POLYETHER IONOPHORES – WHAT ARE THEY, WHAT ARE THE ADVANTAGES AND RISKS OF THEIR USE IN ANIMAL PRODUCTION

IONÓROFOS POLIÉTERES – O QUE SÃO, QUAIS AS VANTAGENS E RISCOS DO SEU USO NA PRODUÇÃO ANIMAL

IONÓROFOS POLIÉTERES: QUÉ SON, QUÉ VENTAJAS Y RIESGOS TIENE SU USO EN LA PRODUCCIÓN ANIMAL

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ABSTRACT

Polyether ionophores are a class of antibiotics used in animal production preventively, therapeutically and as food additives. The main representatives of this class are monensin, lasalocid, narasin, salinomycin and hidramycin. They are used for the prevention and treatment of coccidiosis in birds and calves and, as food additives, improving production performance. In beef cattle farming they help with weight gain and muscle development and in dairy cattle farming they increase milk production, although there is controversy regarding the improvement of solids and fats in the product. Despite the benefits of using ionophores, there are reports, both experimental and accidental, of poisoning caused by them in several animal species as a result of supplementation errors (offering quantities above those recommended for the species), poor homogenization of feed containing the additive and the ingestion of feed intended for cattle by other animals. In addition to the risks of poisoning animals, there is also the risk of poisoning consumers of products coming from animals supplemented with polyether ionophores, making it important to investigate residues of these substances in meat, eggs and milk. This review aims to discuss what polyether ionophore antibiotics are, what are the advantages and risks of their use in animal production, the risks

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of bacterial resistance emerging to these drugs and how this can interfere with human health, in addition to investigating how they occur poisoning in animals and their clinical course.

Keywords: Monensin. Food Additives. Intoxication. Cattle Farming. Anticoccidial.

RESUMO

Os ionóforos poliéteres compõem uma classe de antibióticos utilizados na produção animal de forma preventiva, terapêutica e como aditivos alimentares. Os principais representantes desta classe são a monensina, a lasalocida, a narasina, a salinomicina e a maduramicina. São utilizados para prevenção e tratamento de coccidiose em aves e bezerros e, como aditivos alimentares, atuando na melhora da performance produtiva. Na bovinocultura de corte auxiliam no ganho de peso e desenvolvimento muscular e na bovinocultura de leite aumentam a produção leiteira, havendo controvérsias quanto a melhora de sólidos e gorduras do produto. Apesar dos benefícios do uso dos ionóforos há relatos, tanto experimentais quanto acidentais, de intoxicações ocasionadas por eles em diversas espécies animais em decorrência de erros de suplementação (oferecimento de quantidades acima da recomendada para a espécie), má homogeneização de ração contendo o aditivo e a ingestão de ração destinada a bovinos por outros animais. Além dos riscos de intoxicação de animais, há também o risco de intoxicação de consumidores de produtos advindos de animais suplementados com ionóforos poliéteres, sendo importante a investigação de resíduos destas substâncias em carnes, ovos e leite. Esta revisão tem como objetivo discutir o que são os antibióticos ionóforos poliéteres, quais as vantagens e riscos do seu uso na produção animal, os riscos de surgimento de resistência bacteriana a estas drogas e como isso pode interferir na saúde humana, além de investigar como ocorrem as intoxicações nos animais e seu curso clínico.

Palavras-chave: Monensina. Aditivos Alimentares. Intoxicação. Bovinocultura. Anticoccidiano.

RESUMEN

Los ionóforos poliéteres componen una clase de antibióticos utilizados en la producción animal de forma preventiva, terapéutica y como aditivos alimentarios. Los principales representantes de esta clase son la monensina, la lasalocida, la narasina, la salinomicina y la maduramicina. Se utilizan para la prevención y el tratamiento de la coccidiosis en aves y terneros y, como aditivos alimentarios, actúan mejorando el rendimiento productivo. En la ganadería de corte, ayudan al aumento de peso y al desarrollo muscular, y en la ganadería lechera aumentan la producción de leche, aunque existen controversias en cuanto a la mejora de los sólidos y las grasas del producto. A pesar de los beneficios del uso de ionóforos, existen informes, tanto experimentales como accidentales, de intoxicaciones causadas por ellos en diversas especies animales como consecuencia de errores de suplementación (administración de cantidades superiores a las recomendadas para la especie), mala homogeneización del pienso que contiene el aditivo e ingestión de pienso destinado al ganado vacuno por parte de otros animales. Además de los riesgos de intoxicación de los animales, también existe el riesgo de intoxicación de los consumidores de productos derivados de animales suplementados con ionóforos poliéteres, por lo que es importante investigar los residuos de estas sustancias en la carne, los huevos y la leche. Esta revisión tiene como objetivo discutir qué son los antibióticos ionóforos poliéteres, cuáles son las ventajas y los riesgos de su uso en la producción animal, los riesgos de aparición de resistencia bacteriana a estos fármacos y cómo esto puede interferir en la salud humana, además de investigar cómo se producen las intoxicaciones en los animales y su curso clínico.

Palabras clave: Monensina. Aditivos alimentarios. Intoxicación. Ganadería bovina. Anticoccidiano.

1 INTRODUCTION

In animal production, there is a great search for the improvement of the product and for the intensification of growth and muscle mass gain of the animals, so that they arrive faster and healthier at finishing, as there is a lot of competition between producing countries in the foreign market. Since 1992, Brazil has ranked second in terms of world beef production, with a vast consumer market composed of countries such as China, Hong Kong, the United States and Egypt (Salman et al., 2006; Gomes et al., 2017; Walnut; Ustinova, 2021). Today, most of the Brazilian beef cattle herd is composed of zebu breeds, mainly the Nellore, due to resistance to ecto and endoparasites. However, zebu meat does not have tenderness comparable to European breeds, and it is important to cross the breeds to ensure the tenderness of the meat and marbling, that is, the fat interspersed between the muscles. Zebu genetics and pasture finishing do not favor marbling, making the product leaner, but, through crossbreeding and with the feedlot finishing of some herds, Brazil is able to meet different preferences in the market (Gomes et al., 2017; Medeiros et al., 2021).

Brazil's evolution in beef production was possible due to zootechnical improvements in management, genetics, feeding and animal health promotion. On the topic of feed, emphasis can be placed on feed additives that optimize animal growth, feed conversion and production (Salman et al., 2006; Araújo; Souza, 2016; Gomes et al., 2017; Medeiros et al., 2021).

Production additives are important in weight gain and disease prevention in herds. Among these additives are ionophores, antibiotics with anticoccidial power, which are widely used in the production of chickens and ruminants (Salman et al., 2006). Currently, there are more than 120 types of ionophores, but in Brazil, the Ministry of Agriculture, Livestock and Supply (MAPA) has the use of monensin, nasasin, salinomycin, maduramycin and lasalocid (Nicodemo, 2001; Araújo; Souza, 2016; MAPA, 2020).

Despite the improvement in productivity, the use of feed additives in livestock, especially antimicrobials, has been questioned due to the risk of the emergence of resistant microorganisms that could cause damage to human health. In addition, there is a risk of intoxication of the consumer by certain substances, such as ionophores, which can generate cardiovascular lesions (Spisso; Nóbrega, 2010). As a result, restrictive measures have been adopted regarding the use of these drugs in production animals and acquisition of products of animal origin in which these additives have been used (Salman et al., 2006).

The intoxication of consumers through the ingestion of these substances in products of animal origin is worrying, but there is a greater risk of poisoning of animals that directly consume ionophores in their pure form or mixed with food. There are reports of experimental and accidental poisonings, due to supplementation error, inhomogeneous mixing in rations or offering feed intended for cattle containing ionophores for other species. Some studies report greater sensitivity of some species than others, with the equine species being considered more sensitive with fatal results of poisoning (Bezerra et al., 2000; França et al., 2009; Pavarini et al., 2011; Machado et al., 2018; Brito et al., 2020). Machado et al. (2018) reported an outbreak of poisoning by feed contaminated with ionophores in horses, in which 16 animals, belonging to a group of 27, died. Compared to cattle, buffaloes have a higher sensitivity to higher doses of ionophore antibiotics (Bence et al., 2018; Barbosa et al., 2021). In the swine species, there are few reports of poisoning, which are associated with the concomitant use of other antibiotics that intensify their action (Armién et al., 1997; Carvalho et al., 2019).

The clinical signs caused by poisoning by ionophore polyether antibiotics are similar in different species, being mainly apathy, hyporexia and anorexia, ataxia, muscle weakness, claudication, mucous congestion, sweating, drooling, cardiac arrhythmia, dyspnea, diarrhea, decubitus, hyperthermia and, when pregnant, abortion (França et al., 2009; Machado et al., 2018; Brito et al., 2020). Due to heart failure caused by intoxication, cattle can develop submandibular edema (Resende et al., 2015).

Biochemical findings include elevated creatine kinase (CK) levels (Vargas, et al., 2009; Brito et al., 2020). CK is present in skeletal muscles, myocardium, and brain tissue, and its plasma elevation is strongly related to muscle injuries and, in humans, to myocardial infarction (Cardinet III, 1997). Horses poisoned by monensin have elevated CK and aspartate aminotransferase (AST) in the blood (Pavarini et al., 2011). Resende et al. (2015) reported elevation of CK and AST in ionophore antibiotic poisoned sheep after feed mill sweep ingestion. Buffaloes that received feed for dairy cows containing monensin also showed an increase in CK and AST, demonstrating the occurrence of muscle injury (Bence et al., 2018).

Vargas et al. (2009) demonstrated the possibility of measuring Cardiac Troponin I (cTnI) in poisoned animals, as a way to measure the degree of cardiac damage caused by monensin intoxication, based on the relationship between the increase in cTnI and the reduction of the chamber and the systolic function of the right ventricle. Decloedt et al. (2012) reported increased plasma cTnI concentration and decreased left ventricular contractility in lasalocid-poisoned horses.

Necropsy findings include areas of pallor, degeneration, and necrosis in myocardium and skeletal muscles, hydroperitoneum, hydrothorax, and pulmonary edema (França et al., 2009; Brito et al., 2020; Barbosa et al., 2021). In sheep poisoned by ionophores, congestion may occur in the liver, kidneys and lungs (Resende et al., 2015).

Histopathological examinations of animals poisoned by monensin show degenerative-necrotic lesions of skeletal and myocardial muscles, mononuclear interstitial inflammation and replacement of muscle fibers by fibrous connective tissue, loss of muscle striations causing increased cytoplasmic eosinophilia, floccular necrosis of muscle fibers, renal and hepatic cortical congestion (França et al., 2009; Barbosa et al., 2021). In addition, it is possible to identify the presence of ionophores in the muscle and liver of animals that ingested high doses through the method of analysis by high-performance liquid chromatography (Zavala et al., 2011).

Although it is not common, as ionophores are not used in people, there are two reports of poisoning caused by the ingestion of monensin. The symptoms of poisoning are similar to those that occur in animals, such as myalgia, tachycardia, tachypnea, sweating, and pigmenturia. Laboratory tests confirm the occurrence of rhabdomyolysis and acute renal failure (Caldeira et al., 2001; Kouyoumdjian et al., 2001).

2 IONOPHORES (POLYETHER ANTIBIOTICS)

Polyether ionophores make up a class of antibiotics used as anticoccidials in poultry and ruminant production. It gets its name because of its ionization ability, as its components form fat-soluble complexes with cations and transport them across the lipid membrane of cells. The name polyether is due to the fact that these compounds have cyclic ethers in their molecular structure (Nagajara et al., 1997).

These antibiotics are produced by microorganisms of the genus *Streptomyces* sp. and *Actinomadura* sp. and are categorized into neutral and carboxylic:

- **Neutral:** considered more toxic because they form cationic complexes that disrupt the structure and transport of ions in cell membranes;
- **Carboxyls:** *when* they bind to ions, they form "zwitterionic" molecules, which are neither anionic nor cationic, promoting the diffusion of cations in a neutral way, and are therefore more tolerated in organisms. Thus, they are widely used in the prevention of avian coccidiosis (Ferreira; Pizarro, 2017).

The main representatives of this class are narasin, lasalocid, salinomycin, monensin, senduramycin and maduramycin. In addition to the anticoccidial action, they also act on Gram-positive bacteria and some fungi, interfering with the digestibility of fibers in the rumen (Oliveira; Stasi, 2012; Davis; Gookin, 2018).

Ionophore antibiotics were discovered in the 1950s, and at least 74 of them were discovered in 1951, after lasalocid. At the end of 1960, its anti-coccidial action was recognized

(Nicodemo, 2001; Olive tree; Stasi, 2012; Davis; Gookin, 2018). In the United States, it has been used in extensive cattle farming since 1976 and since 1978 for confined animals (Morais; Berchielli; Reis, 2006).

Regarding the mechanism of action against coccidia, it is known that ionophores have hydrophobic characteristics and therefore can diffuse in the cell membrane, causing alteration in the transport of ions, especially for sodium and potassium, allowing the occurrence of passive diffusion of these compounds through the membrane. In addition, they are able to form lipophilic complexes with alkali metal cations and transport them across membranes. As a consequence of these electrolyte alterations, there is a change in the internal pH, compromising the production of adenosine triphosphate (ATP) by the mitochondria, leading to energy exhaustion, with the entry of water molecules and rupture of the coccidia, which does not have osmoregulatory organelles (Oliveira; Stasi, 2012; Davis; Gookin, 2018; Ferreira; Pizarro, 2021).

Different ionophores have different affinities with different cations. For example, monensin binds to monovalent ions such as sodium (Na) and potassium (K), while lasalocid has a greater affinity for bivalent ions such as calcium (Ca) and magnesium (Mg) (Ferreira; Pizarro, 2017).

Cattle receiving ionophores improve weight gain and feed conversion without changing the amount of feed ingested. This effect occurs due to the change in the rumen microbiota, leading to a change in the proportion of volatile fatty acids (VFA) and ammonia concentration. In addition, it decreases the incidence of rumen lactic acidosis, as it increases rumen pH and inhibits bacteria that produce lactic acid (Oliveira; Stasi, 2012). Just as they are used in birds for the prevention and treatment of coccidiosis, ionophores can be used for the same purpose in calves (Peek, et al., 2018).

Today, these drugs are widely used in the poultry industry and in cattle farming. In poultry farming, they are used because of the resistance generated by other antiprotozoal drugs and their large spectrum of action (Davis; Gookin, 2018).

3 ACTION OF IONOPHORES IN CATTLE

In cattle farming, polyether ionophores are used as feed additives, with the purpose of improving animal performance. The objective of its use is achieved through the selection of the rumen microbiota, as this drug acts on Gram-positive bacteria, inhibiting their growth, thus leaving the environment conducive to a greater growth of the population of Gram-negative, propionic acid-producing bacteria (Viegas et al., 2019). Due to the reduction in the population of Gram-positive acids, there is a decrease in its products, which are acetic, butyric and lactic acids (Morais et al., 2006).

The change in the rumen microbiota causes an improvement in the energy metabolism of the selected bacteria and, consequently, a change in the proportion of volatile fatty acids and a lower production of methane. The decrease in methane production is beneficial for feed conversion, as the production of this gas is responsible for the loss of 2 to 12% of food energy. Another action is the alteration in the metabolism of nitrogen (N) by microorganisms, increasing the amount of protein that reaches the ruminant's intestine and decreasing the absorption of ammonia. The mechanism by which monensin inhibits this protein degradation is not yet clear, but this characteristic is advantageous in the diet of cattle raised on pasture (Nicodemo, 2001; Morais et al., 2006).

With the use of ionophores in the diet of ruminants, some diseases can be avoided, for example, coccidiosis and rumen lactic acidosis. With the decrease in lactic acid production and the increase in rumen pH, the incidence of rumen lactic acidosis can be decreased, thus improving animal performance (Nicodemus, 2001; Morais et al., 2006).

Afonso et al. (2022) induced lactic acidosis in two groups of sheep, a control group and another that received 33 mg/kg of monensin daily per rumen fistula. Acidosis was induced by the administration of sucrose at a dose of 15g/kg of body weight, as a result it was observed that all animals developed rumen lactic acidosis. The difference in the mean pH of rumen juice between the groups was 0.05 higher in the group that received monensin 24 hours after disease induction. In addition, it was noted that the sheep in the treated group recovered more quickly. Research with goats has shown that sodium monensin does not prevent the occurrence of rumen lactic acidosis in this species, nor does it cause changes in hematological parameters when compared to control groups (Miranda Neto et al., 2011; Silva et al., 2013).

4 EFFECT OF IONOPHORES ON BEEF CATTLE

Cattle that get too much concentrate in the diet, when supplemented with ionophores tend to reduce feed intake by 8 to 10%, maintaining or increasing weight gain. On the other hand, feedlot animals that feed mainly on roughage improve feed conversion and weight gain, without modifying the volume of food ingested (Nicodemo, 2001). Bertipaglia and Reis (2008) observed cattle on pasture in different periods of pasture, during the transition from the rainy season to the dry period, greater weight gain was observed in animals supplemented with monensin, even with an 18% decrease in forage intake. With these advantages it is possible to increase the capacity of the paddocks. In addition, they also concluded that monensin is beneficial for rumen fermentation, as it provides an increase in propionic acid and improves the energy efficiency of the rumen environment in heifers on pasture.

Oliveira et al. (2005) sought to demonstrate the influence of monensin on the intake and rumen fermentation of cattle receiving diets with high and low protein content, through the evaluation of rumen fluid. During the experiment, it was proved that monensin decreases the dry matter intake and increases the proportion of propionic acid and reduces that of butyric acid. In addition, associated with a low-protein diet, monensin reduces the concentration of acetic acid, leading to an increase in pH and an increase in microbial protein synthesis. In addition to generating benefits for cattle with weight gain and disease prevention, the use of monensin reduces production costs and brings benefits to the environment with the reduction of methane emissions (Marcucci et al., 2014).

5 EFFECT OF IONOPHORES ON DAIRY CATTLE

Gandra and Rennó (2009), in a study with lactating dairy cows consuming diets with different concentrations of monensin, observed that there was no interference in the weight or body score of the animals. However, there was an increase in milk production and fat and lactose contents. The improvement in milk production and composition is related to the mechanism of action of ionophores in the rumen, as the increased production of propionic acid improves the flow of hepatic glycogen and, consequently, improves production. Possatti et al. (2015) noticed an increase in the amount of total solids in the milk of animals in the initial phase of lactation.

Before the 1990s, there was reluctance to seek benefits from the use of ionophores for dairy cattle, because it was believed that the decrease in food intake caused by these substances and the increase in the production of propionic acid would cause a reduction in milk fat. However, propionic acid is a primary precursor of lactose synthesis and one of the regulators of milk osmolarity during its synthesis, thus increasing cows' milk production. In addition, ionophores act in the prevention of diseases such as ketosis and rumen lactic acidosis, and their use in lactating cattle is beneficial (Nagajara et al.; 1997).

Beckett et al. (1998) compared two groups of cows during pregnancy and lactation, one of these groups received monensin in the diet and the other did not. In this study, no change was observed in the fat and protein content in the milk of cows that received the ionophore.

The administration of monensin to cows in the peripartum was shown to be efficient in preventing ketosis, since it decreases the production of acetate and increases the production of propionic acid in the rumen, which is converted into glucose in the liver. The increase in available glucose avoids hypoglycemia that could lead to the mobilization of lipids from fat deposits causing ketosis (McArt, et al., 2018).

6 RESISTANCE TO IONOPHORES

Due to the mode of action of Polyether Ionophores, it is difficult for coccidia to occur resistance to this pharmacological class. In the 1980s, some ionophore-resistant strains of *Eimeria* spp. were detected. Currently, it is common to identify resistance to these antibiotics and even cross-resistance between them, i.e., strains resistant to an ionophore antibiotic are resistant to other ionophores as well (Davis; Gookin, 2018).

Several studies indicate that some rumen bacteria are capable of adapting and developing resistance to this class of antibiotics. Microorganisms from the rumen fluid of animals adapted to lasaloside showed greater resistance to monensin and lasaloside compared to animals that were not adapted. In addition, it is also suggested that resistance to monensin and lasalocid occur by similar mechanisms, as it was noted that lasalocid-resistant bacteria were also resistant to monensin (Dawson; Boling, 1984; Rumpler et al., 1986; Domescik; Martin, 1999).

There are ruminal bacterial populations that become resistant to ionophores, both Gram-negative and Gram-positive bacteria, and the mechanism of development of this resistance is not known. Aerobic microorganisms and some enzymes can degrade ionophore antibiotics, but these degradation methods do not work in the rumen environment which is anaerobic. Although there are resistant bacteria, it is believed that it is more of a selection that has occurred than a mutation and that genes cannot be transmitted from one bacterium to another. In this way, it becomes difficult for pathogenic bacteria to emerge in humans to these substances, since their therapeutic use is not allowed in human medicine (Russell and Houlihan, 2003).

Gram-negative bacteria do not suffer the action of this drug, because they have a cell wall and an outer membrane composed of proteins, lipoproteins and lipopolysaccharides, which contains channels of approximately 600 Dalton in diameter, through which ionophore molecules are unable to pass (Morais et al., 2006).

Despite the low risk of generating bacterial resistance that negatively interferes with human and animal health, ionophore antibiotics should be used with caution and more research on the subject should be developed.

7 TOXICITY OF IONOPHORES

Ionophores are rapidly excreted after consumption, but when the recommended daily intake is exceeded, their accumulation in tissues can occur and their toxic effects appear both in animals and in humans who consume the products from these animals. Signs of intoxication usually appear at the beginning of supplementation or due to miscalculations in the amount to be offered. Poisonings present as inappetence, anorexia, apathy, necrosis of skeletal muscles and degenerative cardiomyopathy (Nicodemo, 2001). There are reports of poisoning in several species, including pigs (Armién et al., 1997), cattle (Brito et al., 2020), horses (Pavarini et al., 2011), poultry (Pavarini et al., 2011; Zavala et al., 2011) and dogs (Bosch et al., 2018), and there are even reports in the literature of human poisoning in an adolescent who ingested 500mg of monensin and died after 11 days (Caldeira et al., 2001).

There are species that are highly susceptible to ionophore poisoning, with the equine species being considered the most sensitive. In intoxicated animals, the clinical signs observed are: colic, sweating and ataxia of the pelvic limbs, resulting from muscle and myocardial degeneration caused by the drug. In histopathology, skeletal muscle necrosis and focal degenerative cardiomyopathy are notable (Davis; Gookin, 2018).

Poisonings occur accidentally, especially in the most sensitive species, due to access to feed with the addition of these drugs for ruminants (Davis; Gookin, 2018). Seeking to reproduce an accident that occurred with horses that received monensin feed, Bezerra Jr. et al (2000) experimentally poisoned seven horses offering different amounts of the diet and a premix with different frequencies during the day. In this experiment, two animals died, two were euthanized due to the severity of the signs they developed, one fell ill and recovered, and two others did not develop signs of intoxication. In five of the seven animals used in the experiment, an increase in CK activity was observed as a result of muscle degeneration.

In comparative experimental poisoning, the buffalo species proved to be more sensitive to monensin than the bovine species. A group of seven buffaloes, which received the same daily doses of the drug as the group of four cattle, presented apathy, anorexia, diarrhea, dyspnea, locomotor problems, sialorrhea, and jugular vein distension. The blood of the animals was collected before the beginning of the experiment and 3, 6 and 9 days after the beginning of the ionophore administration. There was a progressive increase in the concentration of CK in buffaloes, while in cattle there was an increase at first, but as the days went by the concentration of the enzyme stabilized. None of the cattle died, however, in four buffaloes the poisoning was fatal and the necropsy findings were myopathy and cardiomyopathy, hemorrhage, congestion and pulmonary emphysema, and fibronecrotic enteritis (Rozza et al., 2007).

These additives should be used with caution on properties and employees who will administer these compounds to animals should be aware of the fatal poisoning that doses higher than indicated can cause. In addition, feed mills that add ionophores to feed formulas must also continuously inspect the product, thus preventing quantities greater than those indicated for animals from being added to the feed or that homogenization is not adequate.

8 TOXICITY OF IONOPHORES IN CATTLE

Too many ionophores are potentially toxic to cattle, especially calves. Its ingestion together with macrolide antibiotics can potentiate the effects of monensin and cause intoxication. The clinical signs caused by intoxication are: anorexia, diarrhea, fever, dyspnea, lethargy, central neurological signs (in calves) and heart failure. Poisoned animals present plasma elevation of cTnI (Cardiac Troponin I), hemorrhage and necrosis of myocardium and skeletal muscles, ascites and hydrothorax. The treatment of poisoned animals is supportive, and vitamin E and Selenium can be used (Thompson and Goodrich, 2018).

Brito et al. (2020) reported a case of ionophore poisoning in calves in Goiás, in which 21 deaths occurred in a herd composed of 900 animals that had been introduced on the property 14 days ago. As clinical signs, these cattle presented ataxia, muscle weakness, rigid gait, decubitus, bilateral jugular distension and death. Biochemical tests showed an increase in the concentration of CK and lactate dehydrogenase (LDH) in the serum of these animals. At necropsy of one of the animals, 800 mL of serous fluid was found in the thoracic cavity and 100 mL inside the pericardium, and histopathology showed necrotizing and degenerative myopathy. In addition, in hepatic and muscle fragments, amounts higher than those allowed for monensin were revealed in these organs, thus confirming intoxication by the additive.

Varga et al. (2009) in an experimental study evaluated ten cows poisoned by monensin by means of electrogardiogram, echocardiogram, biochemical tests, including cTnI measurement, and *postmortem* examination. In this research, a pilot study was carried out with two animals, in which one received a dose of 30mg/kg of monensin and the other 40mg/kg. The next study was carried out with 8 animals given a dose of 50 mg/kg of monensin. As a result, a positive correlation was found between the increase in plasma cTnI concentration 24 hours after ingestion of the ionophore antibiotic, the increase in CK 72 hours after intoxication, the decrease in the left ventricular shortening fraction and the lesions corresponding to myocardial necrosis.

The way of offering monensin to cattle can predispose to poisoning. In 2016, in Goiás, the death of five Nellore cattle in a herd of 160 animals was reported. Before death, the animals had a staggering gait, reluctance to walk, weakness and muscle tremors. Through the clinical investigation, it was revealed that the animals were receiving an amount of monensin above that indicated for the species, which is 10 mg/kg/day. The environment in which the animals were made it difficult to transport the supplements, so much so that the producer tried to solve the problem by offering a greater amount of the ionophore, in addition, the pasture was in poor condition, factors that favored the greater intake of the additive, culminating in intoxication. It is estimated that the animals ingested 671.87 mg per day. In biochemical examinations of the surviving animals, an increase in the enzymes CK and LDH was observed (Marcelino et al., 2017).

Polyether ionophores are antibiotics that can cause myocardial lesions when administered at higher doses than recommended, which can cause arrhythmias and increased plasma cTnI (Peek and Buczinski, 2018). In calves, monensin poisoning can cause neurological signs that resemble meningitis, but without infectious involvement or failure to transfer passive immunity (PEEK, et al.; 2018).

In Brazil, monensin is marketed under the name of Rumensin® and its recommendation for use is 50 to 100mg/head/day in the first five to seven days of use, and can reach up to 400mg/head/day after adaptation (Scot consultoria, 2006). The commercial name of lasalocid is Taurotec® and the recommended daily dose is 0.4g to 0.8g per day for suckler calves, 0.6g to 1.5g per day for growing animals and 1g to 2g for finishing cattle. For animals finishing in confinement, the daily dose can be up to 2.4g per day, the same dosage applies to lactating cows (Zoetis).

9 RESIDUES OF POLYETHER IONOPHORES IN ANIMAL PRODUCTS

There is great concern about the presence of residues of veterinary drugs in products of animal origin, not only because of the possibility of bacterial resistance, but also because some substances cause damage to the health of consumers. Because of this, there must be control over the residues of additives and medicines in the products (Spisso; Nóbrega, 2010; Lima et al., 2018). The use of antimicrobials in the treatment and prevention of diseases in animals and humans has often been linked to the emergence of bacterial strains resistant to various antibiotics, so it is necessary to control these substances in products of animal origin, such as milk, eggs, and meat (Lima et al., 2018).

Food safety is controlled by the Risk Analysis determined by the *Codex Alimentarius*. Such evaluation is divided into stages, through which the identification of the hazard, the characterization of the hazard are carried out; the assessment of exposure and the characterization of risk. With these evaluations, it is possible to determine variables such as the Acceptable Daily Intake (ADI) value of a substance and the Maximum Residue Limits (MRL) allowed in products (Codex Alimantarius Coission, 2010).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is a body that recommends to the Codex committee MRL values for residues of veterinary drugs on food (Spisso; Nóbrega, 2010). JECFA has determined MRLs for monensin and narasine. For monensin, an MRL of 10µg/kg was determined in muscle, liver and kidneys of chickens, quails and turkeys and an MRL of 100 µ/kg for fat. For Narasin, an MRL of 15µg/kg was determined in muscle, liver and kidneys of chickens and pigs and 50µg/kg in fats.

ADI values for polyether ionophores were determined by the Scientific Committee for Animal Feed (SCAN) of the European Union (EU) and by the European Food Safety Authority (EFSA), and currently 2.5 µg/Kg for lasalocid, 1 µg/kg and 1.25 µg/kg for maduramycin and senduramincin, respectively. EFSA also determined values for salinomycin (5 µg/Kg), narasin (5 µg/Kg) and monensin (3 µg/Kg). But there is a wide variety of limits determined in different countries for ionophore ADI (Scientific Committee On Animal Nutrition, 1982; European Food Safety Authority, 2004a; 2004b; 2004c, 2004d; Spisso; Nóbrega, 2010).

In Brazil, the agency that controls the presence of veterinary drug residues in products of animal origin is the National Health Surveillance Agency (ANVISA), establishing ADI and MRL for food (Lima et al. 2018). Thus, there are MRL values defined for lasalocid, maduraminica, monensin, narasin, and senduramycin, which can be seen in table 1 Such values are adopted by ANVISA, based on international documents.

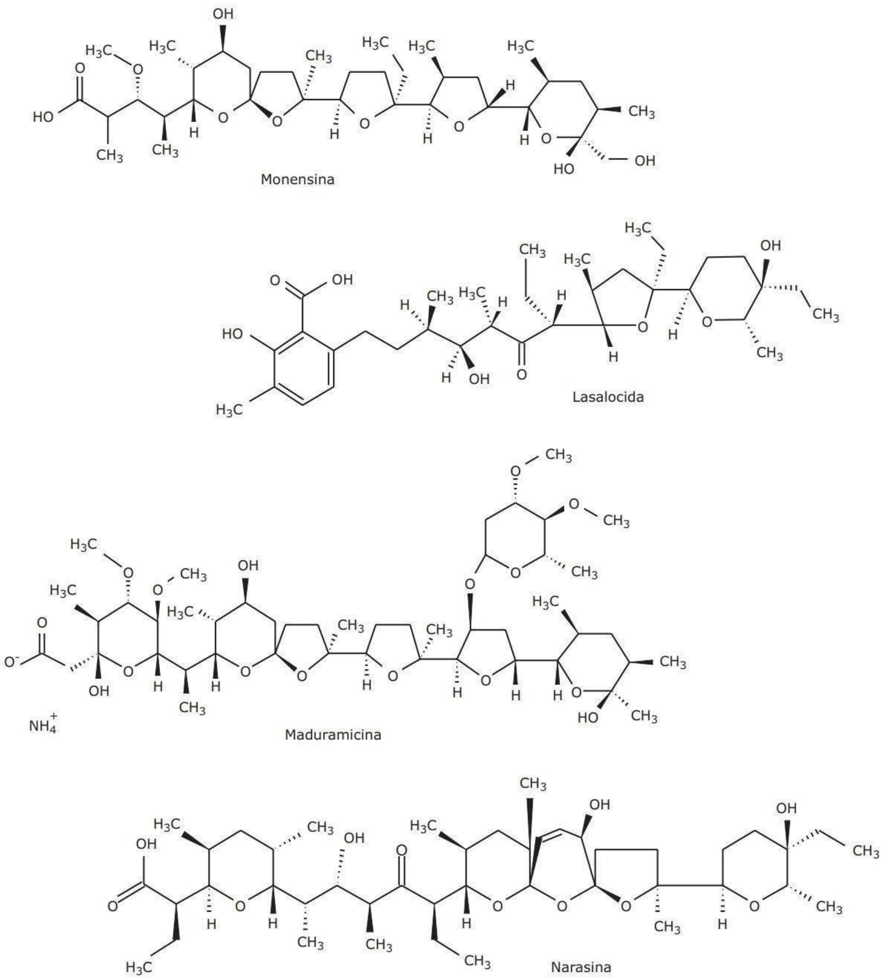
Despite the determination of MRLs for several products of animal origin, it is noted that there are no determined values for the presence of ionophore residues in eggs. In order to investigate traces of these antibiotics in eggs, Spisso and Nóbrega (2010) used eggs purchased in the metropolitan region of Rio de Janeiro to investigate the presence of polyether ionophores in these products. As a result, salinomycin was detected in 21% of the samples.

There are few existing analytical methods for the detection of ionophores in milk. In order to investigate the presence of ionophores in whole UHT milk, Pereira et al. (2015), analyzed 102 samples of the product, detecting the presence of monensin in 14% of the samples, but the concentration of this antibiotic was lower than that recommended by *the Codex Alimentarius* and the European Community. The 2018 *Codex alimentarius* update maintained the MRL of 2 µg/kg monensin in milk.

It is noted that there are still failures in the detection of traces of veterinary medications in products of animal origin, such failures must be corrected in order to protect the health of the final consumer, as some substances, such as ionophores, for example, can cause damage to health through serious poisoning when consumed in large quantities, causing disorders in myocardium and skeletal muscle.

Figure 1

Molecular structure of the main polyether ionophores



Source: Oliveira; Stasi, 2012.

Table 1

Ionophore antibiotics and their respective producing microorganisms and deficiency period in meat

Ionophore	Producing microorganism	Grace Period
Monensin	*Streptomyces cinnamonensis*	3 days
Lasalocida	*Streptomyces lasaliensis*	5 days
Narasina	*Streptomyces aureofaciens*	5 days
Salomycin	*Streptomyces albus*	5 days
Maduramycin	*Actinomadura yumaense*	5 days

Adapted from: Nagaraja et al., 1997; Ferreira; Pizarro, 2017.

Table 2

Maximum Residue Limits (MRL) values adopted by the National Health Surveillance Agency (ANVISA) for Ionophore Antibiotics used in Brazil

Ionophore	Animal Species	Fabric	MRL (µg/kg)	Reference
Lasalocida	Cattle	Muscle	10	I
		Liver	100	
		Kidney	20	
Maduramycin	Poultry	Muscle	240	USA
		Liver	720	
		Skin	480	
		Fat	480	
Monensin	Cattle	Muscle	10	CODEX
		Liver	100	
		Kidney	10	
		Fat	100	
		Milk	2	
	Sheep and Goats	Muscle	10	CODEX
		Liver	20	
		Kidney	10	
		Fat	100	
	Chicken, Turkey and Quail	Muscle	10	CODEX
		Liver	10	
		Kidney	10	
		Fat	100	
Narasina	Cattle	Muscle	15	CODEX
		Liver	50	
		Kidney	15	
		Fat	50	
	Swine	Muscle	15	CODEX
		Liver	50	
		Kidney	15	
		Fat	50	
	Chicken	Muscle	15	CODEX
		Liver	50	
		Kidney	15	
		Fat	50	
Senduramycin	Poultry	Muscle	130	USA
		Liver	400	

Source: Adapted from Lima et al., 2018; MS and VISA, 2019

10 CONCLUSION

The use of Polyether Ionophore Antibiotics brings many benefits to animal feed, improving feed conversion, optimizing weight gain and preventing diseases. However, its use must be controlled to reduce the risks both to the health of animals and to the health of consumers of products from these individuals, which may contain drug residues. The main risks related to the use of ionophores in the diet of herds are the poisoning of animals and consumers of the products and the generation of bacterial resistance.

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