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Review

The use of antimicrobial agents in broiler chickens

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ABSTRACT

Antimicrobial agents are essential tools for treating and controlling bacterial infections in poultry production. Veterinarians have a huge responsibility when using antimicrobials in poultry producing meat and eggs for human consumption. The term 'judicious use' of antimicrobials implies the optimal selection of drug, dose and duration of antimicrobial treatment, along with a reduction in inappropriate and excessive use as a means of slowing the emergence of antimicrobial resistance.

The proper use of antimicrobials depends on the knowledge of interrelationships between bacteria, antimicrobial, host and consumer. This article reviews the anatomical–physiological features of poultry relating to drug disposition as well as the pharmacological and therapeutic characteristics of the most commonly used antimicrobials in broiler chickens. Doses frequently employed for flock treatment are presented as are accepted withdrawal times.

Introduction

Poultry meat and eggs are major food sources for the world's rapidly expanding population; considering that production costs are low (compared to, for example, pork) and the virtual absence of religious restrictions, the poultry industry is probably the most widespread food production industry worldwide. The global chicken meat and global egg markets have grown over the 5-year period from 2006–2010 by 19% and 9.52%, respectively (FAO Statistical Yearbook, 2013). Commercial poultry production is a very intensive animal agricultural system, and one poultry house or barn can contain as many as 100,000 commercial layers or broilers. This means that disease control/prevention at all levels must be a major focus for the poultry veterinarian.

Antimicrobial agents are critically important in the prevention and treatment of diseases in poultry production. In spite of scientific (and also political) debates and controversy regarding the potential consequences on public health of the use of antimicrobial agents in animals (Turnidge, 2004; Hao et al., 2014), it is impossible to imagine a sustainable poultry industry without antimicrobial use. In this context, it is vital to understand the interrelationships between bacteria, antimicrobial agents, host and consumer in designing rational drug administration schedules.

The present article will consider key anatomical–physiological features of poultry in relation to drug disposition. Also, the pharmacological and therapeutic characteristics of the most commonly used antibiotics are reviewed. This is a huge subject and clearly it is not possible to analyse all of the important issues in depth. There are, however, a number of excellent reviews that can be consulted and which complement the present paper (see, for example, Agunos et al., 2012, 2013; Goetting et al., 2011; Vermeulen et al., 2002).

Specific characteristics of poultry related to drug pharmacokinetics

Every species has some pharmacokinetic peculiarity that determines drug disposition patterns. Poultry are no exception. Knowledge of the origin of these characteristics is fundamental for a rational design of dosing schedules.

Oral absorption of drugs

In terms of physiological functions, the digestive system in birds is the principal feature that distinguishes them from mammals. To understand the nature of the absorption process, and its effects on drug disposition after oral administration, a brief review of gastrointestinal anatomy and physiology in poultry is necessary.

The gastrointestinal tract (GIT) in birds has profound anatomical and physiological differences compared to the mammalian GIT, and these significantly influence the pharmacokinetic processes of most drugs. Birds have neither lips nor teeth, and therefore do not have the ability of grinding feed in the oral cavity. Unlike mammals, there is no sharp distinction between the pharynx and mouth (absence of soft palate); the combined avian oral and pharyngeal cavities are referred to as the oropharynx. As with other granivorous (seed-eating) birds, poultry show well-developed salivary glands that are located on the roof and floor of the mouth. Although some

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species, such as sparrows, secrete considerable amounts of amylase, the secretion of salivary amylase in poultry is very low (Denbow, 2000).

The chicken's oesophagus has a total length of around 140 mm and is divided into a cervical and a thoracic region; the crop is a vertical diverticulum of the cervical portion of the oesophagus that functions as a food store. Although drug absorption from the crop is minimal or absent, its influence on the temporal pattern of drug absorption is important. In general, dry feed remains in the crop longer than wet feed. Mean retention time can be as short as 3 h but may be up to 20 h (Vermeulen et al., 2002).

The pH of the crop in chickens is around 4.5, and is more acidic than in other bird species such as turkeys (pH 6) (Denbow, 2000), or pigeons (pH 6.3) (Herpol and van Grembergen, 1967). For some antimicrobial agents, such as the tetracyclines, this offers an advantage since precipitation at this site is not common. It is important to bear in mind that all tetracyclines precipitate at a pH near the isoelectric point, around 5.5 (Mitscher et al., 2013), therefore precipitation is common in the crops of pigeons and turkeys, but not chickens. On the other hand, the presence of *Lactobacillus* spp. flora in the crop (Hilmi et al., 2007) can interfere with the absorption of some antimicrobial agents, such as macrolides, due to their capability to metabolise this group of antimicrobials (Dutta and Devriese, 1980).

The avian stomach consists of two chambers, namely, the proventriculus (pars glandularis), the site of acid secretion, and the gizzard (pars muscularis) that functions in mechanical digestion and is the site of gastric proteolysis. The pH of the proventriculus and gizzard is 4 and 2.5, respectively (Svihus, 2011), and the mean retention time in the whole stomach is 40–71 min (Van Der Klis et al., 1990).

The small intestine is sometimes divided into the duodenum, jejunum and ileum, although these are not distinguishable based on histology or gross observation. Intestinal pH varies with the location, and is around 6 in the first segment increasing to 7.3 in the last portion (Herpol and van Grembergen, 1967). The intestinal flora in the adult chicken contains large numbers of *Lactobacillus* spp. and it is important to be aware of this due to the microorganism's capacity to metabolise macrolide–lincosamide–streptogramin antibiotics. On the other hand, enterocytes are rich in cytochrome P-450 enzymes, especially CYP3A (Antonovic and Martinez, 2011), so, for antimicrobial agents that are substrates for these enzymes (macrolides, lincosamides), a first pass metabolism can take place at this level leading to reduced bioavailability.

The presence of efflux pumps (P-glycoprotein) at the apical surface of enterocytes in the duodenum, jejunum and ileum has been reported (Haritova et al., 2010) adding another factor that could interfere with the absorption of some antimicrobial agents such as fluoroquinolones, oxytetracycline, doxycycline and, to a lesser extent, macrolides when administered orally (Haritova, 2008). An interesting paper published by Guo et al. (2013) reported the age dependency of P-glycoprotein expression in poultry enterocytes, demonstrating an influence in lowering the bioavailability of enrofloxacin in 4 week-old compared to 8 week-old broilers.

Drug elimination in poultry

As with mammals, most drugs are eliminated in birds by a combination of biotransformation (mainly hepatic) and renal excretion. Phase I and phase II reactions have been reported in birds. In both birds and mammals, enzyme systems involved in phase I reactions include cytochrome P450 (CYP450), flavine monoxygenases and monoamine oxidases.

Of all these enzymatic systems the cytochrome superfamily is the most frequently involved. In chickens, at least 41 putatively fully functioning CYP genes have been reported (Nelson, 2009). Cytochrome 1A4/5 and CYP3A37 have been identified in the turkey as 'orthologues' (genes in different species that encode for proteins that generally share similar functions) of the human CYP1A2 and CYP3A4, respectively. The latter cytochromes are involved in the biotransformation of a large number of human drugs currently on the market. In phase II reactions, the main difference from mammals is that poultry mainly use the ornithine path for conjugation instead of the glucuronide reaction. Renal excretion processes have important differences compared to mammals as a consequence of the anatomical and functional differences between kidneys.

In birds, nephrons resemble those of reptiles with only 20–30% of nephrons possessing loops of Henlé. Functionally, the glomerular filtration rate in chickens is almost half of that of mammals with very low or absent tubular reabsorption. Also, the characteristic renal portal system present in birds must be considered since it can reduce the bioavailability of drugs administered intramuscularly.

Drug administration method in poultry

Differences in the modalities of drug administration across species depend on animal and management husbandry procedures. In poultry, antimicrobial agents can be administered either individually or, more often, at a flock level. Individual administration has the advantage that only sick animals are treated, using the correct dose. However, it is time- and labour-consuming if large numbers need treatment and it is stressful on animals and staff. On the other hand, flock treatment is easy to perform, as large numbers of birds can be promptly treated and the medication can be given in the early stages of a disease outbreak. However, the dose will not be homogeneous in all the treated birds.

For drug administration at flock level, the oral route is chosen because it enables large numbers of birds (sometimes several thousand) to be treated conveniently and cheaply at the same time. Considering organoleptic and physicochemical properties (water solubility, stability, palatability etc.), antimicrobial agents can be administered via drinking water or medicated feed. The selection of the appropriate modality is based on the final objective of the administration, namely, (1) disease treatment (therapeutic), (2) disease control (metaphylactic: the application of antimicrobials to groups of animals at times when only single animals of the group present symptoms of the disease, but it is expected that most of the group will become affected) or (3) disease prevention (prophylactic: a solely preventive measure. It should be used with discretion, since this may provide the basis for selection of resistance among pathogenic bacteria).

Drinking water is the preferred mode of administration, because diseased birds usually tend to stop eating but will often continue to drink (Esmail, 1996).

Drinking water medication has several advantages in relation to therapeutic and metaphylactic treatment, such as low cost, ease of administration, immediate therapeutic care for all diseased or endangered birds in the flock, and in addition a quick change of drug and/or dose is possible (Vermeulen et al., 2002). The main disadvantages are related to the several factors that influence individual animal water intake, including biological (bodyweight, age, and gender), environmental (lighting period, environmental temperature) and management factors (flock size, composition of the diet).

An alternative to the drinking water is the administration of a drug through the food via pre-mix formulations. In contrast to water that is offered ad libitum, food may be given and is ingested in a restricted way, and competition exists between birds. Therefore, the pecking order that influences food intake will modulate drug exposure and unavoidably lead to differences of medication ingestion between individuals. Toutain et al. (2010) have indicated that the use of medicated feed in food animals has been associated with imprecise drug intake, leading to under- or over-administration of drugs.