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NEW DRUGS, NEW APPROACHES FOR ANTIMICROBIAL THERAPY

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INTRODUCTION

Treatment of common infections in small animals have been investigated to provide us with established regimens and approved drugs. 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.

NEW DRUGS

Cephalosporins

We are familiar with the cephalosporins commonly referred to as the 1st- generation cephalosporins represented by the oral drugs cephalexin (Keflex) and cefadroxil (Cefa-Tabs, Cefa-Drops), and the injectable drug cefazolin. These drugs have a spectrum of activity that includes staphylococci, streptococci, and many of the enteric gram-negative bacilli. However, resistance among gram-negative bacteria develops easily, primarily from synthesis of β-lactamase enzymes that can hydrolyze these drugs. Extended-spectrum cephalosporins include cephalosporins from the 2nd, 3rd, and 4th generation. The situations in veterinary medicine in which extended-spectrum cephalosporins are most often used are for treatment of bacterial infections that are resistant to other drugs. The bacteria often identified in these resistance problems have been *Escherichia coli, Klebsiella pneumoniae, Enterobacter* species, *Proteus* species (especially indole-positive), and *Pseudomonas aeruginosa*.

Of the 2nd -generation cephalosporins, the ones used most often in veterinary medicine are cefoxitin and cefotetan. Their use has been valuable for treating organisms resistant to the 1st-generation cephalosporins or in cases in which there are anaerobic bacteria present. Anaerobic bacteria such as those of the *Bacteroides fragilis* group can become resistant by synthesizing a cephalosporinase enzyme. Cefoxitin and cefotetan, which are in the cephamycin group, are resistant to this enzyme and may be active against these bacteria. Therefore, these drugs may be valuable for some cases such as septic peritonitis that may have a mixed population of anaerobic bacteria and gram-negative bacilli.

The 3rd-generation cephalosporins are the most active of the cephalosporins against gram negative bacteria, especially enteric bacteria that are resistant to other cephalosporins. Almost all drugs in this group (exceptions discussed below) should be administered IV or IM. For convenience, some have been administered to animals SC. But one should be warned that the IM or SC administration of these drugs could be irritating and painful. One of the most frequently administered drugs in this group is cefotaxime (Claforan) because of its potency and activity against most enteric gram-negative bacteria and some streptococci. Compared to other cephalosporins, ceftazidime is the most active against *Pseudomonas*, against which all of the other cephalosporins, except cefoperazone, have little or no activity. Since the drugs mentioned are all injectable, there has been a need for an oral extended-spectrum cephalosporin. Of the ones available, cefixime (Suprax) has been used in dogs because it is one of the few 3rd-generation cephalosporins that can be administered orally. The doses have ranged from 5 to 10 mg/kg twice daily orally. Another oral 3rd-generation cephalosporin that has become recently popular is cefpodoxime proxetil (human brand name, Vantin). This drug has a longer half-life than other cephalosporins and can be administered once-daily for some infections, and twice daily for infections that are more serious. A dose used in dogs and cats, (extrapolated from the human dose) is 5-10 mg/kg orally every 12 hours, but 5 mg/kg orally once a day also has been used for highly susceptible bacteria.

The most recent development in this class is the 4th-generation cephalosporins. 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 has the advantage of 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).

Carbapenems

The carbapenems are beta-lactam antibiotics that include imipenem-cilastatin sodium (Primaxin), meropenem (Merrem), and most recently, ertapenem (Invanz). Imipenem is administered with cilastatin to decrease renal tubular metabolism. Cilastatin does not affect the antibacterial activity. Imipenem has become a valuable antibiotic because it has a broad spectrum that includes almost all bacteria that may be 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 it's 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. Resistance to carbapenems has been extremely rare in veterinary medicine.

The disadvantages of carbapenems include induction of resistance, inconvenient administration, and high cost. For imipenem, a common dose for small animals is 10 mg/kg q8h. One of the adverse effects caused from imipenem therapy is seizures. Meropenem, one of the newest of the carbapenem class of drugs has antibacterial activity approximately equal to, or greater than imipenem. Other characteristics are similar to imipenem. Its 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 (Bidgood & Papich, 2002), the recommended dose is 12 mg/kg every 8 hours SC, or 24 mg/kg IV, every 8 hours. 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.

Ertapenem is the newest drug in this class. It has a longer half-life in people and can be administered once a day. Experiments are underway in animals to determine the optimum dosing. Ertapenem has good activity against most gram-negative organisms, except *Pseudomonas aeruginosa.*

Fluoroquinolones

The fluoroquinolones include enrofloxacin, marbofloxacin, difloxacin, and orbifloxacin, which are currently approved for small animals. In the U.S., all of these drugs are approved for dogs; orbifloxacin, marbofloxacin, and enrofloxacin are approved for cats. Enrofloxacin 100 mg/mL injection is approved for cattle. A topical formulation of enrofloxacin and silver sulfadiazine (Baytril Otic) is registered for treating otitis in dogs. (A topical form of marbofloxacin is registered for treating otitis in Europe.) The mechanism of action and important pharmacological properties have been reviewed elsewhere (Papich & Riviere, 2001). There are several other fluoroquinolones approved for use in human medicine (ciprofloxacin, lomefloxacin, enoxacin, ofloxacin), and until now their use has been limited in veterinary medicine. However, a generic formulation of ciprofloxacin has become available that is less expensive than the brand name version. This has increased veterinary interest in its use. Ciprofloxacin is as active as the veterinary fluoroquinolones against most organisms, and more active against some gram-negative bacteria, especially *Pseudomonas aeruginosa*. Dosing regimens have not been established through clinical trials for ciprofloxacin. In cats and dogs the oral absorption is much less than the available veterinary fluoroquinolones. Oral absorption of ciprofloxacin in dogs and cats is approximately 50%, compared to near complete absorption of the veterinary drugs. This difference should be accounted for in dosing regimens in order to achieve comparable plasma concentrations as other drugs.

Other fluoroquinolones available for use in human medicine have addressed the deficiencies in the spectrum of activity for older fluoroquinolones. The deficiencies include gram-positive cocci, and anaerobic bacteria. The newest generations of fluoroquinolones (referred to by some authors as the 3rd-generation fluoroquinolones) include trovafloxacin, grepafloxacin, gatifloxacin, sparfloxacin, and moxifloxacin. Two of these, trovafloxacin and grepafloxacin, have already been discontinued for use in people because of adverse effects (abnormal cardiac rhythms and hepatic injury). The new generation of fluoroquinolones, with substitutions at the C-8 position, (C-8 methoxy for example) have as their advantage a broader spectrum that includes anaerobic bacteria and gram-positive cocci. They are less active against enterococci (*Enterococcus faecalis* and *Enterococcus faecium*), however. The difference in spectrum of activity is largely caused by increased activity against the DNA-gyrase of gram-positive bacteria, rather than activity against Topoisomerase IV, which is the target in gram-positive bacteria for the older quinolones (Pestova et al, 2000), but other factors also may play a role. There are no drugs of this group registered for veterinary use. Premafloxacin was examined for its potential in veterinary medicine, but not available. Moxifloxacin has been used on a limited basis for treatment of infections in dogs and cats caused by bacteria that have been refractory to other drugs. Anecdotally, it has been used with some success and has been well-tolerated.

New Macrolides and Derivatives

Erythromycin is an effective drug that has been available for many years. However, it has disadvantages, which include a narrow antibacterial spectrum, adverse gastrointestinal effects (nausea and vomiting), poor oral absorption, short half-life, and need for frequent dosing intervals. There are now new derivatives of this macrolide drug that are designed to improve therapy and produce fewer adverse reactions. Azithromycin (Zithromax) is the first drug in the class of azalides. (Lode et al, 1996) Azalides are derived from erythromycin and these drugs share a similar mechanism of action. (Erythromycin is a 14 member ring, and azithromycin has a 15 member ring structure.) The important difference between azithromycin and erythromycin is better oral absorption, it is better tolerated, has a much longer half-life (especially in tissues), and has a slightly broader spectrum of activity. The primary pharmacokinetic difference between azithromycin and erythromycin is the long half-life and high concentration in tissues. The tissue concentrations of azithromycin can be as much as 100 x serum concentrations and the concentrations in leukocytes may be 200x the concentrations in serum.

Azithromycn is active against gram-positive aerobic bacteria (staphylococci and streptococci) and anaerobes. The activity of azithromycin against staphylococci is not superior to erythromycin, but it has activity against intracellular organisms such as *Chlamydia*, and *Toxoplasma*. (Clinical efficacy against these pathogens has not been confirmed, however.) It is also active against mycobacteria and *Mycoplasma*. There are no published clinical reports that have demonstrated the effective use of azithromycin in dogs, cats, horses, and birds but the use is increasing.

In dogs and cats it has been used to treat animals with *Bartonella* infections, even though effectiveness is difficult to assess. It has also been used to treat respiratory infections in cats, but there have been no trials showing superiority over older drugs.

Because of the long half-life and persistence of drug in tissues, the regimen employed in people is to administer a dose once daily for 3 to 5 days, at which time effective drug concentrations are expected in tissues for up to 10 days.

In dogs, doses of 5-10 mg/kg once daily, orally for 1 to 5 days has been suggested. In cats, doses of 5 mg/kg once daily, or every other day, orally for 1 to 5 days have been used.

In some dogs and cats, doses as high as 15 mg/kg per day have been administered. It is available in a 250 mg capsule, tablets, and an oral suspension.

OTHER NEW DRUGS

Oxazolidinones

Linezolid (Zyvox): Linezolid is the first in the class of oxazolidinones to be used in medicine. It is currently being used in people to treat vancomycin resistant gram-positive infections caused by enterococci and streptococci. Linezolid inhibits protein synthesis by binding to the bacterial ribosome. It has activity against staphylocci and enterococci. Linezolid is absorbed orally and also is administered IV. Linezolid is available in 600 mg tablets ($53 per tablet!), oral suspension, and injection.

Streptogramins

Two streptogramin compounds are currently marketed in a combination of 30:70 quinupristin:dalfopristin called Synercid. These compounds were approved specifically for treating infections caused by *Enterococcus faecium,* and *Staphylococcus aureus* that are resistant to penicillins and vancomycin. Quinupristin and dalfopristin act in a synergistic manner to inhibit protein synthesis. In addition to *Enterococcus faecium*, and *Staphylococcus*, streptogramins also have activity against *Mycoplasma* and *Clostridium*.

The clinical use of Synercid has not been reported in veterinary medicine. The use of this combination has been limited to human hospitals in which nosocomial organisms can cause serious resistance problems. It must be administered IV through a large central vein. Adverse effects have been common. Current cost of treatment is very expensive, for example, $3,000 per treatment.

Daptomycin

Daptomycin (Cubicin) is a new cyclic lipopeptide antibiotic. It is only used for staphylococcal, streptococcal, and enterococcal infections that are resistant to other drugs. It can only be given IV (dose in humans is 4 mg/kg IV once daily). The spectrum includes methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S. aureus*, vancomycin-resistant *S. aureus*, penicillin-resistant *Streptococcus pneumoniae*, and ampicillin- and vancomycin-resistant enterococci. There are no reports of its use in veterinary medicine. Cost for four day treatment in people is $480.00.

Ketolides

Telithromycin (Ketek) is the first of a new class of drugs called ketolides. They have some similarities to the older macrolide compounds (eg. erythromycin), with slightly improved spectrum and tolerability. Ketolides are semisynthetic derivatives of macrolides and block protein synthesis at a similar target as for macrolides.

Telithromycin is available as an oral tablets that is used in people primarily for respiratory tract infections and sinus infections, for example those caused by *Streptococcus pneumoniae* or *Haemophilus influenzae*. It is also active against *Staphylococcus aureus* and intracellular pathogens such as *Chlamydia*. It has a long half-life of 10-13 hours in people with high tissue and leukocyte concentrations. It is given at a dose of 10 mg/kg once daily orally. There are no reported veterinary uses.

NEW APPROACHES

In addition to new drugs used in veterinary medicine, new approaches have been used as well. These have not been rigorously evaluated for efficacy, long term safety, or effect on emergence of resistance. Some of the approaches to recurrent infections have been to either administer long-term, low dose antibiotics on a chronic regimen, or, to administer regular therapeutic doses intermittently (eg, once per week) on a long-term basis. This approach has been used to treat recurrent urinary tract and skin infections, especially in immunosuppressed patients.

An additional approach used for recurrent urinary tract infections has been to administer urinary antiseptics such as methenamine (methenamine hippurate, or methenamine mandelate) on a long-term basis. This drug is metabolized to formaldehyde in acidic urine and may inhibit growth of organisms in the urine. Another human drug used in women, fosfomycin, also has been used intermittently to decrease recurrent infections caused by *E. coli*.

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