INTRODUCTION

Antibiotic therapy has made many advances that has given veterinary medicine a large number of effective drugs and provided pharmacokinetic and pharmacodynamic information to guide dosing. Improved techniques for bacterial identification and susceptibility testing have helped to provide information for the most appropriate drug selection. This presentation will review the current concepts that guide antibiotic therapy in veterinary medicine and provide important strategies for effective dosing.

BACTERIAL SUSCEPTIBILITY

Most bacteria that cause infections come from the following list: *Staphylococcus intermedius*, (and occasionally other staphyloccoci) *Escherichia coli*, *Klebsiella pneumoniae*, *Pasteurella multocida*, beta-hemolytic streptococci, *Pseudomonas aeruginosa*, *Proteus mirabilis* (and occasionally indole-positive *Proteus*), *Enterobacter* spp and *Enterococcus* spp. If the bacteria are accurately identified, antibiotic selection is simplified because the susceptibility pattern of many organisms is predictable. For example, if the bacteria is likely to be *Pasteurella*, *Streptococcus*, or *Actinomyces*, susceptibility is expected to penicillin or an aminopenicillin such as ampicillin, amoxicillin, or amoxicillin-clavulanic acid (Clavamox).
Usually Susceptible Bacteria

Staphylococcus isolated from small animals is most likely to be *S. pseudintermedius* rather than *S. aureus*. (Note that previously identified *Staphylococcus intermedius* probably have been misidentified and are now referred to as *S. pseudintermedius* by many laboratories. This species of *Staphylococcus* will usually have a predictable susceptibility to β-lactamase resistant β-lactam antibiotics such as amoxicillin combined with a β-lactamase inhibitor (Clavamox), or first-generation cephalosporin such as cephalexin or cefadroxil, or the third-generation cephalosporins, cefovecin (Convenia) and cefpodoxime (Simplicef). *Staphylococcus* also is susceptible to oxacillin and dicloxacillin but these are not used as commonly in small animal medicine. Reports of studies on *S. pseudintermedius* have shown that, despite frequent use of the above mentioned drugs in small animals, the incidence of resistance has not increased (Lloyd, et al, 1996; Pinchbeck et al, 2007). Most staphylococci are also sensitive to fluoroquinolones. The majority of staphylococci are sensitive to lincosamides (clindamycin, lincomycin), trimethoprim-sulfonamides, or erythromycin, but resistance can occur in as high as 25% of the cases. These rates of susceptibility do not diminish the important emergence of methicillin-resistant *Staphylococcus* in companion animals (Weese 2005). Reports of these isolates are becoming more frequent and methicillin-resistant *Staphylococcus aureus* (MRSA) in human hospitals, and in the community has reached alarming rates.

If the bacteria is an anaerobe (for example, *Clostridium, Fusobacterium, Prevotella, Actinomyces, or Porphyromonas*) predictable results can be attained by administering a penicillin, chloramphenicol, metronidazole, clindamycin, amoxicillin-clavulanic acid, or one of the second-generation cephalosporins such as cefotetan or cefoxitin. Metronidazole is consistently highly active against anaerobes including *B. fragilis*. The activity of first-generation
cephalosporins, trimethoprim-sulfonamides/ormetoprim-sulfonamides, or fluoroquinolones for an anaerobic infection is unpredictable. If the anaerobe is from the *Bacteroides fragilis* group, resistance may be more of a problem because they produce a beta-lactamase that may inactivate 1st generation cephalosporins and ampicillin/amoxicillin. Some of these *Bacteroides* may also be resistant to clindamycin. More resistant strains of *Bacteroides* have been observed in recent years (Jang et al 1997).

**Problem, or Resistant Bacteria**

If the organism is *Pseudomonas aeruginosa, Enterobacter, Klebsiella, Escherichia coli,* or *Proteus*, resistance against many common antibiotics is possible and a susceptibility test is advised. For example, a report showed that among nonenteric *E. coli*, only 23% were sensitive to a 1st generation cephalosporin and less than half were sensitive to ampicillin. In the same study, 13%, and 23% were intermediate or resistant to enrofloxacin, and orbifloxacin, respectively (Oluoch, et al 2001). In urinary tract infections (Torres et al, 2005) half of the *E. coli* were resistant to cephalexin, and only 22% were sensitive to enrofloxacin. Based on these data as well as other studies, for initial therapy we usually expect the gram-negative enteric bacteria to be susceptible to fluoroquinolones and aminoglycosides. An extended-spectrum cephalosporin (second- or third-generation cephalosporin) usually is active against enteric-gram negative bacteria, but will not be active against *Pseudomonas aeruginosa*. If the organism is a *Pseudomonas aeruginosa*, inherent resistance against many drugs is common, but it may be susceptible to fluoroquinolones, aminoglycosides, or extended-spectrum penicillin such as ticarcillin or piperacillin. In one published study, the *in vivo* activity was examined in 23 strains of *Pseudomonas*: 19 *Ps. aeruginosa, 3 Ps. fluorescens* and one *Pseudomonas spp.* The most
Effective antibiotics were tobramycin (100% susceptible), marbofloxacin (91.3%) and ceftazidime (91.3%). Ticarcillin and gentamicin, showed good activity (86 and 65.2% respectively). Lower susceptibility was found with enrofloxacin (52.1%) (Martin Barrasa et al, 2000). Isolates of *Pseudomonas aeruginosa* from otitis media showed that 97% were susceptible to ceftazidime, and 81% to carbenicillin (Colombini et al 2000). Fewer were susceptible to enrofloxacin (51%) and gentamicin (68%). In a study that isolated *Pseudomonas aeruginosa* from the skin and ears of dogs, the pattern of resistance is similar (Petersen et al, 2002). There were no trends identified, and most isolates were susceptible to ciprofloxacin, piperacillin, ticarcillin, amikacin, and gentamicin (enrofloxacin was not tested). However, isolates from the ears tended to be more resistant than isolates from the skin, with lower susceptibility to topical drugs such as gentamicin.

When administering a fluoroquinolone to treat *Pseudomonas aeruginosa* the high-end of the dose range is suggested. Of the currently available fluoroquinolones, (human or veterinary drugs) ciprofloxacin is the most active against *Pseudomonas aeruginosa*, followed by marbofloxacin, enrofloxacin, difloxacin, and orbifloxacin (Rubin et al, 2008).

**Bacterial Susceptibility Testing**

Bacterial susceptibility to drugs has traditionally been tested with the agar-disk-diffusion test (ADD), also known as the Kirby-Bauer test. With this test, paper disks impregnated with the drug are placed on an agar plate and the drug diffuses into the agar. Activity of the drug against the bacteria correlates with the zone of bacterial inhibition around the disk. The inoculation variables must be well controlled and the test must be performed according to strict procedural guidelines (CLSI, 2007; Lorian, 1996). The precise incubation time (usually 18 to 24 hours),
selection and preparation of the agar, and interfering compounds should be known. The ADD test results are qualitative (that is, it determines only resistant vs sensitive) rather than providing quantitative information. If this test is performed using standardized procedures, it is valuable, even though it may sometimes overestimate the degree of susceptibility.

**MIC Determination**

It is becoming more common for laboratories to directly measure the minimum inhibitory concentration (MIC) of an organism with an antimicrobial dilution test. The test is usually performed by inoculating the wells of a plate with the bacterial culture and dilutions of antibiotics are arranged across the rows. The MIC can be directly determined by observing the lowest concentration required to inhibit bacterial growth.

Resistance and susceptibility are determined by comparing the organism's MIC to the drug's breakpoint as established by the Clinical and Laboratory Standards Institute (CLSI) – formerly known as the National Committee for Clinical Laboratory Standards (NCCLS) (CLSI 2007). After a laboratory determines an MIC, it may use the CLSI “SIR” classification for breakpoints (S, susceptible; I, intermediate, or R, resistant). *Susceptible* and *Resistant* are self-explanatory. The *intermediate category* is intended as a buffer zone between susceptible and resistant strains. This category reflects the possibility of error when an isolate has an MIC that borders between susceptible and resistant. The intermediate category is not intended to mean “moderately susceptible.” If the MIC value is in the intermediate category, therapy with this drug at the usual standard dosage is discouraged because there is a good likelihood that drug concentrations may be inadequate for a cure.
PENETRATION TO THE SITE OF INFECTION

For most tissues, antibiotic drug concentrations in the serum or plasma approximate the drug concentration in the extracellular space (interstitial fluid). This is because there is no barrier that impedes drug diffusion from the vascular compartment to extracellular tissue fluid (Nix et al, 1991). There is really no such thing as “good penetration” and “poor penetration” when referring to most drugs in most tissues. Pores (fenestrations) or microchannels in the endothelium of capillaries are large enough to allow drug molecules to pass through unless the drug is restricted by protein binding in the blood. Tissues lacking pores or channels may inhibit penetration of some drugs (discussed below).

Diffusion Into Tissues

Diffusion of most antibiotics from plasma to tissues is limited by tissue blood flow, rather than drug lipid solubility. This has been called perfusion-rate limited drug diffusion. If adequate drug concentrations can be achieved in plasma, it is unlikely that a barrier in the tissue will prevent drug diffusion to the site of infection as long as the tissue has an adequate blood supply. Rapid equilibration between the extracellular fluid and plasma is possible because of high surface area:volume ratio (high SA:V). That is, the surface area of the capillaries is high relative to the volume into which the drug diffuses. Drug diffusion into an abscess or granulation tissue is sometimes a problem because in these conditions drug penetration relies on simple diffusion and the site of infection lacks adequate blood supply. In an abscess, there may not be a physical barrier to diffusion – that is, there is no impenetrable membrane – but low drug concentrations are attained in the abscess or drug concentrations are slow to accumulate because in a cavitated lesion there is low surface area to volume ratio (low S:V ratio).
In some tissues a lipid membrane (such as tight junctions on capillaries) presents a barrier to drug diffusion. This has been called *permeability-rate limited* drug diffusion. In these instances, a drug must be sufficiently lipid-soluble, or be actively carried across the membrane in order to reach effective concentrations in tissues. These tissues include: the central nervous system, eye, and prostate. A functional membrane pump (p-glycoprotein) also contributes to the barrier. There also is a barrier between plasma and bronchial epithelium (blood:bronchus barrier). This limits drug concentrations of some drugs in the bronchial secretions and epithelial fluid of the airways. Lipophilic drugs may be more likely to diffuse through the blood-bronchus barrier and reach effective drug concentrations in bronchial secretions.

**Urinary Tract**

High antibiotic concentrations achieved in renal tubules and the urine after routine therapy with modest doses of antibiotics is often sufficient to cure lower urinary tract infections, even those that are caused by organisms identified on a susceptibility test as “intermediate” in sensitivity (Lees & Rogers, 1986; CLSI 2007). Urine concentrations of antibiotics are at least 100 x the corresponding plasma concentrations because of the tubular concentration. When the infection is confined to the lower urinary tract, these high concentrations are an advantage (Stamey, et al. 1974). Cures of urinary tract infections are possible, even when the antibiotic levels do not attain concentrations high enough for a systemic infection. However, clinicians should be aware that if the concentrating ability of the kidneys is compromised, antibiotic concentrations in the urine may be low. Patients may have dilute urine because of renal disease, or treatment with corticosteroids, fluid therapy, or diuretics.

When the renal tissue is involved, high urine drug concentrations offer no advantage.
Drug concentrations in renal tissue – which are equivalent to the renal lymph concentrations – are correlated to plasma drug concentrations, not the drug concentrations in the urine. Therefore, consideration must be given to drugs that attain high concentrations in the renal tissue and that can be administered at doses and intervals that are optimum to achieve the pharmacokinetic-pharmacodynamic relationships for a clinical cure.

**Intracellular Infections**

Most bacterial infections are located extracellular, and a cure can be achieved with adequate drug concentrations in the extracellular (interstitial) space rather than intracellular space. Intracellular infections present another problem. For drugs to reach intracellular sites, they must be carried into the cell or diffuse passively. Generally, lipid-soluble drugs are best able to diffuse through the cell membrane for intracellular infections. Examples of drugs that accumulate in leukocytes, fibroblasts, macrophages, and other cells are fluoroquinolones, lincosamides (clindamycin, lincomycin), macrolides (erythromycin, clarithromycin), and the azalides (azithromycin) (Pasqual, 1995). β-lactam antibiotics and aminoglycosides do not reach effective concentrations within cells. Intracellular organisms such as *Brucella*, *Chlamydia*, *Rickettsia*, *Bartonella* and *Mycobacteria* are examples of intracellular pathogens. Staphylococci may in some cases become resistant to treatment because of intracellular survival. Fluoroquinolones and tetracyclines such as doxycycline are frequently administered to treat *Rickettsia* and *Ehrlichia* infections. There is good evidence for efficacy of doxycycline or fluoroquinolones (enrofloxacin is the only one tested) for treating *Rickettsia*, but only doxycycline should be considered for its efficacy for treating canine ehrlichiosis.
PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) OPTIMIZATION OF DOSES

To achieve a cure, the drug concentration in plasma, serum, or tissue fluid should be maintained above the minimum inhibitory concentration (MIC), or some multiple of the MIC, for at least a portion of the dose interval. Antibacterial dosage regimens are based on this assumption, but drugs vary with respect to the peak concentration and the time above the MIC that is needed for a clinical cure. Pharmacokinetic-pharmacodynamic (PK-PD) relationships of antibiotics attempt to explain how these factors can correlate with clinical outcome (Nicolau et al. 1995, Hyatt et al. 1995). Shown on Figure 1 are some terms used to describe the shape of the plasma concentration vs time profile. The $C_{\text{MAX}}$ is simply the maximum plasma concentration attained during a dosing interval. The $C_{\text{MAX}}$ is related to the MIC by the $C_{\text{MAX}}$:MIC ratio. The AUC is the total area-under-the-curve. The AUC for a 24 hour period is related to the MIC value by the AUC:MIC ratio. Also shown in Figure 1, is the relationship of time to MIC measured in hours ($T > \text{MIC}$).

Antibiotics have been classified as being either bactericidal or bacteriostatic, depending on their action on the bacteria. However, the distinction between bactericidal and bacteriostatic has become more blurred in recent years. Drugs traditionally considered bactericidal can be ‘static if the concentrations are low. Alternatively, drugs traditionally considered ‘static, can be ‘cidal against some bacteria and under optimum conditions. Rather than bacteriostatic or bactericidal, drugs are now more frequently grouped as either concentration-dependent or time-dependent in its action. If concentration-dependent, one should administer a high enough dose to maximize the $C_{\text{MAX}}$:MIC ratio or AUC:MIC ratio. If time-dependent, the drug should be administered frequently enough to maximize the $T > \text{MIC}$. For some of these drugs the AUC/MIC also predicts clinical success. Examples of how these relationships affect drug
regimens are described below:

**Aminoglycosides**

Aminoglycosides (eg, gentamicin, or amikacin) are concentration-dependent bactericidal drugs, therefore the higher the drug concentration, the greater the bactericidal effect. An optimal bactericidal effect occurs if a high enough dose is administered to produce a peak of 8-10x the MIC. This can be accomplished by administering a single dose once daily. This regimen is at least as effective, and perhaps less nephrotoxic, than lower doses administered more frequently (Freeman et al, 1997). Our current regimens in small animals employ this strategy. The single daily dose is based on the drug’s volume of distribution (calculated using the area method). A once daily dose for gentamicin is 5-8 mg/kg for cats, and 10-14 mg/kg for dogs, once daily. An appropriate dose for amikacin is 10-15 mg/kg for cats and 15-30 mg/kg for dogs once daily. The efficacy of these regimens has not been tested for conditions encountered in veterinary medicine, but the relationships are supported by experimental evidence. These regimens assume some competency of the immune system. If the animal is immunocompromised, one may consider a more frequent interval for administration. In animals with decreased renal function, longer intervals may be considered.

**Fluoroquinolones**

For the fluoroquinolone antimicrobials, as reviewed by Hyatt et al (1995), Dudley (1991), and recently by Wright et al (2000) and Papich & Riviere (2001) investigators have shown that either the peak plasma concentration above bacterial minimum inhibitory concentration (MIC), also known as the C\text{MAX}:MIC ratio, or the total AUC above the MIC (also
known as the AUC:MIC ratio), may predict clinical cure in studies of laboratory animals, and in a limited number human clinical studies. There are no published studies involving dogs or cats that indicate which of these parameters is the best predictor of clinical cure, or what the respective target ratios might be. Therefore, the optimum value for these surrogate markers has not been determined for infections in dogs or cats. However, derived from other studies, a $C_{\text{MAX}}$:MIC of 8-10, or a AUC:MIC of greater than 125 have been associated with a cure. As reviewed by Wright et al (2000), for some clinical situations AUC:MIC ratios as low as 30-55 for a clinical cure, since the study in which 125 was cited involved critically ill human patients. This difference may also be organism specific.

Sensitive bacteria from small animals are expected to have an MIC for fluoroquinolones in the range of 0.125 mg/mL, (+/- one dilution) (Pirro et al 1999). Using this value for MIC, the administration of the lowest label dose of any of the currently available fluoroquinolones usually meets the goal of a $C_{\text{MAX}}$:MIC ratio or a AUC:MIC ratio in the range cited above. To take advantage of the wide range of safe doses for fluoroquinolones, low doses have been administered to treat susceptible organisms with low MIC, such as *E. coli* or *Pasteurella*. But, for bacteria with a higher MIC, (for example gram-positive cocci) a slightly larger dose can be used. To achieve the necessary peak concentration for a bacteria such as *Pseudomonas aeruginosa*, that usually has the highest MIC among susceptible bacteria, the highest dose within a safe range is recommended. Bacteria such as streptococci and anaerobes are more resistant and even at high doses, a sufficient peak concentration or AUC:MIC ratio will be difficult to achieve.

**Beta-lactam antibiotics**

$\beta$-lactam antibiotics such as penicillins, potentiated-aminopenicillins, and cephalosporins
are slowly bactericidal. Their concentration should be kept above the MIC throughout most of the dosing interval (long T>MIC) for the optimal bactericidal effect (Turnidge 1998). Dosage regimens for the β-lactam antibiotics should consider these pharmacodynamic relationships. Therefore, for treating a gram-negative infection, especially a serious one, some regimens for penicillins and cephalosporins require administration 3 to 4 times per day. Some long-acting formulations have been developed to prolong plasma concentrations. Some of the third-generation cephalosporins have long half-lives and less frequent regimens have been used for some of these drugs (for example cefpodoxime proxetil, cefotaxime and ceftiofur). (However, the long half-life for ceftriaxone in people does not occur in animals because of differences in drug protein binding.) Gram-positive organisms are more susceptible to the β-lactams than are gram-negative bacteria and lower doses and longer intervals are possible when treating these bacteria. Additionally, because antibacterial effects occur at concentrations below the MIC (post antibiotic effect or PAE) for Staphylococcus, longer dose intervals may be possible for staphylococcal infections. For example, cephalexin or amoxicillin-clavulanate have been used successfully to treat staphylococcal infections when administered only once daily (although twice-daily administration is recommended to obtain maximum response). Cefpodoxime proxetil (Simplicef) is effective for once-daily administration, which is due to both high activity (low MIC values) and a longer half-life compared to other cephalosporins.

**Other Time-Dependent Drugs**

The drugs such as tetracyclines, macrolides (erythromycin and derivatives), sulfonamides, lincosamides (lincomycin and clindamycin), and chloramphenicol derivatives act in a time-dependent manner against most bacteria. Either time above MIC (T>MIC) or total
drug exposure, measured as AUC/MIC, has been used to predict clinical success for these drugs.

The time-dependent activity is demonstrated by studies in which effectiveness is highest when the drug concentrations are maintained above the MIC throughout the dosing interval. Drugs in this group should be administered frequently to achieve this goal. However, a property of some is that they persistent in tissues for a prolonged time, which allows infrequent dosing intervals. The macrolide derivative azithromycin (Zithromax) has shown tissue half-lives as long as 70-90 hours in cats and dogs, permitting infrequent dosing. Tissue concentrations of trimethoprim-sulfonamides persist long enough to allow once-daily dosing for many infections. Most published dosage regimens are designed to take the pharmacokinetic properties of these drugs into account.

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INTRODUCTION

Treatment of common infections in small animals has been reported to provide guidelines and established regimens. Drug manufacturers have produced several important drugs to treat the most common infections encountered in small animals. However, the drugs and approaches to therapy are more limited when the infection is more refractory, resistant, or is associated with another complicating factor. Susceptibility of the most common isolates has been documented well enough to make sound judgments and empirical antimicrobial drug choices. However, when the patient has a refractory and/or resistant infection, or is seriously ill with an infection, other strategies and drugs may be necessary. As with many new treatments, there are few veterinary clinical studies to support a recommended use and dose and many of these details have been extrapolated from human medicine.

TREATING RESISTANT GRAM-NEGATIVE BACTERIA

The most common resistant gram-negative bacteria in veterinary small animal medicine are the gram-negative bacilli, especially the enteric isolates. The most common resistant gram-negative bacilli that we encounter in small animal medicine is *Escherichia coli*. In some hospitals, there have been outbreaks of *Klebsiella pneumoniae*, *Enterobacter*, and indole-positive *Proteus*, but *E. coli* remains as the most common. Wild-type strains of *E. coli* should respond to third-generation cephalosporins, fluoroquinolones, and
aminoglycosides. Many are susceptible to amoxicillin-clavulanate (Clavamox), or ampicillin-sulbactam (Unasyn) combinations. Drugs that are not expected to have good activity against the wild type strains are first-generation cephalosporins, ampicillin/amoxicillin, or macrolides.

After a susceptibility report is available, one may find that the only drugs to which some gram-negative bacilli are sensitive are extended-spectrum cephalosporins, penems (carbapenems), or amikacin. The injectable cephalosporins most often used are cefotaxime and ceftazidime, although individual veterinary hospitals have utilized others in this group. These drugs are expensive, injectable (except for the oral exception discussed below), and must be administered frequently.

The activity of the oral third-generation cephalosporin, cefpodoxime proxetil (Simplicef) is variable among gram-negative bacteria. To treat the indications for which it is registered in dogs (skin infections), it can be given once a day orally at a dose of 5-10 mg/kg. Its absorption from oral administration is approximately 35%, which is good compared to other oral third generation cephalosporins. It is excreted mostly in the urine with a half-life of 5.6-6 hours (Brown et al, 2007). The long half-life and concentrations in interstitial fluid of dogs account for the once-daily dosing (Papich et al, 2007). Since cefpodoxime is excreted in the urine, it may have efficacy against urinary tract infections, but clinical results have not been reported.

Cefpodoxime is more active than many other third-generation cephalosporins against *Staphylococcus*. However, it is not active against *Pseudomonas aeruginosa*, Enterococcus, or methicillin-resistant *Staphylococcus*. One should be aware that the break-point for susceptibility is lower than for other third-generations cephalosporins. Therefore, it is possible for a bacterial isolate to be sensitive to cefotaxime or ceftazidime (breakpoint 8 µg/mL) but resistant to cefpodoxime (breakpoint 2 µg/mL) (CLSI 2007). Specific disks are
suggested for testing bacterial isolates, rather than relying on the results from other cephalosporins.

In the spring of 2008 cefovecin (Convenia) was registered by the FDA-CVM for use in dogs and cats for treatment of skin infections. In December of 2006 cefovecin (Convenia) was introduced to small animal medicine in Europe and in Canada in October 2007. There have also been pharmacokinetic studies (Stegemann et al 2006ab) published for dogs and cats, pharmacodynamic studies published (Stegemann et al, 2006c), and clinical efficacy studies in dogs and cats (Stegemann et al, 2007ab; Passmore et al, 2007; Six et al, 2008). In the clinical studies, cefovecin was compared to another active antimicrobial (cefadroxil, cephalaxin, or amoxicillin-clavulanate) and non-inferior to these other drugs.

In dogs and cats, cefovecin is registered in Europe and Canada for treatment of skin infections. In dogs it is also registered for urinary tract infections. In Europe, but not Canada, it is also registered for urinary tract infections in cats. The approved label dose in these countries is 8 mg/kg SC, once every 14 days. The studies published show efficacy with a 14 day interval for administration. The injection may be repeated for infections that require longer than 14 days for a cure (eg, canine pyoderma). The registration in the United States lists treatment of skin infections in dogs and cats and therapeutic concentrations are maintained for an interval of 7 days. Drug concentrations persist long enough for a 14 day interval for some indications.

The long duration of action is attributed to the long half-life in dogs and cats. Cefovecin is > 99% protein bound in cats and >98% in dogs. With such a small fraction unbound (fu) there is little drug available for excretion. Subsequently, the terminal half-life is approximately 7 days in cats and 5 days in dogs. Effective concentrations can be maintained in the tissue fluid for the entire 14 day interval, or longer (Stegemann et al, 2006ab). Cefovecin is a third-generation cephalosporin. Therefore, against many bacteria, it
is more active with lower MIC values than first generation cephalosporins. This was demonstrated for pathogens from Europe and the United States (Stegemann et al, 2006c, Six et al, 2008). Cefovecin MIC<sub>90</sub> values were 0.25 µg/mL for *Staphylococcus intermedius* compared to 2 µg/mL for cephalaxin and cefadroxil. As a 3<sup>rd</sup>-generation cephalosporin, it is expected to have even greater activity against gram-negative bacteria as was demonstrated by the MIC<sub>90</sub> values of 1 µg/mL compared to 16 µg/mL for cephalaxin and cefadroxil (Six et al, 2008). Other MIC comparisons are provided in the tables in the paper by Stegemann et al (2006c). Susceptibility breakpoints are not yet set for this drug by the Clinical Laboratory Standards Institute (CLSI 2007, formerly NCCLS), but based on the distribution of organisms reported (Stegemann et al. 2006c) ≤ 2.0 µg/mL should be considered.

The first 4th generation cephalosporin is cefepime (Maxipime). It is unique from other cephalosporins because of its broad spectrum of activity that includes gram positive cocci, enteric gram negative bacilli, and *Pseudomonas*. It even has activity against some extended-spectrum β-lactamase (ESBL) producing strains of *Klebsiella* and *E. coli* that have become resistant to many other β-lactam drugs and fluoroquinolones. Except for one investigation in dogs, adult horses, and foals, the use of cefepime has been limited in veterinary medicine (Gardner, et al. 2001), and there has been recent concern about the mortality associated with its use in human medicine (Yahav, et al, 2007).

The carbapenems have been valuable for treatment of resistant gram-negative bacteria. The carbapenems are β-lactam antibiotics that include imipenem-cilastatin sodium (Primaxin), meropenem (Merrem), and most recently, ertapenem (Invanz). All three have activity against the enteric gram-negative bacilli. Resistance (carbapenemases) among veterinary isolates has been very rare. Imipenem is administered with cilastatin to decrease renal tubular metabolism. Imipenem has become a valuable antibiotic because it has a broad spectrum that includes many bacteria resistant to other drugs (Edwards & Betts, 2000).
Imipenem is not active against methicillin-resistant staphylococci or resistant strains of *Enterococcus faecium*. The high activity of imipenem is attributed to its stability against most of the β-lactamases (including ESBL) and ability to penetrate porin channels that usually exclude other drugs (Livermore 2001). The carbapenems are more rapidly bactericidal than the cephalosporins and less likely to induce release of endotoxin in an animal from gram-negative sepsis.

Some disadvantages of imipenem are the inconvenience of administration, short shelf-life after reconstitution, and high cost. It must be diluted in fluids prior to administration. Meropenem, one of the newest of the carbapenem class of drugs (some experts consider it a 2nd -generation penem) and has antibacterial activity greater than imipenem against some isolates. One important advantage over imipenem is that it is more soluble and can be administered in less fluid volume and more rapidly. For example, small volumes can be administered subcutaneously with almost complete absorption. There also is a lower incidence of adverse effects to the central nervous system, such as seizures (Edwards & Betts, 2000). Based on pharmacokinetic experiments in our laboratory (Bidgood & Papich, 2002), the recommended dose for Enterobactericeae and other sensitive organisms is 8.5 mg/kg SC every 12hr, or 24 mg/kg IV every 12 hr. For infections caused by *Pseudomonas aeruginosa*, or other similar organisms that may have MIC values as high as 1.0 mcg/mL: 12 mg/kg q8h, SC, or 25 mg/kg q8h, IV. For sensitive organisms in the urinary tract, 8 mg/kg, SC, every 12 hours can be used. In our experience, these doses have been well-tolerated except for slight hair loss over some of the SC dosing sites.

Aminoglycosides are still valuable for treating gram-negative bacilli that are resistant to other drugs. They are rapidly bactericidal, less expensive than injectable drugs listed above, and can be administered once-daily. Among these, amikacin is the most active. Therefore, it is often the first choice in small animal medicine. It has been administered
once-daily for systemic infections IV, IM, or SC. There are two important disadvantages to systemic use of aminoglycosides: (1) Treatment usually must extend for at least two weeks or longer. Risk of nephrotoxicosis is greater with longer duration of treatment. (2) Activity of aminoglycosides is diminished in the presence of pus and cellular debris (Konig et al 1998). This may decrease their usefulness for the treatment of wound and ear infections caused by *Pseudomonas aeruginosa*. To decrease the risk of drug-induced nephrotoxicosis, therapeutic drug monitoring and careful evaluation of renal function during its use is recommended.

Infections caused by *Pseudomonas aeruginosa* present a special problem because so few drugs are active against this organism. Of the β-lactam antibiotics, a few are designated as anti-*Pseudomonas* antibiotics. Those with activity against this organism include the ureidopenicillins (mezlocillin, azlocillin, piperacillin) and the carboxylic derivatives of penicillin (carbencillin, ticarcillin). These derivatives are available as sodium salts for injection; there are no orally-effective formulations in this class, except indanyl carbencillin (Geocillin, Geopen) which is poorly absorbed and not useful for systemic infections. These drugs are more expensive than the more-commonly used penicillins, and must be administered frequently (eg, at least 4 times daily) to be effective. Ticarcillin is available in combination with the β-lactamase inhibitor clavulanic acid (Timentin). Because these drugs degrade quickly after reconstitution, observe the storage recommendations on the package insert to preserve the drug’s potency.

Of the cephalosporins, only the 3rd-generation cephalosporins, ceftazidime (Fortaz, Tazidime), cefoperazone (Cefobid), or cefepime (Maxipime), a 4th-generation cephalosporin, have predictable activity against *Pseudomonas aeruginosa*. Ceftazidime has greater activity than cefoperazone and is the one used most often in veterinary medicine. These drugs must all be injected, and are usually given IV, although SC, and IM routes have been used. As
with the penicillins, frequent administration is necessary. As mentioned previously, the β-lactam antibiotics with greatest activity against *Pseudomonas aeruginosa* are the carbapenems. Ertapenem is a new addition to the class of carbapenems but it does not have anti-*Pseudomonas* activity. Aminoglycosides are active against most wild-type strains of *Pseudomonas aeruginosa*. Against resistant isolates, amikacin and tobramycin are more active than gentamicin, and resistance is less likely to these drugs (Petersen et al, 2002). Of the currently available fluoroquinolones, (human or veterinary drugs) ciprofloxacin is the most active against *Pseudomonas aeruginosa*, followed by marbofloxacin, enrofloxacin, difloxacin, and orbifloxacin (Rubin et al, 2007).

**TREATMENT OF RESISTANT GRAM-POSITIVE BACTERIA**

**Resistant Staphylococcus**

Staphylococcal resistance can be caused by altered penicillin-binding proteins (for example the resistance carried by the gene mecA). These are known as methicillin-resistant staphylococci – MRS (Gortel et al, 1999; Deresinski 2005; Jones et al, 2007). If it is *S. aureus* the term methicillin-resistant *S. aureus* (MRSA) is used. Bacteria previously identified as *Staphylococcus intermedius* are most likely *Staph. pseudintermedius* and any future studies and papers will likely use the new terminology (Sasaki et al, 2007). Other *Staphylococcus* species also have been identified among veterinary isolates, such as coagulase-negative *Staphylococcus*. Oxacillin is now used more commonly than methicillin as the marker for this type of resistance, and resistance to oxacillin is equivalent to methicillin-resistance. The mecA gene and methicillin resistance appears to be increasing in veterinary medicine based on the number of reports in the last several years. If staphylococci are resistant to oxacillin or methicillin, they should be considered resistant to all other β-lactams, including cephalosporins and amoxicillin-clavulanate (eg, Clavamox), regardless of
the susceptibility test result. Adding a β-lactamase inhibitor will not overcome methicillin resistance. Unfortunately, these bacteria often carry co-resistance to many other non-β-lactam drugs, including clindamycin, fluoroquinolones, macrolides, tetracyclines, and trimethoprim-sulfonamides. Use of fluoroquinolones and cephalosporins has been linked to emergence of resistance of methicillin-resistant staphylococci (Dancer, 2008). Because susceptibility to non-β-lactam antibiotics is unpredictable, a susceptibility test is needed to identify which drug to use for these infections. Clindamycin, chloramphenicol, rifampin, and trimethoprim-sulfonamides are drugs to consider for these infections if a susceptibility test can confirm activity. However, in some instances the only drug that is active for treatment will be a glycopeptide such as vancomycin (Vancocin) or the oxazolidinone, linezolid (Zyvox). Vancomycin can only be administered by intravenous infusion. Linezolid is the first in the class of oxazolidinones to be used in medicine and it is used in people to treat resistant gram-positive infections caused by enterococci and streptococci. It can be administered IV or orally and has excellent absorption, but is extremely expensive. Nevertheless, veterinary patients have been treated with this medication with good success.

**Resistant Enterococcus**

Enterococci are gram-positive cocci that have emerged as important causes of infections, especially those that are nosocomial. The most common species identified are *Enterococcus faecalis* and *E. faecium*. *Enterococcus faecalis* is more common, but *E. faecium* is usually the more resistant. Wild-strain enterococci may still be sensitive to penicillin G and ampicillin, or amoxicillin. However, the enterococci have an inherent resistance to cephalosporins and fluoroquinolones. These strains also are usually resistant to trimethoprim-sulfonamide combinations, clindamycin, and erythromycin. Susceptibility test results for cephalosporins, β-lactamase resistant penicillins (eg, oxacillin), trimethoprim-
sulfonamide combinations, and clindamycin can give misleading results (CLSI, 2008). Even if isolates are shown to be susceptible to a fluoroquinolone, this class of drugs may not be a good alternative for treatment.

In human medicine frequent use of fluoroquinolones and cephalosporins (both of which have poor activity against enterococci), has been attributed to emergence of a higher rate of enterococcal infections. Evidence to document this trend is limited in veterinary medicine, but one study from a veterinary teaching hospital indicated increased rate of enterococcal urinary tract infections (Prescott, et al, 2002). Treatment of Enterococcus is frustrating because there are so few drug choices. If the Enterococcus isolated is sensitive to penicillins, one should administer amoxicillin or ampicillin at the high-end of the dose range. When possible, combine an aminoglycoside with a β-lactam antibiotic for treating serious infections. Occasionally, one of the carbapenems (imipenem-cilastatin) or an extended-spectrum penicillin (eg, piperacillin) can be considered for treatment of *E. faecalis* (but not *E. faecium*). When enterococci are present in wound infections, lower urinary tract, peritoneal infections, and body cavity infections (eg, peritonitis), the organism may exist with other bacteria such as gram-negative bacilli, or anaerobic bacteria. In these cases, there is evidence that treatment should be aimed at the anaerobe, and/or gram-negative bacilli and not directed at the enterococcus. Treatment cures are possible if the other organisms are eliminated without specific therapy for enterococcus (Bartlett et al 1978). As mentioned above for resistant Staphylococcus, sometimes the only active drug will be a glycopeptide or the oxazolidinone linezolid. Disadvantages of these drugs were discussed above.

**RESISTANT / REFRACTORY URINARY TRACT INFECTIONS**

Urinary tract infections that are refractory, recurrent, and/or caused by resistant bacteria can be frustrating cases in veterinary medicine. Some of these patients are
immunocompromised, diabetic, receiving corticosteroids, or have underlying neurological disease. The secondary UTI associated with diabetes and other underlying problems often are often occult (McGuire, et al, 2002; Torres et al, 2005). Clinical signs may be minimal or may be attributed to underlying disease or drug therapy, and white blood cells (WBC) and bacteria may be found in very minimal concentration in dilute urine. Treatment of complicated UTI must be based on urine culture and sensitivity, and even with this information it can be very difficult to eradicate infection (Sequin et al, 2003). After initiating antimicrobial therapy, follow-up urine culture should be obtained after approximately one week to be sure of antimicrobial efficacy in vivo. Culture should be repeated approximately one week after antibiotics are discontinued, and again several weeks later if immunocompromise continues. The antibiotics already discussed above can have an important role in treating these difficult-to-treat urinary tract infections. In some cases, antibiotics alone are not sufficient and urinary antiseptics are used.

Use of Urinary Antiseptics

For frequent recurrent UTI, once acute infection is resolved urinary antiseptics or daily antimicrobial administration may be useful to prevent re-infection. However, the ideal urinary antiseptic has not been identified in veterinary medicine (Sequin et al 2003). Drugs used for this purpose include nitrofurantoin (Macrodantin) and methenamine (methenamine hippurate or methenamine mandelate). Nitrofurantoin has caused adverse gastrointestinal effects in animals. Methenamine is converted to formaldehyde—which is naturally antibacterial—in acidic urine. However, for the conversion to be effective the urine pH must be low, in the range of 5 to 6. Depending on the animal’s diet and other medications, urinary pH consistently in this range may not occur in all animals. Drugs or natural compounds that decrease the virulence of uropathogens, such as fosfomycin tromethamine (Monural), or
cranberry juice also have been used in dogs with recurrent, or refractory, urinary tract infections. Cranberry juice (or its extract) contains a proanthocyanindin that inhibits the attachment of bacteria to the urinary mucosa (Howell et al, 2007). Its efficacy has not been reported in animals. Veterinarians and pet owners should be warned that products marketed as cranberry juice, or its extract, are highly variable in content. Cranberry may help to prevent but not treat urinary tract infections in women. Veterinarians may wish to refer interested pet owners to the web site at the National Center for Complimentary and Alternative Medicine (NCCAM), http://nccam.nih.gov/health/cranberry/. Fosfomycin tromethamine can be antibacterial and also decrease virulence of uropathogens. In people it is used as a one-time administration for uncomplicated urinary tract infections in women (Monural 3-gram packet taken once with water). The efficacy has not been evaluated in animals.

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GLUCOCORTICOIDS:

Glucocorticoids are the most consistently effective drugs available for the treatment of various forms of inflammation in animals. However, their potent anti-inflammatory effects and immunosuppressive actions must be balanced by the multiple side-effects produced by these drugs. Glucocorticoids exert their action via binding to intracellular receptors, translocating to the nucleus, and binding to receptor sites on responsive genes (Rhen & Cidlowski 2005), where they modulate the transcription of glucocorticoid-responsive genes (Barnes, 2006; Hayashi et al, 2004; Rhen & Cidlowski 2005). By regulating glucocorticoid-responsive genes, protein synthesis is altered which affects cell function. For controlling inflammation, the major effect of corticosteroids is inhibition of the synthesis of inflammatory proteins. These effects may be mediated by the interaction of glucocorticoids with activator protein-1 (AP-1) and nuclear factor κ-B (NF κ-B).

Clinical use: planning corticosteroid therapy:

For short-term therapy (less than two weeks), glucocorticoids can be used daily at anti-inflammatory doses without serious long-term side effects. If long-term therapy is not needed, the medication can be discontinued abruptly with little chance of a rebound effect from adrenal
suppression. For long-term, chronic therapy, glucocorticoid doses should be titrated to the lowest dose that is effective and, if possible, these drugs should be administered every other day (EOD).

**Choice of a corticosteroid:**

Prednisolone, prednisone, methylprednisolone, or triamcinolone are the most common choices because they are intermediate-acting steroids and can be used on an every-other-day (EOD) schedule. Initial (induction) dosages (prednisone or prednisolone) for anti-inflammatory activity are approximately 1 mg/kg/day for 5 to 10 days then the dose is gradually lowered to approximately 1 mg/kg every-other-day for another 5 to 10 days and eventually to 0.5 mg/kg, EOD. These are typical anti-inflammatory maintenance dosages, although in some patients it may be possible to lower the dose further. There can be wide variation of response among individuals and doses should be titrated for each patient.

**Differences Among Species:**

Cats often require higher dosages than dogs, sometimes twice as much as dogs, possibly owing to differences in receptors (van den Broek, et al, 1992). Prednisolone is preferred over prednisone in cats. In cats, there is evidence that either oral absorption of prednisone is poor, or once it is absorbed, there is a deficiency in the ability to convert to prednisolone as well as other animals (Graham-Mize & Rosser, 2004).

Cats are also more resistant to the adverse effects than are dogs, but cats are still susceptible to severe adverse effects from chronic administration. Repository forms of methylprednisolone acetate (Depo-Medrol) have been administered to cats, at dosages of 20
Adrenal recovery following glucocorticoid therapy:

After short-term glucocorticoid therapy, HPA axis recovery occurs quickly, and the medication can be discontinued abruptly. After long-term therapy it may take longer for adrenal gland recovery and a withdrawal syndrome may be observed in animals after glucocorticoids are discontinued. However, even after chronic treatment, adrenocortical recovery may occur within a few weeks. In healthy dogs, complete HPA-axis recovery was evident two weeks after cessation of daily prednisone administration (Moore & Hoenig, 1992). In another study, recovery occurred one week following discontinuation of every-other-day prednisolone administration (Brockus et al 1999).

Recovery of adrenal function after long-term glucocorticosteroid therapy can be variable among animals. Veterinarians should advise animal owners of the possibility of adrenal suppression following discontinuation of corticosteroid therapy. Patients should be monitored for signs of adrenocortical insufficiency (lethargy and weakness, for example), and supplement animals with physiologic dosages of a short to medium-acting corticosteroid as needed, especially at times of stress (Romatowski, 1989). Because the usual physiologic secretion of cortisol is 1 mg/kg/day, this translates to a dose for glucocorticoid supplementation of 0.2 to 0.25 mg/kg of prednisolone/day.

Inhaled Corticosteroids:

Glucocorticoids are among the most valuable drugs for managing asthma in people. For people, a metered-dose inhaler is used to deliver the drug topically in order to avoid systemic
adverse effects. According to one review, inhaled corticosteroids are the most effective agents available for the symptomatic control of asthma and improvement in pulmonary function (Busse & Lemanske, 2001). Examples of aerosolized corticosteroids are beclomethasone (Beclovent), flunisolide (Aerobid), fluticasone (Flovent), triamcinolone (Azmacort), and budesonide (Pulmicort). Fluticasone is the most potent (18 x dexamethasone) and is usually the one used in veterinary medicine (see accompanying table). When glucocorticoids are delivered topically with these devices, systemic adverse effects are minimized, but not eliminated.

**Small Animal Use:** Metered-dose inhalers have been successfully used in small animals, particularly cats. For this use, a chamber with a valve on one end, fitted with a mask (for example the OptiChamber by Respironics and AeroKat by Trudell Medical International) has been used to deliver the drug. Budesonide or fluticasone are most often administered because of their high potency and low systemic effects. Fluticasone has been used most often. In people it has a systemic absorption of only 18-26%, but there are extensive first pass effects preventing systemic blood concentrations if it is swallowed after delivery. Therefore, the systemic action – and adverse effects – is expected to be small. A typical dose for fluticasone for a cat is 110 µg (one puff from a 110 µg metered dose inhaler) per day. Higher dose inhalers that deliver 220 µg are also available. In a recent study (Cohn et al, 2008) three doses (44, 110, and 220 mcg per cat) twice daily via metered dose inhaler were equivalent in an experimental model of feline asthma. When asthmatic cats were given inhaled corticosteroids twice a day and allowed 5-7 breaths (10 sec) from the chamber, it reduced the need for oral prednisolone. After 10 days, the patient may be re-evaluated and frequency of administration reduced.

In one study, inhaled fluticasone reduced bronchial hyper-responsiveness and bronchoconstriction in cats with bronchitis with a dose of 250 µg per cat daily (Kirschuink et al,
This dose also decreased inflammatory cells and prostaglandins in bronchoalveolar lavage fluid. In cats, flunisolide was studied for its systemic effects after administration by inhalation (Reinero et al, 2006). Although there was some suppression of the hypothalamic-pituitary-adrenocortical axis (indicating some systemic absorption), the systemic effects on immune cells were observed.

**Budesonide (Entocort EC):**

Budesonide is a locally-acting corticosteroid. It has been used in people, but there has been only limited use in small animals. Budesonide granules are contained in an ethylcellulose matrix that is coated with methacrylic acid polymer. This coating does not release the drug until the pH > 5.5. In the proximal intestine the pH is low and it gradually increases in the distal intestine to attain a pH above 7. Therefore, the drug is not released until it reaches the distal GI tract. If a portion of the drug is absorbed, 80-90% is inactivated by metabolism 1st pass effects. Therefore, systemic glucocorticoid effects are minimized. In humans it has been as effective as other drugs for treatment of Crohn’s disease. It is available in a 3 mg capsule and is used in people at a dose of 9 mg/day.

*Use of Budesonide in Animals:* There is only limited experience with budesonide in dogs and cats, but some animals have benefited from its administration. There is some systemic absorption as evidenced by decreased response to ACTH after 30 day treatment to dogs at 3 mg/m², but other side effects were not observed (Tumulty et al, 2004).

**LEUKOTRIENE INHIBITORS:**

Leukotrienes, such as LTD₄ contribute to airway inflammation by increasing migration of
eosinophils, cause bronchoconstriction, and increase airway wall edema. Inhibitors or blockers of leukotrienes have been used to treat airway diseases. These were discussed by Peters-Golden & Henderson (2007). The leukotrienes have not been demonstrated to be important mediators in feline asthma (Norris et al, 2003). Therefore, these inhibitors may not have a role in feline respiratory disease.

**Lipooxygenase inhibitor: Zileuton (Zyflo7):**

Zileuton is an oral drug for treating asthma in people. It inhibits the enzyme 5-lipoxygenase and thereby inhibits synthesis of inflammatory leukotrienes. This drug has broader actions than the leukotriene receptor blockers because it inhibits effects of both LTB₄ and the cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄). However, it has been less effective than leukotriene receptor blockers (see below) because at the doses administered, it does not achieve complete suppression of the 5-lipoxygenase enzyme. In people, the safety profile has not been as good as the receptor blockers (see below). The effectiveness of zileuton for respiratory diseases in animals has not been reported. Treatment of other diseases in animals (eg, allergic skin disease) have been investigated, but it has not been effective.

**Leukotriene receptor blockers:**

Zafirlukast (Accolate7), pranlukast, and montelukast (Singulair7) are leukotriene receptor blockers that have been used as oral drugs for treating asthma. They block the cysteinyl leukotriene receptor, therefore blocking the effects of LTC₄, LTD₄, and LTE₄ – primarily at the CysLT₁ receptor site – but these drugs do not block receptor for the leukotriene LTB₄. (The CysLT₁ receptor mediates sustained bronchoconstriction, mucus secretion, and edema in the
airways (Peters-Golden & Henderson, 2007). These drugs have been generally well tolerated in people, but there are some drug interactions with zafirlukast (inhibition of CYP-450 enzymes). Montelukast seems to have fewer adverse effects in people and less risk of drug interaction than zafirlukast. The use of these drugs has not been reported to be effective for treating respiratory diseases in animals. Doses in animals are not established but the dose in people for zafirlukast is 20 mg/person twice daily and for montelukast is 5 mg for children and 10 mg for adults.

**Dual blockers:**

The only dual blocker of prostaglandins and leukotrienes (COX and LOX) is the NSAID tepoxalin (Zubrin). It is currently registered as an oral treatment for arthritis in dogs. It is not known if the anti-leukotriene effect will be beneficial in patients with respiratory disease.

**ANTIHISTAMINES**

Antihistamines fall into two primary classes, the H1- and H2-receptor antagonists (Simons & Simons, 1994; Papich, 1999). These were reviewed by Simons (2004). The H2-receptor antagonists include cimetidine, ranitidine, and famotidine. Although H2-receptor antagonists have some effects on vessels during inflammation, they are not used as sole treatments for allergic or inflammatory conditions. There also are H3 and H4 - receptors, but since drugs to antagonize the effects at these sites have not been identified, they will not be discussed here.

The H1-antagonists have been divided into the first-generation antihistamines (eg, chlorpheniramine, diphenhydramine, and hydroxyzine) and the second-generation antihistamines
(eg, cetirizine, desloratadine, fexofenadine, terfenadine, astemizole, and loratadine). The first-generation antihistamines are generally the older familiar drugs. The second-generation antihistamines are the newer, non-sedating antihistamines. This group includes most of the newer antihistamines introduced since 1981. Some of these drugs are related: cetirizine is a metabolite of hydroxyzine; diphenhydramine is a metabolite of dimenhydrinate; desloratidine is a metabolite of loratadine.

The primary difference between the first- and second-generation antihistamines is that the second-generation antihistamines lack the antimuscarinic properties and do not cross the blood-brain barrier as easily as first-generation antihistamines. Therefore these drugs lack the central-nervous system side effects – particularly sedation – that is common with the first-generation antihistamines. It has been reported that second-generation antihistamines are less effective than first-generation drugs in dogs for treating pruritus (Paradis, 1996). However, this should be re-evaluated. Hydroxyzine, which is reported to be effective in some dogs is almost completely metabolized to cetirizine (a second-generation antihistamine) in dogs (Bisikova et al, 2008).

Astemizole and terfenadine have been discontinued in the U.S. Astemizole and terfenadine are both similar in structure (also structurally related to haloperidol, a butyrophenone antipsychotic). All three agents have been associated with torsades de pointes, an abnormal cardiac conduction in people.

Clinical Use:

Antihistamines have been used in an attempt to control pruritus and skin inflammation in animals, but their success has not been overwhelming (DeBoer & Griffin, 2001). An evidence-based review was published by Olivry et al (2003). The conclusions pointed out that in some
reports the incidence of response is approximately the same as a placebo. Several of the reported studies are uncontrolled, or the studies are not published in reviewed sources. Nevertheless, these drugs are used by dermatologists to decrease the reliance on corticosteroids or used in conjunction with other anti-inflammatory medications. As reported by Zur and colleagues (Zur, et al, 2002), dermatologists will often try 3 to 5 antihistamines in two week trials to find the one that is most effective for a patient. As expected, because of these individual variations, there also are a variety of results reported.

Clemastine (Tavist), an ethanolamine antihistamine, is one of the most commonly used in dogs (Paradis et al 1991) even though there is reliable evidence that it is not absorbed orally (Hansson et al 2004). Chlorpheniramine, diphenhydramine, and hydroxyzine also may be effective in dogs (Scott & Buerger, 1988). Hydroxyzine administered at a dose of 1 mg/kg orally or IV to dogs inhibited the wheal and flare response from histamine, but this effect was entirely caused by the metabolite cetirizine (Bisikova et al, 2008). Trimeprazine, a phenothiazine derivative with antihistamine effects, has little effect on its own, but is among the most effective drugs when combined with a corticosteroid. In the study cited previously (Zur et al 2002), hydroxyzine, diphenhydramine, chlorpheniramine, and clemastine were evaluated in a retrospective study. Overall, 54% of the dogs had a good to moderate response. In that study, diphenhydramine and hydroxyzine were the most often used, and the most often effective. Chlorpheniramine and clemastine also have been reported to reduce pruritus in cats.

**Combinations with other drugs:**

Some studies have shown that combinations of antihistamines with fatty acids or other drugs may improve efficacy. There may be a synergistic effect of antihistamines (eg, clemastine,
chlorpheniramine) in combination with n-3/n-6 fatty acids (Paradis, et al, 1991), and evidence for a synergistic effect with fatty acids and corticosteroids. When antihistamines (trimeprazine) were combined with corticosteroids in one report, the effective dose of prednisone was lowered (30% reduction) (Paradis, et al, 1991). The product Temaril-P contains a fixed combination of an antihistamine and corticosteroid.

**CYCLOSPORINE:**

Cyclosporine is a fat-soluble, cyclic polypeptide fungal product with immunosuppressive activity. It has been an important drug used in humans, primarily to produce immunosuppression in organ transplant patients. It has gained recognition for veterinary use because of availability of a veterinary formulation of cyclosporine (Atopica).

Cyclosporine binds to a specific cellular receptor on calcineurin and inhibits the T-cell receptor-activated signal transduction pathway. Particularly important are its effects to suppress interleukin-2 (IL-2) and other cytokines, and block proliferation of activated T-lymphocytes. The action of cyclosporine is more specific for T-cells as compared to B-cells. One important advantage in comparison to other immunosuppressive drugs – especially corticosteroids – is that it does not cause significant myelosuppression or suppress nonspecific immunity.

**Clinical Use**

Cyclosporine has been used for a number of diseases in veterinary medicine. Many of these diseases have been dermatologic, as reviewed by Robson & Burton, (2003). In dogs, when used in the treatment of perianal fistulas, (Mathews et al 1997; Griffiths et al 1999) an 85% healing rate was found in one study (Mathews, et al 1997) (2.5-6 mg/kg/day); in sebaceous
adenitis, good response was reported in one case (Carothers et al 1991); and in idiopathic sterile nodular panniculitis, excellent results were seen in 2 reported cases which were followed for 6 months following discontinuance of the cyclosporine (Guaguere 2000).

**Use for Immune-mediated diseases:**

Cyclosporine has been used for treatment of a variety of immune-mediated diseases that include immune-mediated hemolytic anemia (IMHA), inflammatory bowel disease (IBD) (Allenspach et al 2006), and immune-mediated polyarthritis, and aplastic anemia (AA). For most of these diseases there is incomplete evidence to document efficacy.

**Atopic dermatitis:**

The most common use of cyclosporine has been for treatment of atopic dermatitis, for which there is a registered formulation. The use has been reported and reviewed in other papers. In clinical trials, the efficacy of cyclosporine was not statistically different than prednisolone (Olivry et al 2000, 2002, Steffan et al, 2003). In one of the studies, in the cyclosporine-treated dogs, the dose was started at 5 mg/kg/day for four weeks, but eventually half of the dogs were adjusted to an every-other-day dose, and one-quarter of the dogs were given cyclosporine at 5 mg/kg only twice a week.

**Use in Cats:**

For organ transplantation in cats (Mathews and Gregory, 1997) a dose of 3 mg/kg q12h was used to achieve blood concentrations of 300-500 ng/ml. Cats undergoing organ transplantation usually receive 3-4 mg/kg oral, q12h (Kadar et al 2005) to achieve trough blood
concentrations of 500 ng/mL. For treatment of inflammatory disease in cats, including eosinophilia granuloma complex, lower doses are possible. A good response to a dose of 25 mg/cat was seen in 6 cases of eosinophilic plaque and 3 cases of oral eosinophilic granuloma (Guaguere & Prelaud, 2000). In the report by Vercelli et al, 2006) cats with allergic pruritus were improved with 8 mg/kg oral q24h. Cats with plasmacytic stomatitis, and feline allergic disease have also showed improvement with oral administration of cyclosporine (Vercelli, et al 2006).

One of the capsule sizes is 25 mg size and a common is 25 mg/cat, once daily. (Smaller capsules are also available for veterinary use) The most common adverse effects are anorexia, vomiting, and refusal to eat their food if cyclosporine is mixed with food. Toxoplasmosis has been reported in cats treated with cyclosporine, presumably due to the immunosuppression.

**Formulations and Pharmacokinetics**

The introduction in late 2003 of *Atopica* represents the first oral veterinary formulation of cyclosporine. The formulation is exactly the same as Neoral (microemulsion), except that there is a greater variety of capsule sizes available (10, 25, 50, and 100 mg). Absorption, kinetics, and dissolution are the same as for Neoral.

The pharmacokinetics of cyclosporine in treated animals has been examined (Steffan et al, 2004). Cyclosporine is metabolized in the intestine and liver to several metabolites. Twenty-five to 30 such metabolites have been identified. The pre-hepatic intestinal enzymes account for significant metabolism of cyclosporine (Wu et al 1995), and systemic absorption in dogs is only 20-30% (Myre et al 1991). Systemic absorption in cats is similar at 25-29% (Mehl et al, 2003). The intestinal metabolism by cytochrome P-450 enzymes (CYP) and the efflux caused by
intestinal p-glycoprotein (P-gp) account for most of the loss in systemic availability after oral administration. Drug enzyme inhibitors such as ketoconazole, diltiazem or the flavonoids in grapefruit juice can inhibit the pre-systemic metabolism and produce a profound increase in systemic availability of cyclosporine. For example, 5-10 mg/kg of ketoconazole once daily can decrease the dose of cyclosporine because clearance is reduced by 85% (Myre et al 1991).

**Adverse Effects and Precautions**

Cyclosporine can cause vomiting, diarrhea, anorexia, secondary infections, and gingival hyperplasia. Hyperplastic skin lesions have occasionally developed in dogs treated with cyclosporine (Favrot et al, 2005). Papillomavirus can be detected in some skin lesions. Tremors or shaking have been observed in dogs administered high doses.

The most common clinical problem with cyclosporine in dogs that has been cited in the clinical trials (Olivry et al, 2000, 2001, 2002; Steffan et al 2003) is gastrointestinal problems. Vomiting, anorexia, and diarrhea can be seen. When anorexia and vomiting are reported, veterinarians have tried various interventions such as lowering the dose, or administration of the dose with some food. However, whether this decreases the efficacy of the drug should be considered. Feeding will reduce the amount of cyclosporine absorbed in dogs by 15-20%, but it is unlikely that this decrease will be severe enough to affect efficacy. Nephrotoxicity, once a problem with older forms, is rare with current formulations. Secondary malignancies are a possible complication to long-term therapy but have not been reported in dogs or cats.

**Drug Interactions:**
Several drugs may interact with cyclosporine. For example, co-administration of ketoconazole to treat secondary fungal infections will decrease metabolism of cyclosporine (Myre et al 1991). Ketoconazole has been used deliberately to reduce the need for cyclosporine in some investigations (Patricelli et al, 2002) and clinically doses have been reduced by 1/3 of the original dose when administered with ketoconazole. In one study with cyclosporine in the treatment of perianal fistulae, the dose of 1 mg/kg cyclosporine combined with 10 mg/kg ketoconazole was used. The author felt that a dose of 0.5 mg/kg combined with 10 mg/kg ketoconazole also could be used (Mouatt, 2002). Erythromycin, grapefruit juice, and diltiazem also may inhibit cyclosporine metabolism and increase blood concentrations.

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COMMON MYTHS ABOUT DRUG THERAPY IN SMALL ANIMALS

Mark G. Papich, DVM, MS, Professor of Clinical Pharmacology, Diplomate ACVCP
North Carolina State University, Raleigh, North Carolina, USA

INTRODUCTION

In small animal antimicrobial therapeutics there are several unsubstantiated recommendations, misconceptions, and myths that persist. Data is now available through microbiologic and pharmacologic studies to dispel many of these old thoughts and concepts. For the instances when there is not specific data to prove or disprove the value or harm of a drug treatment, we can make some educated predictions based on our evaluation and interpretation of experimental data, even when it has been derived from human or laboratory animal studies.

This presentation will focus on antibiotic drugs. One of the major controversies is that of administration of antibiotics to food-producing animals. However, this discussion will focus on small animals, primarily dogs and cats. In addition, time will not allow an exploration of other areas for which there is controversy, and perhaps unproven treatments: alternative and complimentary medical therapies and holistic treatments.

CAN ANTIBIOTICS BE COMBINED THAT ARE BACTERICIDAL AND BACTERIOSTATIC?

Drug combinations can improve therapy by providing a synergistic effect and broadening the spectrum. Occasionally, it is necessary to administer drug combinations because the infecting pathogen is not known and the clinician desires to target several different potential
pathogens. When prescribing combinations of antibiotics, a frequent concern is that drugs administered may produce both a bactericidal and bacteriostatic effect. Will this produce an interaction that will compromise effective therapy? There are no documented situations in veterinary medicine in which these combinations produce a less effective interaction. This recommendation is primarily taken from a clinical study in children treated with penicillin and tetracycline published over 50 years ago. This study has not been repeated in other clinical situations. The line separating bacteriostatic and bactericidal antibiotics is becoming more blurred. Drugs now are usually referred to as time-dependent or concentration-dependent. Macrolides, chloramphenicol, and tetracyclines are more bacteridical than once thought, but are time-dependent in their action. There is no documented problem with combining these drugs with other drugs such as beta-lactam antibiotics or fluoroquinolones in the same patient. For example, there is no known interaction from administering doxycycline to a patient (to treat a suspected tick-borne pathogen) in combination with a fluoroquinolone, penicillin, aminoglycoside, or cephalosporin. Likewise, combining two drugs with a different spectrum (clindamycin + fluoroquinolone) broaden the spectrum of activity with no evidence of interaction.

ANTIBIOTIC SUSCEPTIBILITY INFORMATION. IS IT ALWAYS RELIABLE?

The susceptibility data derived from a bacterial isolate should help to guide therapy with the appropriate antibiotic. Unfortunately, sometimes this data is not as reliable as we would like. For companion animals, veterinary-specific MIC breakpoints have only been established for the four licensed fluoroquinolones (enrofloxacin, difloxacin, marbofloxacin, and orbifloxacin), gentamicin, cefpodoxime proxetil, ampicillin (urinary tract infections only), and clindamycin
(dogs only). Until veterinary-specific breakpoints are established for other antibiotics used in companion animals, we will continue to rely on the human breakpoints for drugs such as amikacin, amoxicillin-clavulanate, other cephalosporins, chloramphenicol, erythromycin, carbapenems (imipenem), penicillins, sulfonamides, potentiated sulfonamides, and tetracyclines. Similarities in pharmacokinetics and pathogen susceptibilities between humans and animals allow for an acceptable approximation to extrapolate human breakpoints to animal situations for many drugs until veterinary-specific standards are available. However in other situations, human-derived breakpoints are not appropriate for interpretation because the breakpoint is much higher than concentrations that can be achieved clinically. For example, there is evidence that cephalosporin breakpoints should be lower that the criteria currently used (Kahlmeter, 2008). Subsequently, an organism considered “sensitive” by a human standard breakpoint, may not be susceptible under veterinary use conditions.

**IS AN ANTIBIOTIC WITH HIGH VOLUME OF DISTRIBUTION / HIGH LIPOPHILICITY SUPERIOR?**

The pharmacokinetic term *volume of distribution* is only a measure of the proportion of drug concentration in plasma relative to the dose. A high volume of distribution implies that the drug has distributed outside of plasma, possibly intracellular. Highly lipophilic drugs have the ability to penetrate membranes and these are the antibiotics most often associated with a high volume of distribution. A high volume of distribution does not necessarily imply that the drug has high tissue penetration. Tissue concentrations are rarely measured for many antibiotics, but the plasma concentration usually reflects the drug concentration in extracellular tissue fluid.
Many effective drugs have low lipophilic characteristics and a relatively low volume of distribution, yet they are highly effective. The explanation for this observation is that most infections encountered in veterinary medicine are extracellular. It is not necessary for an antibiotic to penetrate cells or membranes to be effective (provided that if it is an oral drug it can be absorbed). Studies in our laboratory showed that volume of distribution and lipophilicity did not determine the extent of antimicrobial drug distribution to the tissue fluid (Bidgood & Papich, 2005). Lipophilicity and high volume of distribution are highly over-rated terms to measure the effectiveness of antibiotics.

**WILL HIGHLY PROTEIN BOUND ANTIBIOTICS CAUSE A DRUG INTERACTION FROM DRUG DISPLACEMENT FROM A BINDING SITE?**

Protein-binding displacement reactions are rare and undocumented in veterinary medicine. Certain drugs are known to displace drugs from protein binding sites and increase the fraction of drug unbound. But for most drugs, the amount of protein in the plasma (and subsequently the number of available drug binding sites) greatly exceeds the concentration of drug in the plasma and binding is rarely saturated. Interactions that involve displacement of protein-bound drugs are therefore rare unless there is severe hypoproteinemia or the drug is so highly protein bound that it occupies most of the binding sites.

It is listed on some highly protein bound antibiotic labels that an interaction may be possible when combining the antimicrobial with another highly protein bound drug such as ketoconazole, NSAIDs, doxycycline, or furosemide. But in vivo interactions from these drugs are not documented. The activity of a drug in plasma is dependent on the concentration of free (unbound) drug in plasma, not necessarily the free fraction. Although protein binding
displacements and interactions may affect the free fraction, they rarely affect the free concentration. Only drugs that are highly protein bound (approximately greater than 85%), exhibit high clearance, administered IV, and have a low therapeutic index are likely to be involved in protein binding interactions of clinical significance. Few drugs meet these criteria. Frequently cited reviews (Toutain & Bousquet-Melou, 2003; Benet & Hoener, 2002) have illustrated that drug protein binding interactions may not have consequences that were once thought to be important. As concluded in their paper titled Changes in plasma protein binding have little clinical relevance, the authors stated, “… although changes in plasma protein binding can have an important influence on individual pharmacokinetic parameters, we have shown that changes in plasma protein binding will usually not influence the clinical exposure of a patient to a drug.” (Hoener & Benet, 2002).

ARE COMPOUNDED ANTIBIOTICS EQUIVALENT TO BRAND NAME DRUGS?

Compounding is the practice of modifying a dose form in order to facilitate administration to a patient. Compounding can be a therapeutic necessity in some veterinary patients because there may be a lack of availability of medications to treat the variety of diseases in our patients. For example, human dose formulations must be modified to administer to a dog, cat or exotic animal. Sometimes compounding is performed to ease administration, mask a bitter taste, or accommodate an animal’s small size. Compounding is allowed by federal law, provided that it is performed on a patient by patient basis and other restrictions are met. The FDA Center for Veterinary Medicine currently restricts compounding from bulk chemicals containing the active pharmaceutical ingredient when an FDA approved drug is available, especially if it is performed on a large scale.
Compounded formulations may provide an equivalent therapeutic response to a proprietary formulation in many instances. However, there may be problems with solubility, stability, and potency for some drugs. These problems were discussed in more detail in a recent AAPS review article that may be accessed electronically and contains links to relevant FDA guidances and federal legislation (Papich, 2005).

The inactive ingredients and excipients added to drug formulations are done so to ensure the stability of the drug, provide an optimum chemical environment, pH, or increase the ease of packaging or handling. Adding other chemicals, flavorings, vehicles, or interfering with protective coatings of tablets in the course of compounding may interfere with the stability of the drug, decreasing its potency, oral absorption, and efficacy. The most common interaction is that from a change in pH. When veterinarians compound formulations in their own practices, or write an order for this to be done in a pharmacy, they should be cognizant of the potential interactions and alterations that may compromise the stability and potency of the active ingredient. Drugs known to be compromised when compounded for animals include omeprazole, pimobendan, fluoroquinolone antimicrobials, diazepam, and antifungal drugs (eg, itraconazole). Itraconazole, for example is unstable and insoluble. Compounded formulations do not produce equivalent blood concentrations as the proprietary formulation of Sporanox. Fluoroquinolone are subject to chelation with cations (eg, Fe^{3+}, Ca^{++}, Al^{3+}, Mg^{+3}) that may be added as a supplement. The chelation will inhibit oral absorption.

There may be clues that compounding has affected drug quality, purity, or potency. Oxidation is often visible through a color change (color change to pink or amber for example). Loss of solubility may be observed through precipitation. Some drugs are prone to hydrolysis from moisture. A rule-of-thumb for veterinarians is that if a drug is packaged in blister packs or
moisture proof barrier, it is probably subject to loss of stability and potency if mixed with aqueous vehicles. This applies to some β-lactam antibiotics (for example amoxicillin-clavulanate). If compounded formulations of solid dose forms show cracking or “caking”, or swelling, the formulation has probably accumulated moisture and may have lost potency. Another rule-of-thumb is that if the original packaging of a drug is in a light-protected or amber container it is probably prone to inactivation by light. Vitamins, cardiovascular drugs, and phenothiazines are labile to oxidation from light during compounding. Also, as a general rule, if an antibiotic is available in a powder that must be reconstituted in a vial or oral dispensing bottle prior to administration, it should not be mixed with other drugs.

**CAN DRUGS BE ADMINISTERED TRANSDERMALY?**

To meet the growing demands for more transdermal medications for pets, compounding pharmacies have prepared existing drugs (both human and veterinary drugs), into transdermal formulations. Most drugs cannot be absorbed across the skin without some enhancement. Their lipophilicity or solubility characteristics otherwise prevent the drug from penetrating the skin. Therefore, veterinary compounding pharmacies have mixed drugs with “penetration enhancers” (PE) to facilitate transdermal absorption. The most popular of the PE used by veterinary pharmacists is pleuronic lecithin organogel (PLO), which is lecithin (derived from eggs or soybeans) mixed with isopropyl palmitate and a poloxamer (Pluronic). The ingredients in PLO act as surfactants, emulsifiers, and solubilizing agents. There is little data available to suggest that drugs applied in a PLO vehicle are actually absorbed systemically in animals. Most published reports of transdermal application of drugs to cats showed that absorption was incomplete, nonexistent, or highly inconsistent among cats. Drugs examined so far have
included enrofloxacin, glipizide, dexamethasone, buspirone, amitriptyline, fentanyl, morphine, fluoxetine, and diltiazem (Nolan et al. 2002; Hoffman et al. 2002). Glipizide was absorbed poorly in cats, with bioavailability only 4%-30% of that observed from the oral formulation (Bennett et al. 2005). Fluoxetine transdermal bioavailability was only 10% of that compared to oral absorption of an approved human formulation. However, if a large dose was administered (10 times the oral dose), plasma concentrations equal to that achieved after oral administration were achieved (Ciribassi et al., 2002), although repeated topical application caused dermatitis.

While in a pharmacokinetic investigation, methimazole was shown to be poorly absorbed (Hoffman, et al. 2002; Trepanier 2002), clinical investigations provided evidence of efficacy with repeated transdermal applications (Sartor et al, 2004; Hoffman et al. 2001). When dexamethasone was topically administered in PLO, there was negligible absorption in cats (Willis-Goulet et al. 2003). Systemic absorption from topically applied amitriptyline or buspirone in a PLO vehicle was poor and should not be considered a reliable route for treatment (Mealey et al, 2004). Other drugs formulated in a PLO which have been poorly absorbed are morphine, fentanyl, and enrofloxacin (data presented as abstracts in previous ACVIM Forum).

Drug absorption through the skin is actually more challenging than expected. The barriers of stratum corneum, hair, and first-pass metabolism limit this route. In addition, some drugs may not be soluble or compatible in a transdermal vehicle. Many drugs are not potent enough to be delivered in the small volume (often 0.1 mL) required for practical transdermal therapy.

Despite the limitations presented by these challenges, it should not discourage further development in this area. There are some advantages and several opportunities. For some drugs, transdermal delivery bypasses the intestinal and hepatic first-pass effects (first-pass presystemic
metabolism) and produces greater systemic concentrations than oral administration.

Transdermal application of drugs also can improve pet owner compliance in a difficult-to-medicate cat or dog. Transdermal medications may eliminate the irritation that causes vomiting, as well as stomach and esophageal lesions. Esophageal lesions and strictures have been observed in cats after oral capsules or tablets have become lodged in the esophagus.

Transdermal drugs also decrease the invasiveness of injections that can cause pain, and injection-site lesions. If the transdermal formulation can slowly release the medication, such as from the reservoir of a transdermal patch system, or from a depot in the lipid layer of the skin, it offers additional advantages. Slow-release drugs would give veterinarians the ability to treat patients that cannot be handled or medicated frequently, such as fractious cats, exotic and zoo animals, or livestock. These challenges are as yet unmet, except for a few products adapted for use from human medicine (eg, fentanyl patches, nitroglycerin transdermal ointment).

ELEVATIONS IN LIVER ENZYMES INDICATE THAT THE LIVER MAY NOT METABOLIZE SOME DRUGS AND CERTAIN DRUGS SHOULD BE AVOIDED

Liver enzymes alone are not a sensitive predictor of capability to metabolize drugs. A chemistry panel is a common component of the evaluation of patients. It is part of routine senior care management, preanesthetic screening, or the minimum database for a sick patient. Increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activities are common findings. While elevated enzymes may be indicative of liver disease, they are not predictive of hepatocellular dysfunction. Increased transaminase activity indicates leakage of the hepatocellular enzymes from the hepatocytes. Increased serum activities may indicate hepatocellular membrane damage, hepatocellular necrosis, or increased hepatocellular enzyme
activity secondary to enzyme induction. Membrane damage is the most common reason for elevations in ALT and AST, but enzyme elevations alone may not indicate significant liver disease. It is common for animals with intestinal disease, such as inflammatory bowel disease, or metabolic diseases, such as hyperthyroidism or diabetes mellitus, to have increased transaminase activity. The history of treatment with such drugs as nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, anticonvulsants, anthelmintics, antibiotics, imidazole antifungals, and antithyroid drugs should be explored. Increased activity of the hepatic isoenzyme alkaline phosphatase (ALP) can be caused by drug therapy or cholestasis. The clinically significant isoenzymes of ALP are hepatic, bone-derived, and corticosteroid-induced (C-ALP). These isoenzymes have a half-life of approximately 72 hours in dogs, but half-life is significantly less than in cats. Disease affecting the liver or biliary tree may commonly increases concentrations of ALP. Disease that increases bone turnover increases osseous ALP, and the presence of exogenous or endogenous corticosteroids induces increased concentrations of C-ALP. Even short courses of glucocorticoids can produce significant increases in C-ALP activity that may remain elevated for a month or more after the medications are discontinued (Ginel et al, 2002).

Increased ALP activity is a common finding on the chemistry panel of older dogs. The hepatic isoenzyme becomes increasingly more active and elevated as dogs age (Syakalima et al 1997). When elevations are observed without proportional increases in transaminase activity, liver disease is probably less likely than corticosteroid influences, such as hyperadrenocorticism or exogenous corticosteroid administration. Other poorly understood derangements of adrenal steroid hormones are increasingly being recognized as causes of ALP activity increase in senior dogs (Frank et al, 2003; Sepesy et al, 2006).
If liver disease is present, can medications be administered? Liver disease may have a variable effect on drug clearance; thus, the change in drug disposition is difficult to predict and almost impossible to quantify. No tests of hepatic function reliably predict drug clearance. Drug clearance by the liver is determined by both hepatic blood flow and the organ's intrinsic ability to extract the drug. Although this is a useful physiologic basis for describing organ clearance, the parameters of organ blood flow and extraction ratio are not easily determined in pharmacokinetic experiments, unless special sampling methods are used. Likewise, loss of hepatic function is not easily determined clinically. A biopsy may not even predict the loss of hepatic function. As a result, it is difficult to formulate individualized drug protocols. Liver disease and loss of function cannot be as easily quantified in animals as can loss of renal function. This complicates dosing adjustments for patients with liver disease. In reality, hepatic drug clearance is remarkably preserved in animals with liver disease. Severe cirrhosis is probably the only disease in which hepatic drug clearance is consistently reduced for most drugs. In one recent report, the investigators concluded that there was wide variation in the changes in hepatic drug enzyme activity associated with liver disease (Frye et al, 2006). For some drugs, changes in drug metabolizing activity occurred early in liver disease; for other drugs the changes were not observed until late stages of liver disease. This was demonstrated in a study in which they showed that Cytochrome P450 metabolizing enzymes were differentially affected by the presence of liver disease (Frye et al, 2006). Therefore, metabolism of drugs varies with both the severity of the liver disease and the specific enzymes responsible for metabolism.

**IS TRAMADOL A NEW MIRACLE TREATMENT FOR PAIN?**
There are no efficacy studies yet available to indicate the value of tramadol for treating pain in animals. Tramadol has gained recent popularity because the generic formulations are very inexpensive, and safety problems have not apparently been an issue. Although there is encouraging anecdotal information regarding its clinical efficacy for treating some painful conditions in animals, there are – at this date – no controlled published trials of efficacy. The pharmacokinetic data available from animals and experience in people also suggest that its use may be promising. Tramadol is a unique oral analgesic drug that currently is not registered as a controlled substance. It has become available in generic form, and is inexpensive. The exact mechanism of action for tramadol is uncertain but there is probably more than one mechanism that contributes to its clinical effects. Tramadol has some mu-opioid receptor action, and it also inhibits the reuptake of norepinephrine (NE), and serotonin (5-HT). One of the isomers has greater effect on serotonin reuptake and greater affinity for mu-opiate receptors. The other isomer is more potent for norepinephrine reuptake and less active for inhibiting serotonin reuptake. Taken together, the effects of tramadol may be explained through inhibition of serotonin reuptake (similar to fluoxetine and other antidepressant drugs), action on alpha-2 receptors (similar to medetomidine and xylazine), and activity for opiate mu-receptors (similar to morphine). Although tramadol is a weak opioid compared to morphine, the metabolite (desmethyltramadol, also called M1) may have greater opiate effects than the parent drug (for example, 200x in opiate receptor binding).

Studies completed at NCSU (Kukanich & Papich, 2004) have shown that tramadol is absorbed orally in dogs and was well-tolerated. Dogs produce sufficient metabolite (M1) that may contribute to the analgesic effects. Clearance is higher than in people, which will necessitate a higher dose for dogs. Although safety and efficacy studies are not available, based
on pharmacokinetic studies we have recommended doses of 5 mg/kg every 6 to 8 hours orally in dogs.

In cats, safe and effective doses still need to be defined. In one study in cats (Papich et al 2007) a dose of 4 mg/kg (oral tablet) produced adequate concentrations of the parent drug and metabolite (M1) but there was high variation among cats. It was also observed to be unpalatable and some cats developed dysphoric reactions. Compared to dogs, cats have a longer half-life for both the parent drug and metabolite. Cats also produce a higher proportion of the M1 metabolite compared to dogs. Because the M1 metabolite has been associated with opiate-mediated effects, this may potentially be a cause for observed dysphoric effects in cats.

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