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COCCIDIOSTATS IN TREATING COCCIDIOSIS

S u m m a r y

Coccidiostats are a group of veterinary antibiotics, the residues of which in, e.g. meat or other edible tissues, are potentially dangerous to human health and life. Thus, it is important to effectively prevent intoxications. For that purpose it is essential to gather data on those antibiotics. Coccidiostats are used mainly in treating and preventing coccidiosis – a disease of the intestinal track of animals, especially of the poultry, caused by parasitic protozoans of the *Eimeria* genus. Two major groups are used – polyether ionophores and chemical coccidiostats, which differ in origin and mechanisms of action. Their application is governed by the Regulation (EC) No 1831/2003 of the European Parliament and of the Council, in which the application of the following 11 coccidiostats was authorized: salinomycin, narasin, monensin, maduramicin, semduramicin, lasalocid, robenidine, nicarbazin, halofuginone, diclazuril and decoquinate. Each of the mentioned coccidiostat present in the products of animal origin can lead to intoxication resulting from production errors and poor manufacturing practices. The effects of those compounds in food include symptoms such as: polyneuropathy, rhabdomyolysis, hypercalcaemia, respiratory failure and even death of patients. The coccidiostats are irreplaceable in treating coccidiosis, which can always be associated with the possibility of their occurrence in food. The present-day methods used to identify these medicines make it possible to monitor the products as regards the occurrence thereof and to reduce the risk of exceeding safe dose limits as set out in the relevant legal acts.

Key words: coccidiostats, veterinary medicines, products of animal origin, food safety

Introduction

Coccidiostats are veterinary medicines used to treat and prevent coccidiosis, a common disease of breeding animals. The widespread use thereof raises general interest owing to the potential harmfulness of residues of those drugs in food products of animal origin.

The objective of the paper is to provide the most important information on the currently used coccidiostats, their mechanism of action and potential toxicity, and to highlight the presence of these drugs in modern animal husbandry. The intent of pre-

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senting the knowledge on this subject is to raise the recipients' awareness of this group of substances and to give an introduction to a deeper study of the subject.

Coccidiosis

Coccidiosis is caused by protozoans of the *Eimeria* genus. In particular, it affects poultry and ruminating animals. It often occurs when inbreeding is carried under high moisture and temperature conditions. The level of basic hygiene and the density of animals per area unit are factors to increase the risk of infections. Main species to affect poultry are *E. acervulina*, *E. brunetti*, *E. mitis*, *E. necatrix*, *E. praecox*, *E. tenella* and *E. maxima*. There are also other species that affect specifically turkeys, such as *E. meleagrimiti*, and rabbits, such as *E. stiedae* [35].

An infection begins with the ingestion of parasites in the form of oocyst from faeces of infected animals. The ingested parasites release sporozoites and they attack the intestinal ephitelium. Then, after a few asexual life-cycles, merozoites, which were formed in the host, differentiate into sexual forms – male microgametes and female macrogametes. After fertilization by microgametes, macrogametes produce oocysts, which are shed in faeces. The disease manifests itself as severe diarrhoea, a poor weight gain and sometimes it ends in death [39]. The symptoms are caused by inflammation of the mucous membrane of small intestines, set off by the intense proliferation of coccidia in the epithelium cells [35]. As a result the efficiency of breeding is decreased.

History of coccidiosis treatment

For many years coccidiosis has been a major cause of low productivity of the poultry production. In the 20th century, along with the increased poultry breeding level on the poultry farms, the number of infection outbreaks also increased. In those days efficient methods of prophylaxis and treatment were not available, therefore the only recommendation for breeders was to improve their hygiene procedures on the farms. Unfortunately it was impracticable to rear birds in absolute isolation from their faeces, since it precluded the disease eradication on farms [10]. The first change in the poultry production was the introduction of sulfaquinoxaline in the United States of America in the 1940s. That drug was initially intended to treat malaria, however its high toxicity to humans excluded it from the widespread use. Fortunately it was found to be effective against *Eimeria spp.* among the fowls [7]. The drug was extensively incorporated into the poultry feedstuffs; this quickly led to drug resistance against parasites, which was reported in the 1950s.

A milestone in overcoming coccidiosis was the introduction of monensin, the first ionophore coccidiostat, onto American market in the 1970s; monensin turned out to be much more effective against protozoa than sulfaquinoxaline [35]. The first report about

monensin appeared in 1967 when Agratrap isolated it from *Streptomyces cinnamonensis* in the Lilly Research Laboratories. Since then the ionophore coccidiostats have been in the spotlight of scientists looking for new antibiotics and this quickly led to the discovery of other coccidiostats of this group [1].

In the European Union the first admission of monensin as a feed additive was granted by the Regulation (EC) No 1831/2003 of the European Parliament and of the Council in 2003 [17, 34]. However it was not the first coccidiostat approved for the use in the European Union; the Council Directive 70/524/EEC of 23 November 1970 [13] provided for the use of coccidiostats such as decoquinate and nicarbazin.

It could be predicted that, along with the increased use of single coccidiostats, the resistance against them would increase too. Hence more efficient multi-component products began to be sold more often, e.g. Eli Lilly's Maxiban. Furthermore, alternative methods of dealing with coccidiosis began to be sought. In 1992 vaccines were developed based on the precocious oocysts of the parasite strains. However they weren't very popular, because they were species-specific and unavailable for all the types of animals. At present there is only one vaccine authorized in the EU [35]. There were also acidifiers, enzymes and probiotics used to create barriers in the animals' digestive system in order to fight coccidiosis, although with a poor effect [35]. There are some novel reports on how to treat coccidiosis using herbal substances, however this issue is at the stage of discussion and investigation [28].

At present there are 11 coccidiostats authorized for the use in the EU; they were granted different permits for different species und under certain conditions of their use. They are regarded to be the most effective drugs in treating coccidiosis and are permitted for chickens, turkeys and rabbits. These are ionophores: monensin sodium, lasalocid sodium, maduramicin ammonium, narasin, salinomycin sodium, semduramicin sodium, and chemical coccidiostats: decoquinate, robenidine hydrochloride, halofuginone, diclazuril and nicarbazin [35].

Modes of action of coccidiostats

Coccidiostats can be divided into two classes. The first class includes natural substances produced by bacteria of the *Streptomycetaceae* family; they are called polyether ionophores. They are composed of tetrahydrofuran rings conjugated into spiroketal moieties. The second group consists of synthetic coccidiostats (also called chemicals): guanidines, triazines, quinolones, pyridines, alkaloids or/and thiamine analogues [12].

The ionophore antibiotics have two modes of action (MoA), but both of them lead to the same effect – a change in the concentration ratios of ions on the both sides of the cell membrane. Under the first MoA two particles of the antibiotic dimerize and create a channel to transport cations across a lipid bilayer [28]. Under the second MoA the ionophores in an anionic form bind the cations and actively carry the ions through a

cell membrane. After passing through the membrane to the cytoplasm they release the cations [3].

When in a physiological state, the cells efficiently defend themselves against the mentioned effect. Na^+/K^+-ATPase and Ca^{2+}/Mg^{2+}-ATPase control the ion concentrations on the two sides of the cell membrane. According to what was said before, the ionophore antibiotics change those concentrations. For example lasalocid increases the concentration of Na^+ and Ca^{2+} in the cell; this leads to a simultaneous efflux of K^+ ions. The Ca^{2+} cations overload disrupts the functioning of mitochondria; this decreases the energy production and leads to necrosis. A high concentration of Ca^{2+} is also considered to be a cause of apoptosis owing to the activation of dedicated endonucleaes. Furthermore, a high ratio of influx into the efflux of Na^+ ions disrupts the physiological ion concentrations on the both sides of the cell membrane. To restore a normal state an increased energy expenditure for ATPases is required. However when this ratio is too high, the cell is not able to maintain a proper ionic gradient and lyse. At the end high concentrations of Na^+ and Ca^{2+} cause the osmosis to increase, the cell to swell and to burst [20].

Chemical coccidiostats have various mechanisms of action. Decoquinate disrupts the electron transport in the protozoan mitochondria and inhibits the development of parasite [40]. Robenidine and nicarbazin are said to inhibit energy production in mitochondria, although its mode of action needs more investigation. In the reference literature there is very little information on MoA of halofuginone and diclazuril [9].

Legislation

The usage of coccidiostats was established by the European Union in 1970 by the Council Directive 70/524/EEC [13]. In 2003 this document was reviewed and replaced by the Regulation (EC) 1831/2003 of the European Parliament and of the Council [34]. Since then the ionophoric antibiotics: salinomycin, narasin, monensin, maduramicin, semduramicin and lasalocid have been permitted for the use as feed additives as have the synthetic coccidiostats: robenidine, nicarbazin, halofuginone, diclazuril and decoquinate [34, 35]. It is required by the European Union that its member states control residues of these drugs in food and assess their safety, which is supervised by the European Food Safety Authority (EFSA). The newly introduced coccidiostats must have their MRL (Maximum Residue Limit) determined before being introduced into the animal feed [27].

The European Commission released a report on the use of coccidiostats as feed additives in 2008. In the absence of efficient alternatives it was recommended to continue to maintain the authorization for the use of coccidiostats despite their numerous side effects [19, 35].

Nowadays there are 18.3 million of 40.7 million tonnes of annually produced feed for chickens, turkeys and rabbits, which contain coccidiostats [14]. It is important that the authorization for the use of coccidiostats in feedstuff is granted for target animal species, which usually cover chickens for fattening and chickens for rearing, but not laying hens [14]. Therefore, when the coccidiostats are detected in eggs, there is a very high probability of error during feeding procedures.

The coccidiostats are increasingly administered to animals worldwide and the result is the unavoidable presence thereof in food; on the other hand the awareness of harmfulness of those medicines raises and the search for quality and safety of food products goes on [25].

Toxicity

Coccidiostats are potentially harmful to health of animals and humans, and to their lives. At the beginning of the application of coccidiostats their toxicity mechanisms were monitored among the breeding animals as were the ionophores affecting nervous tissues. According to numerous research studies, the intoxication usually occurred as soon as the safe doses of medicines administered were exceeded, e.g. salinomycin poisoning in turkeys [32] or in rabbits [30], or monensin poisoning in broiler chickens [8]. Dogs [38] and horses can be poisoned by coccidiostats after an accidental exposure to them [27]. The most typical clinical symptoms are anorexia, diarrhoea, lack of motor coordination, stiff walking and reluctance to move, muscle tremor, myoglobinuria, depression and exhaustion. Ionophore poisoning can cause rapid death within 7 h or a chronic disease with symptoms of congestive heart failure [29].

Since the late 1990s the interest in the presence of coccidiostats in food has started to grow owing to the increasing number of reports on food contamination with nicarbazin and lasalocid [12]. Coccidiostats occur in the food of animal origin because of the non-compliance with grace periods and the contamination of the supposedly drug-free (non-medicated) animal feeding stuffs by coccidiostats. Also simple human errors or underdeveloped production processes and handling procedures can cause contamination. It is also possible to transfer those drugs between animals (animal-to-animal route) by ingestion of faeces [22].

Acute intoxications in humans are rare but possible. The symptoms of human poisoning are similar to those of animals. In 2000 in Brazil a 17-year old boy died after consumption of monensin. He appeared in the hospital with the symptoms of sickness, nausea and abdominal pain. Two days after his treatment began, the weakness and severe muscle pains appeared followed by tachycardia and drowsiness. Over the next few days an acute renal failure and pulmonary congestion developed in the patient and he died. The post mortem examination revealed that myoglobinuria was the main cause of his death [24].

In 2004 in New Zealand a worker in an animal feed factory accidentally swallowed a small amount of salinomycin and very quickly thereafter had nausea, shortness of breath and dizziness. Half an hour after swallowing salinomycin the patient was found to be agitated and he complained about leg weakness and photophobia. A neurological examination revealed a bilateral leg weakness. The patient re-arrived in the emergency department 14 days after swallowing with increasingly severe pain in his two legs. Here he stayed 40 days to recover and was finally discharged. The symptoms of pain and the weakness of his legs were associated with prolonged rhabdomyolysis [38].

In 2005 in India a maduramicin intoxication case was described. Several patients consumed a contaminated food product and within 4 h they developed vomiting and weakness of their legs. Next, a series of other symptoms developed such as polyneuropathy, rhabdomyolysis, hypercalcaemia and respiratory failure; finally 2 patients died [37].

Those few examples show that the introduced safety procedures are effective in preventing food contamination with coccidiostats and in keeping the concentration rates of those drugs in food at a safe level. On the other hand the growing food production forces the development of other more effective methods to detect and control both the coccidiostats and their consistent implementation. There are reports showing that the cooking of contaminated food poorly decreases concentrations of those drugs [36, 41]. Furthermore, the ionophores have a narrow range of safety and this increases the likelihood of intoxication [4]. The cases presented highlight the need for effective food screening for the presence of coccidiostats.

Determination methods

In 1969 Hammond and Weston [18] presented a thin-layer chromatography-based technique to detect decoquinate, amprolium, ethopabate, clopidol, buquinolate and aklomide in animal feeding stuffs; it was one of the first attempts to analyse samples with coccidiostats. To identify the coccidiostats, the values of retardation factors of these substances were compared with the reference values. Though the method didn't provide any quantitative determination, thus it was impossible to apply it for the purpose of confirming the safety of the detected dose. Moreover, that method involved 6 coccidiostats that are not in use anymore except for decoquinate.

At the turn of the 1980s-1990s the application of high-performance liquid chromatography (HPLC) coupled with UV detection became regularly used, so in 1985 Blanchflower, Rice and Hamilton [6] could report one of the first quantitative methods employed to determine coccidiostats. Monensin, narasin and salinomycin were extracted using methanol and separated by means of a reversed-phase HPLC. The detection limit of the assay was 0.25 mg kg^{-1} as for monensin and 0.5 mg kg^{-1} as for narasin and

salinomycin. The recoveries ranged from 95 to 108 %. However the method covered only ionophore coccidiostats and a derivatization technique with vanillin was necessary to detect them with UV.

Nowadays mass spectrometry is constantly used to precisely determine coccidiostats. Takatsuki, Suzuki and Ushizawa [42] were the first to present the incorporation of mass spectrometry for the purpose of determining coccidiostats. In paper of 1986 they described the application of gas chromatography coupled with mass spectrometry only to confirm the occurrence of monensin in a sample of chicken tissues. The quantitative determination of monensin residues was performed by LC with fluorometric detection. The detection limit was 1 ppb in the chicken tissues. The recoveries ranged from 46.5 to 77.6 % depending on the fortification levels.

Under the Council Directive 96/23/EC of 1996 the member states of the European Union were required to monitor poultry meat for the residues of banned hormones and legal veterinary medicines like coccidiostats [21]. From that moment many research centres started to develop methods to determine coccidiostats and the safety of food became a frequent issue in scientific periodicals [15, 16, 26].

Since several years the LC-MS/MS based methods to determine coccidiostats have undergone an intensive development and now they are considered to be methods of choice for the identification of those medicines. In the novel methods the main emphasis is on the improvement of sample preparation procedures and on the broadening the range of substances under determination.

In 2009 Stubbings and Bigwood [39] reported an LC-MS/MS procedure with the use of a modified QuEChERS sample preparation for 7 coccidiostats extracted from chicken meat. In 2012 Chico et al. [11] presented a method to determine 9 coccidiostats in eggs. Ethyl acetate was used as an extraction solvent with clean-up based on a gel permeation chromatography (GPC). In turn in 2016 Piątkowska et al. [31] developed a method to simultaneously determine 14 coccidiostats in fresh eggs. The samples were extracted using 0.1 % formic acid in acetonitrile : water (8 : 2) with EDTA added and cleaned using a solid phase extraction with Hybrid SPE cartridges. In 2017 Barreto et al. [2] used an extraction with acetonitrile followed by a low-temperature clean-up and centrifugation. The supernatant was collected and evaporated to dryness. They determined 14 coccidiostats in a poultry muscle and eggs. An interesting innovation was presented in 2019 by Klimek-Turek et al. [23], who applied simple procedures with a thin-layer chromatography to inexpensively and quickly prepare samples of coccidiostats. Future methods using molecularly imprinted polymers (MIP) to determine coccidiostats seem to be promising provided those special sorbents are less expensive [33]. An interesting trend is also the establishment of some new alternative methods, such as a flow cytometry-based immunoassay, to quantitatively determine coccidiostats [5].

Conclusions

The widespread use of coccidiostats in animal husbandry is burdened by a risk of occurrence of undesirable effects for consumers of the products of animal origin. An additional burden is the absence of satisfactory alternative to those drugs. Furthermore there is a potential risk of contaminating the environment with coccidiostats. Only the responsible use of those medicines can significantly reduce the risk of occurrence of those health hazards.

The developed determination methods are reliable and precise enough to be used for routine testing of food for the presence of coccidiostats.

Currently the coccidiostats are the most effective treatment of coccidiosis and, according to new research studies, they can be used also against multi-resistant bacteria.

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KOKCYDIOSTATYKI W LECZENIU KOKCYDIOZY

S t r e s z c z e n i e

Kokcydiostatyki to grupa antybiotyków weterynaryjnych, których pozostałości, na przykład w mięsie czy innych jadalnych tkankach, są potencjalnie niebezpieczne dla zdrowia i życia ludzi. Ważne jest zatem, by skutecznie zapobiegać zatruciom. W tym celu należy koniecznie gromadzić dane na ich temat. Kokcydiostatyki stosowane są głównie w leczeniu i profilaktyce kokcydiozy – choroby jelit zwierząt, przede wszystkim drobiu, wywołanej przez pasożytnicze pierwotniaki z rodzaju *Eimeria*. Używane są dwie główne grupy – jonofory polieterowe i kokcydiostatyki chemiczne, które różnią się pochodzeniem i mechanizmem działania. Ich stosowanie jest regulowane Rozporządzeniem (WE) nr 1831/2003 Parlamentu Europejskiego i Rady Unii Europejskiej, w którym zezwolono na stosowanie 11 kokcydiostatyków: salinomycyny, narazyny, monenzyny, maduramycyny, semduramycyny, lasalocydu, robenidyny, nikarbazyny, halofuginonu, diklazurilu i dekokwinatu. Każdy z wymienionych kokcydiostatyków zawartych w produktach pochodzenia zwierzęcego może prowadzić do zatrucia będącego rezultatem błędów i złych praktyk produkcyjnych. Skutkiem obecności tych związków w żywności mogą być takie schorzenia, jak: polineuropatia, rabdomioliza, hiperkalcemia, niewydolność oddechowa, a nawet śmierć pacjentów. Kok-

cydiostatyki są niezastąpione w leczeniu kokcydiozy, co zawsze może się wiązać z możliwością ich wystąpienia w żywności. Współczesne metody oznaczania omawianych leków pozwalają na monitorowanie produktów pod względem ich obecności i zmniejszają ryzyko przekraczania bezpiecznych dawek określonych w odpowiednich aktach prawnych.

Słowa kluczowe: kokcydiostatyki, leki weterynaryjne, produkty pochodzenia zwierzęcego, bezpieczeństwo żywności