



Doramectin intoxication in malnourished 15-month-old cattle¹

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ABSTRACT.- Machado M., Riet-Correa F., Pedroso P.M.O. & Macêdo J.T.S.A. 2022. **Doramectin intoxication in malnourished 15-month-old cattle.** *Pesquisa Veterinária Brasileira* 42:e07102, 2022. Graduate Program in Animal Sciences in the Tropics, Faculdade de Medicina Veterinária e Zootecnia, Universidade Federal da Bahia, Av. Adhemar de Barros 500, Ondina, Salvador, BA 40170-110, Brazil. E-mail: franklinrietcorrea@gmail.com

Macrocyclic lactones are widely used as endectocides in farm animals. Intoxications occur in situations of overdose and/or malnutrition, in young animals, and in genetically sensitive breeds. We describe the intoxication by doramectin in malnourished 15-month-old cattle that received 1.6 times the recommended dose. The animals presented salivation, ataxia, motor incoordination, reluctance to move, and sternal recumbency. Two animals recovered spontaneously; one died and was necropsied. No gross or microscopic changes were observed. This study suggests that doramectin may cause intoxication when administered to malnourished cattle in doses higher than those recommended and that knowing the history is essential to establish a diagnosis.

INDEX TERMS: Cattle, doramectin, neurological signs, toxicity.

RESUMO.- [Intoxicação por doramectina em bovinos malnutridos de 15 meses de idade.] As lactonas macrocíclicas são amplamente utilizadas como endectocidas em animais de produção. Casos de intoxicação ocorrem em situações de sobredosagem e/ou desnutrição, em animais jovens ou em raças geneticamente suscetíveis. Descreve-se a intoxicação por doramectina em bovinos desnutridos, com 15 meses de idade, que receberam uma dose 1,6 vezes maior que a dose recomendada. Os animais apresentaram salivação, ataxia, incoordenação motora, relutância em se movimentar e decúbito esternal. Dois animais se recuperaram espontaneamente; um morreu e foi necropsiado. Não foram observadas alterações macro e microscópicas. Esse relato sugere que a doramectina pode causar intoxicação em bovinos desnutridos quando administrada em doses maiores que as recomendadas e que o histórico é fundamental para estabelecer o diagnóstico.

TERMOS DE INDEXAÇÃO: Bovinos, doramectina, sinais neurológicos, toxicidade.

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INTRODUCTION

Macrocyclic lactones are broad-spectrum endectocides widely used in animal production to control arthropods and nematodes. This pharmacological class is divided into two groups: avermectins (e.g., ivermectin, abamectin, doramectin, eprinomectin, and selamectin) and milbemycin (e.g., moxidectin) (Campbell 2012).

These molecules act by supporting the inhibitory action of the gamma-aminobutyric acid (GABA) neurotransmitter, which promotes the opening of chloride channels in the cell, leading to neuronal hyperpolarization and culminating in the inhibition of nerve transmission (Ayres & Almeida 2002). The use of these substances in vertebrate animals does not typically produce intoxication due to the protection P-glycoprotein provides, which prevents the passage of these substances through the blood-brain barrier (Ayres & Almeida 2002, Fromm 2004). However, intoxication by macrocyclic lactones occurs in mammals when higher-than-recommended doses are administered to young (Salman et al. 2022) or malnourished animals (Riet-Correa 2007).

In Brazil, abamectin intoxication frequently occurs in calves under three months of age (Riet-Correa 2007, Guizelini et al. 2020, Borges et al. 2021). The use of abamectin in cows with suckling calves has caused intoxication and death in their calves under 50 days of age (Borges et al. 2021). Goats under one week of age and malnourished cattle were affected by moxidectin intoxication (Riet-Correa 2007), and

piglets were intoxicated by ivermectin (Silva et al. 2018). Doramectin intoxication has not been described in cattle. The objective of this study is to describe the epidemiological and clinicopathological findings of doramectin intoxication in malnourished cattle.

MATERIALS AND METHODS

Sample collection and epidemiological and clinical data were obtained during a visit to a farm with a history of cattle exhibiting neurological signs after doramectin administration. Veterinarians from the "Secretaria de Estado da Agricultura, Abastecimento e Desenvolvimento Rural" of the Distrito Federal (State Department of Agriculture, Supply and Rural Development - SEAGRI/DF) referred the case to the "Universidade de Brasília", "Laboratório de Patologia Veterinária" (Veterinary Pathology Laboratory - LPV/UnB) for a diagnostic solution. One animal died. During necropsy, fragments of several organs were collected, fixed in 10% formalin, routinely processed for histology, embedded in paraffin, and stained with hematoxylin and eosin (HE). Additionally, samples from the central nervous system were sent for a direct fluorescent antibody test for rabies.

RESULTS

On a farm located in the municipality of Planaltina (15°38'35.8" S 47°32'53.9" W), Distrito Federal, Brazil, three male cattle (Bovines A-C), mixed breed, aged 15 months and weighing approximately 150kg (i.e., body condition score of 2 on a scale of 1 to 5) exhibited neurological signs. On physical examination, the animals were emaciated with prominent ribs, transverse processes, and retracted flanks. The animals had recently been purchased at an auction, and upon arrival at the farm, they received 5ml of a high-concentration doramectin-based commercial product (3.5g/100ml) intramuscularly. The dose recommended by the manufacturer is 1ml per 50kg of body weight. After 24 hours of drug administration, Bovines A-C showed sialorrhoea, ataxia, and incoordination. Bovine C showed more severe clinical signs in addition to a reluctance to move, sternal recumbency, and prostration. Bovines A and B spontaneously recovered after two days and Bovine C died after the same clinical course. No gross or microscopic changes were observed. The central nervous system samples tested negative for rabies by a direct fluorescent antibody test.

DISCUSSION

The diagnosis of doramectin intoxication was based on the history of a drug overdose in malnourished animals, characteristic clinical signs of macrocyclic lactone intoxication, and the absence of gross and microscopic changes in the necropsied animal. These findings are similar to the cases previously described in the literature on intoxication by other macrocyclic lactones (Seixas et al. 2006, Riet-Correa 2007).

The clinical manifestations associated with macrocyclic lactone intoxication consist of depression, staggering gait, ataxia, recumbency, and sialorrhoea and are similar to those observed in the animals in the present case. Macrocyclic lactones promote the inhibitory action of the GABA neurotransmitter, which may lead to generalized muscle hypotonia and cause the death of intoxicated animals. Most animals recover with or without supportive treatment, and lethality ranges from 50-100% (Riet-Correa 2007, Guizelini et al. 2020). Considering

the weight of the animals (150kg), the therapeutic dose of doramectin indicated would be 3ml; however, the bovines received a dosage compatible with animals weighing 250kg, 1.6 times more than the recommended dose. These findings characterize overdose of the drug, an essential epidemiological factor for the occurrence of outbreaks associated with mass deworming of animals (Seixas et al. 2006, Riet-Correa 2007).

Young (Seixas et al. 2006) or malnourished (Riet-Correa 2007) animals are susceptible to macrocyclic lactone intoxication even when receiving manufacturer-recommended doses. The overdose of the drug in the malnourished animals may have contributed to the intoxication and the fatal outcome of one of the affected animals. Another aspect of intoxication by macrocyclic lactones is a genetic predisposition, as seen in Murray Gray cattle, which are particularly sensitive to developing intoxication because they do not have P-glycoprotein (Seixas et al. 2006).

Macrocyclic lactones are highly lipophilic compounds with a high affinity for adipose tissue and the central nervous system, which gives these molecules a long persistence in the animal's body and increases the residual effect (Merola & Eubig 2012). The relationship of body condition with macrocyclic lactone intoxication is controversial. It has been suggested that the animal's diet and body condition may influence the occurrence of intoxication. Obese dogs intoxicated with moxidectin took longer to eliminate the compound (i.e., the animal remained exposed for an extended time to the compound with toxic potential) (Merola & Eubig 2012). However, obesity may have a protective effect, as the animal has an increased deposition of the compound in adipose tissue and, consequently, lower plasma concentrations may not cause intoxication. In contrast, malnourished animals may have hypoproteinemia, which results in a lower number of plasma proteins for binding to macrocyclic lactones (Merola & Eubig 2012). In this way, the drug would have a higher free plasma concentration, resulting in more severe signs of intoxication. The influence of body condition on macrocyclic lactone intoxication should therefore be considered.

Overdosage of macrocyclic lactones has often been reported as a condition for the occurrence of intoxication, but age, predisposed breeds, and body condition score must also be considered. Recently, abamectin intoxication was reported in suckling calves after treatment of their dams (Borges et al. 2021). Intoxication by macrocyclic lactones occurs under various conditions and often in outbreaks, leading to economic losses for owners.

The varied and nonspecific clinical signs and the absence of pathological findings make the diagnosis of macrocyclic lactone intoxication a challenge (Guizelini et al. 2020). The association of the history of overdose with the clinical course and the absence of gross and microscopic lesions are decisive to the diagnosis of the intoxication. As previously observed in moxidectin intoxication, lean animals appear more susceptible to macrocyclic lactone intoxication (Riet-Correa 2007). In this present case, the dose 1.6 times higher than the recommended does not seem to be the sole triggering factor for intoxication, which does not occur in animals with the favorable nutritional status treated with this dose. Doramectin has a safety margin of 25 times the recommended dose in adult cattle and three times in calves (Lanusse et al. 2009). The occurrence of intoxication with doses considered within the

safety margin in lean 15-month-old bovines suggests that the main triggering factor of intoxication in this outbreak was the animals' nutritional status. This condition has been described previously in malnourished cattle up to seven months of age intoxicated by moxidectin (Riet-Correa 2007). Due to the low number of affected animals and because there are no other animals for comparison, it is not possible to make further comparative speculations.

Although macrocyclic lactones are used on a large scale in animal production due to their efficacy, prolonged action, and safety margin, cases of intoxication frequently occur in Brazil, especially with abamectin in calves (Riet-Correa 2007, Guizelini et al. 2020). As well as botulism, urea or organochlorine intoxication, intoxication by macrocyclic lactones should be a differential diagnosis of diseases affecting the nervous system that do not produce gross or microscopic changes in ruminants. Macrocyclic lactone intoxication in malnourished cattle is likely underdiagnosed, as many animals recover spontaneously. More studies should be conducted to determine malnourished animals' susceptibility to macrocyclic lactones.

CONCLUSION

Doramectin is potentially toxic to malnourished cattle that receive an overdose of the drug.

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

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