CHAPTER

17

ANTIMICROBIAL THERAPY

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Microbial diseases are common in companion and aviary birds, and careful drug selection and delivery can greatly influence the outcome of many clinical cases. In contrast to mammals in which it may be possible to try an empirical treatment regimen, birds are often presented in an advanced state of illness, necessitating immediate and correct diagnosis and treatment. For best results, antimicrobial therapy should be maximized early in the disease process.

Published avian drug doses are often based on clinical experience or data extrapolated from other species. Suggested doses may or may not be optimal, and avian veterinarians should be attentive to the possible toxic effects or lack of efficacy when treating birds with empirically derived doses. Sub-therapeutic dosing can result in treatment failure and encourage the development of microbial resistance. Excessive drug treatment may be toxic and damage the kidneys or liver. In particular, care should be extended when treating rare birds in which the effects of a specific drug have not been investigated.

The goal of antimicrobial therapy is to aid elimination of the infecting organism from the host. Antibiotics play only a partial role in this process, and the host immune system is usually required to resolve an infection. Supportive care is therefore an important component of the overall therapeutic plan. The clinical outcome of using an antimicrobial agent depends upon the intrinsic susceptibility of the agent and microbiological activity of the drug (efficacy), the ability of the drug to reach the site of infection at adequate concentrations (pharmacodynamics), and the ability of the drug to kill the pathogen without harming the host (selective toxicity). Other considerations include the route and frequency of administration, cost and ability of the bird owner to accomplish the treatment regimen. Because birds are often presented in a state of advanced illness and immunosuppression, the best drug should be given via the best route to maximize the chances for treatment success. A general approach to the treatment of microbial diseases is provided in Table 17.1.

Factors Influencing Selection of an Antibiotic

There are no exact criteria to determine which antibiotic is best for each situation. Some of the important factors influencing the rational selection of an antibiotic are discussed below.

TABLE 17.1 General Approach to Treatment of Bacterial Diseases

1. **Identify** the pathogen and location of infection.
2. **Determine** the antimicrobial susceptibility of the isolate if the susceptibility cannot be predicted.
3. **Select** an antimicrobial drug based on susceptibility, ability to reach the site of infection, available routes of administration, required frequency of administration and minimal toxicity to the host.
4. **Determine** if it is feasible for the bird owner to complete the treatment regimen.
5. **Treat** with appropriate antibiotics.
6. **Maintain** host defenses by reducing stress and maximizing supportive care.
7. **Find** and **eliminate** the source of bacteria.
8. **Decontaminate** the bird's environment.

Antimicrobial Spectrum

The target organism must be susceptible to the antibiotic at concentrations achievable at the site of infection if treatment is to be effective. Some microbial organisms have predictable susceptibility. For example, all strains of chlamydia are presumed to be susceptible to tetracyclines. If chlamydiosis is diagnosed, it is rational to begin therapy without a susceptibility test. Unfortunately, the most common infectious agents in psittacine birds (gram-negative bacteria, streptococcus and staphylococcus) have unpredictable antimicrobial susceptibilities, and an in vitro susceptibility test is required to aid drug selection.

Laboratories can determine the antimicrobial susceptibility of a bacterial isolate by two primary methods: disk diffusion and dilution tests. The Kirby-Bauer disk diffusion susceptibility test is a semiquantitative method, and the test organism is classified as susceptible, of intermediate susceptibility, or resistant to the drug. It is important to understand that the classification "susceptible" is based on the

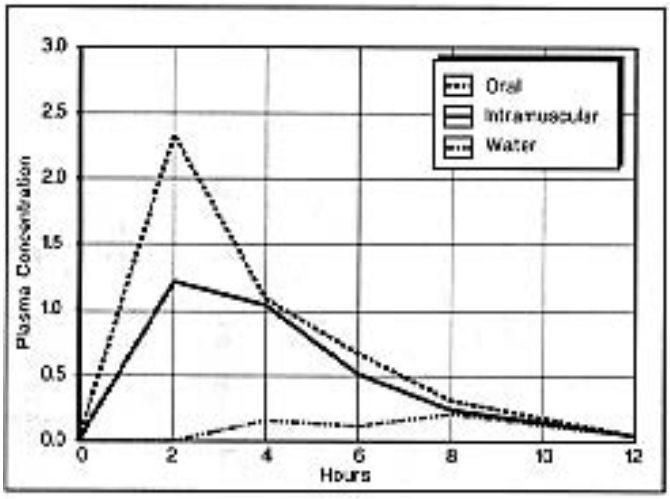

FIG 17.1 Plasma concentrations of enrofloxacin in African Grey Parrots vary with the route of administration. Bacteria must be highly susceptible (MIC <0.05 μg/ml) to be effectively treated with water-based administration.

antibiotic serum concentrations that are achieved by a *standard treatment regimen in humans* (or a test animal if the drug is veterinary-labeled). A pathogen that is classified as susceptible by an *in vitro* test will be susceptible in the bird only if similar concentrations are maintained at the site of infection. As explained below, the achievable drug concentrations are influenced by many factors including dose, frequency and route of administration. Therefore, if a disk diffusion susceptibility test indicates that an organism is resistant, treatment with that drug will not be successful. If the test indicates the organism is susceptible, then treatment *may* be successful if drug concentrations similar to those in humans are achieved in the bird.

Antimicrobial susceptibility tests using dilution methods determine the minimal inhibitory concentration (MIC) of the antibiotic. Since the MIC is quantitative, it allows the clinician to select the drug to which the organism is *most* susceptible and provides a better prediction of treatment success. An example illustrates how disk diffusion and dilution tests differ. When using a disk diffusion test to determine microbial susceptibility to enrofloxacin, all isolates with a zone of inhibition corresponding to an MIC of 2 μg/ml (based on achievable concentrations in dogs) would be reported as susceptible. It would not indicate if the organism was at the low end of susceptibility (0.03 μg/ml) or the high end (2.0 μg/ml). If a dilution susceptibility test were performed, the precise MIC for that organism would be determined. Figure 17.1 illustrates the plasma concentrations

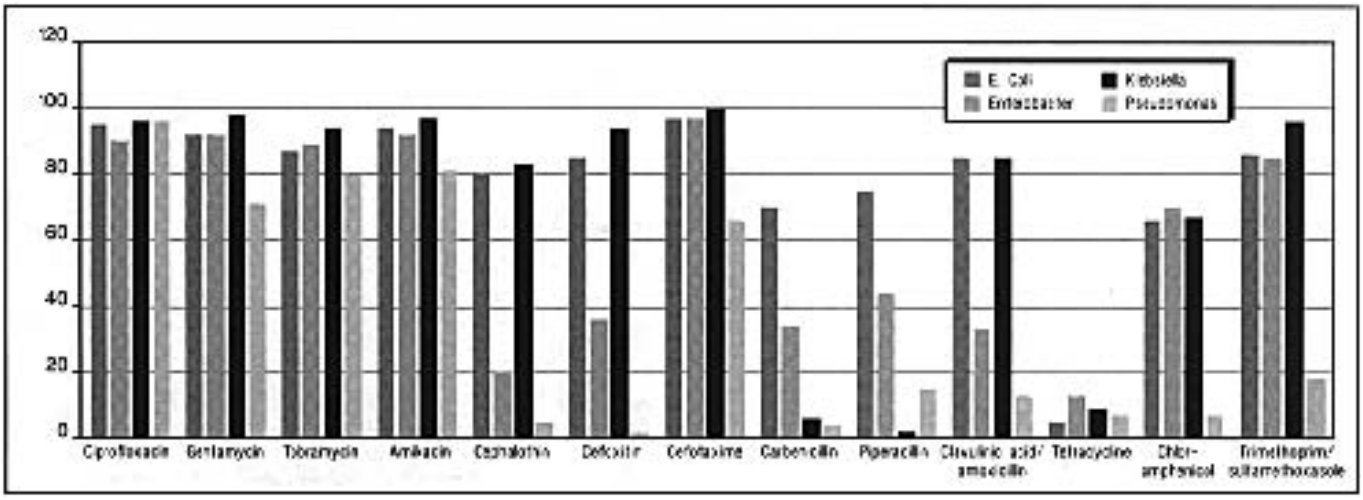

FIG 17.2 Susceptibility of gram-negative bacteria to commonly used antibiotics in one study of psittacine birds.

achieved when enrofloxacin is administered to African Grey Parrots by intramuscular, oral (gavage) or water route. This data shows that isolates with an MIC of 1-2 μg/ml would not be successfully treated by enrofloxacin in African Grey Parrots under any circumstances; oral and IM administration would be effective against isolates with an MIC < 1.0 μg/ml; and water administration would be effective only against isolates with an MIC < 0.05 μg/ml. The dilution test enables selection of a drug and route of administration that will have a high likelihood of success. Information on the pharmacokinetics of antibiotics in avian species is expanding, making decisions based on MIC data increasingly possible and effective.

In a severely ill patient, or in one that has an infection in an area that is difficult to culture, it may be necessary to start treatment without the benefit of a culture and susceptibility test. In these cases it is helpful to know the common causes of infection and the antimicrobial drugs most likely to be effective. There are many exceptions to the comments made below; however, following these suggestions can result in successful therapy. Figure 17.2 displays the predictive efficacy for using various antimicrobial drugs to treat gram-negative bacteria isolated from psittacine patients at the Veterinary Teaching Hospital, College of Veterinary Medicine, North Carolina State University. Antimicrobial susceptibility patterns vary geographically, so this data may not be applicable to all areas.

The most common causes of primary and secondary microbial infections in psittacine birds are gram-negative bacteria, chlamydia and yeast. Gram-negative bacteria are frequently resistant to routine antibiotics (eg, ampicillin, tetracycline, chloramphenicol and erythromycin); however, most isolates are susceptible to trimethoprim/sulfa combinations, enrofloxacin, amikacin, and the advanced generation cephalosporins (eg, cefotaxime) and penicillins (eg, piperacillin). Yeast are usually confined to the alimentary tract and can be readily identified by performing a Gram's stain of a fecal smear. Most yeast are susceptible to treatment with nystatin, ketoconazole or fluconazole. Chlamydia are susceptible to treatment with tetracyclines.

CLINICAL APPLICATIONS

- Prolonged tetracycline therapy may be catabolic, cause immunosuppression, reduce normal gut flora or render a bird more susceptible to secondary pathogens.
- Nystatin must come in direct contact with yeast to be effective. If nystatin is delivered by gavage tube, infections in the mouth will not be treated.
- Medicated food and water are traditionally favored routes for poultry but seldom achieve therapeutic drug concentrations in companion and aviary birds.
- Birds receiving antibiotics should be monitored for secondary infections with cloacal cultures and fecal Gram's stains.
- Trimethoprim/sulfadiazine is often effective for treating gram-negative infections in nestling birds.
- Critically ill birds should be treated via parenteral routes to establish effective drug concentration quickly.
- On a body weight basis, a 0.05 ml injection in a canary is equivalent to a 40 ml injection in a 25 kg dog.
- Given orally, the IM formulation of enrofloxacin produces therapeutic plasma concentrations.

Less common infectious agents of psittacine birds are gram-positive bacteria (*Staphylococcus aureus* and some *Streptococcus* spp.), mycoplasma, systemic fungi and mycobacteria. Many of the *S. aureus* and streptococcus isolates tested by the author are susceptible to cephalexin or cephalothin. Mycoplasma are presumed to be susceptible to enrofloxacin, tetracyclines and tylosin. Systemic fungal infections are difficult to treat under any circumstances and require multiple drug therapy with amphotericin B and itraconazole, fluconazole or flucytosine. Mycobacteria are extremely difficult to eliminate. *Mycobacterium avium* can cause fatal infections in immunosuppressed humans, and therapeutic management must be considered with caution (see Chapter 33). A summary of the susceptibilities of common avian infectious agents to antimicrobial therapy is given in Table 17.2.

Pharmacodynamics of the Drug

Antibiotics penetrate tissues differently, so the site of infection will also influence drug selection. Most bacteria remain extracellular while causing infection; however, there are a few notable exceptions (eg, salmonella, mycobacteria and some staphylococci). Treatment of intracellular infections may require drugs that are highly lipophilic and can penetrate cells (eg, chloramphenicol). Polar drugs (eg, the beta lactams and aminoglycosides) are frequently excluded from pharmacologically privileged spaces such as the cerebrospinal fluid (CSF) and ocular fluids.

Conditions at the site of infection are also important. Exudates, abscesses and granulomas create a hostile environment for the action of antibiotics. Perfusion of fibrous tissue is limited, and this may prevent the drug from reaching the site of infection. Changes in pH, oxygen tension, binding by intracellular proteins and slow microbial division may reduce antimicrobial activity. Surgical drainage or removal of an infected mass may be required before antibiotics can be effective.

The pharmacokinetics of the drug are also important. With bacteriostatic drugs, it is desirable to maintain the concentration of drug above the bacterial MIC for at least half of the dosage interval, and preferably throughout the interval, if this is attainable and not toxic. With most bacteriocidal drugs, it is not necessary to maintain the drug above the MIC for the entire dosage interval; however, if concentrations drop below the MIC for too long, the bacteria will multiply, and a "break-through bacteremia" may occur. Drugs with a short half-life, like the beta lactams, must be given frequently to maintain effective concentrations.

Pharmacokinetic information is invaluable and has become available for specific drugs in some avian species, but it is likely that the use of extrapolated drug treatment regimens to untested species will continue to be a common practice in avian medicine. The extrapolation of pharmacokinetic data to untested species is complicated by the fact that there may be differences in the way that even individuals and closely related species absorb and excrete antimicrobial drugs.[15] For example, the aminoglycosides are excreted unchanged by the kidney, and the pharmacokinetics are similar across species lines. The recommended dose and elimination half-life are similar in cockatiels and macaws despite a 10-fold difference in body weight. The pharmacokinetics of drugs that are metabolized show greater variability.

For some drugs there is good correlation between dose and metabolic rate calculations based on body size. It has been suggested that the techniques of "allometric scaling" be used to extrapolate the doses of these drugs from human and mammalian medicine to birds.[15,55] Although allometric scaling has validity for some compounds, veterinarians should be aware of its limitations. Evaluation of drug excretion and potential metabolic pathways are important, as numerous exceptions to scaling exist — some with potentially toxic results. For example, the elimination half-life of chloramphenicol in budgerigars is twice as long as in macaws, despite a 30-fold difference in body weight. In this instance, scaling a dose from a macaw to a budgerigar would result in toxic doses, while scaling from a budgerigar to a macaw would result in completely ineffective doses. Unexpected differences are also seen with doxycycline. The elimination half-life of orally administered doxycycline in Goffin's Cockatoos is approximately 20 hours, but in similarly sized Orange-winged Amazon Parrots it is approximately 10 hours.[19] Finally, scaling of a compound with a narrow therapeutic range such as gentamicin could result in potentially lethal dosage recommendations if the drug is scaled from doses from small to large species. Allometric scaling is a useful tool when pharmacokinetic data is not available, but it should be used with caution and the effects of dosing closely monitored. The adverse effects of improper antimicrobial therapy are discussed below in the section on toxicity and side effects.

Route of Administration

Selecting the route of drug administration in birds requires careful consideration. Available routes include medicated water, medicated food, oral, intramuscular, intravenous, subcutaneous, intraosseous, intratracheal, inhalation and topical. Factors to consider when selecting a route include: 1) The severity of the infection. Critically ill birds should be treated with parenteral medications to establish effective drug concentrations quickly. 2) The number of birds to be treated. Medicated food or water may be the only practical way to treat multiple-bird flocks (Figure 17.3). 3) The availability of appropriate drug formulations. 4) The frequency of administration, resultant stress to the bird and the labor involved in completing the treatment regimen. 5) The ability of the owner to complete the treatment regimen.

As noted previously, the route of delivery greatly influences the drug concentration achieved in the host. For example, Figure 17.1 shows that the concentration of enrofloxacin achieved in African Grey Parrots by offering medicated water is one-tenth of that achieved by oral or parenteral administration. This data must be considered when interpreting antimicrobial susceptibility tests, as the achievable drug concentrations will depend on the route of administration.

The advantages and disadvantages of various routes are discussed below. In general, medicated food and water are traditionally favored routes for poultry but seldom achieve therapeutic drug concentrations in companion and aviary birds. Most serious microbial infections must be treated by the oral or a parenteral route.

Water-based Drug Administration

- ***Advantages:*** It is easy, handling of the birds is not required and the birds will self-medicate several times daily. The presence of medication may decrease disease transmission via contaminated drinking water.

- ***Disadvantages:*** Consumption is erratic and therapeutic serum concentrations are rarely achieved, especially during the night when less water is consumed. Medicated water is often unpalatable, and reduced water consumption not only decreases therapeutic drug concentrations but may also result in decreased water consumption and dehydration. Many antibiotics are not stable or soluble in water.

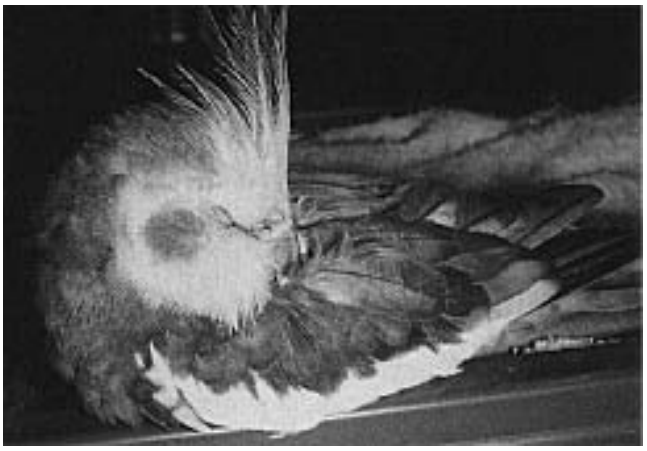

FIG 17.3 An adult cockatiel with a three-day history of anorexia was found on the bottom of the enclosure. Depression is a hallmark clinical sign of septicemia. These emergency cases usually require parenteral administration of broad-spectrum antibiotics, parenteral fluid therapy and corticosteroid administration to prevent endotoxic shock due to degenerating gram-negative bacteria.

- ***Comments:*** At first glance, medicated water would appear to be the ideal way to medicate many avian species. Unfortunately, with a few exceptions, medicated water will not adequately treat most companion and aviary bird diseases. Psittacine birds simply fail to drink enough water to consume adequate doses of most antimicrobial drugs, especially if they are ill. If water is consumed, low drug concentrations are usually sustained in the bird because small amounts of drug are consumed often. Only highly susceptible bacterial infections in a stable patient should be treated in this manner. Water-based drugs should not be used in sick birds where the rapid establishment of therapeutic drug concentrations is required. Water-based medications can be used as an adjunct to direct drug administration or in situations where direct medication is impossible. Water-based drugs are most successful against mild infections of the alimentary tract where the drug may have a local effect in the gut.

There are some specific drugs and therapeutic situations where water-based administration may be successful. Enrofloxacin may successfully treat highly susceptible gram-negative bacteria (MIC <0.05 μg/ml). Sulfachlorpyridizine may be effective against alimentary tract infections caused by highly susceptible strains of *Escherichia coli*. Spectinomycin may be effective against alimentary tract infections caused by highly susceptible strains of *E. coli*. Nitrofurazone may slow the spread of salmonella within a flock. Aminoglycosides (eg, gentamicin, neomycin and amikacin) are not absorbed but may have

a local effect against pathogens in the gut. Tetracyclines may slow the spread and alleviate clinical signs in birds with chlamydiosis but will not consistently clear birds of infection. Tetracyclines degrade rapidly in water. Chlorhexidine may inhibit the spread and severity of candida infections of the alimentary tract.

Food-based Drug Administration

- ***Advantages:*** It is easy, the birds will self-medicate several times daily, capture and handling are not required and food consumption is often more consistent than water consumption. It may be possible to medicate nestling birds by adding medication to the food of their parents.

- ***Disadvantages:*** Food often reduces drug absorption and sick birds consume less food, especially if the medicated ration is unpalatable. As with medicated water, it is difficult to achieve therapeutic concentrations with food-based administration. Psittacine birds are notorious for refusing new foods and may reject even palatable medicated rations if the diet must be changed to provide a food that will carry the drug.

- ***Comments:*** Powders, ground tablets and oral suspensions can be added to a palatable food vehicle such as cooked mashes, rolled corn, canned and frozen vegetables or fruit mixtures. A cooked mash containing 13% dry oatmeal and 29% each cooked kidney beans, rice, and corn is nutritious and well accepted by many psittacine birds. If a favorite treat food is well accepted and quickly consumed, it may be possible to lace it with the divided daily drug dose and offer it several times daily. If the drug must be added to food consumed on an intermittent basis throughout the day, the total daily dose plus extra (based on wastage and estimated reduced drug availability) should be placed in the amount of food the bird will consume in one day. As with medicated water, the achievable serum drug concentrations are usually much lower than those reached with oral or parenteral administration, so only highly susceptible bacteria should be treated with food-based medications.

  Formulated diets containing chlortetracycline are commercially available and can be used to treat chlamydiosis. Chlortetracycline-impregnated millet seed[a] is also available and is readily accepted by budgerigars and finches. These products sustain chlortetracycline blood concentrations of 0.5-1.5 μg/ml when fed with diets containing < 0.7% calcium. It is also possible to prepare a medicated mash using powdered chlortetracycline.

  Research on developing doxycycline-medicated diets illustrates the importance of standardizing the components of a medicated ration. Consumption of the diet determines the amount of drug ingested and is dependent on energy content, palatability and familiarity of the diet. For example, cockatoos receiving ad libitum diets medicated with identical concentrations of doxycycline (0.1%) achieved toxic plasma concentrations (8-10 μg/ml) when fed a medicated corn and soybean mash, adequate concentrations (1-2 μg/ml) when fed a medicated rice, corn, bean, and oatmeal mash, and low concentrations (< 0.5 μg/ml) when fed medicated pellets. The primary difference among these diets is the energy content. Drug concentrations for medicated feed cannot be extrapolated from one diet to another without knowing the energy content and palatability of the diets.

Oral Medication

- ***Advantages:*** A precise dose can be administered and, because many drugs are available as oral suspensions in flavored pediatric strengths, dosing is easy. Sick birds frequently require assisted feedings, and these drugs can easily be added to the feeding formula.

- ***Disadvantages:*** Unless the bird is tame and finds the medication palatable, the bird must be captured and fully restrained to deliver the medication. This is stressful, and some birds will refuse to swallow medications or may aspirate them into the nasal passages. It is often necessary to pass a tube and deliver oral drugs into the crop of recalcitrant birds. Drug selection is restricted since not all drugs are absorbed orally (eg, aminoglycosides, advanced generation penicillins and cephalosporins). Some birds, (eg, macaws) may regurgitate medications delivered per os.

- ***Comments:*** It is surprisingly difficult to force psittacine birds to accept oral medications. Bird owners may initially be able to administer the drug, but as treatment progresses the bird may become more difficult to medicate. Sometimes the stress of handling exceeds the benefits of the drug itself. Acceptance can be improved if the drug is mixed with a palatable vehicle such as lactulose syrup or fruit juice. Oral suspensions and solutions are appropriate for use in all birds; tablets and pills are probably not appropriate for use in birds with a crop. Capsules that rapidly dissolve can be used in those birds that are "pillable" (eg, pigeons, waterfowl and gallinaceous birds).

Intramuscular Injection

- ***Advantages:*** An exact dose can be administered, and absorption is usually rapid. The bird must be captured, but restraint time is minimal.

- ***Disadvantages:*** Not all antibiotics can be given IM, and injections may be painful and cause muscle necrosis (Figure 17.4). The volume of injected fluid must be carefully monitored in small patients.

- ***Comments:*** Intramuscular injection is often the quickest and least stressful method of directly administering drugs to companion birds. It is often easier to administer drugs IM than orally, and most bird owners can be taught to perform this procedure. The proximal two-thirds of the pectoral muscles provide the optimal injection site. Drugs injected into the muscles of the legs may pass through the renal portal system first, clearing the drug before it can reach the systemic circulation. Injection sites can be rotated to avoid excess trauma in one area. Short, 26 ga x ⅜" intradermal needles or insulin syringes work well.

  Intramuscular injection may not be feasible in all birds. Nestling birds of all species have relatively little pectoral muscle mass, and it is easy to pierce the sternum, which is non-ossified at this age. Ratites, even as adults, lack large pectoral muscles. Owners of racing pigeons, raptors and some game birds may refuse to give medications IM in the breast because they fear muscle damage will interfere with flight or normal activity.

  The injection volume in relation to body size must also be considered. For example, on a body weight basis, a 0.05 ml injection in a canary is equivalent to a 40 ml injection in a 25 kg dog. Injection volumes in psittacine birds should be small but permit accurate measurement of the medication.

Subcutaneous Injection

- ***Advantages:*** An accurate dose and large volumes can be administered. This is a good site for fluid administration if the bird is not volume depleted or severely dehydrated. The best sites are the groin and dorsal cervico-thoracic area.

- ***Disadvantages:*** Full restraint is required. Birds have very thin skin and fluid will often leak out of the injection site. Irritating drugs may cause skin necrosis and ulceration.

- ***Comments:*** The subcutaneous route is not ideal but can be used for irritating drugs when muscle necrosis or injection trauma is to be avoided. This site is often used by pigeon and game bird breeders.

FIG 17.4 Muscle necrosis secondary to a single IM injection of ticarcillin. Many of the drugs available for parenteral administration in birds can cause mild to severe muscle necrosis.

Intravenous Injection

- ***Advantages:*** An exact dose can be given and therapeutic levels are rapidly achieved.

- ***Disadvantages:*** The bird must be fully restrained; anesthesia may be helpful. Because avian veins are fragile, leakage of drug from the vessel and hematoma formation are common.

- ***Comments:*** Intravenous injection should be reserved for emergencies and one-time drug administration. Veins may also be needed for blood withdrawal for diagnostic tests. The right jugular, superficial ulnar, basilic vein on the ventral humerus and superficial plantar veins are most accessible. Intravenous catheters are available but are potentially dangerous to leave in unattended birds. Intravenous fluids can be delivered as a slow bolus at a dose of 10 ml/kg without pulmonary compromise.

Intraosseous Injection

- ***Advantages:*** If repeated drug administration is required the intraosseous route may be selected (Figure 17.5). The intraosseous route allows stable access to the intravascular space. A cannula can be inserted and used for repeated fluid or drug administration. If properly bandaged, psittacine birds will usually tolerate cannulas for short periods of time. Intraosseous cannulas are well tolerated in raptors, pigeons, waterfowl and other less temperamental species. The

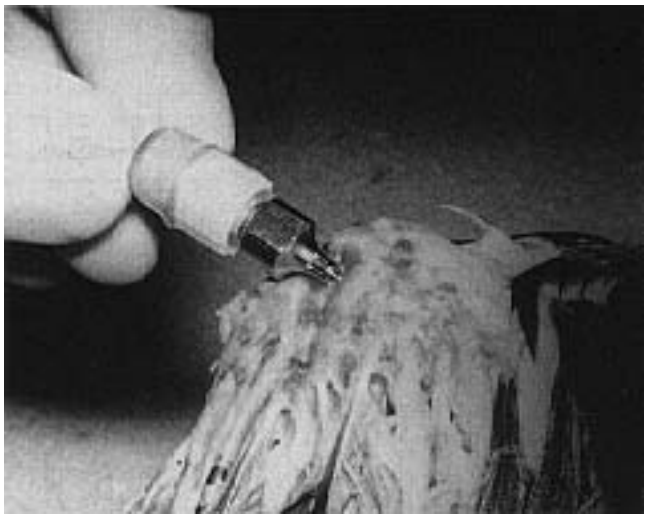

FIG 17.5 It may be safe to deliver some drugs designed for IV administration through indwelling intraosseous cannulas. If several days of therapy are necessary, the cannula can be placed in the ulna. For birds that need only a single administration of a drug that must be given slowly (most IV products), a cannula can be placed in the tibia. It has not been determined which of the IV drug preparations can safely be delivered through IO cannulas.

distal ulna and proximal tibia are the best locations for cannulation.

- ***Disadvantages:*** Only fluids or non-irritating drugs should be delivered via intraosseous cannulas. Sterility is critical, as infection may result in osteomyelitis.

Nebulization

- ***Advantages:*** Nebulized antibiotics are useful for pulmonary, sinus and trachea infections, and are often combined with mucolytic and penetrating agents (eg, DMSO) to break down caseous material and increase antibiotic uptake. Simple humidification of the lungs is also helpful. Therapeutic serum levels are seldom achieved but effective concentrations may be achieved in restricted sites in the upper respiratory tract.

- ***Disadvantages:*** At rest, there is little or no air exchange in much of the respiratory tract. It has been suggested that only 20% of the respiratory tract would be reached by nebulization.[2] The nebulized particle size should be less than 1-3 μm. Nebulization should usually be combined with systemic therapy.

Topical Medications

- ***Skin:*** Topical medications should be used carefully and sparingly. Oily and toxic compounds should be avoided, as they will mat the feathers and be ingested when the bird preens. A water-soluble formulation should be selected if available. If it is necessary to use greasy compounds, the site should be bandaged or the bird collared to prevent preening and ingestion. Propylene glycol can be added to some preparations (eg, ivermectin) to allow systemic absorption of cutaneously applied drugs.

- ***Eye:*** Liquid eye drops retard corneal healing less than ointments but must be given more frequently. Ointments should be applied very sparingly, as excess ointment will cause matting and loss of feathers surrounding the eye. Misting the eye with a water-soluble, topical spray may also be effective. Subconjunctival injections may be considered for delivering repository drugs.

- ***Nasal Flushes:*** Nasal irrigation can be very helpful for treating upper respiratory infections. Antibiotics can be added to flushing solutions, but in many cases unmedicated saline works as well. Isotonic solutions should be delivered with minimal pressure to avoid damage to inflamed tissues.

- ***Infraorbital Sinus Injection:*** Sinus injection is useful for flushing and delivering medication into the infraorbital sinus in birds with sinusitis. The injection is made at the level of the commissure of the beak, just ventral to the zygomatic arch, the same site as for cytologic sampling (see Chapter 10). Care must be taken not to penetrate the globe of the eye. If sinusitis has resulted in blockage of the outflow tracts, low volumes of fluid must be slowly injected to prevent exophthalmus. Only non-irritating drugs should be used.

- ***Intratracheal*** (through the glottis): This is an effective route for delivering amphotericin B to birds suffering from tracheal and pulmonary aspergillosis.

Toxicity and Adverse Effects of Antimicrobial Therapy

All antimicrobial drugs have the potential to harm the host. Direct toxic effects and the reduction of normal alimentary tract flora can occur even when antibiotics are used properly, requiring that birds should be monitored during treatment. Treatment failure and the development of resistant strains of bacteria occur most often when drugs are used improperly. Because the interplay between effective treatment, toxicity and adverse side effects is complex, the use of antimicrobials in birds should be pursued with caution, and routine prophylactic treatment of birds without a clear indication of infection is not suggested in any circumstance.

Misuse of antimicrobials can have serious consequences, especially in an avicultural facility or multiple-bird household. Selection of the wrong agent can result in treatment failure and spread of disease-causing organisms by the inappropriately treated bird. Use of low-dose administration (eg, drinking water-based) often generates resistant strains of bacteria that may become established in the aviary. This, coupled with the stress and adverse effects of drug delivery on normal flora, can actually make a disease problem worse rather than better. When prescribing antimicrobials, it is important to explain to the client the necessity of giving the full treatment regimen without skipping doses, even if the bird improves before treatment ends. This is necessary to prevent a recurrence of the infection and generation of resistant strains of bacteria.

Direct Toxic Effects

Drug toxicity varies with the compound, dose and physiologic status of the patient. Toxic effects of specific agents are listed in the section below, but some generalities can be made. The beta lactam antibiotics have relatively few direct toxic effects. The aminoglycosides are nephrotoxic at therapeutic doses and should be used with extreme caution in juvenile and dehydrated birds. Sulfa drugs should also be used cautiously in birds that are uricemic, because they are potentially nephrotoxic in dehydrated animals and are metabolized via the same metabolic pathway in the liver as uric acid. The fluroquinolones cause defects in the articular cartilage of some species of growing animals (eg, dogs, pigeons and horses) but not others (eg, cats). These effects are both species- and dose-dependent. To date, toxic effects have not been proven in psittacine birds treated with recommended doses of fluroquinolones.

Adverse Effects on Normal Alimentary Tract Flora

Most of the antibiotics used in avian practice are broad spectrum and their use will reduce or eliminate normal alimentary tract flora. Normal flora help reduce infection by potentially harmful microorganisms by competing for nutrients and occupying cellular attachment sites. Eliminating normal flora may render the bird more susceptible to colonization by potential pathogens such as yeast, viruses and gram-negative bacteria. Birds receiving antibiotics should be monitored for secondary infections with cloacal cultures and fecal Gram's stains.

Inappropriate antimicrobial therapy may potentiate an infection if the pathogen is resistant but the drug selected eliminates normal flora. This will favor growth of the pathogen in a competition-free environment (eg, digestive tract, skin, nasal passages). For this reason, drugs and the route of administration should be selected with care, and non-specific prophylactic use of antimicrobials should be avoided. It may also be advisable to culture the cloaca prior to antimicrobial treatment of all birds, even if the alimentary tract is not the primary site of infection. If potential pathogens are isolated, the treatment regimen should include a drug that will be effective for these organisms as well as the primary pathogens; otherwise minor alimentary tract pathogens may proliferate and cause illness if the competition from normal flora is eliminated. Environmental sources of harmful microorganisms should be eliminated during antimicrobial treatment by improving husbandry. Young and immunocompromised birds should be monitored every day during antimicrobial therapy to prevent potential yeast infections.

Treatment Failure

Birds are perceived to be masters at hiding their signs of disease and are often in an advanced state of illness by the time they are presented for treatment. It is important to establish a correct diagnosis and implement an effective treatment plan early in the disease process because there is seldom time to simply try a drug and see what happens. If the wrong drug or route of administration is selected, or if the problem is not due to a microbial infection, the bird may die while waiting to determine if prophylactic therapy is successful.

Some pet stores may sell over-the-counter (OTC) antibiotics with label claims that they are beneficial for treating a variety of avian respiratory and gastrointestinal complaints. Most of these products contain tetracycline, erythromycin or a sulfa drug, and are compounded for water administration. These products are *seldom* effective at the doses and routes recommended, and many bird owners waste valuable time attempting treatment with these products before consulting an avian veterinarian. By the time the bird receives appropriate care, it is usually too late. Bird owners should be educated to avoid these useless medications and to use more effective diagnostic and therapeutic methods with their pets.

Development of Resistant Strains of Bacteria

Bacteria develop resistance to drugs by two primary methods: transfer of plasmids and chromosomal mutation. These methods may: 1) induce production of an enzyme that degrades the antibiotic; 2) alter membrane permeability and therefore prevent the

antibiotic from penetrating the bacteria; or 3) create an alternate metabolic pathway that bypasses the action of the antibiotics. Plasmids are cytoplasmic bundles of nucleic acid that can be transferred among different species of bacteria, and are therefore the most important mechanism of developing, maintaining and transferring resistance in a bacterial population. Resistance is most common among gram-positive and gram-negative bacteria and less common in anaerobes, chlamydia and yeast.

Sub-therapeutic treatment can encourage the development of resistant bacteria. If low antibiotic concentration is achieved at the site of infection (such as typically occurs with water-based treatment regimes), only the highly susceptible bacteria will be killed. The remaining resistant bacteria will then multiply to use the space and nutrients formerly consumed by the susceptible bacteria. Over time, resistant bacteria may become established in a hospital or aviary. Sub-therapeutic or random non-specific treatment would be considered worse than no treatment at all if resistant bacterial strains are generated at the same time normal alimentary tract flora is reduced.

Cost

The small size of most avian patients makes it possible to economically use antibiotics that would be too expensive in traditional small animal species. This permits use of a variety of advanced generation antibiotics, especially among the beta lactams. In appropriate situations, these antibiotics are quite effective; however, they should not be used inappropriately, or microbial resistance will occur.

Antibacterial Therapy

The following sections were written to provide concise, practical information about the pharmacology and use of antimicrobial drugs in birds, primarily psittacines. More exhaustive reviews of drug pharmacology and use in poultry are available in the references (see Chapter 18).[47,51]

Fluoroquinolones

Pharmacology

The fluoroquinolones are a relatively new class of antimicrobial drugs that inhibit bacterial gyrase, the enzyme responsible for coiling DNA within the bacterial nucleus. They are bactericidal, widely distributed to tissues and the extracellular space, and are excreted primarily through renal tubular secretion and glomerular filtration. There is some hepatic metabolization, and enrofloxacin is partially metabolized to ciprofloxacin, an equipotent metabolite. Fluoroquinolones are generally well tolerated, although gastrointestinal upset and anorexia have been occasionally reported, and they may induce seizures in seizure-prone animals. High-dose or prolonged treatment may cause permanent articular defects in growing juveniles of certain species, including dogs, pigeons and horses.[36]

Use in Companion Avian Medicine

- ***Enrofloxacin:*** Enrofloxacin is currently the only veterinary-labeled fluoroquinolone. It has excellent activity against mycoplasma, some gram-positive bacteria and most gram-negative bacteria. Resistance of *Pseudomonas* spp. is occasionally seen. Enrofloxacin is highly active against most Enterobacteriaceae recovered from psittacine birds. It reduces clinical signs in birds infected with *Chlamydia psittaci*, but anecdotal comments indicate that enrofloxacin treatment does not routinely clear the carrier state. Currently, only tablets and IM preparations are available in the United States. A water-soluble liquid is available in some countries.

Studies on the single-dose kinetics of enrofloxacin in healthy African Grey Parrots, Blue-fronted and Orange-winged Amazons, and Goffin's Cockatoos indicate that a dose of 7.5-15 mg/kg administered IM or PO BID should maintain effective concentrations in these species.[26,27] Elimination in the African Grey Parrot was more rapid than in the Amazon parrot or cockatoo. For highly susceptible bacterial infections (MIC $\leq$ 0.03 µg/ml) in the Amazon parrot and cockatoo, SID therapy may be adequate. Intramuscular injection achieves greater peak concentrations (3-5 µg/ml versus 1-1.5 µg/ml with oral administration at 15 mg/kg), but concentrations after two to four hours are similar to those achieved with oral administration of the water-soluble solution. The IM formulation causes irritation at the site of injection, but given orally, the IM formulation induces higher peak plasma concentrations (1.5-2.5 µg/ml at 15 mg/kg) than the water-soluble formulation.

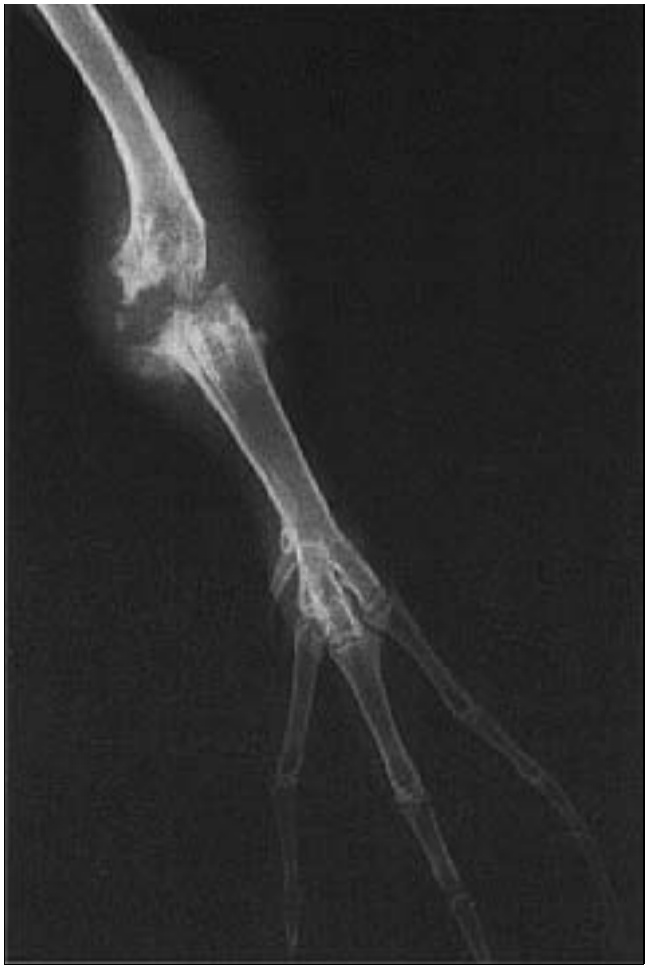

FIG 17.6 A duck with osteomyelitis of the tibiotarsal/tarsometatarsal area. Surgical debridement and long-term antibiotic therapy are usually required to resolve bone infections.

Mean plasma concentrations of approximately 0.1 μg/ml were maintained in African Grey Parrots fed drinking water medicated at 0.19-0.38 mg/ml. These concentrations might be effective for highly susceptible gram-negative bacteria.[25] Effective clearance of gram-negative bacteria from psittacine birds has been reported using IM (10 mg/kg SID) or water-based administration (100-200 ppm) for ten days.[36] Combination therapy in Senegal Parrots treated with enrofloxacin-medicated drinking water (100 ppm) and ketoconazole (30 mg/kg PO SID) for 10 days produced evidence of renal toxicity.[36] The half-life of enrofloxacin in pigeons was 2.6-4.7 hours with tissue concentrations exceeding those of serum in one hour. Recommended doses are 5 mg/kg, BID IM, PO or SC, or 100-200 ppm (0.1-0.2 mg/ml) in the drinking water for highly susceptible bacteria.[14]

Enrofloxacin and ciprofloxacin have been widely used in psittacine nurseries without reports of side effects. However, the drug should be used with caution in growing birds since toxic effects are species-specific and dose-related, and the drug has not been studied in all species. There have been scattered, anecdotal reports of aggressive, irritable behavior in adult Amazon parrots treated with quinolones.

- ***Ciprofloxacin:*** Ciprofloxacin is a human-labeled fluoroquinolone with an antibacterial spectrum and pharmacology similar to enrofloxacin. Ciprofloxacin tablets appear to be more water soluble than enrofloxacin. Ciprofloxacin has not been shown to have a therapeutic advantage over enrofloxacin.

Comments

The fluoroquinolones, especially enrofloxacin, are among the most effective drugs for treating gram-negative bacterial infections (Figure 17.6). Effective treatment with BID (or in some species, SID) administration is a clear advantage over some other antibiotics. Enrofloxacin can be administered orally but is bitter, and many birds will refuse to accept it. It may be necessary to dilute the drug in a palatable vehicle such as fruit juice or lactulose syrup, or to deliver it via a gavage tube. The major disadvantage to parenteral administration is intramuscular pain and irritation at the site of injection.

Penicillins

- ***Characteristics:*** The penicillins are beta lactam antibiotics. They inhibit the formation of the bacterial cell wall and are bactericidal for growing and dividing organisms. The spectrum and route of administration vary with the generation of the product. Older agents, such as ampicillin and amoxicillin, are effective against many gram-positive and some gram-negative organisms, and are available in oral and injectable formulations. Later-generation penicillins such as ticarcillin and piperacillin have enhanced activity against gram-negative bacteria, including *Pseudomonas* spp., but are primarily available in parenteral formulations.[40]

Penicillins are widely distributed to the extracellular space but poorly penetrate the CSF. Excretion is rapid (half-lives are usually less than 60 minutes) and is accomplished primarily through renal tubular secretion and glomerular filtration. Penicillins are considered relatively nontoxic, although allergic reactions (anaphylaxis) can occur. Procaine penicillin may cause adverse reactions in small patients (eg,

finches, canaries, budgerigars and cockatiels) due to the procaine component. Penicillins have reduced efficacy in the presence of overwhelming numbers of organisms ("inoculum effect"). Penicillins are synergistic when combined with aminoglycosides, and this combination can be used to treat severe infections, especially those caused by *Pseudomonas* spp.. These two agents should not be combined in the same syringe or the aminoglycoside will be inactivated.

Use in Companion Avian Medicine

- ***Natural Penicillins:*** Natural penicillins have a narrow spectrum restricted to *Pasteurella* spp. and some gram-positive organisms with MIC's less than 1 μg/ml. They are rarely used in avian medicine due to the availability of more effective drugs.

- ***Ampicillin / Amoxicillin:*** Many gram-positive bacteria are susceptible to ampicillin and amoxicillin, but most gram-negative isolates are resistant at concentrations achievable in birds. Oral absorption of ampicillin is highly erratic, so treatment failures are common even when laboratory tests suggest the isolated organisms are susceptible. Tests in chickens and ducks indicate that oral amoxicillin induces double the plasma concentrations of oral ampicillin.[37] Parenteral administration results in much higher and more consistent plasma concentrations. Ampicillin sodium doses of 100 mg/kg IM induced mean peak plasma concentrations of 60 μg/ml that declined to 0.65 μg/ml in four hours in Blue-naped Parrots. Based on this study, and another in Amazon parrots, it was recommended that ampicillin be dosed at 150 mg/kg PO QID.[17] Clark suggested that ampicillin in birds may be eliminated via hepatic and intestinal routes, in addition to renal excretion.[9]

- ***Ticarcillin:*** The pharmacology of ticarcillin is similar to that of carbenicillin; however, it is often two to four times more active against *Pseudomonas* spp. It is available for parenteral administration only.

- ***Piperacillin:*** In humans, piperacillin has greater activity against more gram-negative bacteria than other penicillins. It is widely used by avian veterinarians to treat systemic gram-negative bacterial infections. It is available for parenteral administration only. Serum and intestinal concentrations of piperacillin after an IM dose of 100 mg/kg in budgerigars were very high, and doses up to 1000 mg/kg did not induce clinically apparent toxic effects.[32] The half-life of piperacillin in Blue-fronted Amazon Parrots dosed with 100 mg/kg IM was less than 30 minutes, and doses of 75-100 mg/kg IM administered three to six times daily have been recommended.[23] Higher and more frequent doses should be used in more severe infections.

- ***Clavulinic Acid:*** Clavulinic acid has no antimicrobial activity of its own, but when combined with a penicillin, it inhibits beta-lactamase, a bacterial enzyme that inactivates many penicillins. Formulations combining clavulinic acid with amoxicillin or ticarcillin are available. Reports of use in birds are rare, but this drug may offer safe, effective activity against gram-negative and gram-positive pathogens.

Comments

Early generation penicillins are appropriate for treating infections caused only by highly susceptible pathogens. The advanced generation penicillins have an excellent gram-negative spectrum and are appropriate for treating severe infections caused by these organisms. Penicillins have a very high therapeutic index, an advantage when treating patients with compromised renal or hepatic function. A major disadvantage of using penicillins is the frequency of administration required to maintain effective concentrations.

Cephalosporins

Pharmacology

Like penicillins, the cephalosporins are beta lactam antibiotics; they share similar pharmacology but differ in spectrum.[41] Cephalosporins inhibit the formation of the bacterial cell wall and are bactericidal for growing and dividing organisms. They are widely distributed in the extracellular space, but most products poorly penetrate the cerebrospinal fluid and other pharmacologically privileged spaces. Excretion is primarily through renal tubular secretion and glomerular filtration. Cephalosporins are considered to be relatively nontoxic. They are classified into first, second and third generation products. In general, first generation products are effective against many gram-positive and some gram-negative bacteria, while increasing generations demonstrate enhanced gram-negative activity but reduced activity against gram-positives. Like the penicillins, cephalosporins also suffer from the "inoculum effect," and show reduced activity in the presence of overwhelming numbers of organisms. They are potentially synergistic when combined with aminoglycosides.

Use in Companion Avian Medicine

- ***First Generation Agents*** (eg, cephalexin and cephalothin): The antimicrobial spectrum of first genera-

tion agents includes most gram-positive cocci, some gram-negative bacteria and some anaerobes. Oral cephalexin is readily absorbed after oral administration in quail, ducks, cranes and emus. Doses of 35-50 mg/kg QID for larger birds and BID to TID for smaller birds have been recommended.[42] Cephalothin is available as a parenteral formulation, and, based on single-dose studies, therapeutic concentrations should be maintained with doses of 100 mg/kg IM QID in pigeons, cranes and emus, and BID to TID in quail and ducks. The author has successfully treated psittacine birds with cutaneous infections caused by *S. aureus* using administration of cephalexin at a dose of 100 mg/kg PO TID for 14-21 days.

- ***Second generation agents*** (eg, cefoxitin and cetaxitin) have increased gram-negative activity and are available primarily in parenteral formulations. There are few reports of their use in birds. Presumably, the pharmacology would be similar to first and third generation products.

- ***Third generation agents*** (eg, cefotaxime and ceftriaxone) have an expanded gram-negative spectrum (including increased activity against *Pseudomonas* spp.) and variable activity against gram-positive bacteria. Cefotaxime is unusual among cephalosporins because it penetrates the CSF in effective concentrations. Ceftriaxone has an extended half-life in humans (eight hours versus one hour for most other cephalosporins); however, the half-life is the same as other cephalosporins in Amazon parrots.[23] Doses of 75-100 mg/kg IM given three to six times daily should maintain effective plasma concentrations. These agents are mostly available in parenteral formulations; the use of newer drug preparations that can be given orally has not been reported in birds.

Comments

Recommendations are similar to the penicillins. First generation products have shown good activity against staphylococcus infections of the alimentary tract and skin of birds. The third generation products have an excellent gram-negative spectrum. Cephalosporins have a high therapeutic index, an advantage when treating patients with compromised renal or hepatic function. A major disadvantage of using cephalosporins is the frequency of administration required to maintain effective plasma concentrations.

Aminoglycosides

Pharmacology

The aminoglycoside antibiotics interfere with bacterial protein synthesis and are bactericidal.[42] They are not absorbed from the GI tract and must be administered parenterally. Aminoglycosides are confined to the extracellular space and poorly penetrate the eye and cerebrospinal fluid. Excretion is almost exclusively by glomerular filtration. Aminoglycosides must penetrate the bacterial cell wall to interfere with protein synthesis. This process requires oxygen, so aminoglycosides are not active against anaerobes or at sites with low oxygen tension (eg, large abscesses). Although aminoglycosides are poorly bound to blood proteins, they are extensively bound to intracellular proteins and may be inactivated in proteinaceous environments such as abscesses and exudates.

The aminoglycosides are relatively toxic when compared to other antibiotics. Nephrotoxicity and ototoxicity are relatively common, even in humans where dosage regimens are tailored for individual patients. The nephrotoxicity associated with recommended dosage regimens and short-term treatment is usually reversible once treatment stops. Chronic renal dysfunction occurs when high-dose or prolonged therapy is attempted. Since excretion is dependent on glomerular filtration, aminoglycosides should be used with caution in dehydrated patients. Another side effect, neuromuscular synaptic dysfunction and paralysis, can occur if the drug is given intravenously at a rapid rate.

Use in Companion Avian Medicine

- ***Early Generation Aminoglycosides:*** Streptomycin, dihydrostreptomycin, neomycin and kanamycin have limited spectrum and greater toxicity, and are seldom used systemically in birds. Neomycin is used in topical and ocular formulations and can be administered orally to sterilize the gut.

- ***Gentamicin:*** Gentamicin is effective against many gram-negative and gram-positive bacteria. It is more toxic than amikacin, and signs of nephrotoxicity (eg, polyuria and polydipsia) are often encountered even when birds are treated with low doses. The degree of toxicity varies with individuals and species. For example, toxic reactions were more severe in Rose-breasted Cockatoos than in Scarlet Macaws treated with 5 mg/kg IM BID for seven days (Figure 17.7). The cockatoos remained polyuric for more than 30 days after treatment ended.[24] Based on these studies, gentamicin doses of 2.5-5 mg/kg IM BID should pro-

vide efficacious plasma concentrations and reduce toxicity. Variability in toxicity has also been demonstrated in raptors. Renal toxicity was found in Lanner Falcons treated with 5 mg/kg/day for four days,[18] and doses of 10 mg/kg administered BID for five days in Great Horned Owls produced reactions ranging from no signs to death. Doses similar to those in psittacine birds (2.5 mg/kg IM TID) are recommended for raptors.[4] Previously recommended doses (10 mg/kg IM TID) are excessive and may cause severe toxicity and death.

- ***Tobramycin:*** The pharmacology of tobramycin in mammals is similar to that of gentamicin, but it has greater activity against *Pseudomonas* spp. and some other gram-negative bacteria. Pharmacology studies in birds are lacking, but it is probably similar to gentamicin. In dogs and humans, tobramycin is considered slightly less toxic than gentamicin but more so than amikacin. The estimated dose for tobramycin is 2.5-5 mg/kg IM BID.

- ***Amikacin:*** Amikacin has excellent activity against many gram-negative bacteria, including some strains that are resistant to gentamicin and tobramycin. Amikacin is approximately four times less active than gentamicin but is correspondingly less toxic, so higher doses can be used safely. Amikacin causes fewer toxic side effects and is the aminoglycoside of choice for use in birds.

  Pharmacokinetic studies have been completed in several psittacine species. Doses of 13 and 20 mg/kg IM in healthy Blue-fronted Amazon Parrots produced peak plasma concentrations of 40 and 75 µg/ml respectively that declined to zero by eight hours.[20] When these doses were administered for seven days, mild signs of toxicity (polyuria) occurred but rapidly resolved when treatment ended. Similar single-dose pharmacology was observed in cockatiels, Goffin's Cockatoos,[20] and Orange-winged Amazon Parrots and in African Grey Parrots.[28] Based on these studies, amikacin doses of 10-15 mg/kg IM administered BID or TID should provide effective plasma concentrations for most susceptible gram-negative bacteria. The higher end of the dosage range should be used with more resistant organisms, sites of infection with poor perfusion or in critically ill patients. In dehydrated birds and those with compromised renal function, the dose should be reduced or a less toxic drug selected.

Comments

The aminoglycosides are excellent drugs for treating resistant gram-negative bacterial infections in birds. They are active against *Pseudomonas* spp., especially when combined with a third generation cephalosporin (eg, cefotaxime) or late generation penicillin (eg, piperacillin). However, these two agents must not be combined in the same syringe. Aminoglycosides should be avoided or used with care in dehydrated patients. Amikacin is currently the aminoglycoside of choice for avian use because of its broad spectrum and reduced toxicity compared to other aminoglycosides.

Tetracyclines

Pharmacology

Tetracyclines interfere with bacterial protein synthesis and are bacteriostatic.[43] In mammals, they are effective against a broad spectrum of gram-positive and some gram-negative bacteria. It is difficult to achieve concentrations that are effective for treating bacterial infections in companion and aviary birds, and tetracyclines are primarily used to treat chlamydiosis and mycoplasmosis. Tetracyclines are lipid soluble and are widely distributed to tissue. They are mostly available as oral formulations. Injectable formulations are available for some compounds but cause necrosis at the site of injection. Oral absorption is generally good except in the presence of cations such as calcium or magnesium, which chelate tetracyclines. The route of excretion varies with the compound. Oxytetracycline and chlortetracycline are excreted primarily by hepatic metabolism and renal excretion; minocycline is metabolized by the liver and excreted in the bile; and doxycycline is excreted as an inactive conjugate in the feces. Toxicity varies with the compound used, species of animal and duration of treatment. Tetracyclines will chelate calcium in the teeth and bone. GI upset and photosensitization have been reported. Prolonged treatment may have catabolic and immunosuppressive effects, reduce normal gut flora and render the animal more susceptible to opportunistic infections.

Use in Companion Avian Medicine

- ***Chlortetracycline:*** Diets containing 1% chlortetracycline are recommended for treating psittacine chlamydiosis in the United States.[12] Diets containing 0.5% chlortetracycline have been shown to be effective in Europe. Powdered chlortetracycline can be added to a cooked mash, or medicated pellets are commercially available. The efficacy of these diets

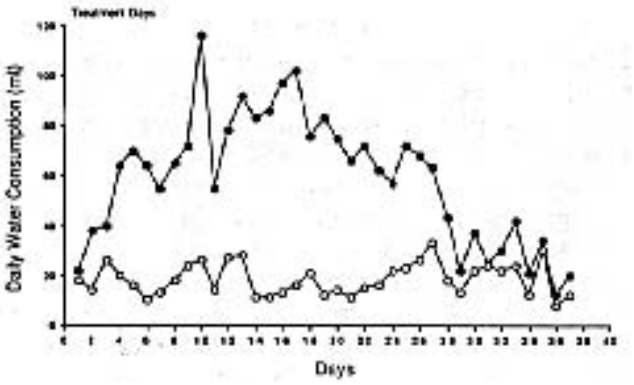

FIG 17.7 Adverse effects of gentamicin in Scarlet Macaws (open circles) and Rose-breasted Cockatoos (Flammer, et al: Am J Vet Res 51[3]:406, reprinted with permission).

will vary with the nutritional composition of the ration. Birds will tend to consume less of a diet with a high-energy content (eg, formulated diets) and more if the energy content is reduced (eg, cooked corn mashes). Although medicated diets may be successful in reducing the clinical signs of chlamydiosis, common sequelae to treatment include diet refusal, starvation, treatment failures and secondary microbial infections.[21]

- ***Oxytetracycline:*** Water-soluble formulations of oxytetracycline are available, but oral absorption is poor. A long-acting injectable formulation[c] is available and may maintain plasma concentrations effective for controlling chlamydiosis in Goffin's Cockatoos for two to three days; however, this drug preparation is irritating and will cause necrosis at the injection site.[22] The single dose kinetics of intramuscular injection has been investigated in pheasants, Great Horned Owls and Amazon parrots.[59] It can be nebulized for treating respiratory infections, but must be dosed every four to six hours.[16]

- ***Minocycline:*** This drug has an extended half-life in mammals. It has been used experimentally to coat millet seeds and treat chlamydiosis in small psittacine birds.[54]

- ***Doxycycline:*** Doxycycline has a prolonged half-life and differs from conventional tetracyclines because it is more lipophilic. The half-life varies with the species. At oral doses of 50 mg/kg, the half-life averages ten hours in cockatiels and Amazon parrots and greater than 20 hours in cockatoos and macaws.[19] This is the drug of choice for treating chlamydiosis, and oral dosage recommendations are: 40-50 mg/kg PO BID in cockatiels and Blue-fronted and Orange-winged Amazons; 25 mg/kg PO BID in African Grey Parrots, Goffin's Cockatoos and Blue and Gold and Green-winged Macaws. In untested species it is impossible to precisely extrapolate dosages; however, 25-30 mg/kg is the recommended starting dose in cockatoos and macaws, and 25-50 mg/kg is recommended in other species.

If regurgitation occurs, the dose should be reduced by 25% or divided and administered BID. Hepatotoxicity, as detected by elevated AST and LDH tests, may occur in macaws. Dosage recommendations for treating chlamydiosis in psittacine birds with injectable doxycycline (Vibravenös formulation only!) is 75-100 mg/kg IM every five to seven days. In macaws, the lower dose and more frequent administration should be administered in the last three weeks of treatment.[29] There have been anecdotal reports of use of pharmacist-compounded injectable doxycycline products; however, kinetic studies are lacking and it is impossible to extrapolate dosage schedules from one formulation to another.

Comments

In companion and aviary birds, tetracyclines are primarily used to treat chlamydiosis and, to a lesser extent, mycoplasmosis and pasteurellosis. Dosage regimens are based on attaining sustained blood concentrations of 1 μg/ml — a concentration thought to inhibit chlamydiosis.[1]

Trimethoprim / Sulfonamide Combinations

Pharmacology

A combination of trimethoprim and a sulfonamide is synergistic, as both drugs interfere with microbial folic acid synthesis.[7] This combination has good efficacy against many gram-positive and gram-negative bacterial pathogens, with the exclusion of *Pseudomonas* spp. Use of these drugs in combination has largely replaced use of either component alone for treatment of systemic bacterial infections. This combination is probably bacteriostatic at the doses used in birds. Oral and parenteral formulations are available and readily absorbed. The sulfa drugs are primarily distributed to the extracellular space, while trimethoprim is more lipophilic and has good tissue penetration. Excretion is primarily renal, and the degree of hepatic metabolism varies with the species. A number of side effects, including rashes, photosensitization, arthritis and hepatic disorders, have been reported in mammals but not in birds.

Use in Companion Avian Medicine

The pharmacology of trimethoprim/sulfonamide combinations has been investigated in poultry,[65] geese[52] and pigeons,[13] but not in psittacine birds. Empirical doses of 16-24 mg/kg trimethoprim/sulfonamide (oral solution) administered BID, and 8 mg/kg IM (40 mg/ml trimethoprim + 200 mg/ml sulfadiazine) BID have been widely used clinically with good success.

Trimethoprim and sulfonamide combinations have few toxic effects, but many birds (especially macaws) suffer GI upset and will regurgitate one to three hours after an oral dose. The incidence of GI upset can be reduced if the drug is added to a small amount of food or if the dose is reduced. Sulfonamides form crystals and damage renal glomeruli in dehydrated birds and those with compromised renal function. The injectable product may cause irritation and necrosis at the site of injection.

Two formulations are available, each combining trimethoprim with a different sulfa drug. There is no clear advantage for either preparation. Trimethoprim/sulfadiazine (veterinary formulation) is available in injectable and oral forms. Trimethoprim/sulfamethoxazole (human formulation) is available in oral suspension.

Comments

Trimethoprim/sulfadiazine is an excellent broad-spectrum bacteriostatic drug. It is often the drug of choice when using the oral route to deliver antibiotics (eg, treating gram-negative infections in nestling birds).

Macrolides and Lincosamides

Pharmacology

The macrolides and lincosamides interfere with bacterial protein synthesis, are bacteriostatic and share similar pharmacology.[6] Their spectrum of action includes gram-positive bacteria, pasteurella, bordetella, some mycoplasma and obligate anaerobic bacteria. Injectable formulations are available but are seldom used in birds due to irritation and necrosis at the site of injection. Oral absorption is good in mammals, but there are few pharmacokinetic studies in birds. All are well distributed to tissues and eliminated primarily by hepatic metabolism. Toxicity is usually limited to gastrointestinal irritation and vomiting.

Use in Companion Avian Medicine

The primary uses for the macrolides are to treat gram-positive infections in finches, suspected or confirmed mycoplasma in psittacine birds and gram-positive or anaerobic osteomyelitis. These drugs are also active against *Campylobacter* spp. and *Clostridia* spp. Clindamycin is the most active of the listed drugs.

- ***Tylosin:*** The pharmacokinetics of intramuscularly administered tylosin has been studied in quail, pigeons, cranes and emus.[38] Peak concentrations of 3-5 µg/ml were achieved, and doses of 15-25 mg/kg TID to QID were recommended, with the cranes receiving the lower dose. Unfortunately, tissue necrosis at the site of injection would preclude a multi-day treatment regimen using the IM formulation at this frequency. Effective pulmonary concentrations were achieved with nebulization of 1 gram tylosin in 50 ml dimethyl sulfoxide (DMSO) for one hour.[39] Treatment of conjunctivitis in cockatiels with a tylosin and water spray has been suggested.[33]
- ***Erythromycin:*** Erythromycin is active against campylobacter and mycoplasma. Dosages have been investigated in pigeons,[44] but it is rarely used in companion and aviary birds. In humans, erythromycin is active against chlamydia, but it is not likely to eliminate this organism in birds at accepted avian dosages. A water-soluble powder has been used to treat mild respiratory infections in psittacine birds at a rate of 500 mg/gallon of water but is of questionable efficacy. A popular over-the-counter product[b] is available for medicating drinking water, but it is doubtful that this product achieves plasma concentrations effective for treating most microbial infections in companion birds.
- ***Clindamycin:*** Clindamycin is the most active of the macrolides mentioned. It is used to treat anaerobic infections and osteomyelitis caused by susceptible gram-positive pathogens. The author treated osteomyelitis in a macaw with a combination of enrofloxacin and clindamycin for seven months without detectable toxic effects.
- ***New Macrolides:*** Research on treating *Chlamydia trachomatis* infection in humans has focused on the use of new macrolide (azalide) antibiotics (ie, azithromycin and clarithromycin). These drugs are well tolerated and have a prolonged tissue half-life. Studies in humans have demonstrated that a single dose of either drug is as effective in eliminating *C. trachomatis* infection as a seven-day course of doxycycline. The

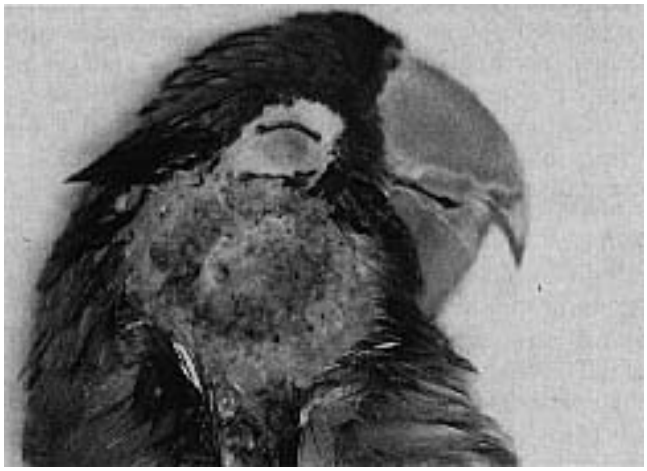

FIG 17.8 Bacterial-induced pruritic dermatitis that was responsive to systemic antibiotic therapy. Many cases of bacterial dermatitis recur when therapy is stopped (photo courtesy of Louise Bauck).

disposition and safety of these drugs in birds remain to be investigated.

- ***Lincomycin:*** Lincomycin is usually combined with spectinomycin and has been used in finches to treat respiratory and alimentary tract infections caused by gram-positive bacteria and mycoplasma in other species.

Chloramphenicol

Pharmacology

Chloramphenicol interferes with bacterial protein synthesis and is bacteriostatic.[58] Its antimicrobial spectrum includes many gram-positive and some gram-negative bacteria. It will inhibit chlamydial growth and alleviate clinical signs in infected birds, but will not routinely clear a bird of infection. Oral and parenteral formulations are available; however, oral absorption is highly erratic. Chloramphenicol is highly lipid-soluble and is widely distributed to most tissues, including the central nervous system. Tissue concentrations often exceed serum levels. The route of excretion varies with different species, but in most cases it is metabolized by the liver.

Potential toxic effects include reversible dose-related bone marrow depression, inhibition of hepatic microsomal enzyme synthesis, inhibition of host protein synthesis resulting in decreased wound healing and decreased immunoglobulin synthesis.[58] In a small percentage of the human population, non-dose-related, irreversible, aplastic anemia may occur, even with mild cutaneous contact. For this reason, clients are instructed to handle this drug carefully and wear gloves when treating birds.

Use in Companion Avian Medicine

- ***Oral Formulation*** (palmitate ester): This formulation is readily accepted by most birds but achieves erratic blood concentrations.[10] It is infrequently used in avian medicine due to the potential toxicity in humans and the availability of more effective oral drugs (eg, trimethoprim/sulfa combinations and enrofloxacin).

- ***Injectable Formulations*** (succinate, propylene glycol-based): These formulations yield more predictable serum concentrations than the oral preparations. The succinate formulation yields lower serum concentrations, but is less irritating to muscle. There is wide pharmacokinetic variation among species. For example, the elimination half-life in budgerigars was longer than in macaws.[10] Doses of 50 mg/kg IM TID are recommended for most psittacine birds.

Comments

Use of chloramphenicol has been largely replaced by other antibiotics that are more effective and can be administered less frequently. Chloramphenicol is still useful for treating infections caused by susceptible intracellular bacteria (eg, salmonella) and where penetration into the central nervous system is desired. Chloramphenicol is bacteriostatic and is probably not the drug of choice for initial treatment of severe, life-threatening infections.

Antifungal Therapy

The most common fungal infections encountered in psittacine birds, raptors and waterfowl are candidiasis (usually confined to the alimentary tract) and aspergillosis (respiratory and cutaneous).[47] Other fungal infections such as cryptococcosis, sporotrichosis, blastomycosis and histoplasmosis are infrequently encountered.

Historically, nystatin, flucytosine and amphotericin B have been widely used in birds. Development of the orally active, broad-spectrum azole antifungals (first

ketoconazole and more recently, fluconazole and itraconazole) may offer similar or greater efficacy, easier administration and lower toxicity. The major drawback to the use of azoles is the lack of pharmacokinetic and toxicologic information to guide dosage selection. However, empirical doses have been established, and use of these drugs is becoming established in avian medicine. As with antibacterial agents, spectrum, ability to reach the site of infection, route of administration and potential toxicity are important considerations when selecting an antifungal agent.

Nystatin

Pharmacology

Nystatin is a polyene antimicrobial that disrupts the fungal cell membrane by substituting for ergosterol.[48] It is effective against most strains of candida and some other yeasts, although clinical evidence suggests resistant yeast strains may occur in some psittacine nurseries.[46] It is not absorbed from the GI tract and is available for oral or topical use only. Nystatin is relatively nontoxic due to the lack of systemic absorption, and is suitable for treating alimentary tract infections caused by candida and other susceptible yeast. It must come in direct contact with the yeast to be effective. Treatment failures may occur if the nystatin is delivered via a tube or syringe to the back of the oral pharynx, bypassing more rostral sites of infection in the mouth.

Use in Companion Avian Medicine

Nystatin is a highly useful drug for yeast infections that are confined to the alimentary tract. It has low toxicity and is safe for use in nestling birds. Some birds suffer GI upset and may regurgitate following repeated or large doses. With oral infections, nystatin or a more potent topical drug (eg, amphotericin B cream) can be applied directly to the lesions. If resistance or a non-alimentary tract infection is encountered, a systemically active antifungal should be used.

Nystatin dosage recommendations have been empirically derived but are supported by effective, long-term clinical use. Individual birds can be treated with 300,000 IU/kg orally BID or TID for five to ten days. Nystatin can also be added to hand-feeding formulas for prophylactic treatment in nurseries experiencing chronic yeast problems. If the yeast is highly susceptible to nystatin, food-based administration will be effective. A nystatin feed premix[d] has been used to medicate a mash diet to treat flocks.

Amphotericin B

Pharmacology

Amphotericin B is a polyene antimicrobial drug that disrupts the fungal cell membrane by substituting for ergosterol.[3] It is active against most of the yeast and fungi of medical importance. Resistance by some strains of *Aspergillus* spp. has been reported in man and other animals. Comparison studies in humans have shown that amphotericin B is still one of the most efficacious antifungal drugs, especially for chronic infections and infections in immunocompromised hosts. Clinical data demonstrating improved efficacy when amphotericin B is combined with flucytosine or an azole antifungal are conflicting, but combination therapy is a common practice for treating serious fungal infections in humans. Amphotericin B is not well absorbed after oral administration and is too irritating for intramuscular or subcutaneous injection; thus, it must be delivered intravenously or used topically. It is widely distributed to tissue and extracellular spaces where it is metabolized and slowly excreted in the urine. Amphotericin B is highly nephrotoxic in mammals, although this can be reduced by instituting a step-wise dosing scheme based on renal function calculated from creatinine clearance levels.

Use in Companion Avian Medicine

Amphotericin B is one of the drugs of choice for initially treating serious, systemic fungal infections. Major disadvantages are potential toxicity and the need for IV administration. It has been used in combination with flucytosine in raptors and swans with fair results.[48] A new, orally active azole, itraconazole, may offer similar activity or may potentiate the effects of amphotericin B.

Amphotericin B can be nebulized or injected into an affected air sac for respiratory infections. It can also be injected through the glottis or administered transtracheally to treat tracheal and syringeal aspergillosis. A topical cream in a plasticized base is available for treatment of topical lesions and oral candidiasis.

The pharmacokinetics of amphotericin B in turkeys and selected raptors indicate that these birds eliminate the drug much more rapidly than mammals.[52] Based on these findings and clinical experience, doses of 1.5 mg/kg IV BID are recommended. Pharmacokinetic data in psittacine birds is lacking. Long-term use in raptors was not associated with nephrotoxicity, so the drug may be safer in avian than mammalian species.[49] However, until more informa-

tion on avian use is available, patients receiving this drug should be monitored for signs of nephrotoxicity (polyuria and uricemia).

Flucytosine

Pharmacology

Flucytosine is converted by the liver to 5-fluorouracil, and exerts its antifungal effect by inhibiting DNA synthesis.[34] It is always used in combination with amphotericin B in humans, and this combination is considered useful for treating candida and cryptococcus infections. Resistance develops quickly when the drug is used alone. It is well absorbed orally, shows little protein binding and is widely distributed to tissues that are difficult to penetrate such as the CSF, eye and joints. This drug is excreted almost entirely unmetabolized in the urine, and dosage modifications are necessary in patients with reduced renal function. Dose-related, reversible bone marrow depression is the major toxic change seen in humans, presumably due to the conversion of flucytosine into 5-fluorouracil by GI tract bacteria. Hepatotoxicity and GI toxicity are occasionally reported in mammals.

Use in Companion Avian Medicine

Flucytosine has been used singly as a prophylactic treatment to prevent aspergillosis in highly susceptible avian species undergoing stress (eg, hospitalization of swans) and in combination with other drugs to treat respiratory aspergillosis. *In vitro* susceptibility of eleven strains of *Aspergillus fumigatus* indicated that flucytosine doses of 20-30 mg/kg QID would maintain inhibitory plasma concentrations.[49] Because reported *in vitro* susceptibility data varies greatly, a combination of flucytosine, amphotericin B and rifampin has been suggested for treating respiratory aspergillosis in raptors.[48] Clinically, doses of 50 mg/kg orally BID for two to four weeks appears to prevent aspergillosis when prophylactically administered to swans (Degernes L, unpublished). Flucytosine has been safe for long-term use (two to four weeks) in raptors and waterfowl.[49] Rosskopf, et al. reported successful treatment of esophageal and subcutaneous aspergillosis in a cockatoo using a combination of flucytosine (65 mg/kg orally BID) and ketoconazole (20 mg/kg orally BID) for approximately one month.[53]

Recently available azole compounds may replace flucytosine with drugs that are safer and more effective.

Ketoconazole

A major breakthrough in antifungal therapy occurred in 1979 with the release of the azole drug ketoconazole, the first orally active, systemic antifungal with a broad spectrum. Further research resulted in release of fluconazole in 1990 and itraconazole in 1992. All three of these drugs are labeled for human use only. Older azole antifungals, miconazole and clotrimazole, are suitable for intravenous and topical use only and are more toxic than more recently available drugs.

The use of the azole antifungals in veterinary medicine has been reviewed.[30] They inhibit synthesis of the primary fungal sterol, ergosterol, which is important in fungal cell membrane integrity. This is accomplished by inhibition of a P_{450} enzyme system, and the relative potency of the azoles is determined by their affinity for this P_{450} enzyme moiety. Vertebrates also have a P_{450} enzyme system, and the selective toxicity of the azoles depends on their relative specificity for binding fungal P_{450} enzymes. Potential toxic effects of interfering with vertebrate P_{450} enzymes include decreased synthesis of cholesterol, cortisol and reproductive steroid hormones. Ketoconazole has the least affinity and specificity and is therefore considered less active and potentially more toxic than fluconazole and itraconazole; however, it is still a highly useful drug. All three azoles are fungistatic and several days of therapy are needed to achieve steady-state concentrations.

Pharmacology

Ketoconazole is effective against many of the yeast and fungi of medical importance, but *Aspergillus* spp. are often resistant.[45] It is readily absorbed in an acid environment such as exists in the stomach following a meal. It is widely distributed to tissues but is highly protein-bound and does not significantly penetrate into the cerebrospinal or ocular fluids. It is eliminated via hepatic metabolism, and significant interactions occur with drugs that inhibit or induce hepatic enzyme metabolism (eg, rifampin and barbiturates). Ketoconazole is considered more toxic than either itraconazole or fluconazole. Reports of toxicity are rare in birds, but anorexia, vomiting, jaundice and elevated liver enzymes have been reported in other animals. Long-term use in dogs has resulted in decreased cortisol levels and decreased testosterone synthesis.

Ketoconazole is available in 200 mg tablets. Crushed tablets can be compounded with 0.15% methylcellu-

lose into an oral suspension that is stable for six months if refrigerated. Ketoconazole is water insoluble unless in an acid environment. Medicated water is therefore of questionable benefit except for infections caused by highly susceptible yeast that are limited to the GI tract.

Use in Companion Avian Medicine

Ketoconazole is currently the most widely used, least expensive, orally available and systemically active antifungal. It is useful for treating resistant yeast infections and yeast infections where systemic drug delivery is required. It is not usually effective against aspergillosis alone, but may have a synergistic effect when combined with other antifungals.

Limited pharmacokinetic studies have been performed in pigeons and cockatoos.[35] Following oral administration at 30 mg/kg, peak concentrations were achieved in 0.5 to 4 hours and the elimination half-life was 2 to 3.8 hours in pigeons and 3.8 hours in Moluccan Cockatoos. No significant toxic reactions were seen in pigeons given 30 mg/kg orally BID for 30 days or Amazon parrots treated with 30 mg/kg BID for 14 days. Because absorption is increased in an acid environment, ketoconazole should be administered with food. It is not necessary to pre-dissolve the drug in acid.

Tracheal aspergillosis in an Amazon parrot was treated using ketoconazole (approximately 25 mg/kg orally BID for 14 days) and intratracheal amphotericin B (50-75 mg/kg SID for seven days).[53]

Itraconazole

Pharmacology

Itraconazole is a triazole that was recently licensed for use in humans in the United States.[30] It is similar to ketoconazole but has 5 to 100 times greater potency, better *in vitro* and *in vivo* activity against aspergillus infections and meningeal cryptococcoses, and fewer side effects. It is insoluble in water, highly lipophilic and is well absorbed if taken with a meal. It is highly protein-bound and widely distributed to tissues. Tissue concentrations (especially fat, liver, adrenal cortex and skin) are substantially greater than plasma concentrations, and therapeutic concentrations are maintained longer in tissue than in plasma. The volume of distribution greatly exceeds body water (11-17 l/kg). It is poorly distributed to CSF, ocular fluids and plasma. It is degraded by hepatic metabolism, and the primary route of elimination is via the bile. Elimination half-life in man is longer than for ketoconazole (17 to 25 hours versus 8 hours), and steady-state concentrations are achieved in approximately six days. Itraconazole is considered safe for long-term treatment in humans at a dose of approximately 4-6 mg/kg/day, and dogs receiving up to 40 mg/kg/day for three months did not show signs of toxicity.[60] Maternal toxicity, embryo toxicity and teratogenicity were absent in mice treated with 10 mg/kg/day, but did occur when the dose was increased to 40 and 160 mg/kg; use in pregnant animals is not recommended.[61]

In man, itraconazole has shown promising results for treating aspergillosis; however, there are conflicting reports when efficacy is compared to other drugs (primarily amphotericin B and flucytosine). Even with prolonged treatment (eg, several months), relapses and treatment failures are common. If reports in the literature are any indication, itraconazole alone or in combination with amphotericin B appears to be the treatment of choice for aspergillosis in humans.

There is limited data on the use of itraconazole in animals. It was as effective as ketoconazole when used for three months in cats with cryptococcosis, but less toxic.[44] Variable success has been seen with itraconazole used to treat superficial dermatophyte infections and systemic blastomycosis.[5] It was unsuccessful as a sole treatment in resolving four cases of canine nasal aspergillosis; better success was achieved in another study when itraconazole was combined with topical enilconazole infusion.[64]

Use in Companion Avian Medicine

Reports of itraconazole use in birds are limited, but it has been used to treat aspergillus and candida infections in macaws and penguins.[31] A severe *Candida krusei* tracheitis was resolved in a Blue and Gold Macaw that received itraconazole at 10 mg/kg/day for 35 days. Presumed ocular aspergillosis in a King Penguin was successfully resolved after treatment with 8 mg/kg/day for 29 days. Two penguins with candida infections of the uropygial gland were successfully treated with 10 mg/kg/day for 20 days. A Gentoo Penguin with a pulmonary aspergilloma showed marked improvement and reduction in the size of the aspergilloma after receiving itraconazole at 8.3 mg/kg for 30 days and 17 mg/kg for an additional 19 days. However, the bird died from cerebral aspergillosis three weeks after therapy ended. In man, pulmonary aspergillosis is treated for six to nine months, so the treatment failure in this case may have been due to the short duration of therapy.

Fluconazole

Pharmacology

Fluconazole is a synthetic bistriazole that became available in the United States in 1990.[30] *In vitro* potencies are up to 100 times greater than ketoconazole. Most yeast and fungi of medical importance are susceptible to fluconazole *in vitro*. *In vivo*, it has excellent activity against yeast and variable activity against aspergillus. In contrast to ketoconazole and itraconazole, fluconazole is highly water soluble and is readily absorbed from the GI tract regardless of acidity or food intake. It is not highly protein-bound and penetrates the CSF, brain tissue, ocular fluids and sputum; the volume of distribution is similar to body water (0.7 l/kg). It is eliminated primarily by the kidney, and the prolonged serum half-life of 4 to 5 hours in rats and mice, 14 hours in dogs, and 22-30 hours in humans is presumably due to tubular reabsorption. The dose should be modified if renal function is impaired. Fluconazole alters the kinetics of drugs that undergo hepatic metabolism, but not to the degree described with ketoconazole. The manufacturer recommends giving a double loading dose during the first 24 hours, because five to seven days are needed to achieve steady-state concentrations in man. Fluconazole is well tolerated in humans, although mild GI, CNS and skin reactions are occasionally reported. Hematologic abnormalities are rare. Doses of 30 mg/kg/day in dogs caused increased hepatic fat and hepatic weight.

Clinical studies in humans are still investigating the efficacy of fluconazole *in vivo*. It has been highly successful for treating tissue candida and coccidiomycosis infection and variably successful for treating pulmonary aspergillosis. It is probably the drug of choice in situations where penetration into the CSF is desirable.

Clinical studies in animals with fluconazole are even more limited. Six of ten dogs with nasal aspergillosis were successfully treated with 2.5-5 mg/kg/day orally for eight weeks.[56] Fluconazole was considered effective treatment in animal models for blastomyces, cryptococcus, candida, coccidioides and histoplasma infection. As with clinical trials in humans , fluconazole was variably effective against aspergillosis.[30]

Use in Companion Avian Medicine

Juvenile psittacine birds treated with fluconazole were found to be fecal negative for yeast as determined by Gram's stain; clearance of yeast required 48 hours.[2] Based on this limited study, dosage recommendations of 2-5 mg/kg/day were suggested. Transient regurgitation, increased AST and LDH levels were observed in some birds. Further studies are needed to establish the safety and efficacy of fluconazole in birds.

Enilconazole

Pharmacology

Enilconazole is an imidazole antifungal agent with a broad spectrum. It is not approved for use in the United States. It is poorly soluble and its use is limited to topical application and inhalation. Inhalation of burned enilconazole has been used to treat aspergillosis in poultry.[50] It has also been infused into the nasal passages and sinuses to treat canine nasal aspergillosis.[57] Reports of use in companion and aviary birds are lacking.

Summary of Antifungal Treatment

Spectrum, ability to reach the site of infection, route of administration and potential toxicity are important considerations when selecting an antifungal agent. Spectrum is difficult to determine for antifungal drugs because the methods for *in vitro* testing are expensive, are poorly standardized and there is often little correlation between *in vitro* and *in vivo* efficacy. This makes drug selection somewhat empirical, but some generalities can be made. Most candida are susceptible to nystatin, and almost all yeast of medical importance are susceptible to ketoconazole, itraconazole, fluconazole and amphotericin B. In human and animal studies, itraconazole and fluconazole are more active than ketoconazole, with itraconazole showing greater activity against aspergillosis, and fluconazole showing greater activity against yeast infections. A combination of amphotericin B and flucytosine or an azole, or an azole and flucytosine may provide better efficacy than either drug alone.

The ability of the drug to reach the site of infection is also important. Nystatin is not absorbed from the alimentary tract and must come in contact with the yeast. Systemic infections by hypheal fungi (eg, aspergillus) usually cause a granulomatous response that inhibits drug penetration to the site of infection. Ketoconazole and itraconazole are highly protein-bound and develop high tissue concentrations, but are found in low concentrations in the CSF and ocular fluids. In contrast, fluconazole is water-soluble, minimally protein-bound, and able to treat the CNS, eye and sputum. In general, fungal infections require

TABLE 17.2 Susceptibility of Common Avian Infectious Agents to Antimicrobial Therapy

ANTIBACTERIAL	G^- bacteria	Pseudomonas	G^+ bacteria	Mycoplasma	Chlamydia	Anaerobes
Amikacin	+++++	+++	+++	–	–	–
Ampicillin / Amoxicillin	+	–	+++	–	–	–
Chloramphenicol	+	–	+++	–	+	–
1st generation Cephalosporins	+	–	+++++	–	–	–
3rd generation Cephalosporins	+++++	+++	+	–	–	–
Enrofloxacin	++++	+	+++	+++++	+	–
Gentamicin	+++	+++	+++	–	–	–
Macrolides (Tylosin, Clindamycin)	+	–	++++	+	–	++++
New Macrolides	–	–	++++	+	possible	++++
Tetracycline	+	–	+	++++	+++++	–
Trimethoprim / Sulfa	++++	–	++++	–	–	–

ANTIFUNGAL	Yeast	Aspergillus	Other Fungi
Amphotericin	+++++	++++	+++++
Fluconazole	++++	+++	–
Flucytosine	+++++	+	+++++
Itraconazole	++++	+++++	+++++
Nystatin	++++	–	–

+++++ = most isolates susceptible; ++++ = many isolates susceptible; +++ = some isolates susceptible; ++ = few isolates susceptible; + = almost no isolates susceptible

longer treatment periods than bacterial infections. Sometimes many months of therapy are needed to control aspergillosis.

Finally, the route of administration and potential toxicity are important considerations. All of the antifungal drugs mentioned are delivered orally with the exception of amphotericin B, which must be administered IV. Nystatin is virtually nontoxic. Ketoconazole has greater potential toxicity than either itraconazole or fluconazole, especially if long-duration and high-dose therapy are used. Drug interactions should also be considered. Ketoconazole and fluconazole may significantly alter the hepatic metabolism of drugs such as barbiturates and rifampin.

Nystatin is the drug of choice for uncomplicated yeast infections of the alimentary tract. It is inexpensive and virtually nontoxic. Resistant or severe yeast infections can be treated with ketoconazole or fluconazole. Ketoconazole is less expensive but potentially more toxic; few side effects have been observed when used for fewer than two to three weeks. Systemic yeast infections can be treated with either ketoconazole, fluconazole or itraconazole, depending on the site of infection.

Drug selection for treatment of aspergillosis infections is more problematic. Cutaneous aspergillosis is probably best treated with fluconazole or itraconazole (ketoconazole might be effective in limited cases). Topical administration of enilconazole or miconazole may also be effective. Severe pulmonary or disseminated aspergillosis carries a poor prognosis for recovery regardless of the treatment program. Amphotericin B is the primary drug of choice for chronic infections and infections in immunocompromised patients because it rapidly develops fungicidal concentrations. Prior to the availability of the new azole antifungals, a combination therapy with amphotericin B, flucytosine and rifampin was recommended. Based on human clinical studies, it is probably more effective to use amphotericin B in combination with itraconazole for initial treatment, and then continue long-term treatment for months with itraconazole alone. Flucytosine also has substantial anti-aspergillus activity and may be preferable if there is CNS involvement. Intratracheal ad-

ministration of amphotericin B is very useful when treating syringeal or tracheal infections. Systemic infections caused by other fungi (eg, mucormycosis and cryptococcosis) can be treated in the same manner as systemic aspergillosis.

Antifungal drug research is currently an active field, spurred by the increasing numbers of opportunistic fungal infections in immunocompromised human HIV patients. New drugs may soon be available.

Products Mentioned in the Text

a. Keet Life, Hartz Mountain, Harrison, NJ
b. Ornacin, Mardel Laboratories, Glendale Heights, IL
c. LA-200, Pfizer Laboratories, New York, NY
d. Myco 20, Squibb Laboratories, Princeton, NJ
e. Bactrim, Roche, Nutley, NJ

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