Antibiotics in Avian Species

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Bacterial infections are commonly diagnosed and treated with antibiotics in the avian species. Infected birds can spread zoonotic diseases such as influenza, psittacosis, pasteurellosis, and campylobacteriosis to humans, especially if they are in close contact with them, such as pet-owner settings, zoos, or pet shops. The elimination of bacterial infections in birds is therefore important for both human and avian health.

Keywords: antibiotic ; bird ; dosing

1. Drug Disposition and Pharmacokinetic Parameters in Birds

To understand the pharmacokinetic profiles of drugs in avian species, it is important to first understand the pertinent physiological and behavioural traits of birds that can affect the absorption, distribution, metabolism, and excretion of a drug.

The avian stomach is made up of two sections, namely the proventriculus and the gizzard. The proventriculus secretes digestive enzymes while the gizzard is responsible for mechanical digestion and absorption by grinding and crushing food. Birds with softer diets such as carnivorous birds tend to have thin and poorly muscled gizzard walls while insectivorous, herbivorous, and granivorous birds have highly differentiated stomachs with more powerful gizzards, for triturating tougher stomach contents [1]. This could potentially affect drug absorption as efficient mechanical digestion can increase the surface area of the drug presented to the intestines for absorption.

In avian species, the impact of fed or fasted status on the absorption of a drug is accentuated due to the presence of the crop along the oesophagus. In a fasted bird, ingested food bypasses the crop and travels directly into the stomach. However, if the gizzard is filled, food consumed will then be diverted into the crop where there is minimal absorption and stored until contractions discharge food boluses into the lower oesophagus [1]. Absorption mainly occurs in the small intestine [2], and a delayed movement of food from the crop will result in delayed absorption. The digestive system of birds who pursue active prey (raptors) also tend to have shorter intestinal transit times as a reduced ingesta mass aids flight performance [3]. As the transit time determines the duration of the drug at the absorption site, a shorter transit time may lead to a poorer absorption of drugs in birds. The eventual fraction of drug that is systemically absorbed is indicated by the PK parameter of bioavailability, F.

The distribution of a drug largely depends on its physicochemical properties, such as its partition coefficient and acid dissociation constant (pKa). Other factors affecting the distribution of a drug also include the presence of influx or efflux transporters [4], and organ or tissue blood flow [5]. The primary PK parameter, apparent volume of distribution (V), is the fluid volume that a drug seems to be distributed in to account for the observed plasma concentration. It is dependent on the extent of tissue and plasma protein binding [5]. Plasma protein albumin has a high affinity for acidic and neutral drugs, while α1-acid glycoprotein is an important binding protein for basic drugs [6].

The clearance of a drug can be via the metabolism of excretion. In drug metabolism, Phase I reactions add or expose -OH, -SH, $-NH_2$, or -COOH functional groups. Phase II reactions couple the drug (or its metabolites) with large, often water-soluble polar molecules [7], so as to render them soluble enough to be excreted in urine. Avian liver enzymes are capable of both Phase I and II reactions [7], which make drugs and their metabolites more water-soluble to be excreted via urine. Relative to mammals, birds tend to have relatively lower levels of cytochrome P450 (CYP450) proteins [8]. This phenomenon is especially witnessed in the marine-eating and raptor species of birds.

In birds, kidney nephrons are mostly reptilian-type, which lack a loop of Henle and are less able to concentrate urine than mammalian-type nephrons [2]. However, avian kidneys are able to vary their glomerular filtration rate (GFR) to a much larger extent than mammals, by up to 65% in states of dehydration [9]. Additionally, birds excrete nitrogenous waste as uric acid [10][11], unlike urea in mammals and humans. This is significant as the excretion of insoluble uric acid reduces water

loss and the water requirement of the animal, especially in water-scarce areas. However, in states of renal dysfunction, insoluble uric acid build-up may result in a more rapid manifestation of clinical symptoms such as kidney failure and gout. Avian species also have a renal portal system which is absent in humans, where blood from the caudal half of the body passes through the kidneys before re-joining the systemic circulation [12]. As a result, renally cleared drugs which are intramuscularly administered into the leg may be more rapidly eliminated and result in low bioavailability due to the first-pass effect [13] if it reaches the renal system before entering circulation. This is likely significant as intramuscular injections are usually administered to birds into the pectoral muscle [14]. However, this factor has not been extensively investigated to date.

Clearance (CL) and the apparent volume of distribution (V) of a drug are two primary PK parameters that impact the half-life of a drug. The overall exposure of the animal to a drug can be gleaned from the area under the curve (AUC) parameter.

2. Types of Antibiotics

Antibiotics can be classified based on their PD properties [15]. The first group consists of concentration-dependent antibiotics such as the aminoglycosides and fluoroquinolones. Concentration-dependent antibiotics should be given once daily at the highest possible dose as their bactericidal effect increases with increasing C_{max}, and they possess a significant post-antibiotic effect (PAE). To achieve clinical response, a C_{max}:MIC value of 8–10 is desirable for aminoglycosides [16][17] and an AUC:MIC value of >100–125 h [17] or ≥125 h [16] is desirable for fluoroquinolones according to animal and human clinical studies. The second group consists of time-dependent antibiotics such as beta-lactams. These antibiotics have minimal PAE and their bactericidal action depends on the T > MIC. To achieve an optimal bactericidal effect, T > MIC should be ≥50–80% of the dosing interval [16], or ≥40–50% of the dosing interval [17] according to animal and human studies. The third group consists of antibiotics such as the tetraycyclines and clindamycin. These antibiotics can display time- or concentration-dependent activity depending on the dose used and the pathogen it is targeting. They have a long-to-moderate PAE and their efficacy depends on the AUC:MIC achieved [16][17]. However, the optimal AUC:MIC target is unknown and animal studies have used targets ranging from 13 to 40 h [17][18].

3. Fluoroquinolones

Fluoroquinolones are broad-spectrum antibiotics which have potent bactericidal activity against Gram-negative *Enterobacteriaceae*. Some also have activity against selected Gram-positive bacteria and *Pseudomonas* spp. In humans, most fluoroquinolones are well-absorbed orally, have high volumes of distribution, and are predominantly cleared by the kidneys [19]. In avian medicine, enrofloxacin and marbofloxacin are the two most commonly used [20][21] and studied fluoroquinolones. They are used to treat avian respiratory and alimentary diseases caused by bacteria such as *Chlamydia psittaci*, *Pseudomonas aeruginosa*, and *Salmonella* spp.

4. Aminoglycosides

Aminoglycosides are bactericidal agents that are primarily active against aerobic Gram-negative bacilli such as *Escherichia coli* and *Pseudomonas aeruginosa*. In humans, aminoglycosides are poorly absorbed from the gastrointestinal (GI) tract as they are polar cations but are well intramuscularly absorbed. These drugs do not undergo significant metabolism, are primarily excreted by renal filtration, and have a low volume of distribution [19]. In avian medicine, amikacin and gentamicin are the two most commonly used and studied aminoglycosides as amikacin produces the least adverse effect and gentamicin is the least costly [20][21].

5. Cephalosporins

Cephalosporins are bactericidal agents that are classified into different generations based on their antimicrobial activity. Third-generation cephalosporins are broad-spectrum antibiotics that are highly active against *Enterobacteriaceae* such as *Escherichia coli*, *Klebsiella* spp., and *Salmonella* spp. In humans, most cephalosporins are well absorbed after oral administration, primarily excreted by the kidneys, well-distributed throughout the body, and undergo minimal metabolism [19].

6. Tetracyclines

Tetracyclines are bacteriostatic agents which inhibit the growth of bacteria. They are mainly active against Gram-negative organisms. In humans, the absorption of most tetracyclines from the GI tract is incomplete and can be inhibited by the

presence of divalent and trivalent cations. However, doxycycline has good oral absorption that is unaffected by the presence of food. Tetracyclines have a high volume of distribution and are predominantly eliminated by the kidneys, with the exception of doxycycline, which is excreted mostly unchanged in the bile and urine [19].

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