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Review

Macrolides and lincosamides in cattle and pigs: Use and development of antimicrobial resistance

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ABSTRACT

Macrolides and lincosamides are important antibacterials for the treatment of many common infections in cattle and pigs. Products for in-feed medication with these compounds in combination with other antimicrobials are commonly used in Europe. Most recently approved injectable macrolides have very long elimination half-lives in both pigs and cattle, which allows once-only dosing regimens. Both in-feed medication and use of long-acting injections result in low concentrations of the active substance for prolonged periods, which causes concerns related to development of antimicrobial resistance.

Acquired resistance to macrolides and lincosamides among food animal pathogens, including some zoonotic bacteria, has now emerged. A comparison of studies on the prevalence of resistance is difficult, since for many micro-organisms no agreed standards for susceptibility testing are available. With animal pathogens, the most dramatic increase in resistance has been seen in the genus *Brachyspira*. Resistance towards macrolides and lincosamides has also been detected in staphylococci isolated from pigs and streptococci from cattle. This article reviews the use of macrolides and lincosamides in cattle and pigs, as well as the development of resistance in target and some zoonotic pathogens. The focus of the review is on European conditions.

Introduction

Macrolides are classified according to the number of atoms which comprise the lactone ring, ranging from 12 to 16 members (Yao and Moellering, 2007) (Table 1). The first macrolide intended for food animal use was spiramycin, which was introduced in the early 1960s, followed by erythromycin and tylosin in the early 1970s (Prescott, 2008). The most recent macrolide to be approved in the EU was tildipirosin in 2011. Semi-synthetic, new generation macrolides, the azalides, were introduced into human medicine in the early 1990s (Ballow and Amsden, 1992; Bryskier and Butzler, 2003). The first azalide for animal use, gamithromycin, was approved for use within the European Union (EU) in 2008.

Lincomycin and its semi-synthetic derivatives clindamycin and pirlimycin, belong to the lincosamides. In addition, streptogramins (A and B) are classified along with macrolides and lincosamides (Edelstein, 2004). The only streptogramin used for animals is

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[1] See: http://www.eucast.org/expert_rules/.

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Table 1
Macrolides and related compounds and their approval for animal use in the EU (EMA/CVMP/SAGAM, 2011).

Macrolides			Lincosamides	Streptogramins (A,B)
14-Membered ring	15-Membered ring	16-Membered ring		
Clarithromycin	Azithromycin	Josamycin	Clindamycin[b]	Pristinamycin
Erythromycin[a]	Gamithromycin[a]	Mideacamycin	Lincomycin[a]	Quinupristin/dalfopristin
Oleandomycin	Tulathromycin[a]	Miocamycin	Pirlimycin[a]	Virginiamycin[c]
Roxithromycin		Rokitamycin		
Telithromycin[a]		Spiramycin[a]		
		Tildipirosin[a]		
		Tilmicosin[a]		
		Tylosin[a]		
		Tylvalosin[a]		

[a] Substances approved for veterinary use in one or more member states in the EU (having marketing authorisation [MA]).
[b] Only approved for small animal use.
[c] Not any longer approved in the EU.

virginiamycin, which, until 1998, was approved in the EU as a feed additive for production enhancement of food animals; it is still approved for this use in the US.

Macrolide antimicrobials inhibit bacterial protein synthesis via binding to the 50S subunit of the ribosome. They bind preferentially to the 23S rRNA of the 50S subunit, which overlaps with the binding site of lincosamides and streptogramin B, but differs from those of phenicols like chloramphenicol, and pleuromutilins. Due to this similar mechanism of action, resistance is also often linked, and macrolides, lincosamides and streptogramins B are often referred to as the MLS_B group. Macrolide and lincosamide (ML) antibacterials have generally a bacteriostatic action, which is mainly time-dependent (Giguère 2013a, 2013b). Some new generation macrolides can have bactericidal activity against some bacterial species, in laboratory conditions, although this effect is limited compared with other classes of antimicrobials (Seral et al., 2003).

ML antimicrobials are active against many Gram-positive bacterial genera such as *Streptococcus*, *Staphylococcus*, *Enterococcus* and *Trueperella* (*Arcanobacterium*), as well as against Gram-negative organisms, like *Actinobacillus*, *Haemophilus*, *Histophilus*, *Mannheimia*, *Pasteurella*, *Moraxella*, *Bordetella*, *Campylobacter* and *Lawsonia*. Anaerobes including *Fusobacterium*, *Clostridium* and *Bacteroides* spp. are usually susceptible. In addition, the spectrum covers spirochaetes (*Leptospira*, *Brachyspira*), and *Mycoplasma*. However, substantial differences exist between macrolides in their activity against different organisms (Hardy et al., 1988; Bryskier and Butzler, 2003). The spectrum of activity of lincosamides is similar but not identical than that of macrolides; for example, *Enterococcus faecalis* is intrinsically resistant to lincosamides (Roberts, 2008). Lincosamides have low activity against Pasteurellaceae (Giguère 2013b).

In vitro susceptibility testing for ML antimicrobials is problematic for many bacterial species, since guidelines for determination of minimal inhibitory concentrations (MIC) do not include all micro-organisms (Schwarz et al., 2010; CLSI, 2013). Comparison of resistance data is also difficult because different antimicrobials are often tested and criteria for interpretation may differ.

Macrolides penetrate well into tissues (Giguère 2013a; Rose et al., 2013). ML build up high intracellular concentrations and accumulate within phagocytes (Scorneaux and Shryock, 1999). The actual efficacy of bacterial killing within cells has not been unambiguously demonstrated (Madgwick et al., 1989; Barcia-Macay et al., 2006). After oral administration, macrolides are absorbed incompletely. Lincosamides are absorbed well when given orally to monogastric animals. ML antibiotics are eliminated mainly by the liver, with a variable part of the drug excreted in bile as the parent drug or metabolites. This leads to enterohepatic cycling and long terminal half-lives.

Semi-synthetic macrolides are very long-acting, due to their low clearance rates. For example, the elimination half-life of tulathromycin in cattle and swine is close to 4 days and that of gamithromycin in cattle is >2 days. The most recently authorised macrolide, tildipirosin, has the longest terminal half-life, approximately 9 days in cattle and >4 days in swine. Quantifiable concentrations of gamithromycin and tildipirosin are present for >2 weeks in plasma and 3–4 weeks in the lung (Giguère et al., 2011; Menge et al., 2012). Severe tissue irritation, causing pain and inflammation, is a common problem of all macrolides, particularly when administered parenterally (Giguère 2013a).

Use of ML antimicrobials in cattle and pigs

By 2013, eight macrolides and two lincosamides were authorised for use in food animals in some or all EU member states (Table 1). In the EU, ML are available for parenteral administration, including intramammary use, and for oral use including premix formulations. ML are used widely for the treatment of common infections in food-producing animals, and have been categorised as critically important in veterinary medicine by the World Organisation for Animal Health (OIE) (Collignon et al., 2009).

Use of macrolides as growth promoters began at the same time as therapeutic use, with spiramycin and tylosin being used within the EU until 1998 (Council Regulation EC2821/98 of 17 December 1998). The first injectable, long-acting macrolide with a one-dose only regimen for food animal use was tilmicosin. Other macrolides authorised with this regimen are tulathromycin, gamithromycin and tildipirosin. The total number of available ML products varies between EU member states from 5 to 183 products containing macrolides (Fig. 1) and from 1 to 32 products containing lincosamides. More than 60 combination products containing macrolides and other antimicrobials are available in the EU; in addition, numerous lincomycin products exist as combinations (EMA/CVMP/SAGAM, 2011). Most often macrolides are combined with colistin or aminoglycosides, but in some products also with sulfonamides, trimethoprim, oxytetracycline, or ampicillin. The approved duration of treatment for some in-feed products is long, up to 4–5 weeks in some cases.

In a recent report (EMA/ESVAC, 2013), data on the sales of antibacterials in 25 European countries were analysed in a harmonised manner using population correction unit (PCU) as an estimate of the eligible animal population. In Fig. 2, data on the sales of ML in different European countries in 2011 are presented. Usage of ML varies greatly between countries, as does proportion of total antimicrobial sales which are ML (ranging from 4% in Sweden to 14% in Denmark), with pigs being the main target species for ML use. The use of different pharmaceutical forms of ML also differs widely between countries (EMA/ESVAC, 2013). For macrolides, sales