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Natural and experimental salinomycin poisoning associated with the use of florfenicol in pigs[1]

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ABSTRACT.- Carvalho A.Q., Wisser C.S., Manfioletti G.O., Rigo N., Cristani J. & Traverso S.D. 2022. **Natural and experimental salinomycin poisoning associated with the use of florfenicol in pigs.** *Pesquisa Veterinária Brasileira 42:e06839, 2022.* Laboratório de Produção e Sanidade Animal, Universidade do Estado de Santa Catarina, Av. Luis de Camões 2090, Conta Dinheiro, Lages, SC 88520-000, Brazil. E-mail: amanda.queiroz@ifpr.edu.br

This study describes the spontaneous and experimental salinomycin poisoning associated with the use of florfenicol and warns about the effects of the administration of antibiotics to animals that receive ionophores in the feed as growth promoters. A batch with 1,200 finishing pigs fed a diet containing 30ppm of salinomycin received florfenicol (60ppm via feed) to control respiratory diseases. Twenty-seven pigs had difficulty walking, tip-toe walking, muscle tremors, and anorexia seven days after the start of treatment. Twenty-two animals died, 10 recovered, and two were sent to the Laboratory of Animal Pathology of CAV-UDESC to be necropsied. The experimental reproduction of the disease was carried out to clarify the possible influence of florfenicol on salinomycin poisoning using 12 pigs divided into four groups with three animals each, treated for 16 days with diets containing no additives (Group 1), 50ppm of salinomycin (Group 2), 40ppm of florfenicol (Group 3), and 50ppm of salinomycin and 40ppm of florfenicol (Group 4). Only animals in Group 4 became ill. The clinical disease was reproduced from the ingestion of 24.67mg/kg/LW of salinomycin and 19.74mg/kg/LW of florfenicol. Both natural and experimental salinomycin poisoning associated with the use of florfenicol caused a condition of myopathy characterized in histology by hyaline degeneration and floccular necrosis of skeletal fibers, with macrophage infiltrate, associated with the figures of regeneration in skeletal muscles and multifocal areas of the proliferation of fibroblasts, being more intense in the *longissimus dorsi* and semimembranosus muscles. Therefore, florfenicol can cause the accumulation of ionophore salinomycin in the animal organism, resulting in a condition of toxic myopathy.

INDEX TERMS: Experimental intoxication, florfenicol, salinomycin, natural intoxication, swine, salinomycin poisoning, myotoxicity, pig breeding, ionophore antibiotics, toxicology.

RESUMO.- [Intoxicação natural e experimental por salinomicina associada ao uso de florfenicol em suínos.] O presente trabalho descreve as intoxicações espontânea e experimental por salinomicina associada ao uso de florfenicol e alerta sobre os efeitos da administração de antibióticos aos animais que recebem ionóforos na ração como promotores de crescimento. Um lote com 1.200 suínos em fase de terminação, alimentados com ração contendo 30ppm de salinomicina, recebeu florfenicol (60ppm via ração) para o controle de doenças respiratórias. Sete dias após o início do tratamento, 27 suínos apresentaram dificuldade de locomoção, "caminhar em brasa", tremores musculares e anorexia. Vinte e dois animais morreram, 10 recuperaram-se e dois foram encaminhados ao Laboratório de Patologia Animal (CAV-UDESC) para serem necropsiados. Para esclarecer a possível influência do florfenicol na toxicidade da salinomicina foi realizada a reprodução experimental da doença utilizando 12 suínos, divididos em 4 grupos com 3 animais cada, tratados por 16 dias com rações contendo: Grupo 1 = sem aditivos, Grupo 2 = 50ppm de salinomicina, Grupo 3 = 40ppm de florfenicol e Grupo 4 = 50ppm de salinomicina e 40ppm de florfenicol. Somente os animais do Grupo 4 adoeceram. A doença clínica foi reproduzida a partir da ingestão de 24,67mg/kg/PV de salinomicina e 19,74 mg/kg/PV de florfenicol. Tanto a intoxicação natural

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quanto a experimental por salinomicina associada ao uso de florfenicol provocaram um quadro de miopatia caracterizado na histologia por degeneração hialina e necrose flocular das fibras esqueléticas, com infiltrado macrofágico, associada às figuras de regeneração na musculatura esquelética e áreas multifocais de proliferação de fibroblastos, sendo mais intensas nos músculos *longissimus dorsi* e semimembranoso. Conclui-se que, o florfenicol tem a capacidade de ocasionar o acúmulo do ionóforo salinomicina no organismo animal, resultando em um quadro de miopatia tóxica.

TERMOS DE INDEXAÇÃO: Intoxicação experimental, florfenicol, salinomicina, intoxicação natural, suínos, intoxicação por salinomicina, miotoxicidade, suinocultura, antibióticos ionóforos, toxicologia.

INTRODUCTION

Salinomycin is an ionophore antibiotic used in pigs as a growth promoter (Rutz & Lima 2001) and preventively to control the clinical signs of enteric diseases caused by bacteria of the genus *Brachyspira* (Hampson et al. 2006). Properly used, ionophores are effective in both indications, but they are myotoxic in excessive doses (Novilla 1992).

Salinomycin facilitates ionic flow through the cytoplasmic and mitochondrial membranes (Mitani et al. 1976). Poisoning is due to high Na^+ concentrations in the cytosol, which causes an increase in the cytosolic Ca^{2+} level through Na^+/Ca^{2+} exchangers in the plasma and mitochondrial membranes. Thus, the increase in the Ca^{2+} level induces cell apoptosis (Boehmerle & Endres 2011).

Spontaneous toxic myopathy in pigs due to salinomycin has been reported by several authors (Dost 1978 apud Ganter et al. 1995, Wanner 1984, Kavanagh & Sparrow 1990, Ganter et al. 1995, Carvalho et al. 2021). Poisoning by ionophore antibiotics can occur due to flaws in the mixing of the drug with the feed (Ganter et al. 1995), mistake in the doses (Rollinson et al. 1987), use in more sensitive non-target species (Griffiths et al. 1989, Salles et al. 1994), or normal doses associated with drugs that enhance their effects (Ganter et al. 1995). These associations have been described since the 1980s (Dost 1980 apud Ganter 1995) and continue to be reported (Carvalho et al. 2021), and may occur due to the interaction of tiamulin with salinomycin (Bouwkamp & Vries 1991, Ganter et al. 1995), with monensin (Laczay et al. 1990) and with narasin (Carpenter et al. 2005); in the association between chloramphenicol with monensin (Friedman et al. 1998) and lasalocid (Broz & Frigg 1987); in the concomitant use of macrolide antibiotics associated with monensin (Basaraba et al. 1999), narasin and salinomycin (Laczay et al. 1989) and in the combinations of sulfaquinoxaline with monensin (Laczay et al. 1990), narasin and salinomycin (Laczay et al. 1989).

The potentiation of ionophore antibiotics with toxic myopathy was reported in pigs in the association of tiamulin with monensin (Drake 1981), narasin (Carpenter et al. 2005), and salinomycin (Wanner 1984, Miller et al. 1986, Ganter et al. 1995, Carvalho et al. 2021).

Florfenicol is an antibiotic used in intensive pig farming to treat respiratory diseases, urinary tract infections (Priebe & Schwarz 2003, Kehrenberg et al. 2004), and enteric desorders (Synen et al. 2002, França & Guedes 2008). It is a fluorinated derivative of chloramphenicol, with characteristics similar to the original compound (Pentecost et al. 2013), and can be used as an alternative to chloramphenicol. Currently, there are no reports of toxic myopathy in the literature associating the interaction of florfenicol with ionophore antibiotics.

This study aimed to report an outbreak of spontaneous and experimental toxic myopathy in pigs due to the concomitant administration of salinomycin and florfenicol.

MATERIALS AND METHODS

In 2009, a pig batch with motor difficulties was observed on a farm located in the mountainous mesoregion of Santa Catarina state, Brazil. The animals were fed diets containing salinomycin and additionally received florfenicol to treat respiratory problems. Two pigs were sent to the "Laboratório de Patologia Animal" (LAPA-CAV-UDESC) for necropsy exam. The sick animals were necropsied and samples of viscera, central nervous system, heart, and skeletal muscles (semitendinosus, *longissimus dorsi*, intercostal, diaphragm, masseter, and subscapularis) were collected, fixed in 10% formalin, routinely processed for histological examination, and stained with hematoxylin and eosin (HE). Epidemiological data on the disease were obtained from the responsible technician. The clinical and pathological condition was compatible with toxic myopathy.

The disease was experimentally reproduced to clarify the possible influence of florfenicol on salinomycin poisoning using 12 pigs with an average weight of 59.58kg and divided into four groups with three animals each, treated during 16 days with diets containing no additives (Group 1, with Pigs 1, 2, and 3), 50ppm of salinomycin (Group 2, with Pigs 4, 5, and 6), 40 ppm of florfenicol (Group 3, with Pigs 7, 8, and 9), and 50ppm of salinomycin and 40ppm of florfenicol (Group 4, with Pigs 10, 11, and 12).

The animals were fed three times a day. The feed was weighed before the supply and the leftovers were collected and weighed to control daily feed intake. Animal behavior was evaluated daily during feed supply, with appetite and movement observed. The animals that fell ill during the experiments were euthanized for necropsy and collection of material for histological examination. The skeletal (tongue, masseter, diaphragm, intercostal, biceps femoris, brachial biceps, *longissimus dorsi*, semimembranosus, semitendinosus, gastrocnemius, gluteus medius, accessory gluteal, subscapularis, deltoid, triceps, and supraspinatus) and cardiac muscles were dissected and collected separately for quantitative analysis of the lesion. The animals that did not get sick were incorporated into the pig production chain destined for slaughter in a slaughterhouse.

RESULTS

Spontaneous poisoning

The spontaneous outbreak occurred in a farm with 1,200 finishing pigs with 95 days of age and average batch weight of 61kg, which were housed in pens with 50 animals and received a diet containing 30ppm of salinomycin (via nucleus) as a growth promoter for 10 days. Respiratory diseases were controlled using 60ppm of florfenicol (via feed). Seven animals were found in the decubitus position on the seventh day of treatment after the inclusion of florfenicol in the diet. In the subsequent weeks, 27 animals were observed with limited mobility, tip-toe walking, muscle tremors, and anorexia. Twenty-two animals died, ten recovered, and two (Pig 1 and Pig 2) were necropsied. The feed containing florfenicol and salinomycin was removed from the animals' feed after the beginning of the first clinical signs and replaced by another without microbial additives. The symptoms lasted for up to

10 days and the morbidity, lethality, and mortality indices reached 2.84, 64.7, and 1.83%, respectively. All pigs in the batch were sent for slaughter after the drug withdrawal period. Pig 1 was euthanized on the day of arrival at LAPA and Pig 2 ten days later. The necropsy showed asymmetric areas of pallor interspersed with apparently normal areas in the muscles of the pelvic limbs in both pigs and the *longissimus dorsi* and diaphragm muscles in Pig 2.

Histology showed hyaline necrosis of skeletal fibers, macrophage infiltrates, and phagocytosis of myofibers in both animals, associated with skeletal muscle regeneration and multifocal areas of fibroblast proliferation in Pig 2. These lesions were more intense in the *L. dorsi* and semimembranosus muscles. In the heart of Pig 1, moderate multifocal cardiomyocyte necrosis with mild macrophage infiltrate and fiber phagocytosis was observed. Macroscopic and histological lesions are shown in the Figure 1-4.

Experimental poisoning

The experimental design of the acute poisoning by salinomycin and florfenicol with the daily and total feed intake, salinomycin, and florfenicol of pigs is shown in Table 1.

The animals in Groups 1, 2, and 3 did not get sick and had an average daily feed intake of 3.2, 3.08, and 3.15kg/day, respectively. Two animals in Group 4 (Pigs 10 and 12) fell ill on the 11th and 16th day after the beginning of the experiment, respectively, and were euthanized five days after the onset of clinical signs. The first clinical sign observed in these animals was a decrease in food intake. Pig 10 had an average daily feed intake of 2.8kg/day up to the tenth day of the experiment and it only ingested 520 grams of feed on day 12. An increase in feed intake was observed in the days following the date of euthanasia, but it has always remained below the average intake observed in the period before the onset of clinical signs. Pig 12 had an irregular feed intake since the beginning of the experiment, but, similar to Pig 10, it presented an abrupt reduction in daily feed intake on

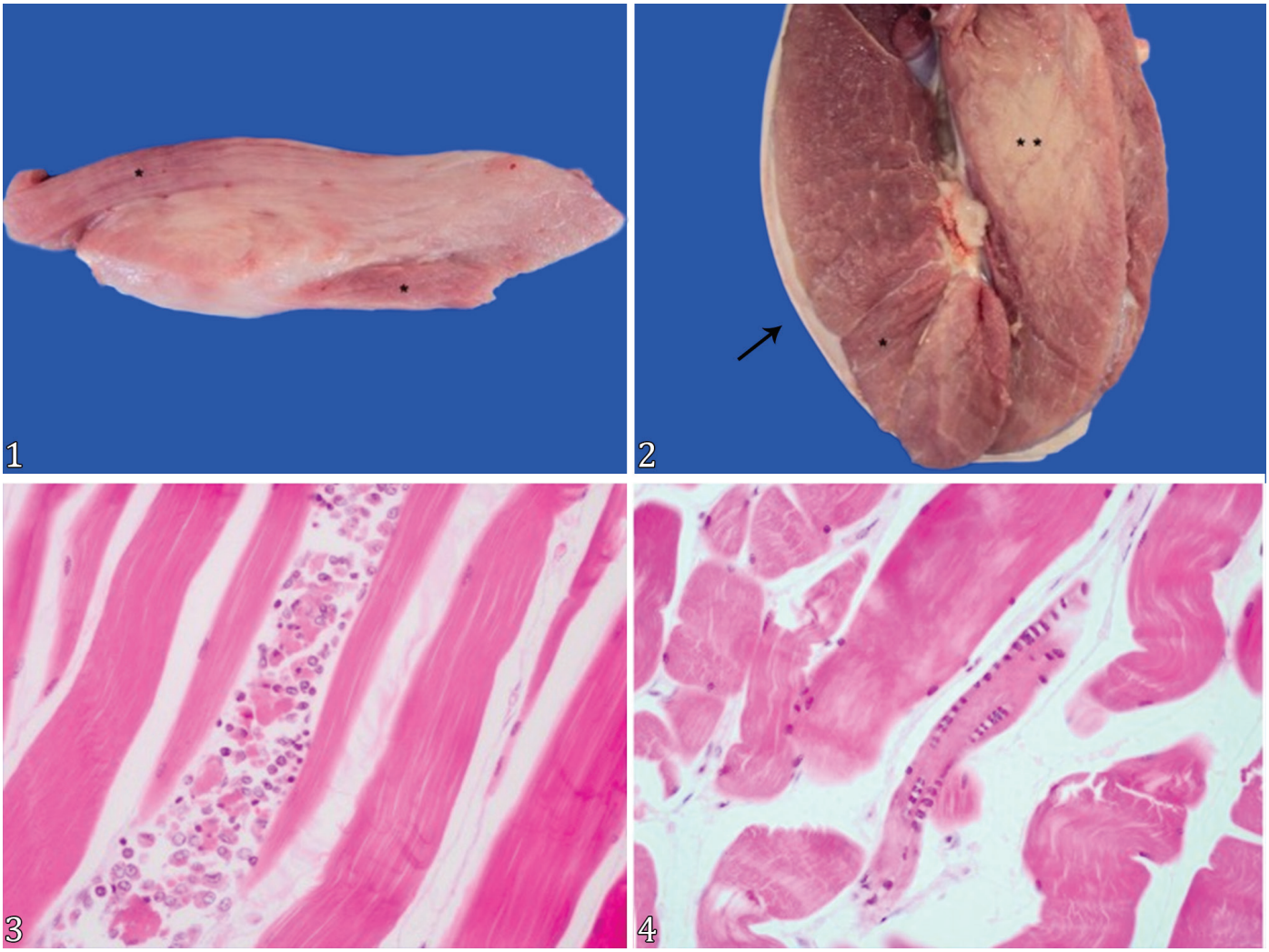

Fig.1-4. Spontaneous poisoning by salinomycin and florfenicol. (**1**) Pig 1: cross-section of the semitendinosus with details of the muscular pallor interspersed with muscles of normal color (*). (**2**) Pig 2: cross-section of the thigh caudal musculature, with skin (arrow), biceps femoris muscle (*), and semitendinosus muscle (**) with pale areas interspersed with areas of normal color. (**3**) Macrophages phagocyting necrotic debris from muscle fibers with evidence of intact sarcolemma and proliferation of satellite cells (Pig 1). HE, obj.20x. (**4**) Skeletal muscle with the formation of myotubes (regenerating fibers) (Pig 2). HE, obj.20x.

the day it fell ill (1.32kg) compared to the last four days of ingestion, that is, a regular average intake of 2.6 kg of feed.

Pig 10 presented clinical symptoms with 11 days of diet intake when it reached the accumulated dose of 24.67mg/kg/LW of salinomycin and 19.74mg/kg/LW of florfenicol, corresponding to a daily intake of 2.01mg/kg of salinomycin and 1.61mg/kg/LW of florfenicol.

The onset of clinical signs in Pig 12 occurred on the 16th day of intake, with an accumulated dose of 40.96mg/kg/LW of salinomycin and 32.8mg/kg/LW of florfenicol and an average daily intake of 2.56mg/kg/LW/day and 2.05mg/kg/day, respectively.

The highest total dose of salinomycin intake in the entire experiment was observed in Pig 6 (Group 2), which was 3.18mg/kg/LW, with a cumulative total of 50.88 mg/kg/LW. The highest dose of florfenicol intake was observed in Pig 7 (Group 3), with 2.25mg/kg/LW/day, corresponding to an accumulated dose of 36mg/kg/LW (Table 1).

In addition to decreased appetite, the animals were reluctant to move, "sitting-dog position," muscle tremors, and tip-toe walking. The necropsy showed mild pallor of the semimembranosus and semitendinosus muscles, accompanied by petechiae and ecchymosis in the muscular fasciae of *L. dorsi* and muscles of the pelvic and thoracic limbs.

Histology showed hyaline necrosis of fibers, severe multifocal infiltrates of macrophages, phagocytosis of myofibers, and regeneration figures in skeletal musculature. Myocardium had a mild cardiomyocyte degeneration, observed in Pig 10 as intracytoplasmic vacuolization and in Pig 12 as eosinophilia of myofibers. Histological lesions of hyaline necrosis in experimental and spontaneous poisoning were more intense in the skeletal muscles *L. dorsi* and semimembranosus.

Macroscopic and histological lesions of experimental poisoning are shown in Figure 5-6. Clinical signs, macroscopic and histological lesions observed in experimental poisoning by salinomycin and florfenicol was similar to that observed in animals of spontaneous poisoning.

DISCUSSION

This is the first report of ionophore poisoning associated with the use of florfenicol in pigs, and it serves as an alert for the importance of care in providing antibiotics to all species that receive ionophores as growth promoters. Although the morbidity and mortality indices were low, the economic significance of poisoning is not only reduced by mortality, but also by a reduction in the weight gain of sick animals and mainly the early slaughter of the entire batch as a control measure. An outbreak of salinomycin associated with tiamulin in pigs showed a reduction of around 32% in pig meat production in the delivery of the batch to a slaughterhouse, which corresponded to approximately 37,520kg less production (Carvalho et al. 2021). Prevention through the administration of the correct ionophore dose, with homogeneous distribution in the feed and care regarding drug interaction, must be

Table 1. Acute experimental salinomycin and florfenicol poisoning: experimental design with total feed intake and daily intake in mg/kg/live weight of salinomycin and florfenicol

Group	Control			Salinomycin (50ppm)			Florfenicol (40ppm)			Salinomycin (50ppm) + Florfenicol (40ppm)		
Swine	1	2	3	4	5	6	7	8	9	10	11	12
Weight (kg)	54	57	81	79	59.5	41	58.5	49.5	65	63	59.5	48
Total FC (kg)	54.8	46.48	53.96	58.84	47.46	41.76	52.62	41.24	57.62	37.96	49.44	39.32
Salinomycin DI mg/kg/pv	-	-	-	2.33	2.49	3.18	-	-	-	2.01	2.60	2.56
Florfenicol DI mg/kg/pv	-	-	-	-	-	-	2.25	2.08	2.22	1.61	2.08	2.05

FC = feed consumption, DI = daly intake.

Fig.5-6. Acute experimental poisoning by salinomycin and florfenicol. (**5**) Pig 10: swine in sitting-dog position. (**6**) Accessory gluteal muscle with marked multifocal segmental floccular necrosis. HE, obj.40x.

strictly followed because there is no treatment for animals poisoned (Nogueira et al. 2009).

Epidemiological data (pigs fed a diet containing salinomycin and which additionally received florfenicol), clinical signs (decreased appetite, reluctance to move, sitting-dog position, muscle tremors, and tip-toe walking), and macroscopic and microscopic lesions, which characterized a multifocal segmental degenerative myopathy and observed in spontaneous and experimental poisoning by salinomycin and florfenicol, are compatible with toxic myopathy and similar to the reports in the literature in cases of poisoning by ionophore antibiotics in pigs (Drake 1981, Wanner 1984, Miller et al. 1986, Van Halderen et al. 1993, Ganter et al. 1995, Plumlee et al. 1995, Miskimins & Neiger 1996, Carpenter et al. 2005, Carvalho et al. 2021).

The appearance of clinical signs in the spontaneous poisoning occurred seven days after the beginning of treatment with florfenicol and from the 11th and 16th days in the experimental poisoning. This fact may be related not only to the individual difference, but also to the time of salinomycin intake. The pigs of spontaneous poisoning received salinomycin in the feed for 10 days before florfenicol administration, but the antibiotics were provided on the same day in the experiment. The individual difference was also observed in the experimental poisoning since one of the three animals in Group 4 (Pig 11) did not become ill. This difference was also reported by Armién et al. (1997), who observed a high lethality index in natural cases and no deaths in the experimental poisoning.

The toxic effects of ionophores are increased when used in association with other drugs, such as chloramphenicol and tiamulin, as both slow down the biotransformation of these antibiotics, delaying their elimination by the animal (Szancer 1989). The doses of salinomycin and florfenicol in both spontaneous and experimental poisoning were in accordance with the manufacturers' recommendations, which is up to 30 or 60ppm of salinomycin depending on the age of the animal and 60ppm of florfenicol.

The lowest dose for disease reproduction was observed in Pig 10, with a concomitant intake of 2.01mg/kg/day of salinomycin and 1.61mg/kg/LW of florfenicol for 10 days. Salinomycin intake by Pig 10 was lower than that of Pigs 4, 5, and 6 (2.33, 2.49, and 3.18mg/kg/LW/day, respectively), which ingested only salinomycin in the diet for 16 days and did not get sick, which indicates the possible influence of florfenicol on the metabolism of salinomycin, as reported for the association between salinomycin and tiamulin (Wanner 1984, Miller et al. 1986, Laczay et al. 1989, Bouwkamp & Vries 1991, Ganter et al. 1995, Carvalho et al. 2021), with macrolide antibiotics and sulfaquinoxaline (Laczay et al. 1989). In addition, the toxic dose observed in the experiment was lower than the spontaneous salinomycin poisoning secondary to the overdose reported by Kavanagh & Sparrow (1990), which was 8mg/kg/LW, corroborating the hypothesis of the interference of florfenicol in the metabolization of this ionophore.

The evolution of the clinical condition and appearance of lesions due to ionophore poisoning varies with the species and dose (Wouters et al. 1997). Carpenter et al. (2005) reported no macroscopic and histology changes due to narasin poisoning associated with tiamulin in pigs, which were restricted to skeletal musculature and characterized by extensive and diffuse degenerative myopathy. Both, spontaneous and experimental poisoning, showed that muscles without apparent lesions in macroscopy had considerable microscopic lesions, which is mainly due to the natural pallor of the pig musculature, making it difficult to observe discrete macroscopic lesions. Another point to be considered is the effect of ionophores on the distribution of sodium, potassium, and calcium ions in myofibers. Ionic disorders can affect muscle function, as calcium ions are essential for processes such as neuromuscular transmission and activation and regulation of muscle contraction (Amend et al. 1980). Thus, the animals can present muscle dysfunctions even when in the absence of macroscopic and microscopic lesions.

Regarding the distribution of muscle lesions, pelvic limb muscles were more affected than thoracic muscles, a characteristic also observed in rabbits due to narasin poisoning (Salles et al. 1994), and similar to that described by Carvalho et al. (2021) in pigs due to salinomycin poisoning associated with tiamulin, in which the most pronounced lesions were in the *longissimus dorsi*, followed by diaphragm and masseter.

The locomotor difficulty, tip-toe walking, muscle tremors, and anorexia are nonspecific clinical signs of muscle diseases, and the differential diagnosis in pigs must consider vitamin E and selenium deficiency and intoxication by plants of the genus *Senna*. Likewise, macro and microscopic lesions are similar to each other in the three diseases, requiring a careful analysis of histology and epidemiology to formulate the etiological diagnosis (Martins et al. 1986, Barros et al. 1990).

Microscopy showed that skeletal muscles were those most affected. This lesion characteristic is important for pigs because it facilitates the microscopic differentiation of vitamin E and selenium deficiency when lesion to the skeletal musculature rarely occurs isolated, and the most common condition of this disease is cardiac (mulberry heart disease) and/or hepatic lesions (hepatosis dietetica) (Van Vleet & Valentine 2007). Also, vitamin E and selenium deficiency occurs mainly in young piglets (6 to 20 weeks of age) in the weaning and nursery phases, differing from the age of administration of salinomycin as a growth promoter in pigs, which is carried out at growth and finishing.

Another common histological lesion due to vitamin E and selenium deficiency is mineralization, which has also been reported in other ionophore poisonings (Armién et al. 1997, Peixoto et al. 2009) and myopathies by plants of the genus *Senna* (Barth et al, 1994, Froehlich 2010, Carvalho et al. 2014). According to McGavin & Zachary (2013), necrotic myofibers are prone to produce mineralization, but it has sometimes been used as a diagnostic aid. The circumstances that determine fiber mineralization are diverse and their occurrence should be considered a non-specific response, an indication of only myofiber necrosis.

Poisoning by plants of the genus *Senna* produces a clinical and pathological condition similar to that of ionophore poisoning, and the distribution of muscle lesions is similar to that of antibiotic poisoning. However, some cases of *Senna* poisoning showed not only classic muscle lesions, but also liver damage (Schmitz & Denton 1977, Martins et al. 1986, Barros et al. 1990, Froehlich 2010, Queiroz et al. 2012). The verification of seeds mixed in the feed and the analysis of the epidemiological data on the supply of ionophore to animals are the most important factors for this differential diagnosis.

CONCLUSION

Pigs that are fed a diet containing salinomycin and receive florfenicol are predisposed to develop toxic myopathy. The confirmatory diagnosis was performed by experimentally reproducing the disease from the intake of 24.67mg/kg/LW of salinomycin and 19.74mg/kg/LW of florfenicol.

Ethics Committee.- This study was approved by the Ethics Committee on Animal Experimentation at the "Universidade do Estado de Santa Catarina" (UDESC) under protocol number 1.06.10.

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Conflict of interest statement.- The authors declare that there are no conflicts of interest.

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