PESQUISA VETERINÁRIA BRASILEIRA
Brazilian Journal of Veterinary Research
ISSN 0100-736X (Print)
ISSN 1678-5150 (Online)

Pesq. Vet. Bras. 44:e07416, 2024
DOI: 10.1590/1678-5150-PVB-7416

Original Article
Livestock Diseases

Anthelmintic intoxication in small ruminants diagnosed in Northeastern Brazil[1]

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The clinical, epidemiological and anatomopathological findings of anthelmintic poisoning in small ruminants diagnosed at the Veterinary Hospital of the Federal University of Campina Grande, Patos, Paraíba, from January 2000 to December 2022 are described. A total of 1,928 necropsies were carried out on small ruminants, of which 1,032 were goats and 896 sheep. Four outbreaks of anthelmintic poisoning were identified in these species: one outbreak of ivermectin in sheep, one outbreak of disophenol in goats and sheep and two outbreaks of nitroxinil in goats. These intoxications accounted for 0.78% and 0.23% of goat and sheep diseases diagnosed routinely. In the case of ivermectin poisoning, the animal had neurological clinical signs, and no macroscopic or histopathological alterations were observed. In the outbreaks of disophenol and nitroxinil, the animals showed anorexia, hyperthermia, tachycardia, tremors, dyspnea, incoordination and limb rigidity. Macroscopically, there were liver and kidney lesions associated with circulatory alterations, such as hemorrhages and edema. Microscopically, necrosis and degeneration of hepatocytes and tubular epithelial cells associated with hemorrhage and congestion were observed. The prevalence of these intoxications in small ruminants is considered low in the Semi-arid Northeast, but outbreaks can occur with high lethality in herds. The main risk factor for the occurrence of intoxications was overdose, combined with other factors such as the age of the animals, high environmental temperature, constant exercise and low body score, which increased the toxicity of anthelmintics.

INDEX TERMS: Poisoning, dewormers, goats, sheep, overdose, disophenol, nitroxinil, ivermectin.

RESUMO.- [**Intoxicações por anti-helmínticos em pequenos ruminantes diagnosticadas no Nordeste do Brasil.**] Descrevem-se os achados clínicos, epidemiológicos e anatomopatológicos das intoxicações por anti-helmínticos em pequenos ruminantes diagnosticadas no Hospital Veterinário da Universidade Federal de Campina Grande, Patos, Paraíba, durante o período de janeiro de 2000 a dezembro de 2022. Foram realizadas 1.928 necropsias de pequenos ruminantes, sendo 1.032 caprinos e 896 ovinos. Destes, foram identificados quatro surtos de intoxicação por anti-helmínticos nessas espécies: um surto de intoxicação por ivermectina em ovino, um surto de disofenol em caprinos e ovinos e dois surtos por nitroxinil em caprinos. Essas intoxicações representaram 0,78% e 0,23% das doenças de caprinos e ovinos diagnosticadas na rotina, respectivamente. Na intoxicação por ivermectina o animal apresentava sinais clínicos neurológicos e não foram observadas alterações macroscópicas e histopatológicas. Nos surtos de disofenol e nitroxinil, os animais demonstravam anorexia, hipertermia, taquicardia, tremores, dispneia,

[1] Received on January 7, 2024.
Accepted for publication on January 31, 2024.
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incoordenação e rigidez de membros. Macroscopicamente observou-se lesões hepáticas e renais associadas a alterações circulatórias como hemorragias e edemas. Microscopicamente observou-se necrose e degeneração de hepatócitos e das células epiteliais tubulares associadas a hemorragia e congestão. A prevalência dessas intoxicações em pequenos ruminantes é considerada baixa no Semiárido nordestino, entretanto, os surtos podem ocorrer com alta letalidade nos rebanhos. O principal fator de risco para a ocorrência das intoxicações foi a sobredosagem aliada aos demais fatores como idade dos animais, temperatura ambiental alta, exercício constante e escore corporal baixo, que provocaram o aumento da toxicidade dos anti-helmínticos.

TERMOS DE INDEXAÇÃO: Intoxicações, vermífugos, caprinos, ovinos, sobredose, disofenol, nitroxinil, ivermectina.

INTRODUCTION

Sheep and goat farming are among the main agricultural activities in the Semi-arid Northeast, and even with the adverse weather conditions, the Northeast stands out in small ruminant farming (IBGE 2023). However, inadequate management practices contribute to the emergence of various diseases that economically affect production in this region, such as gastrointestinal parasites (GIP), which are the most prevalent, morbid and deadly diseases in goat and sheep herds (Salgado & Santos 2016, Salles et al. 2018).

In most cases, parasite control is based on the intensive and continuous use of anthelmintics (Ruas & Berne 2022). The classification of these drugs varies according to their chemical composition into inorganic, natural-organic and synthetic compounds, the latter being the most widely used in the prophylaxis and treatment of parasites in small ruminants (Almeida et al. 2017). Synthetic anthelmintics can be subdivided into phenolic substitutes, salicylanilides, pyrimidines, benzimidazoles, imidazothiazoles, avermectins, milbemycins and aminoacetonitrile derivatives (Almeida et al. 2017, Lanusse et al. 2018).

The indiscriminate use of anthelmintics and the lack of knowledge about the difference in dosage between species has generated populations of resistant helminths. Overdosing is a frequent error in small ruminant farms, resulting in poisoning characterized mainly by neurological and respiratory alterations and malformations in fetuses (Lopes et al. 2014, Almeida et al. 2017). The error in the dose applied to the animals related to the lack of reading of medical leaflets and prescriptions, the overestimation of the animal's weight, defective dosing equipment and the use of dewormers with high doses over an uninterrupted period are considered the main factors related to intoxications (Pohl et al. 2020). In addition, high levels of plasma concentration can occur due to the use of drugs composed of aqueous solutions associated with inadequate routes of administration (Salgado & Santos 2016).

In the Northeastern Semi-arid region, anthelmintic poisoning in small ruminants can occur in the form of outbreaks or isolated cases. However, most have been limited to the description of case reports involving certain groups of drugs (Soares et al. 2001, Lopes et al. 2014, Alves et al. 2018, Campello et al. 2020, Brito Junior et al. 2021), highlighting the need to expand and disseminate more relevant information about this disease in these species. Therefore, this article aimed to characterize the clinical, epidemiological and anatomopathological findings of spontaneous anthelmintic poisoning in small ruminants.

MATERIALS AND METHODS

The study was carried out at the "Laboratório de Patologia Animal" (Animal Pathology Laboratory - LPA) of the "Hospital Veterinário" (Veterinary Hospital - VH) of the "Universidade Federal de Campina Grande" (UFCG), Patos, Paraíba. A retrospective study was carried out to obtain the data. All the cases of spontaneous anthelmintic poisoning in small ruminants were identified and reviewed, based on the necropsy records archived at the LPA, from January 2000 to December 2022.

From the necropsy protocols, clinical and epidemiological data was collected on the size of the herd, the number of sick and dead animals, age, breed, sex, vaccination status, deworming, time of year when the cases occurred, clinical signs and clinical evolution. Macroscopic and histopathological alterations were obtained from the autopsy records of each case. Photographic records were retrieved to complement the macroscopic descriptions of the lesions. In addition, all the histological slides were reviewed, and when necessary, new slides were made from tissues archived in paraffin blocks or material stored in formalin.

RESULTS

From January 2000 to December 2022, 1,928 necropsies were carried out on small ruminants, of which 1,032 were goats and 896 sheep. Four outbreaks of anthelmintic poisoning were identified in these species, consisting of one outbreak of ivermectin poisoning in sheep, one outbreak of disophenol in goats and sheep and two outbreaks of nitroxinil in goats. These intoxications accounted for 0.78% and 0.23% of the goat and sheep diseases diagnosed routinely at the LPA-HV-UFCG during this period, respectively.

The epidemiological data (species, age, breed, time of year when the cases occurred, number of animals in the herd, number of sick and dead animals, and lethality) is described in Table 1.

Ivermectin poisoning

Ivermectin poisoning occurred in a one-month-old male Cariri sheep in the city of Patos/PB. The animal had been weak for 15 days and was treated with calcium and iron. However, after seven days, the animal was dewormed with Ivermic (ivermectin 1%) (the owner was unable to state the dose administered) and showed a staggering gait. Three days later, the sheep received the second dose of the medicine and continued to show the same signs.

The animal was sent to HV-UFCG, and on clinical examination, it showed ataxia, sialorrhea, milk regurgitation and lung crepitation. Supportive treatment was carried out, but the animal died.

Macroscopically, the bladder was full, and there were multifocal to coalescent blackish-red areas in the right cranial lung lobe. Microscopically, the lung showed mild multifocal to coalescing suppurative bronchopneumonia. In all the nervous system sections, the blood vessels had moderate congestion. No changes were observed in the other organs.

Table 1. Epidemiological data on outbreaks of anthelmintic intoxication diagnosed in small ruminants in LPA-HV-UFCG, Patos/PB, January 2000 to December 2022

Anthelmintic	Ivermectin	Disophenol	Nitroxinil	
Species	Sheep	Sheep and goats	Goat	Goat
Age	1 month	Young and adults	2 years	Young and adults
Breed	Cariri	Crossbreed from Saanen, Dorper	Canindé, Boer, Alpina Americana	NDB
Time of year	July/2006	September/2014	March/2019	September/2021
Flock	120	100	120	280
Affected animals (%)	1(0.8%)	26(26%)	19(15.8%)	90(32.1%)
Dead animals	1	17	17	80
Lethality	100%	65.38%	89.47%	88.88%

NDB = no defined breed.

Disophenol poisoning

The outbreak of disophenol poisoning occurred on a rural property in the municipality of Monteiro/PB and was reported by Alves et al. (2018). The herd consisted of 100 animals raised in a semi-extensive system, including goats, sheep and cattle. All the animals were dewormed subcutaneously with the anthelmintic Disofen (disophenol 20%). The goats and sheep received the same dose, differing only in the age of the animals: 2ml for adults (over two years old), 1ml for young animals (over one-year-old) and 0.3ml for lambs and kids (under one year old). Immediately after the application of the drug, 26 animals (14 goats, 11 sheep and one bovine) presented clinical changes characterized by hyperthermia, sialorrhea, muscle tremors, tachycardia, dyspnea and when stimulated, they fell and became rigid. Nine sheep and eight goats died suddenly. The rate of affected animals was 26%, while the lethality rate was 65% (Table 1).

Two adult animals were necropsied: a female Saanen goat and a female Dorper sheep. Macroscopically, pale oral, ocular and vulvar mucous membranes were observed, as well as multifocal areas of hemorrhage in the subcutaneous tissue. The lungs were non-collapsed and heavy with shiny pleural surfaces, and the cut showed a marked amount of foamy fluid in the airways and trachea (edema). The liver was enlarged with a diffusely orange capsular surface and evidence of a lobular pattern (Fig.1 and 2). The subcapsular surface of the kidneys was diffusely pale. A large amount of slightly yellowish fluid was observed in the pericardial sac (hydropericardium). In the heart, multifocal areas of hemorrhage were observed in the walls of the epicardium and endocardium.

Histopathological evaluation of the liver revealed marked centrilobular hepatocellular necrosis associated with hemorrhage and congestion, periportal hepatocellular degeneration (Fig.3) with disorganization of hepatocyte cords and occasional intracytoplasmic eosinophilic spheroids. In the kidneys, there was diffuse and marked necrosis and degeneration of the epithelial cells of the tubules, granular casts and congestion (Fig.4). The lungs showed marked multifocal interalveolar edema and moderate congestion.

Nitroxinil poisoning

The first outbreak occurred in 2019 in the municipality of Prata/PB and was reported by Brito Junior et al. (2021). The anthelmintic Nitromic (nitroxinil 34%) was administered to a herd of 120 goats at a dosage of 0.5ml (17mg/kg) in goats weighing 10kg; 1.5ml (25.5mg/kg) in goats weighing 20kg; and 2ml (22.6mg/kg) for 30kg, subcutaneously. Immediately after applying the drug, around 80 animals in the herd were let out to graze, and 40 remained in the corral. After grazing, all goats were locked in the corral, and 19 of them fell ill; after 1 hour and 30 minutes, one goat died, and the others died approximately 30 minutes apart, with only two animals recovering and totaling 17 deaths in 48 hours after administration (Table 1). Clinically, the animals showed vocalization, abdominal distension, weakness, staggering, falls and anorexia. Deaths only occurred in goats that were put out to pasture after deworming.

Three animals were necropsied, and macroscopically, there were multifocal to coalescent areas of marked hemorrhages of varying sizes in the subcutaneous tissue. In the heart, multiple petechiae were observed in the epicardium. The lungs were non-collapsed, diffusely red and shiny, and on the cut surface, there was a marked amount of foamy liquid in the lumen of the bronchi and trachea (edema). Multifocal to coalescent areas of hemorrhage were noted on the outer surface of the trachea. The liver showed marked and diffuse evidence of the lobular pattern, characterized by a reddish central area delimited by pale areas (Fig.5 and 6). The subcapsular surface of the kidneys was diffusely reddened.

Histopathological evaluation of the liver revealed areas of necrosis associated with moderate hemorrhage and mild hepatocellular degeneration characterized by fine cytoplasmic vacuolization in the centrilobular regions and occasionally extending to the medizonal region (Fig.7). In the kidneys, vacuolar degeneration and necrosis of tubular epithelial cells associated with granular casts in the tubules of the cortical and medullary regions were observed. (Fig.8). There were also multifocal areas of congestion in the cortical and medullary regions and glomerular tuft. The lungs showed diffuse and moderate congestion, as well as multifocal areas of discrete deposition of eosinophilic, amorphous and homogeneous material (edema) obliterating the alveolar lumen, sometimes with a neutrophilic and lymphoplasmacytic inflammatory infiltrate, in addition to fibrin deposition.

The second outbreak occurred in 2021 in the municipality of São José dos Cordeiros/PB. The owner reported that the anthelmintic Nitromic (nitroxinil 34%) was administered subcutaneously to 280 goats at a dosage of 1.5ml in adults and 1ml in young. Shortly after the application, around 90 animals showed anorexia, weight loss, limb stiffness, sitting dog position and self-auscultation, opisthotonus, muscle tremors and pedaling movements. The diet was based on native pasture, corn and mineral salt. The goats had access

to water from a dam. All the animals had been vaccinated for clostridiosis 15 days previously. Of the 90 sick animals, only 10 recovered, totaling 80 deaths (Table 1). Of these four goats, two males and two females, without a defined breed, young and adult, were necropsied.

At necropsy, animals had pale oral and ocular mucous membranes. The fat in the coronary region of the heart had a gelatinous appearance. There was a moderate quantity of yellowish fluid inside the pericardial sac. The lungs were diffusely reddened, and there was a focally extensive reddened and depressed area (consolidation) in the left caudal lobe. The cut surface was diffusely red with foamy liquid content. The kidneys were diffusely reddened. No macroscopic changes were observed in the livers.

Histopathological evaluation of the liver was characterized by centrilobular necrosis and hemorrhage associated with degeneration and congestion. The kidneys showed multifocal areas of mild necrosis and degeneration of the renal tubule epithelium. Cell debris interspersed with finely granular material was seen in the tubular lumen and glomerular congestion. In the lungs, there was a discrete lymphoplasmacytic inflammatory infiltrate around the blood vessels associated with diffuse and moderate congestion, with occasional edema obliterating the alveolar lumen.

DISCUSSION

The diagnosis of ivermectin, disophenol and nitroxinil poisoning in small ruminants was established based on clinical and epidemiological data and anatomopathological findings. In Rio Grande do Sul, anthelmintic poisoning accounts for 0.3% of diseases in sheep (Rissi et al. 2010) and 6.14% in goats (Rosa et al. 2013), and in the Northeast these figures are low compared to other causes of death in small ruminants (Rosa et al. 2013). Although rare, cases of poisoning by anthelmintics have a high lethality rate since, during administration, the doses can be "estimated" or "standardized" in order to facilitate management with animals from the same herd, which often have different weights, resulting in intoxications with high animal mortality (Salles et al. 2018), as can be seen in the

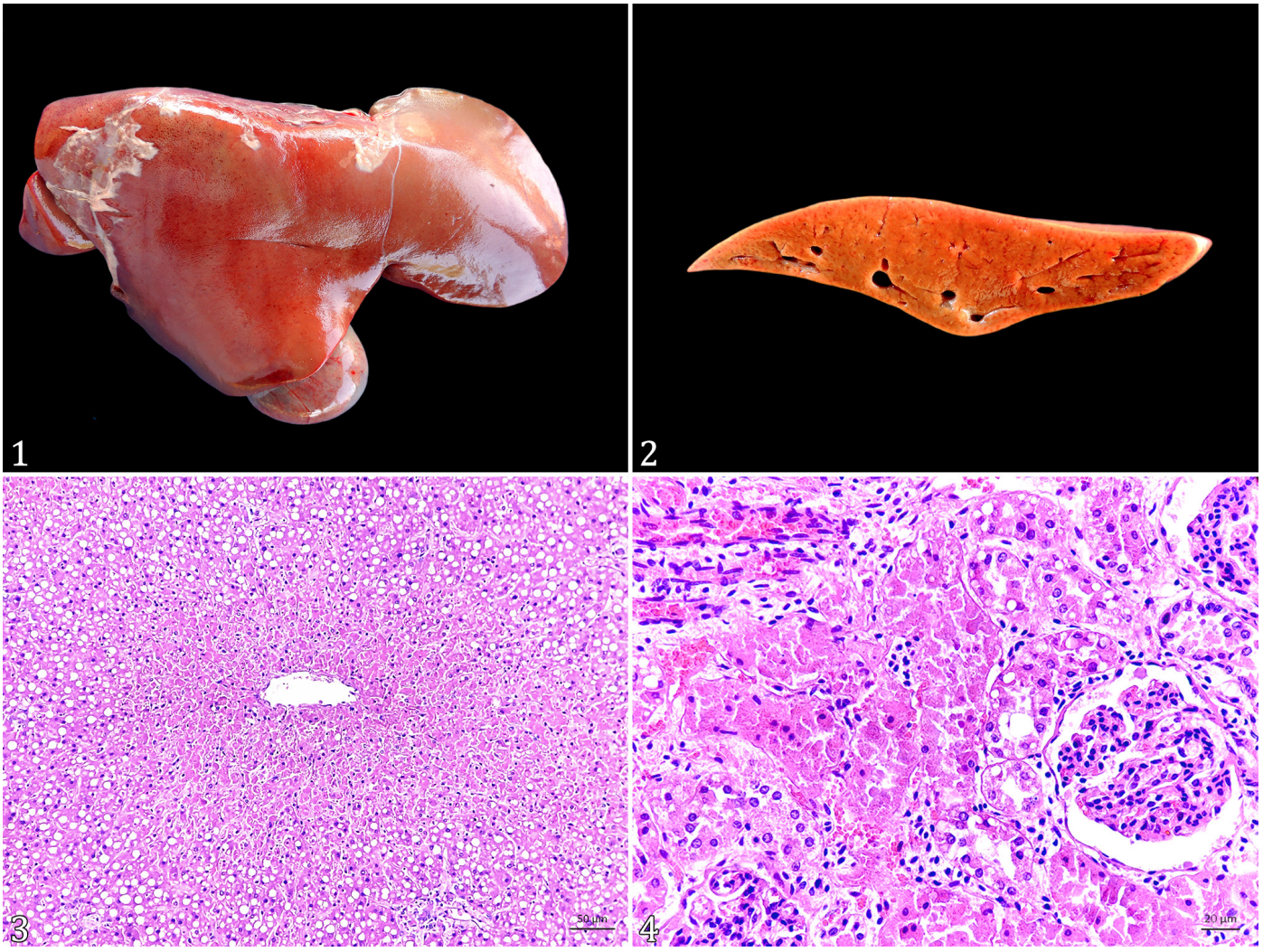

Fig.1-4. Poisoning by disophenol in sheep and goats. (**1**) Liver enlarged with accentuation of the lobular pattern. (**2**) Cut surface of the liver with diffusely orange parenchyma. (**3**) Liver-marked necrosis of hepatocytes in the centrilobular region associated with cytoplasmic vacuolation of hepatocytes in the periportal region. HE, obj.20x. (**4**) Kidney with diffuse and marked necrosis and degeneration of the epithelial cells of the tubules associated with granular casts. HE, obj.40x.

outbreaks caused by disophenol and nitroxinil with high lethality rates.

Generally, the dose of disophenol prescribed for small ruminants is 1ml for every 20kg of live weight (Chagas et al. 2013), so it is suggested that in this case, the weight of the animals may have been overestimated and the dose applied was twice as high as recommended. On the other hand, nitroxinil is a drug that has a low safety margin compared to other anthelmintics and is only indicated for cattle and sheep according to the manufacturer, and the indicated dose for this drug is 0.2ml per 10kg (Campello et al. 2020). In this case, the dosage used in one property was three to four times higher than recommended. In contrast, in the second outbreak, the dosage was calculated according to the age of the animals without correlation with weight. These practices of deworming without specifically assessing the weight of the animals and standardizing the dose by category, totally excluding body mass, are practices commonly employed by small ruminant producers in the Northeastern region.

Ivermectin is a macrocyclic lactone that, when applied in the recommended doses, is safe because its high molecular weight makes it difficult to pass through the blood-brain barrier (BBB) and consequently act on the central nervous system (CNS) (Campbell 2012). However, ivermectin is not indicated for young animals under four months of age because the BBB is underdeveloped and more sensitive to the action of the drug (Almeida et al. 2017), which may have caused poisoning in this case, given that the sheep was only one month old. Generally, the phenolic substitutes disophenol and nitroxinil bind to plasma proteins, especially albumin, and the amount in which this protein is metabolized can influence the elimination rate of the drugs (Ecco et al. 2008). Therefore, animals with a low nutritional status have a lower amount of albumin and, consequently, greater availability of the anthelmintic in the bloodstream (Almeida et al. 2017). In this case, although protein levels were not measured, the animals were very weak with anorexia and weight loss, and it is believed that the nutritional status may have influenced the toxic effect on the tissues, favoring intoxication.

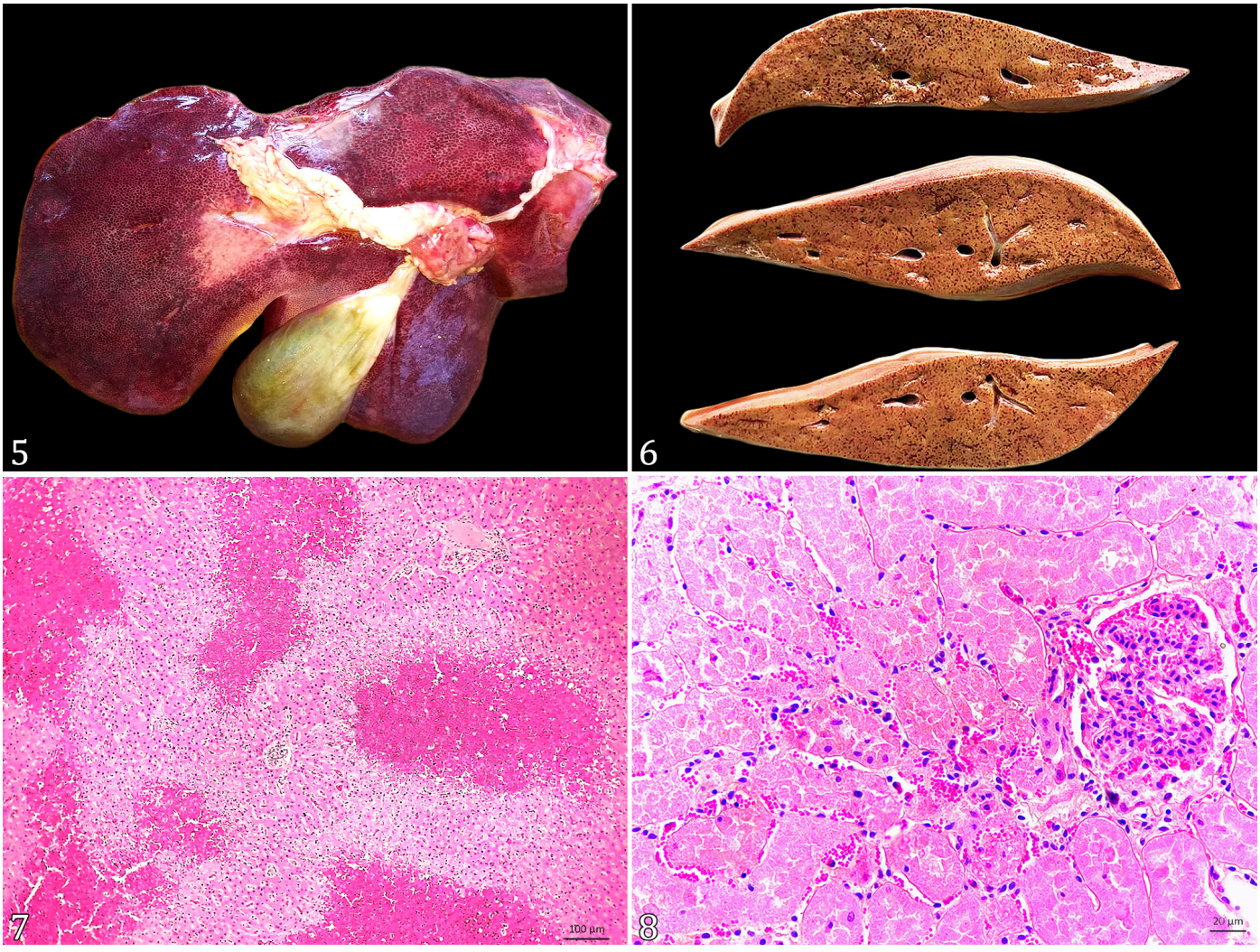

Fig.5-8. Poisoning by nitroxinil at 34% in goats. (**5**) Liver with marked evidence of the lobular pattern. (**6**) Cut surface of the liver with multifocal reddish areas. (**7**) Liver with multifocal to coalescent areas of hemorrhage, necrosis and degeneration of hepatocytes in the centrilobular region. HE, obj.10x. (**8**) Kidney with necrosis of the tubular epithelium associated with granular casts in the cortical region. HE, obj.40x.

Environmental temperature and physical exercise are also considered factors that potentiate disophenol and nitroxinil poisoning since these drugs act by increasing cellular metabolism and the need for oxygen when heat production exceeds physiological dissipation, resulting in severe hyperthermia (Alves et al. 2018). The outbreaks occurred in a semi-arid climate region whose temperatures in September can reach 34.9°C (INMET 2020) and thus contribute to increased metabolism. In addition, the animals were raised in a semi-extensive system, which increases physical activity during grazing. In all cases, the main risk factor for the occurrence of poisonings was the overdose, combined with the other factors already mentioned, the age of the animal, high environmental temperature, constant exercise and low body score, which increased the toxicity of anthelmintics, culminating in intoxication.

The clinical signs presented by the animals during the disophenol intoxication and in the second nitroxinil outbreak were consistent with the descriptions by Soares et al. (2001), Campello et al. (2020) and Brito Junior et al. (2021), respectively. Sheep and goats poisoned by phenolic substitutes show signs of pain, tremors, incoordination, hyperthermia, sweating, tachycardia, polypnea and early rigor mortis shortly after exposure to the drug (Almeida et al. 2017). Therefore, the clinical signs observed in outbreaks of nitroxinil and disophenol poisoning are similar, as they have the same mechanism of action, which consists of uncoupling oxidative phosphorylation causing inhibition of energy metabolism and depletion of ATP (Adenosine Triphosphate) levels, consequently causing tachycardia, polypnea, hyperthermia and convulsions (Soares et al. 2001, Santarém et al. 2008).

Macroscopic and microscopic findings do not occur in ivermectin poisoning in sheep (Campbell 2012); in dogs, it is possible to observe vacuolization of the ganglionic layer and nerve fibers in the retina (Lavadouro et al. 2013). The absence of lesions in sheep and other species is characteristic of poisoning with this medication and assists in the diagnosis. In the outbreaks of disophenol and nitroxinil poisoning, the main macroscopic lesions observed affected the liver and kidneys, associated with circulatory alterations such as hemorrhages and edema in various organs, which were similar to the findings reported by Almeida et al. (2017) and Soares et al. (2001). However, in the second outbreak of nitroxinil poisoning, no characteristic lesions were observed in the necropsies, suggesting that hyperacute cases without macroscopic alterations can occur.

Microscopically, liver injury characterized by centrilobular hepatocellular degeneration and necrosis associated with hemorrhage and congestion is observed in cases of disophenol intoxication (Soares et al. 2001, Alves et al. 2018) and nitroxinil (Campello et al. 2020, Brito Junior et al. 2021). This injury is probably related to the large amount of cytochrome P450 in the hepatocytes of this region, causing cell injury and lower oxygen tension due to the formation of reactive metabolites (Brown et al. 2017), suggesting that the pathogenesis of this intoxication may be similar to acute liver failure. The presence of granular casts in the kidneys reflects kidney damage and decreased glomerular filtration rate, consistent with cases of poisoning by other phenolic substitutes in which there was necrosis and degeneration of the epithelial cells of the tubules, formation of cylinders and congestion (Soares et al. 2001, Alves et al. 2018).

Although the anatomopathological findings are common to other diseases, the association with clinical signs and epidemiological data is fundamental for diagnosing anthelmintic poisoning. Experimental reproduction of intoxication is often used to confirm the diagnosis, especially in the absence of a description of the occurrence of poisoning with a specific medication (Brito Junior et al. 2021). The predominantly neurological clinical signs of ivermectin poisoning must be differentiated from infectious or metabolic diseases that affect the central nervous system of small ruminants. At the same time, intoxications by disophenol and nitroxinil should include hepatotoxic plants (*Crotalaria retusa*, *Cestrum laevigatum* and *Senecio* sp.) and nephrotoxic plants (*Amaranthus spinosus* and *Combretum glaucocarpum)* as the main differential diagnoses (Campello et al. 2020, Brito Junior et al. 2021).

CONCLUSIONS

The main methods used to diagnose anthelmintic poisoning include reports of drug use, clinical signs and anatomopathological findings due to the difficulty in dosing these drugs in the tissues of affected animals.

The prevalence of these intoxications in small ruminants is considered low in the Semi-arid Northeastern. However, outbreaks can result in high lethality with economic losses for the producer.

In cases of disophenol and nitroxinil, when administered in high doses associated with physical exertion, high environmental temperatures and low nutritional status, they result in intoxication in goats and sheep. In addition, attention should be paid to the age of the animals, as some dewormers, such as ivermectin, can cross the blood-brain barrier (BBB) of young animals and initiate intoxication.

Acknowledgments.- The authors are grateful to "Coordenação de Aperfeiçoamento de Pessoal de Nível Superior" (CAPES) and to the productivity scholarship of the "Conselho Nacional de Desenvolvimento Científico e Tecnológico" (CNPq), process number 315813/2023-7.

Financing.- Financial support was provided by the "Coordenação de Aperfeiçoamento de Pessoal de Nível Superior" (CAPES) - financial code 001.

Conflict of interest statement.- The authors declare having no conflicts of interest.

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