Therapeutic Considerations in The Use of Antibacterials

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Combination Therapy

Any discussion of antibiotics must eventually broach the topic of combination therapy. This is a much discussed but little appreciated area because of the lack of good basic information available. The effects of antibiotic combinations are quite specific for individual bacterial species and unfortunately they may have quite diverse effects ranging to antagonism of one another when utilized against other bacteria. To fully appreciate the value of any combination, it would require testing on each bacterial species using a wide range of combination ratios. Because of this variability it is difficult to develop general guidelines. Combinations may be quite helpful for serious illness in the debilitated patient particularly when a mixed bacterial population is involved. The combination may also reduce the development of resistance. The disadvantages of increased risk of adverse drug reactions, potential antagonism between antibiotics and increased expense may be more important than the advantages in many cases.

There is no inherent evil associated with the use of antibacterial combinations. However, in many situations the drugs are so completely misused as to either delude the client or enhance the risk of serious toxicity problems. Adding another drug to a combination does not reduce the need for sound clinical judgment in therapy. There are many disease situations in which the use of more than one antibacterial may be justified. This does not, however, justify the use of some magic elixir dispensed with impunity to every calf off the ramp. One injection of some mystical antibacterial preparation is not only unlikely to be of value but should be a clear signal to the client. Basically antibiotic combinations should be avoided as a *common* practice unless they have shown a clear increase in effectiveness either by your own use or as reported in the literature. Generalizations about various combinations of bactericidal or bacteriostatic antibiotics or admixtures have not proven valid. However, caution should be exercised when using static and cidal drugs together since the likelihood of antagonism is increased. Examples of specific combinations of demonstrated value *(in vitro* or *in vivo)* are shown in Table 1. A second antibiotic may have some influence on the penetration of another antibiotic into the bacterial cell. Penicillins or amphotericin B are thought to exert some effects in increasing the permeability of cells to other antibiotics. A penicillinase resistant penicillin may also be used with another more potent but penicillinase sensitive penicillin. In this case the penicillinase resistant penicillin ties up most of the penicillinase enzyme which prevents degradation of the second more potent penicillin. Methicillin with ampicillin would be an example of this latter practice.

When using antibiotics in combination, some general cautions should be observed. Avoid mixing the drugs directly in a single syringe. A direct reaction with inactivation and/or precipitation may occur. Avoid fixed dosage combinations. Utilize minimal inhibitory concentration (MIC) or sensitivity data for each antibiotic and remember that additive combinations based on *in vitro* testing do not necessarily translate to increased *in vivo* effectiveness. Chloramphenicol and tetracyclines should be used alone unless specific information is known about a combination. Chloramphenicol is antagonistic to aminoglycosides against several bacteria including E. coli. Chloramphenicol, lincomycin and erythromycin (macrolides) all bind to a similar 50 S ribosomal subunit site to initiate their activity, hence they should not be used in combination. The use of more than 2 antibacterials should be approached with more caution. In such cases dosage of antibacterials used may be much more important than adding another drug. Unfortunately in difficult situations it often seems easiest to add another antibacterial to cover the field.

Incompatibilities and Interactions

Antibiotics are frequently administered in parenteral solutions with or without additional drugs. In such instances decomposition of the antibiotic, precipitation and/or an interaction affecting drug disposition may occur. Sterile physiological saline solutions are satisfactory except for methicillin. A 5% dextrose solution is also satisfactory except for ampicillin. In either case, the problem arises only if the antibiotic is added to the solution several hours prior to use. If the solutions are used immediately there is little or no antibiotic inactivation. Mixtures with protein

Table 1 - Antibiotic combination shown effective by *in vitro* or *in vivo* use.

Pencillin G + penicillinase resistant penicillin (cloxacillin, nafcillin)	vs	*Staph* spp, penicillinase producing bacteria
Penicillin G + cephalosporins	vs	*Staph* spp, penicillinase producing bacteria
A penicillin + an aminoglycoside	vs	*listeria monocytogenes*
Ampicillin + an isoxazole penicillin (oxacillin, cloxicillin)	vs	*E. coli, Enterobact., Kleb & Proteus* esp in the urinary tract
Ampicillin + Gentamicin	vs	*Proteus*
Carbenicillin + Gentamicin	vs	*Pseudomonas, Kleb., E. Coli, Proteus*
Cephalosporin + Aminoglycoside Cephalothin + Gentamicin	vs	*E. coli, Kleb., Enterobact.* (Klebsiella)
Lincomycin + spectinomycin	vs	*Mycoplasma, Pasturella*
Tylosin + oxytetracycline	vs	*Pasteurella*

hydrolysates or lipid solutions should be avoided and polymixins, tetracyclines or sulfonamides should not be added to any solutions containing other drugs.

Chloramphenicol and tetracyclines may influence the activity of a number of other drugs by inhibiting liver microsomal metabolism. As a result, the half-life of the 2nd drug may be increased with a concomittant increased risk of toxicity. This has been confirmed for chloramphenicol in increasing phenytoin (Dilantin) toxicity and barbiturate sleeping time. Chloramphenicol and other protein synthesis inhibitors (tetracyclines, etc.) may also decrease the response to vaccines. Activity of both adrenal cortical and reproductive steroids also requires active protein synthesis and may be reduced by chloramphenicol therapy. Several antibiotics including chloramphenicol, tetracycline and rifampin moderately decrease neutrophil chemotaxis and/or phagocytosis when used at high dosages. Aminoglycosides have only a mild influence on these functions.

Most antibiotics are bound to some extent by plasma proteins. Those which are highly or avidly bound may interact with the protein binding (albumen) of other drugs to increase the active free drug concentration of either the antibiotic or the 2nd drug and possibly reduce the half-life (increase clearance because of the increase in free drug). Table 2 lists the antibiotics which are 75% or more protein bound in plasma and examples of other highly protein bound drugs. Protein binding interactions merely indicate a possible effect. Two highly protein bound drugs may or may not compete with one another for sites on the albumen molecule. Some antibiotics such as ampicillin, aminoglycosides (except neomycin), spectinomycin and erythromycin have very low protein binding or are less than 25% bound in plasma.

A further hazard exists between antibiotics and other drugs related to mechanisms of toxicity. A combination of several drugs with similar types of toxicity may result in an increased incidence of toxicity. The use of two oto-toxic drugs such as an aminoglycoside and ethacrynic acid or furosemide may produce an increased problem of toxicity.

Age and Disease Effects

Antibiotic disposition may be markedly altered in the neonate due to the relatively high proportion of extracellular water at birth and the immaturity of renal and hepatic detoxication mechanisms. The immaturity factors are more important for premature birth and low birth weight animals due to overall lower developmental maturity at birth. Drugs which require hepatic transformation and/or glucuronide formation (chloramphenicol) for elimination may have a

Table 2 - Antibiotics and other example substances which are highly protein bound in plasma.

Antibiotics	*Other Compounds*
Cloxacillin	Aspirin
Oxacillin	Phenylbutazone
Doxycycline	Flunixin
Methacycline	Meclofenamate Na
Minocycline	Warfarin-Dicoumarol
Novobiocin	Sulfonamides (not all)
Rifampin	Steroids
	Phenytoin
	Digitoxin
	Quinidine
	Thiopental
	Chlorpromazine
	Bilirubin

longer half-life in the neonate due to a lack of maturity of the requisite enzyme systems. This may be a matter of a few days in normal birth weight foals and calves or up to a few weeks for those with low birth weights. Similarly, drugs cleared by renal elimination may be cleared more slowly with some neonates because renal filtration is low and may not attain adult rates for several weeks. The maturity of herbivores of normal birth weight appears to make this a minor problem of only a few days duration.

Renal disease in the adult animal will produce marked alteration of the half-lives of many antibiotics. A marked decrease in creatinine clearance or elevation of plasma creatinine and blood urea nitrogen (BUN) may be associated with a marked decrease in antibiotic clearance as well as predispose to increased sensitivity to further renal toxicity. The antibiotics of choice for renal insufficiency are listed in Table 3. In some instances the use of particular antibiotics such as gentamicin may be necessitated by bacterial

Table 3 - Influence of renal disease on antibiotic selection

Antibiotics cleared by renal mechanisms	Antibiotics of choice in renal insufficiency
Penicillins	Chloramphenicol
Cephalosporins	Erythromycin or Tylosin
Aminoglycosides	Oxacillin or Cloxacillin
Polymixins	Doxycycline
Tetracyclines	Clindamycin
(except doxycycline)	Pen G*
	Ampicillin*
	Cephalosporins*
	Lincomycin*

* dosage interval must be increased by 2 x if the insufficiency is severe.

sensitivity patterns. In such cases the dosage schedule must be adjusted to allow for the decreased renal clearance. The guidelines for reduction of dosage as recommended in man include reduction of dosage to 1/2 of normal with a BUN of 50-100 mg/dl, 1/4 with a BUN of 100+ and 1/6 with a BUN of 200. For hepatic diseases, antibiotics such as chloramphenicol, tetracyclines, lincomycins, macrolides and rifampin should be avoided to prevent complications due to decreased drug elimination and direct hepatotoxicity.

The gastrointestinal absorption of many drugs is inhibited in the presence of food. This is true for many antibiotics notably the tetracyclines. As a rule, oral antibiotics should be given prior to or several hours after feeding. Chloramphenicol, clindamycin and amoxicillin may be exceptions to this general rule. A particular problem exists with antibiotics administered orally in ruminant neonates. By the second to third week of life, oral chloramphenicol no longer produces appreciable systemic levels unless the method of administration assures the bypassing of the rumen and reticulum. This is probably important for other oral antibiotics that are ineffective in adult ruminants (Ampicillin).

Resistance

The development of bacterial resistance is a constant problem and periodically eliminates the practical use of certain antibiotics against specific diseases. An example would be dihydrostreptomycin against many gram negative organisms *(Salmonella spp.* and *E. coli* especially). Resistance development in gram negative bacteria often involves R factor or plasmid transfer. This is particularly true for enteric organisms and in many cases the bacteria become markedly resistant to multiple antibiotics. This resistance is not readily overcome by increasing the dose antibiotic and requires a change in drug usage patterns. For this reason it may be advisable to change antibiotic use patterns every 2 or 3 years. An example of this would be the general use of tetracyclines, macrolides or sulfonamides for 2 years, then penicillins, dihydrostreptomycin or chloramphenicol for 2 years. Substitutions could be appropriately made or a third group added so that the general widespread use of an antibiotic would occur in only 2 years out of every 4 or 6 years thereby reducing the potential for sustained resistance development.

In many instances particularly in dealing with gram positive organisms the resistant mutations will result in slow stepwise resistance development. In these situations increasing the concentration of antibiotic may be sufficient to overcome the resistance. This may not be as simple a solution as it sounds, because for many antibiotic preparations such as procaine penicillin G., increasing the dose does not always result in a proportional increase in tissue concentration. It may be helpful in many practice areas to periodically carry out culture and sensitivity testing on even routine bacterial infection problems to check for changing patterns of drug sensitivity.

General References

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