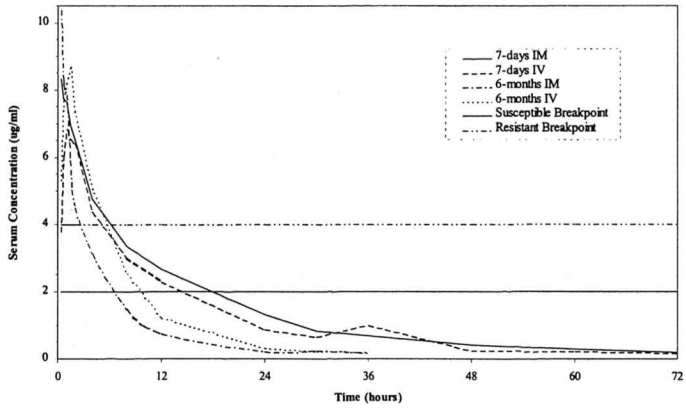

Figure 1. Ceftiofur serum concentrations after 2.2 mg/kg dosing (mean minus 1 SD) adapted from Brown *et al*, 1996.

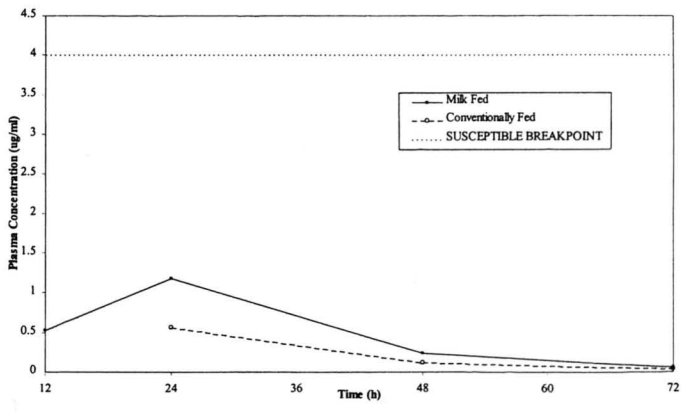

Figure 2. Chlortetracycline in 14-week-old calves (22 mg/kg *per os* in a single dose) Bradley *et al*, 1982.

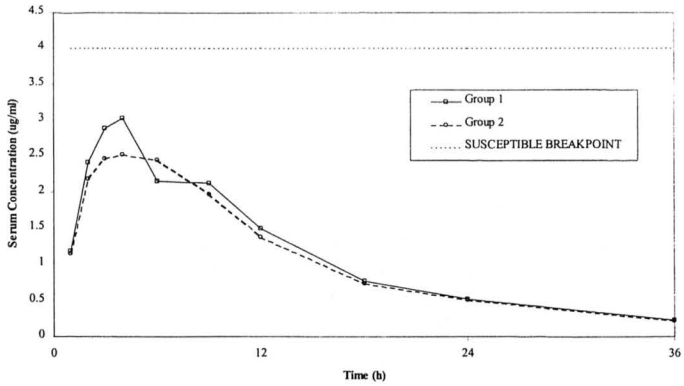

Figure 3. Tetracycline in 100 lb calves: comparison of two manufacturers (one dose, 10 mg/lb, PO) adapted from the FOI Summary, Medico, 1985.

same volume per site as that indicated on the label to make these extrapolations. In addition, the drug must not be bound to tissues (like aminoglycosides in the kidneys), and the elimination half-life must be an estimate of the true terminal half-life.

Conclusion

The bottom line in developing antimicrobial regimens is that given our current understanding of pharmacology and susceptibility testing, we are obligated to utilize this information in order to maximize the efficacy of available drugs.

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