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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.

Over-administration may lead to animal toxicity and the presence of drug residues in meat (Guardabassi and Kruse, 2008); under-administration or inconsistent administration of antimicrobials may lead to treatment failure as well as the emergence of antibiotic-resistant bacterial strains (Lees et al., 2006; Guardabassi and Kruse, 2008).

Subcutaneous (SC) administration is only applied and relevant to the treatment of day-old chicks.

Antimicrobial agents used in poultry

The antimicrobial groups most commonly used in poultry are the betalactams, polypeptides, aminoglycosides and aminocyclitols, macrolides and lincosamides, florfenicol, tetracyclines, sulphonamides, quinolones and fluoroquinolones and ionophores (Hofacre et al., 2013).

Betalactams (penicillins and cephalosporins)

Betalactams are bactericidal; according to their bacterial killing kinetics, betalactams are classified as time-dependent antimicrobial agents, and the ideal dosing regimen would maximise the duration of drug exposure. The length of time that the concentration of an antibiotic remains above the minimum inhibitory concentration (MIC) i.e. the T > MIC, is the parameter that best correlates with efficacy. Maximum killing is seen when the T > MIC is at least 40–60% of the dosing interval (Toutain et al., 2002; McKellar et al., 2004; Lees et al., 2006).

The commonest penicillin used in poultry production is penicillin G, which is especially important for treating clostridial infections causing necrotic enteritis (Gadbois et al., 2008), and pasteurellosis or fowl cholera (Huang et al., 2009; Sellyei et al., 2009); the broader spectrum penicillins, amoxicillin and ampicillin (combined or not with clavulanic acid) are effective for Gram-negative infections such as *Escherichia coli* air sacculitis.

Penicillin G bioavailability after oral administration is higher compared to mammals, probably due to the higher gastric pH. Penicillin G is rapidly absorbed after oral administration, with a peak plasma concentration (T_{max}) of 2 h (Dorrestein et al., 1984) with limited distribution to the extracellular fluid. Different from mammals (in which penicillin is excreted unchanged by urine), the primary excretion route in birds is hepatic, through bile. The elimination half-life most commonly reported is 30 min, although the data were obtained from turkeys (Hirsh et al., 1978).

Amoxicillin is well absorbed after oral administration. However, because its stability in water is poor (Jerzselle and Nagy, 2009) it is normally administered in feed. On the other hand, despite its low bioavailability after oral administration, ampicillin has better stability in water and is generally administered in drinking water. Although ampicillin has lower oral bioavailability (30%) compared to amoxicillin (61%) (Sumano Lopez and Gutierrez Olivera, 2010), absorption is rapid with both compounds (T_{max} 0.5–1 h), with a short elimination half-life (30 min) (Sumano Lopez and Gutierrez Olivera, 2010).

Amoxicillin and ampicillin are indicated for the treatment of secondary infections in chronic respiratory disease caused by *E. coli*, *Pasteurella multocida*, *Salmonella* spp. and also for the control and treatment of necrotic enteritis (*Clostridium perfringens*).

Ceftiofur is the only cephalosporin approved for use in poultry production. As a third generation cephalosporin it is highly effective against Gram-negative bacteria. Ceftiofur is used exclusively for SC injection in day-old chicks in many countries, but is not approved for such use in some countries, for example in Canada (McEwen et al., 2010). It may also be used in poults. Ceftiofur has been administered in-ovo but this extra-label use was banned in the USA in 2012[1] Ceftiofur is indicated for the treatment/control of colibacillosis and yolk sac infections.

Polypeptides

Bacitracin is the only polypeptide antimicrobial agent approved for use in poultry. When given orally, it is not absorbed from the gastrointestinal tract and therefore its effect is local. Bacitracin is available for administration in both drinking water and feed additive formulations. It is commonly administered in feed for preventing/controlling necrotic enteritis (Hofacre et al., 1998). Reported prophylactic and therapeutic doses for zinc bacitracin are presented in Table 1. Administration is continuous, without any required withdrawal time.

Aminoglycosides and aminocyclitols

The aminoglycosides and aminocyclitols are bactericidal drugs with an antibacterial spectrum that includes aerobic Gram-negative bacteria (such as the *Enterobacteriaceae* and *Pseudomonas*) and staphylococci.

According to their bacterial killing kinetics, aminoglycosides and aminocyclitols are classified as concentration-dependent antimicrobial agents, and the ideal dosing regimen would maximise concentrations, because the higher the concentration, the more extensive and the faster is the degree of killing. The ratio area under the plasma concentration vs. time curve from 0 to 24 h/MIC ($AUC_{(0–24)}$/MIC) is the parameter that best correlates with efficacy. Maximum killing is seen when $AUC_{(0–24)}$/MIC is >100. A C_{max}/MIC ratio of at least 8–10 prevents resistance (Toutain et al., 2002; McKellar et al., 2004; Lees et al., 2006).

Only three aminoglycosides are used in poultry, namely, gentamicin, streptomycin and neomycin. Members of this group of compounds are polar bases and are therefore poorly absorbed when administered orally. The primary use of gentamicin in poultry has been by SC injection in day-old chickens (McCapes et al., 1976; Vernimb et al., 1977). After SC administration, bioavailability is 100% (Abu-Basha et al., 2007a). The recommended dose for 1 day-old chickens is 0.2–0.5 mg/chick. However, when administered with Marek's disease vaccine, doses >0.2 mg/chick have been associated with damage to the cell-associated Marek's vaccine (Kinney and Robles, 1994).

Neomycin is not significantly absorbed after oral administration either in feed or water so its effect is local for treating enteric infections, including colibacillosis (Marrett et al., 2000). The recommended doses for prevention/control and treatment are presented in Table 1.

Streptomycin is partially absorbed after oral administration and is indicated for treating systemic *E. coli* infections. Recommended dose and withdrawal time are presented in Table 1.

There are two aminocyclitols approved for use in poultry, namely, hygromycin and spectinomycin. Hygromycin is administered in feed exclusively for its anthelmintic effect. Spectinomycin, due to its low bioavailability after oral administration (Abu-Basha et al., 2007b), is administered in drinking water for local treatment of *E. coli* infections (Goren et al., 1984).

Macrolides, tiamulin and lincosamides

The macrolides most commonly used in poultry are erythromycin, tylosin and tilmicosin. They are considered to be bacteriostatic at therapeutic concentrations, but can be slowly bactericidal, especially against streptococci. Their antimicrobial action is enhanced

[1] See: http://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf (accessed 07 April 2015).

Table 1
Antimicrobial agents used in broiler chickens: mechanism of action, effects, spectrum, dose and withdrawal time.

Antimicrobial	Type/mechanism of action	Disease-bacterial species	Oral dose	Withdrawal time
Betalactams				
Penicillin G	Bactericidals Cell wall synthesis inhibitors	*Staphylococcus* spp.; necrotic enteritis; erysipelas; fowl cholera; fowl coryza	300,000–400,000 IU/L.	1 day
Amoxicillin	Narrow spectrum	*E. coli*; *Pasteurella multocida*; *Salmonella* spp.; necrotic enteritis	10–20 mg/kg feed (100–200 ppm)	5 days
Ampicillin		*E. coli*; *Pasteurella multocida*; *Salmonella* spp.; necrotic enteritis	1.5 g/L	5 days
Ceftiofur		SC injection 1 day-old chickens In-ovo (prohibited in Canada)	(SC) 0.08–0.2 mg/chick	
Polypeptides				
Bacitracin	Bactericidal Cell wall synthesis inhibitor Narrow spectrum	Necrotic enteritis	Prophylactic 55–110 mg/kg feed Therapeutic 200–400 mg/kg feed	0 days
Aminoglycosides				
Gentamicin	Bactericidals	SC injection 1 day-old chickens	(SC) 0.2–0.5 mg/chick	
Neomycin	Protein synthesis inhibitors (30s) Narrow spectrum	Necrotic enteritis	Prophylactic 9.6–19.1 mg/L Therapeutic 35–80 mg/L or 35–226 g/ton	Canada 7 days USA 0 days
Streptomycin		*Staphylococcus* spp.; colibacillosis; necrotic enteritis; fowl cholera; fowl coryza	66–100 mg/L	4 days
Aminocyclitols				
Hygromycin	Bactericidals	Anthelmintic		
Spectinomycin	Protein synthesis inhibitors (30s) Narrow spectrum	*Staphylococcus* spp.; CDR/mycoplasma; colibacillosis; necrotic enteritis; fowl cholera	1 g/L	5 days
Macrolides				
Erythromycin	Bacteriostatics Protein synthesis inhibitors (50s)	*Staphylococcus* spp.; fowl coryza; *Mycoplasma* spp.	92.5–185 g/ton 115.6–250 mg/L	1 days
Tylosin	Broad spectrum	CDR/mycoplasma; necrotic enteritis; fowl coryza	800–1000 g/ton; 500 mg/L	3–5 days
Tilmicosin		*Mycoplasma* spp.; *Pasteurella multocida*; *Ornithobacterium rhinotracheale*	75 mg/L	12 days
Tiamulin		*Mycoplasma* spp.; intestinal spirochaetosis	160–320 mg/kg feed; 250 mg/L	2 days
Lincosamides				
Lincomycin	Bacteriostatics Protein synthesis inhibitors (50s) Broad spectrum	Necrotic enteritis; intestinal spirochaetosis	16 mg/L; 2 g/ton feed	0 days
Fenicols				
Florfenicol	Bacteriostatic Protein synthesis inhibitors (50s) Broad spectrum	Gastrointestinal and respiratory infections; *Actinobacillus* spp.; *Pasteurella* spp.; *Salmonella* spp.; *Streptococcus* spp.	100 mg/L	7 days
Tetracyclines				
Chlortetracycline	Bacteriostatics Protein synthesis inhibitors (30s)	*Staphylococcus* spp.; CDR/mycoplasma; colibacillosis; fowl cholera; fowl coryza	55–220 mg/kg feed 110–280 mg/L	5 days
Tetracycline	Broad spectrum	CDR/mycoplasma; colibacillosis	300 mg/kg feed 45–100 mg/L	7 days
Oxytetracycline		*Staphylococcus* spp.; CDR/mycoplasma; colibacillosis; fowl cholera; fowl coryza	100–400 mg/kg feed 200 mg/L	7 days
Sulphonamides				
Sulphachlorpyridazine	Bacteriostatic Folate antagonists Broad spectrum	Coccidiosis	12.5–62.5 mg/L	2 days[a]
Sulphadimethoxine		Colibacillosis; fowl cholera	250–500 mg/L	5 days[a]
Sulphamethazine		Colibacillosis; fowl cholera; coccidiosis	250–1000 mg/L	10–12 days
Sulphaquinoxaline		Colibacillosis; fowl cholera; coccidiosis	250–400 mg/L	10–14 day
Sulphathiazole		Colibacillosis; fowl cholera	1000 mg/L	10–14 days
Potentiates sulphonamides				
Sulphachlorpyridazine/ trimethoprim	Bactericidal Folate antagonists Broad spectrum	Colibacillosis; fowl cholera	24 mg (total activity)/L	2 days[a]
Sulphadimethoxine/ ormetoprim		Colibacillosis; fowl cholera	113.5–227 g SDMT and 68.1–136.2 g of OMT/ton feed	10 weeks
Sulphaquinoxaline/ trimethoprim		Colibacillosis; fowl cholera	30 mg (total activity)/L	10 days
Fluoroquinolones				
Enrofloxacin	Bactericidal DNA synthesis inhibitor	CDR/Mycoplasma; colibacillosis; fowl cholera	100 mg/L	Banned in USA and Australia EU 3–7 days
Ionophores				
Salinomycin	Disruptors of ions transport into and through biological membranes	Coccidicidals	50–70 mg/kg feed	1 day
Monensin			80–125 mg/kg feed	1 day
Narasin			60–70 mg/kg feed	1 day
Maduramicin			5 mg/kg feed	5 days
Semduramicin			25 mg/kg feed	5 days
Lasalocid			75–125 mg/kg feed	5 days

CDR, chronic respiratory disease; SDMT, sulphadimethoxine; OMT, ormetoprim.
[a] Considering coprophagia associated recycling it is advisable to increase the withdrawal period up to 10 days.
Note: Labelled doses and withdrawal times depends on the country; It is advisable to use, when available, the labelled dose and withdrawal time set in the country.

in alkaline and suppressed in acidic environments, so they are less effective in abscesses or necrotic tissues.

According to their bacterial killing kinetics, macrolides and lincosamides are classified as time-dependent with moderate to prolonged persistent effects. The ideal dosing regimen for these antibiotics maximizes the amount of drug received. Therefore, the $AUC_{(0–24)}$/MIC ratio is the parameter that correlates with efficacy. Maximum killing is seen when $AUC_{(0–24)}$/MIC is >25–35 (Craig, 1998; Lees et al., 2008; Finberg and Guharoy, 2012; Toutain, 2012).

Microbial susceptibility varies between compounds. Erythromycin has activity primarily against Gram-positive bacteria and is used for treating *Staphylococcus aureus* arthritis. Administered orally, the drug is rapidly and almost completely absorbed, with a T_{max} of 1.3 h, a bioavailability of 100% and an elimination half-life of 4 h (Goudah et al., 2004). The recommended dose is presented in Table 1.

Tylosin is reported to be one of the most effective compounds for treating mycoplasma infection in laying hens to restore egg production, reduce transovarial transmission and minimise clinical signs (Kleven, 2008). Since at therapeutic doses macrolides are bacteriostatic, they cannot entirely eliminate *Mycoplasma* spp. infections from a flock, therefore their use is not considered to be a long term solution. Tylosin is also effective for treating clinical and subclinical necrotic enteritis (Collier et al., 2003; Lanckriet et al., 2010). After oral administration absorption is low, with a bioavailability of 30%; T_{max} is 1.5 h and the elimination half-life is 2 h (Kowalski et al., 2001).

Tilmicosin is effective for controlling mycoplasma infections, *Pasteurella multocida* and *Ornithobacterium rhinotracheale* bacterial infections (Abu-Basha et al., 2007c). After oral administration, tilmicosin is rapidly and completely absorbed (T_{max} 4 h, bioavailability 100%) with a slow elimination as reflected by its elimination half-life of 47 h. (Abu-Basha et al., 2007c).

Tiamulin, a pleuromutilin, is highly effective for treating *Mycoplasma* infections (Laber and Schütze, 1977), and avian intestinal spirochaetosis (Burch et al., 2006; Islam et al., 2009). Tiamulin is not approved for use in USA. When using tiamulin it is very important to bear in mind the interaction of this antimicrobial with ionophore anticoccidials (except lasalocid). Tiamulin is a potent inhibitor of CYP3A enzymes and since this enzyme participates in the metabolism of the ionophore, co-administration with tiamulin will lead to a lower metabolic conversion (Nebbia et al., 1999; Szucs et al., 2004). Since ionophores in poultry have a small margin of safety (<1.4), the delayed biotransformation and excretion results in an accumulation of ionophores in the liver and clinical signs of intoxication, which can be fatal.

The only lincosamide approved for use in poultry is lincomycin. It has the same mechanism of action as the macrolides with activity against many Gram-positive and anaerobic bacteria. Although it has good bioavailability after oral administration in feed or drinking water, its major use in poultry is the treatment of enteric infections, such as *Clostridium perfringens*-induced necrotic enteritis and intestinal spirochaetosis (Lanckriet et al., 2010). A combination of lincomycin with spectinomycin (1:3 ratio) is available for the control and treatment of *Mycoplasma* spp. infections. Used alone, withdrawal time is nil.

Florfenicol

Florfenicol (a derivative of chloramphenicol, without the capacity to induce dose-independent fatal aplastic anaemia in humans) is a broad spectrum antimicrobial agent with bacteriostatic effect. Its spectrum of activity includes sensitive Gram-negative bacteria (*E. coli*, *Salmonella*), anaerobes *Chlamydia* spp., *Mycoplasma* spp. and intracellular microorganisms.

Florfenicol is commonly administered to poultry via drinking water. Although it has a relatively high bioavailability, this can be highly variable (from 50 to 94%) (Sumano Lopez and Gutierrez Olivera, 2010), possibly as a consequence of its interaction with gastrointestinal contents and also its incompatibility with hard water (>275 ppm) (Hayes et al., 2003). Based on this, florfenicol efficacy in chickens must, at best, be considered inconsistent.

Nevertheless, florfenicol is indicated for the treatment of respiratory infections due to its high efficacy against *E. coli*, *Pasteurella* spp. and *Haemophilus* spp. The recommended dose in drinking water is 100 mg/L, over 2–4 days, with a withdrawal time of 7 days. In some Latin American countries florfenicol is also administered in feed at a recommended dose of 20–40 ppm (Sumano Lopez and Gutierrez Olivera, 2010). However, a number of studies have shown that this dose is too low, and doses >80 ppm should be used to guarantee efficacy and avoid resistance (Sumano Lopez and Gutierrez Olivera, 2010).

Tetracyclines

Tetracyclines are bacteriostatic antibiotics that interfere with bacterial protein synthesis. They are active against bacteria, protozoa, bacterial L-form, anaerobic and intracellular microorganisms such *Mycoplasma* and *Chlamydia* spp. The main spectrum differences between the drugs are due to their different lipid solubility. This group is probably the one that is most commonly used in poultry production due to its broad spectrum, wide margin of safety and zero day egg withdrawal.

According to their bacterial killing kinetics, tetracyclines are classified as time-dependent with moderate to prolonged persistent effects. The ideal dosing regimen for these antibiotics maximizes the amount of drug received. Therefore, the $AUC_{(0–24)}$/MIC ratio is the parameter that correlates with efficacy. Maximum killing is seen when $AUC_{(0–24)}$/MIC is >30–40. (Craig, 1998; Lees et al., 2008; Finberg and Guharoy, 2012; Toutain, 2012; Papich and Riviere, 2013).

The most commonly used tetracyclines in poultry production are chlortetracycline, tetracycline and oxytetracycline. They have good oral absorption but are chelated in the avian intestines by bivalent cations, such as calcium and magnesium.

Tetracyclines are administered in feed and drinking water. It is important to highlight the low water solubility of these molecules at pH 7; to solve this problem it is advisable to acidify the water with citric acid (5 g of citric acid for each gram of tetracycline to be dissolved in the drinking water) (Pollet et al., 1983).

Tetracyclines are indicated for treating Staphylococci, Mycoplasma, *E. coli*, *Pasteurella multocida* and *Haemophilus paragallinarum*.

Sulphonamides

Although they are the oldest chemotherapeutic agents used for antimicrobial therapy, sulphonamides are still useful for treating or preventing coccidial infections in poultry.

Sulphonamides and diaminopyrimidines, both folic acid synthesis inhibitors, are bacteriostatic drugs, but when combined (as potentiated sulphonamides) are bactericidal and active against *E. coli* and *Pasteurella multocida*.

In poultry, sulphonamides have a narrow margin of safety so their use is limited. Characteristic toxic effects observed in birds are bone marrow suppression, thrombocytopenia and lymphoid and immune depression. Post-mortem changes include haemorrhagic infarcts in the liver and spleen, pale bone marrow, and petechial or ecchymotic haemorrhages in muscles (Frank, 1947; Daft et al., 1989). An additional problem related to sulphonamide use in birds is the potential for presence of prohibitive residues in meat and eggs. The association of sulphonamide elimination in urine and faeces and the coprophagic habits of chickens may lead to recycling, thus increasing drug residence times. To avoid such prolonged residue times it is advisable to increase the withdrawal period of sulphonamides to at least 10 days.

A metabolic interaction between ionophores and sulphonamides has also been reported (Ershov et al., 2001a). As ionophores are inhibitors of CYP3A enzymes, this in turn can result in a lower metabolic conversion of sulphonamides following co-medication.

The drugs of the sulphonamide group which are commonly used in poultry are sulphachlorpyridazine, sulphadimethoxine, sulphamethazine, sulphaquinoxaline and sulphathiazole and the potentiated sulphonamides sulphachlorpyridazine/trimethoprim, sulphadimethoxine/ormetoprim and sulphaquinoxaline/trimethoprim.

Sulphonamides are indicated for the prevention and treatment of coccidia and in outbreaks. They are more effective against intestinal than caecal forms of coccidia.

Sulphonamides are commonly administered in drinking water.

Fluoroquinolones

This group of antimicrobial agents provides some of the most effective antimicrobials for use in poultry. Fluoroquinolones are bactericidal and inhibit bacterial DNA replication and transcription. They are effective against a broad range of important poultry pathogens, including *Mycoplasma*, *E. coli* and *Pasteurella* spp.

According to their bacterial killing kinetics, fluoroquinolones are classified as type I antimicrobials, and the ideal dosing regimen would maximise concentrations, because the higher the concentration, the more extensive and the faster is the degree of killing. The $AUC_{(0-24)}$/MIC is the parameter that best correlates with efficacy. Maximum killing is seen when $AUC_{(0-24)}$/MIC is 125. A C_{max}/MIC ratio of at least 8–10 prevents resistance (Toutain et al., 2002; McKellar et al., 2004; Lees et al., 2006).

The most commonly used of the fluoroquinolones in poultry is enrofloxacin. Older quinolones such as nalidixic acid or oxolinic acid should not be used due to the rapid development of resistance, which can also affect fluoroquinolones (Sárközy, 2001).

Despite their efficacy, the use of fluoroquinolones in poultry is controversial. Australia has never permitted their use in poultry (or indeed in other farm species). Other countries, such as USA, banned the use of fluoroquinolones in poultry 10 years ago, because of concerns about increasing resistance to *Campylobacter* spp. in poultry and humans.[2] Although most countries in the EU still allow the use of fluoroquinolones in poultry, in Finland and Denmark they are banned.

As well as other fluoroquinolones, enrofloxacin has a wide margin of safety, complete and rapid oral absorption and long elimination half-life. It is administered continuously in drinking water and also by pulse dose. The recommended dose is 100 mg/L drinking water for 3–5 days. Single pulse doses must be calculated at the rate of 10 mg/kg. The daily requirement may be added to a maximum of 25% of the estimated daily water consumption. After the medicated water has been consumed, unmedicated water should be provided for the remainder of the day. Withdrawal time varies from 3 to 7 days.

Ionophores

Ionophores are extensively used for preventing coccidial infections in poultry. They have also activity against Gram-positive bacteria, especially *Clostridium perfringens* (Brennan et al., 2001; Lanckriet et al., 2010). They can be subdivided into: monovalent ionophores (salinomycin, monensin, and narasin); monovalent glycoside ionophores (maduramicin and semduramicin), and a divalent ionophore (lasalocid).

Ionophores interfere with the passage of ions across the cell membrane and are therefore coccidicidals (Dusi and Gamba, 1999). It is important to highlight the fact that all compounds share a common mechanism of action, so if resistance develops to one ionophore it will be also apparent with the others (cross resistance). Generally, ionophores have been found safe and effective in birds receiving recommended dosage levels. However, toxic syndromes can result from overdosage and misuse, such as co-administration with fluoroquinolones (Ershov et al., 2001b) and sulphonamides (Ershov et al., 2001a).

Toxic levels of ionophores disrupt potassium and calcium permeability in cells, especially myocytes. Clinical signs of toxicosis vary from anorexia with depression, weakness and reluctance to move to complete paralysis in which birds lie in sternal recumbency with their neck and legs extended (Fulton, 2009).

Conclusions

Veterinarians have a massive responsibility when using antimicrobials in poultry producing meat and eggs for human consumption. 'Judicious use' of antimicrobials implies the optimal selection of drug, dose and duration of antimicrobial treatment, along with a reduction in the inappropriate and excessive use as a means of slowing the emergence of antimicrobial resistance. A fundamental principle common to most guidelines is that the usage of antimicrobials can never replace shortcomings in husbandry, biosecurity measures and prophylactic hygiene on the premises. However, effective preventive medicine and good management can reduce (but may not eliminate) the need for antimicrobial use. Prophylactic or metaphylactic use of antibiotics can be a substantial aid in the control and prevention of diseases (considering the potential for rapid spread on a poultry farm) but the emergence of antimicrobial resistant bacterial strains must be seriously addressed. It is inherently associated with the use of antimicrobials not only in animals (farm and companion) but also in humans.

Use of antimicrobial agents in animals cannot be used as a 'scapegoat' for the emergence of bacterial resistance. Veterinarians must defend the use of one of our most important therapeutic tools, the antimicrobials; this can only be done by responsible, professional prescribing.

Conflict of interest statement

Neither of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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[2] See: http://www.fda.gov/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/ucm042004.htm (accessed 07 April 2015).

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