Monensin

An evaluation of the expert panel of the Netherlands Veterinary Medicines Authority (SDa)

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Members of the SDa expert panel:
I.M van Geijlswijk, PharmD, PhD, hospital pharmacist
Prof. D.J.J. Heederik, PhD, epidemiologist (chairman)
Prof. J.W. Mouton, MD, PhD, medical microbiologist
Prof. J.A. Wagenaar, DVM, PhD, veterinary microbiologist

Samenvatting

Elanco Animal Health heeft in 2013 Kexxtone® op de Europese markt gebracht. Deze intraruminale bolus vermindert het vóórkomen van ketose rond het afkalven bij melkkoeien en vaarzen. De werkzame stof in Kexxtone® is monensin.

Monensin behoort tot de ionoforen, een groep stoffen met antimicrobiële werking die nauwelijks wordt gebruikt in de humane geneeskunde. Er zijn tot nu toe geen genen geïdentificeerd die verantwoordelijk zijn voor bacteriële resistentie tegen ionoforen; resistentie wordt veroorzaakt door een fenotypische verandering in de celwand die reversibel is. Er zijn geen wetenschappelijke aanwijzingen dat het gebruik in dieren significant bijdraagt aan antimicrobiële resistentie bij bacteriën die bij mens en dier voorkomen. Het advies van het SDa Expert panel is om gebruik van monensin in melkvee/vaarzen niet op te nemen in de gebruiksgegevens op dier/bedrijfsniveau. Om in de toekomst in staat te zijn surveillance gegevens te koppelen aan gebruik van monensin is het advies verkoopgegevens van monensin jaarlijks te verzamelen, parallel aan de verkoopdata van andere antibiotica. Omdat deze gegevens tot één fabrikant te herleiden zijn (Elanco) zullen ze niet worden gepubliceerd zolang niet wordt gemonitord op monensin resistentie. Beschikbaarheid geeft het expertpanel van de SDa de mogelijkheid om ontwikkelingen in het gebruik te monitoren.

Summary

In 2013 Elanco Animal Health launched Kexxtone® in Europe. This intraruminal bolus application is designed to reduce the incidence of ketosis metabolic disorder in dairy cattle. The active substance of Kexxtone® is monensin.

Monensin belongs to the ionophores, a group of substances with antimicrobial activity that is only used sporadically in humans. Ionophore resistance appears to be the result of reversible phenotypical changes of the cell wall. Until now there are no genes identified which are responsible for the resistance of bacteria against ionophores. There is no indication that the use of Kexxtone® in animals has a significant contribution on antimicrobial resistance of bacteria in humans and animals. The advice of the SDa Expert Panel is to not include use of Kexxtone® in dairy cattle in the usage data at animal/farm level. To be able in the future to associate surveillance data with the use of Kexxtone® the SDa Expert Panel advices to collect the annual sales data of Kexxtone® parallel to the sales data of other antimicrobials. Because these data can be traced to one supplier (Elanco) they will not be published, as long as monensin resistance is not monitored. Availability of the data gives the expert panel the possibility to monitor the development in use.

1. Background

The increasing antimicrobial resistance in human and veterinary medical care is of global concern. At the national level the Netherlands Veterinary Medicines Authority (SDa) is committed to promote responsible drug use in Dutch animal husbandries in general and especially usage of antimicrobials. In order to reduce antimicrobial use and justify their usage of certain types of antimicrobials, the SDa collects and analyses antimicrobial usage data and defines benchmark indicators for responsible antimicrobial use in animal husbandries. The SDa reports on antimicrobial drug use and changes in use as result of improvement measures implemented by livestock farmers and their veterinarians.

2. Introduction

In 2013 Elanco Animal Health launched a new veterinary medicine in Europe. This bolus application is designed to reduce the incidence of ketosis metabolic disorder in dairy cattle. The bolus, called Kexxtone®, contains the active substance monensin, a monovalent carboxylic ionophore, produced by *Streptomyces cinnamonensi*s (Simjee, Heffron et al. 2012). The product is available as a continuous-release intraruminal device. Continuous release means that monensin is released slowly from the device for approximately 95 days. The product is available in the Netherlands from summer 2013 onward.

Kexxtone® is not classified with an ATCvet code for antimicrobial medicines and as such is not included in the sector quality systems which provide the data to calculate the Defined Daily Dosage per Animal /Y per farm. As a result, the use is not monitored by the Netherlands Veterinary Medicines Authority (SDa). However, as monensin has antimicrobial activity, it is argued that selection for monensin resistance (or co-resistance to other antimicrobials) may pose the same public and animal health threat as other antimicrobial drugs. Therefore there is need to evaluate the possible risks for veterinary and human health through the development of bacterial resistance properties in order to make an evidence-based decision whether including Kexxtone®/monensin use into the SDa monitoring system and DDDA calculations is warranted. We consider in this document the Kexxtone® application, the mechanism of activity, resistance and the potential impact of resistance on human and animal health.

3. Approach

For the purpose of this review, a literature search has been completed to identify the relevant literature from the peer-reviewed research literature and a select number of web-based and practice literature.

Searches for peer-reviewed journal articles were conducted using the Utrecht University online databases in the area of veterinary- and human medicine sciences (PubMed). For more general searches the Google Scholar search engine was additionally used.

4. Kexxtone®

Kexxtone® is a veterinary medicine that contains the active substance monensin. It is used to reduce the incidence of ketosis in dairy cows and heifers which are expected to develop ketosis in the period around calving. Ketosis is a metabolic disorder in which blood glucose levels are low and substances called ketones (such as acetoacetatic acid and β-hydroxybutyrate) resulting from alternative metabolism routes accumulate in the blood (Gordon, Leblanc et al. 2013).

The ultimate effect of monensin within the rumen is a shift in the microbial population resulting in a decrease of the bacteria that produce acetate and butyrate and an increase of bacteria that produce propionate, the gluconeogenic precursor. The result of the shift in the bacterial population within the rumen, an increase in the efficiency of the energy metabolism is improved. In the peri-parturient dairy cow, the positive effects of monensin treatment include reduced blood ketones, increased serum glucose and reduced incidence of ketosis (Duffield 2007).

Kexxtone® is available as a bolus containing 32.4 g of monensin (as monensin sodium). It is indicated for cattle above 300 kg body-weight (dairy cows and heifers) which are expected to develop ketosis in the peri-parturient period. Kexxtone® delivers an approximate average dose of 335 mg of monensin per day for approximately 95 days. The withdrawal period is zero days for milk, meat and offal (European Medicine Agency 2014).

5. Monensin

Monensin is a product of natural fermentation produced by *Streptomyces cinnamonensi*s and belongs to a family of drugs known as polyether antibiotics or ionophores (Butaye et al., 2003). Monensin has been widely used to prevent coccidiosis in poultry since the seventies of the last century (Chapman et al.,, 2010). Antibacterial activity of monensin can be explained by the fact that monensin binds to bacterial cell membranes and interferes with the maintenance of important ion-gradients in the cell which are needed for the transport of nutrients and to generate proton-motive force (Simjee, Heffron et al. 2012). It is a metal/proton anti-porter that can exchange H^+ for either Na^+ or K^+ and thereby changes the pH and the sodium-potassium balance in the cell which may lead to critical disturbances in cellular processes resulting in cell death. Once inserted in the membrane, monensin exchanges intracellular potassium ions for extracellular protons or extracellular sodium for intracellular protons. Because the potassium gradient is greater than the sodium gradient, protons accumulate inside the bacterium (Callaway et al.,2003).

It has been found that monensin is most effective against Gram-positive (Gram+) bacteria. This is explained by the fact that the cell walls of Gram-negative (Gram−) bacteria are more complex and are not porous for large antibiotic molecules and the complexes formed by it. However, the substance can bind to both Gram+ and Gram- bacteria but the cascade of effects has only been shown to occur in Gram+ species (Callaway et al., 2003). Monensin has shown activity against Gram+ bacteria of the genera *Micrococcus*, *Bacillus*, and *Staphylococcus* (Łowicki D 2013).

Studies indicate also anti-viral properties of monensin. Inhibition of vesicular stomatitis and Sindbis virus replication has been demonstrated as well as inhibition of Semliki Forest virus by monensin due to penetration into the target cells. Furthermore it is indicated that monensin decreases DNA synthesis, effectively inhibits the replication, and induces a strong reduction of early viral antigens of murine polyoma virus (Łowicki D 2013).
The effect of antimicrobials as monensin on the prevalence of food-borne pathogens such as *Salmonella* and *E.coli* O157 may have implications for food safety. Studies showed no effect of monensin on growth rate of *E.coli* O157 in ruminal fluid (McAllister, Bach et al. 2006). Conflicting results are presented in surveys about the effect of ionophores on shedding of *E.coli* O157 in cattle. Herriott and colleagues showed in a longitudinal study in 36 Pacific Northwest dairy herds (60 fecal samples/herd monthly for 6 months) a positive association between herd prevalence of *E.coli* O157 in heifers and use of monensin (Herriott et al., 1998). In cattle no association with monensin treatment on the prevalence of *E. coli* O157 in fecal samples of 32 orally challenged finishing steers was found (McAllister, Bach et al. 2006, Jacob, Fox et al. 2008). Also short-term ionophore exposure in lambs did not affect *Salmonella* and *E.coli* O157 fecal shedding or gastrointestinal concentrations (Edrington, Callaway et al. 2003). Taken these results together, overall it seems that short term monensin exposure did not appear to benefit *Salmonella* and *E.coli* O157 populations in the gastrointestinal microbial ecosystem.

5.1 Pharmokinetics

The site of action for intraruminal administered monensin is the gastrointestinal tract. Intraruminal administration of monensin is followed by extensive first pass metabolism which results in low concentrations of monensin in the systemic circulation. Biochemical studies have showed that orally administered monensin is absorbed and extensively metabolized in the liver. Most of the metabolites and parent drug are excreted in the bile and eliminated in the feces (Davison 1984).

Environmental studies indicate that monensin may be of less environmental concern. This is because monensin is biodegradable in manure and soil and because of the biotransformation products have weaker to no antimicrobial properties compared to the parent ionophore (Sun, Cabrera et al. 2014).

5.2 Monensin resistance

Most Gram- bacteria (e.g. *E.coli*, *Salmonella spp*. *Campylobacter spp)* can be considered as intrinsically resistant. *Enteroccus spp* are intrinsically susceptible to monensin. Until now there are no genes identified which are responsible for the ionophore resistance in bacteria. Ionophore resistance seems to be the result of phenotypical changes. No mutations or acquisition of foreign genes are observed (Simjee et al. 2012; Russell and Houlihan, 2003). In studies where measurements were done of monensin-dependent potassium efflux, it was shown that potassium efflux increased rapidly after cattle was supplemented with 350 mg monensin. However when monensin was withdrawn, the potassium efflux returned to its original value indicating that the resistance did not persist when monensin was not present (Lana, Russell 1996). Also in sheep comparable results were found. No adaptation of rumen microbes after a period of 96–146 days of monensin treatment were observed. When monensin was withdrawn from the diet, there was an almost immediate (within a few hours) increase in acetate-to-propionate ratio (Rogers M., Jouany JP., Thivend P., Fontenot JP 1997).

In vivo monensin-exposed isolates of *Clostridium perfringens*, *E. faecalis* and *E. feacium* showed to have the ability to grow in the presence of high monensin concentrations *in vitro*, most likely as the *in vivo* exposure has led to clearly thickened cell wall and a thickening of the glycocalyx. When the exposure was withdrawn the bacterial cell walls returned to their original morphology within a few generations (Simjee, Heffron et al. 2012).

There is no indication that monensin resistance of ruminal bacteria is increasing and that resistance of ruminal bacteria can be transferred between bacteria. Studies showed very little or no monensin resistance in indicator bacteria such as *E. faecium*, *E. faecalis,* and *E. coli* and zoonotic bacteria as *Campylobacter* and *Salmonella* (Butaye, Devriese et al. 2000, Aarestrup, Bager et al. 1998, Butaye, Devriese et al. 2001).

Several European reports focused on salinomycin as ionophore class representative (DANMAP,MARAN), rather than monensin to assess ionophore resistance in *E. faecium* and/or *E. faecalis* recovered from animals. Both salinomycin and monensin are monovalent polyether ionophores. In the last few years consistently no resistance could be shown to salinomycin in *E. faecium* and/or *E. faecalis* recovered from cattle in The Netherlands (Breakpoint 4mg/L) (Maran,) and Denmark (Breakpoint 8mg/L) (DANMAP). However salinomycin resistance of 60.5% was observed in *E. faecalis* recovered from white veal calves in 2012 in The Netherlands. Though these data should be interpret with care because of the low numbers of isolates included (N=5) (MARAN 2013). Resistance to salinomycin in *E. faecium* does occur in broilers and pigs where ionophores are used as coccidiostats. However no resistance of monensin or cross resistance between monensin and other ionophores are observed (Butaye, Devriese et al. 2000). Co-resistance with other antimicrobial agents can be of importance. In Denmark in 2012, 27% of the salinomycin-resistant isolates were also resistant to other antimicrobial agents, especially erythromycin but there are no indications for any functional or genetic association (DANMAP 2012).

6. Monensin use in humans

Monensin has never been used as an antimicrobial in humans (World Health Organization. Seventieth Meeting of the Joint FAO/WHO Expert Committee on Food Additives 2009, Russell, Houlihan 2003). There is very limited data on effects following direct exposure of humans to monensin. However a case report is present of intentional exposure to monensin in a 17-year old male who died from acute rhabdomyolysis with renal failure after ingesting monensin premix (Kouyoumdjian, Morita et al. 2001). Furthermore allergic symptoms including urticaria, swelling of the face or tongue, pruritus, nasal congestion, contact dermatitis and local respiratory irritation have been reported in workers handling monensin (World Health Organization. Seventieth Meeting of the Joint FAO/WHO Expert Committee on Food Additives 2009). In ranchers that fed monensin to cattle headache and dizziness was observed (World Health Organization. Seventieth Meeting of the Joint FAO/WHO Expert Committee on Food Additives 2009).

Although ionophore antimicrobials including monensin are not currently used in humans, salinomycin is under research for cancer therapy (Huczynski 2012). Furthermore, it has been suggested that the antimicrobial effects of ionophores may offer opportunities in the treatment of multi-resistant bacteria (Kevin Ii DA1, Meujo DA, Hamann MT. 2009).

7. Conclusions

Ionophores such as monensin have a distinctly different mode of action compared to other antimicrobial classes. There is no rationale for a mechanism of resistance other than (reversible) glycocalyx formation. Many ruminal bacteria are intrinsically resistant to ionophores even if ionophores are not fed, and ionophore resistance seems to be a phenotypical, reversible effect. Until now there are no genes or mutations identified associated with the ionophore resistance of ruminal bacteria.

Monensin is not used in humans, therefore monensin resistance itself does not pose a direct public health risk. However, co-resistance with other antimicrobial agents can theoretically be of importance and is not well studied.

Given the observations described in this document, use of Kexxtone® in animals is not likely to have a significant impact on the presence of antibiotic resistance in humans and animals.

The advice of the SDa Expert Panel is to not include use of Kexxtone® in dairy cattle in the usage data at animal/farm level. To be able in the future to associate surveillance data with the use of Kexxtone® the SDa Expert Panel advices to collect the annual sales data of Kexxtone® parallel to the sales data of other antimicrobials.

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