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

Pesq. Vet. Bras. 41:e06935, 2021
DOI: 10.1590/1678-5150-PVB-6935

Original Article
Livestock Diseases

Spontaneous and experimental poisoning by nitroxinil at 34% in goats[1]

João Ricardo C. Brito Junior[2]*, Karoline L. Soares[3], Yanca G.S. Soares[4], Flaviane N.L. Oliveira[2], Renato V. Alves[2], Eldinê G. Miranda Neto[5], Antônio Flávio M. Dantas[5] and Glauco J.N. Galiza[5]

ABSTRACT.- Brito Junior J.R.C., Soares K.L., Soares Y.G.S., Oliveira F.N.L., Alves R.V., Miranda Neto E.G., Dantas A.F.M. & Galiza G.J.N. 2021. **Spontaneous and experimental poisoning by nitroxinil at 34% in goats.** *Pesquisa Veterinária Brasileira 41:e06935, 2021*. Laboratório de Patologia Animal, Hospital Veterinário, Centro de Saúde e Tecnologia Rural, Universidade Federal de Campina Grande, Campus de Patos, Avenida Universitária s/n, Bairro Santa Cecília, Patos, PB 58708-110, Brazil. E-mail: joaoricardo055@hotmail.com

This study describes the epidemiological, clinical, and pathological aspects of spontaneous and experimental poisoning by nitroxinil at 34% concentration in goats. The outbreak occurred on a farm in the municipality of Prata, Paraíba state. Nitroxinil was administered to a herd of 120 goats, of which 18 presented with anorexia, vocalization, abdominal distension, weakness, staggering, and falls. Necropsy of three goats revealed that the main lesion was acute liver injury. Histologically the liver showed centrilobular necrosis associated with hemorrhage and hepatocyte degeneration. In the kidneys, tubular nephrosis with granular cylinder formations was observed. The lungs showed multifocal to coalescent areas of moderate interalveolar edema and vascular congestion. Experimental poisoning was carried out in two goats, with the same medication and doses administered on the farm. The experimental goats showed clinical signs and macroscopic and histological changes similar to the spontaneously poisoned goats. The diagnosis of nitroxinil poisoning was made based on epidemiological, clinical, and pathological data, and confirmed by experimental poisoning. The administration of nitroxinil in high doses, associated with high ambient temperature and physical exercises, can cause poisoning with high lethality in goats.

INDEX TERMS: Spontaneous poisoning, experimental poisoning, nitroxinil, goats, anthelmintic, overdose, centrilobular hepatic necrosis, nephrosis.

RESUMO.- [**Intoxicação espontânea e experimental por nitroxinil na concentração de 34% em caprinos.**] Este estudo descreve os aspectos epidemiológicos, clínicos e patológicos da intoxicação espontânea e experimental por nitroxinil na concentração de 34% em caprinos. O surto ocorreu em uma fazenda no município de Prata, Paraíba. Nitroxinil foi administrado a um rebanho de 120 cabras, das quais 18 apresentavam anorexia, vocalização, distensão abdominal, fraqueza, cambaleando e quedas. A necropsia de três cabras revelou que a lesão principal era uma lesão hepática aguda. Histologicamente, o fígado apresentava necrose centrolobular associada a hemorragia e degeneração de hepatócitos. Nos rins, nefrose tubular com formações de cilindro granular foi observada. Os pulmões apresentavam áreas multifocais a coalescentes de edema interalveolar moderado e congestão vascular. A intoxicação experimental foi realizada em duas cabras, com a mesma medicação e doses administradas na

[1] Received on July 16, 2021.
Accepted for publication on August 9, 2021.

[2] Student, Graduate Program in Animal Science and Health, Centro de Saúde e Tecnologia Rural (CSTR), Universidade Federal de Campina Grande (UFCG), Hospital Veterinário Universitário, Avenida Universitária s/n, Bairro Santa Cecília, Patos, PB 58708-110, Brazil. *Corresponding author: joaoricardo055@hotmail.com

[3] Student, Graduate Program in Animal Science, Centro de Ciências Agrárias, Universidade Federal da Paraíba (UFPB), Campus II, Rodovia PB-079 Km 12, Areia, PB 58397000, Brazil.

[4] Lato Sensu Graduate Program, Multiprofessional Residency modality in the Professional Area of Health in Animal Pathology, Centro de Saúde e Tecnologia Rural (CSTR), Universidade Federal de Campina Grande (UFCG), Hospital Veterinário Universitário, Avenida Universitária s/n, Bairro Santa Cecília, Patos, PB 58708-110, Brazil.

[5] Professor, Graduate Program in Animal Science and Health, Centro de Saúde e Tecnologia Rural (CSTR), Universidade Federal de Campina Grande (UFCG), Hospital Veterinário Universitário, Avenida Universitária s/n, Bairro Santa Cecília, Patos, PB 58708-110, Brazil.

fazenda. As cabras experimentais apresentaram sinais clínicos e alterações macroscópicas e histológicas semelhantes às cabras intoxicadas espontaneamente. O diagnóstico de intoxicação por nitroxinil foi feito com base em dados epidemiológicos, clínicos e patológicos, e confirmado por intoxicação experimental. A administração de nitroxinil em altas doses, associada à alta temperatura ambiente e exercícios físicos, pode causar intoxicação com alta letalidade em caprinos.

TERMOS DE INDEXAÇÃO: Intoxicação espontânea, intoxicação experimental, nitroxinil, caprinos, anti-helmíntico, sobredose, necrose hepática centrolobular, nefrose.

INTRODUCTION

Nitroxinil is an anthelmintic that belongs to the group of phenolic substitutes, which includes disophenol and nitroscanate, and is used to control infections by cestodes, nematodes, and trematodes (Lanusse et al. 2018). Phenolic substitutes have a low safety index, and among them, nitroxinil (4-35 hydroxy-3-iodine-5-nitrobenzonitrila), which is mainly indicated for the control of parasites of the genus *Fasciola* (Almeida et al. 2017a), stands out. Nitroxinil is administered to cattle, sheep, goats, and camelids (Rahman et al. 2017).

Animals poisoned by phenolic substitutes present pain, anorexia, dehydration, metabolic acidosis, muscle tremors, incoordination, hyperthermia, sweating, tachycardia, and polypnea (Penumarthy et al. 1975, Liao & Oehme 1980, Osweiler 1998).

Pharmacological intoxication associated with the administration of vermifuges has been described in goats that received high doses of ivermectin (Ali & Samra 1987, Abdou & Sharkawy 2004), tetramisol (Philip & Shone 1967), and disophenol (Soares et al. 2001); however, there are no data in the literature on the occurrence of nitroxinil poisoning in this species. The objective of this paper was to describe the epidemiological, clinical and anatomopathological findings of an outbreak of spontaneous poisoning by nitroxinil at 34%, and experimental poisoning in goats.

MATERIALS AND METHODS

The outbreak occurred in the municipality of Prata, state of Paraíba, on a farm geographically located at latitude 07°41'27" S and longitude 37°04'49" WO. Animal history and clinical data were obtained from the owner. A goat was sent to the University Veterinary Hospital of the "Universidade Federal de Campina Grande" (HVU-UFCG), Campus de Patos/PB, and was subjected to complete blood count and serum biochemistry. Three animals were necropsied, and fragments of organs of the abdominal and thoracic cavities, and nervous system, were collected, fixed in 10% buffered formaldehyde, and subsequently processed for the preparation of histological slides stained in hematoxylin and eosin (HE).

Two 18-month-old Moxotó goats (1 and 2), weighing 21 and 18kg respectively, were used for the experimental poisoning. The goats received 2ml and 1.5ml, respectively, of nitroxinil (doses similar to those administered by the farmer in the spontaneous poisoning). After nitroxinil administration, the goats were subjected to physical effort, and were necropsied after death. Fragments of organs from the abdominal cavity, thoracic and nervous system were collected during necropsy and fixed in 10% buffered formaldehyde. The experiment was registered with the Research Ethics Committee (CEP), and Ethics Committee on the Use of Animals (CEUA) with protocol no. 68-2018.

RESULTS

The outbreak of nitroxinil poisoning occurred after the farmer administered the anthelmintic to all 120 goats in the herd. The drug was administered subcutaneously in the scapular region at the following doses: 0.5mL (17mg/kg) in goats weighing 10kg; 1.5mL (25.5mg/kg) in goats weighing 20kg; and 2mL (22.6mg/kg) in goats weighing 30kg.

After the drug was administered, 80 goats were released to pasture and the remaining 40 goats were kept in the shaded corral. A few hours later, 18 of the 80 goats that were released into the pasture showed anorexia, vocalization, abdominal distension, weakness, staggering and falls. The first death occurred five hours after administration and, on the same day, 13 more goats died. In two days after the application, three more deaths occurred, bringing the total death toll to 17. Clinical signs and death occurred only in goats that were released to pasture. Of the goats that died, a two-year-old Canindé goat (A) and a two-year-old Boer goat (B) were necropsied during the farm visit. A two-year-old Boer goat (C) that received 2ml of nitroxinil was referred to the HVU-UFCG.

Goat C presented an inability to stay in the station, sternal recumbence, self-auscultation posture, opisthotonos, decreased muscle tone of the thoracic and pelvic limbs, mydriasis not responsive to the luminosity test, loss of rumen stratification, abdominal distension, and semi-solid stools. Heart and respiratory rates were found increased by 120bpm (70-90bpm) and 100mpm (25-35mpm), respectively. In the serum biochemistry of Goat C, significant increases in the levels of urea (310.9mg/dL [21.4-42.8mg/dL]), creatinine (5.7mg/dL [1-1.8mg/dL]), and creatinine kinase (CK) (265.2U/L [0.8-8.9U/L]) were observed. The animal was treated with 1.5L of saline (NaCl 0.9%) intravenously (IV), 50mL of IV vitamins and minerals (Hertavita®), 2mL of steroidal anti-inflammatory (Cort-trat®) intramuscularly (IM), 20mL of anti-inflammatory and analgesic (DMSO®) IV, and 0.5L of ruminal fluid via nasogastric tube. The goat died after two days of treatment and was necropsied.

On the necropsy of the three goats, regular body score, and normal oral, ocular, and vulvar mucous membranes, were observed. In the subcutaneous tissue, dark red multifocal areas were observed, mainly in Goat B. The liver of the three goats showed marked, enhanced lobular pattern, characterized by a reddish central area delimited by pale areas that varied from accentuated in Goats A and B, to mild in Goat C (Fig.1-2). The lungs were diffusely bright red and non-collapsed with multifocal areas of hemorrhage around the thoracic aorta. At the opening of the trachea, and when cutting the pulmonary parenchyma, there was a marked amount of foamy liquid (edema). In the heart of the three goats, there were multiple petechiae in the epicardium. The kidneys of Goats A and B were diffusely red on the subcapsular and cut surface.

Microscopically, in the liver of the three goats, necrosis and hemorrhage were observed in the centrilobular regions (Fig.3). The hepatocytes adjacent to the necrotic areas showed slight cytoplasmic vacuolization (Fig.4). In the kidneys, degeneration and necrosis of the tubular epithelium were characterized by hypereosinophilia of the cytoplasm, and pycnotic and karyorrhexis nuclei (Fig.5). In the tubular lumen, cell debris interspersed with finely granular material were observed. In the lungs, diffuse and moderate congestion was observed, in addition to multifocal areas of discrete deposition

of eosinophilic, amorphous, and homogeneous material (edema), obliterating the alveolar lumen.

In experimental poisoning, Goats 1 (21kg) and 2 (18kg) received doses similar to those administered by the owner in the outbreak: 2mL (32.3mg/kg) in Goat 1, and 1.5mL (28.3mg/kg) in Goat 2, by the subcutaneous route in the scapular region. After administration, they were placed in a corral and subjected to physical exercise under the sun for 30 minutes, and subsequently were placed in the stall for observation.

In the experimental poisoning, five hours after administration of the vermifuge, Goat 1 showed clinical signs of apathy, anorexia, ruminal atony, and difficulty in standing. The signs progressed to tachycardia, tachypnea, tympany, lateral torsion of the head, lateral recumbence, muscles tremors and spasms, and vocalization, followed by death. The clinical course was seven hours.

Upon necropsy, the liver had reddish and punctate multifocal areas distributed throughout the parenchyma and on the cut surface. In the heart, there were reddish multifocal areas in the pericardium and the endocardium. The lungs were diffusely bright and not collapsed with reddish multifocal areas, randomly distributed. The kidneys showed slightly reddish capsular surface, slightly pale cortical region, and reddish linear areas in the medullary region.

Microscopically, there was marked centrilobular necrosis in the liver associated with hemorrhage (Fig.6), surrounded by hepatocytes with microvacuolar degeneration in the cytoplasm and discrete mononuclear inflammatory infiltrates. In the medullary region of the kidneys, there were multifocal areas of discrete degeneration and necrosis of the tubular epithelium, characterized by hypereosinophilic epithelial cells with pyknosis and karyorrhexis. In the lung, there was moderate congestion and discrete eosinophilic, amorphous and homogeneous material (edema), obliterating the alveolar lumen.

Goat 2 showed clinical signs of apathy and respiratory difficulty. It died six days after the administration of the vermifuge. Upon necropsy, the lesions observed in the liver and lung were similar to those observed in Goat 1. Kidneys showed pallor in the cortical region and linear reddish areas in the medullary region. Microscopic lesions were also similar, varying with the degree of injury. In the liver, centrilobular necrosis and hemorrhage were moderate. In the kidneys, tubular necrosis was moderate, with regeneration of the tubular epithelium (Fig.7 and 8), characterized by intact basement membranes and karyomegaly. In the tubular lumen there was granular material and cellular debris. In the lungs, there was moderate congestion and edema.

DISCUSSION

The diagnosis of nitroxinil poisoning in goats was based on epidemiological, clinical, and anatomopathological findings, and confirmed by experimental poisoning. Vermifuge poisoning is highly lethal, since during deworming, doses can be "estimated" or "standardized" to facilitate handling with animals from the same herd that often have weight differences (Seixas et al. 2006). On these occasions, there may be overdoses.

The recommended dose of this drug for small ruminants is 10mg/kg (Almeida et al. 2017b, Rahman et al. 2017), while the doses used on the farm were about twice as high as indicated on the package insert. There are no reports of poisoning by this anthelmintic in goats. In sheep, however, incoordination, tremors, decubitus, and death, have been noted in animals that received an overdose (Campello et al. 2020). Nitroxinil is indicated only for cattle and sheep according to the manufacturer of the medication used on the farm (Chagas et al. 2013). The use of vermifuges with a new active principle, or little used in herds, is a common practice in the region, due to the parasitic resistance to the major commercialized anthelmintics (Lima et al. 2010).

In cases of disophenol poisoning, which is a phenolic substitute just like nitroxinil (Almeida et al. 2017a), sheep and goats presented, about three hours after administration, severe pain, muscle tremors, incoordination, hyperthermia, sweating, tachycardia, and tachypnea, in fatal cases (Penumarthy et al. 1975, Soares et al. 2001, Alves et al. 2018). Upon necropsy, hemorrhages in the subcutaneous tissue and hyperemia of the mesentery were also observed after disophenol poisoning in goats (Penumarthy et al. 1975, Soares et al. 2001). Severe liver disease results in a reduction in most clotting factors (Mosier

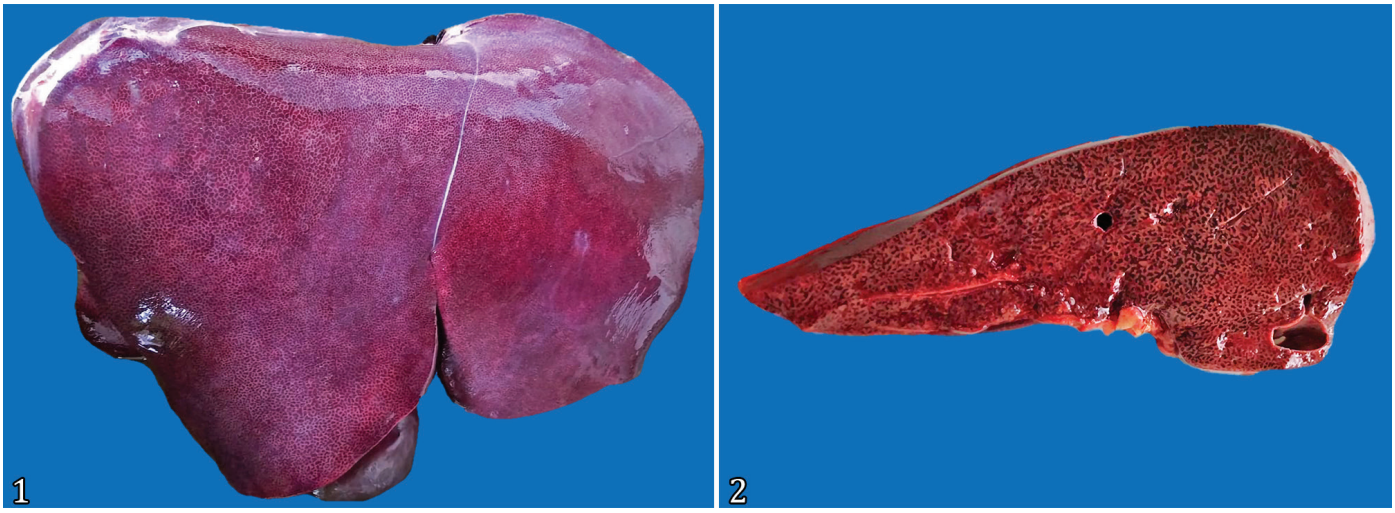

Fig.1-2. Poisoning by nitroxinil at 34% in goats. (**1**) Liver with accentuated lobular pattern. (**2**) Cut surface of the liver with red-black multifocal areas interspersed with pale areas in the parenchyma.

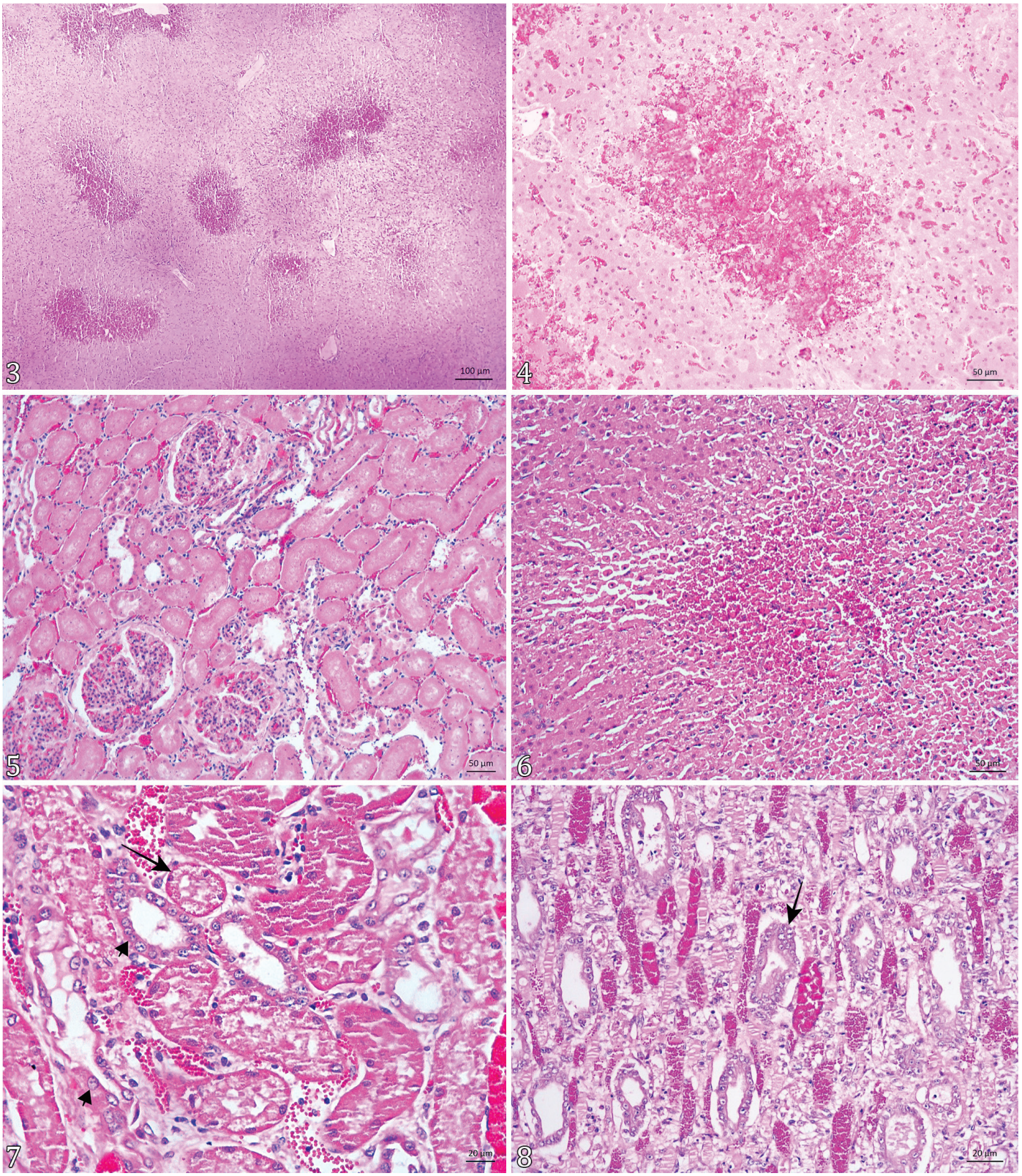

Fig.3-8. Poisoning by nitroxinil at 34% in goats. (**3**) Liver, multifocal areas of necrosis and hemorrhage are seen in the centrilobular region. HE, obj.10x. (**4**) Liver, areas of necrosis and central-lobular hemorrhage are seen surrounded by hepatocytes with vacuolated cytoplasm. HE, obj.20x. (**5**) Kidney, with degeneration and necrosis of the tubular epithelium, characterized by hypereosinophilia of the cytoplasm and pyknosis and karyorrhexis of the nuclei. HE, obj.20x. (**6**) Liver, experimental animal, with necrosis and centrilobular hemorrhage, HE, obj.20x. (**7**) Kidney, experimental animal, with epithelial degeneration and necrosis (arrow), associated with tubular regeneration(arrowhead) in the cortical region. HE, obj.40x. (**8**) Kidney, experimental animal, with marked tubular regeneration (arrow) in the medullary region. HE, obj.40x.

2017), and the acute injury observed in the animals in this study may suggest a decrease in the production of these factors, and the consequent appearance of areas of hemorrhage.

The hepatic alterations found were similar to those described in the literature for poisoning by phenolic substitutes (Soares et al. 2001, Alves et al. 2018), macroscopically characterized by appearance of lobular pattern. Microscopic findings of degeneration, necrosis, and sometimes centrilobular congestion have been described in cases of nitroxinil poisoning in sheep (Campello et al. 2020), and in cases of disophenol poisoning in goats and sheep (Soares et al. 2001, Alves et al. 2018). The acute liver injury characterized by marked centrilobular necrosis is due to the greater amount of cytochrome P450 in the hepatocytes of this region, that induces the formation of reactive metabolites that are responsible for cell damage, in addition to the lower oxygen tension in this zone (Barros 2016, Brown et al. 2017). Based on these observations, it is suggested that the pathogenesis of nitroxinil poisoning may be similar to diseases that present with acute liver failure of toxic origins, such as acute poisoning by hepatotoxic plants (Bezerra et al. 2012).

Edema and pulmonary congestion were seen in all necropsied animals. These lesions have also been described by Campello et al. (2020) and Alves et al. (2018) for nitroxinil toxicosis in sheep, and disophenol in goats and sheep. Tachypnea is a response of the respiratory center (brain stem) primarily associated with increased oxygen consumption and increased blood CO_2 levels (Reece 2006). In addition, the increase in respiratory rate helps dissipate heat mainly during periods of elevated body temperature (Robertshaw 2006). Associated with this, the lack of sufficient ATP decreases the contractile capacity of the heart, increasing the heart rate to compensate for it (Engen 2006); however, due to the low ATP, the cardiac output may continue to decrease, leading to the development of edema and pulmonary congestion.

The increases in the levels of urea and creatinine, metabolites of renal excretion, indicate acute renal injury (Meuten 2015), observed in animals with severe nephrosis. Nephrosis was the main renal disorder seen in goats with an acute condition; however, in a goat that had a longer clinical course, nephrosis was associated with marked tubular regeneration, reinforcing the hypothesis that the drug is capable of inducing both acute and renal liver damage. Tubular regeneration occurs in cases where the basement membranes remain intact and act as a support for tubular regeneration (Breshears & Confer 2018).

Only goats that were released to pasture showed clinical manifestation, possibly associated with high environmental temperature and physical effort. Also, environmental temperature and physical exercise are factors that enhance the onset of the intoxication, since phenolic substitutes increase cell metabolism and the need for oxygen (Legendre 1973). The outbreak occurred in a semi-arid climatic region, where temperatures can reach 33°C (INMET 2010) which, in combination with physical exercise, could have contributed to the increase in the animal's metabolism and, consequently, greater absorption of the vermifuge (Meerdink 1989, Mendonça et al. 2010, Bertoni et al. 2017). Poisoning by other antiparasitic drugs, such as organophosphates and pyrethroids, mainly affect animals that receive an overdose of the drug in combination with high environmental temperature and physical effort (Bertoni et al. 2017).

Pharmacological intoxications in animals occur because of overdose of medications, exceeding the recommended dose several times (Furlan et al. 2009). It is believed that these poisonings occur in a large number of animals, due to the lack of information and neglect in the use of medications (Bertoni et al. 2017). Although the optimal dose of drugs is clearly indicated on the package insert or medical prescription, not weighing the animals, leading to erroneous estimates of weight, or dividing by categories (age and sex), are the main causes of overdose in veterinary medicine (Chagas et al. 2013). Therefore, it is recommended to weigh the animals, as well as observe the route of administration, and indicate the animal species to be treated using the product.

The main differential diagnoses of nitroxinil poisoning in goats include poisoning by hepatotoxic plants such as *Crotalaria retusa* (Maia et al. 2013) and *Cestrum laevigatum* (Peixoto et al. 2000, Brito et al. 2010), and nephrotoxic plants such as *Amaranthus spinosus* and *Combretum glaucocarpum* Mart. (sin.: *Thiloa glaucocarpa*) (Melo et al. 2014, Helayel et al. 2017).

CONCLUSIONS

We concluded that nitroxinil 34%, when administered in high doses associated with high ambient temperature and physical exercise, results in poisoning with high lethality in goats. It is characterized by acute liver necrosis and tubular nephrosis, and should be included as a differential diagnosis of poisoning by hepatotoxic and nephrotoxic plants that affect animals in the region.

Due to the toxicity observed in this outbreak, the drug should be used in the doses recommended by the manufacturer, respecting the indications for each species and the weight of the animals.

Authors' contributions.- Brito Junior J.R.C., Soares K.L, Soares Y.G.S., Oliveira F.N.L., Alves R.V., Miranda Neto E.G., Dantas A.F.M., and Galiza G.J.N contributed to the collection of epidemiological data, observation of clinical signs, experimental reproduction, and necropsy, in addition to contributing substantially to macroscopic and histopathological analysis, drafted and revised the manuscript and its final version.

Acknowledgments.- To the "Coordenação de Aperfeiçoamento de Pessoal de Nível Superior" (CAPES) for the scholarship of the first author.

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

REFERENCES

Abdou K.H.A. & Sharkawy A.A. 2004. Some toxicological studies on ivermectin in goats. Proceedings of the 20 Annual Meeting of the Egyptian Society of Toxicology, Bibliotheca Alexandria, Alexandria University, Alexandria, Egypt, p.18-19.

Ali B.H. & Samra M.T.A. 1987. Some clinico-pathological observations in Nubian goats treated with ivermectin. Revue Élev. Méd. Vét. Pays Trop. 40(2):141-145. <PMid:3453504>

Almeida M.A.O., Ayres M.C.C. & Santarém V.A. 2017b. Agentes anticestódios e antitrematódios, p.849-860. In: Spinosa H.S., Górniak S.L. & Bernardi M.M. (Eds), Farmacologia Aplicada à Medicina Veterinária. 6ª ed. Guanabara Koogan, Rio de Janeiro.

Almeida M.A.O., Ayres M.C.C., Santarém V.A. & Lambert S.M. 2017a. Agentes antinematódeos, p.860-878 In: Spinosa H.S., Górniak S.L. & Bernardi M.M. (Eds), Farmacologia Aplicada à Medicina Veterinária. 6ª ed. Guanabara Koogan, Rio de Janeiro.

Alves R.C., Soares K.L., Olinda R.G., Oliveira R.L., Maia L.A., Oliveira F.N.L., Galiza G.J.N. & Dantas A.F.M. 2018. Surto de intoxicação por disofenol em ruminantes no Estado da Paraíba. Pesq. Vet. Bras. 38(Supl.):326-328. (Resumo)

Barros C.S.L. 2016. Fígado, vias biliares e pâncreas exócrino, p.181-265. In: Santos R.L. & Alessi A.C. (Eds), Patologia Veterinária. 2ª ed. Roca, Rio de Janeiro.

Bertoni E.S., Biondo A.W., Minozzo C.D., Brum J.S., Filho I.R.B. & Perotta J.H. 2017. Intoxicação aguda por organofosforado em bovinos do Paraná, Brasil. Arch. Vet. Sci. 22(4):62-66. <https://dx.doi.org/10.5380/avs.v22i4.56886>

Bezerra C.W.C., Medeiros R.M.T., Rivero B.R.C., Dantas A.F.M. & Amaral F.R.C. 2012. Plantas tóxicas para ruminantes e equídeos da microrregião do Cariri Cearense. Ciência Rural 42(6):1070-1076. <https://dx.doi.org/10.1590/S0103-84782012000600020>

Breshears M.A. & Confer A.W. 2018. Sistema urinário, p.617-681. In: McGavin M.D. & Zachary J.F. (Eds), Bases da Patologia em Veterinária. 6ª ed. Elsevier, Rio de Janeiro.

Brito M.F., França T.N., Oliveira L.I., Ramos A.S., Peixoto T.C. & Aragão A.P. 2010. Intoxicação espontânea por *Cestrum laevigatum* em um caprino no Rio de Janeiro - relato de caso. Braz. J. Vet. Med. 32(1):55-57.

Brown D.L., Vann Wettere A.J. & Cullen J.M. 2017. Hepatobiliary system and exocrine pancreas, p.412-470. In: Zachary J.F. (Ed.), Pathologic Basis of Veterinary Disease. 6ª ed. Elsevier, St. Louis, Missouri.

Campello S., Moraes D.P., Wronski J.G., Assis Brasil N. & Dos Anjos B.L. 2020. Surto de intoxicação por nitroxinil em ovinos. Anais do 8° Salão Internacional de Ensino, Pesquisa e Extensão 8(2). (Resumo)

Chagas A.C.S., Domingues L.F. & Gaínza Y.A. 2013. Cartilha de vermifugação de ovinos e caprinos. Embrapa Pecuária Sudeste, São Carlos, p.1-10.

Engen R.L. 2006. Dinâmica do sistema cardiovascular, p.163-173. In: Reece W.O. (Ed.), Fisiologia dos Animais Domésticos. 12ª ed. Guanabara Koogan, Rio de Janeiro.

Furlan F.H., Licioli J., Borelli V., Fonteque H., Stolf L., Traverso S.D. & Gava A. 2009. Intoxicação por closantel em ovinos e caprinos no Estado de Santa Catarina. Pesq. Vet. Bras. 29(1):98-93. <https://dx.doi.org/10.1590/S0100-736X2009000100014>

Helayel M.A., Ramos A.T., Goloni A.V., Veiga A. P.M., Moron S.E., Viana R.H.O. & Carvalho Júnior C.P. 2017. Intoxicação espontânea por *Combretum glaucocarpum* Mart. [sin.: *Thiloa glaucocarpa* (Mart.) Eichler] (*Combretaceae*) em bovinos. Ciênc. Anim. Bras. 18:1-8. <https://dx.doi.org/10.1590/1089-6891v18e-31906>

INMET 2010. Gráficos climatológicos. Instituto Nacional De Meteorologia, Ministério de Pecuária e Abastecimento, Brasília, DF.

Lanusse C.E., Alvarez L.I. & Virkel G.L. 2018. Anticestodal and antitrematodal drugs, p.1081-1101. In: Riviere J.E. & Papich M.G. (Eds), Veterinary Pharmacology and Therapeutics. 10ª ed. Wiley Blackwell, New York.

Legendre A.M. 1973. Disophenol toxicosis in a dog. J. Am. Vet. Med. Assoc. 163(2):149-150. <PMid:4717119>

Liao J.T. & Oehme F.W. 1980. Literature reviews of phenolic compounds. I. Phenol. Vet. Human Toxicol. 22(3):160-164. <PMid:7404980>

Lima W.C., Athayde A.C.R., Medeiros G.R., Lima D.A.S.D., Borburema J.B., Santos E.M., Vilela V.L.R. & Azevedo S.S. 2010. Nematóides resistentes a alguns anti-helmínticos em rebanhos caprinos no Cariri Paraibano. Pesq. Vet. Bras. 30(12):1003-1009. <https://dx.doi.org/10.1590/S0100-736X2010001200001>

Maia L.A., Lucena R.B., Nobre V.M.T., Dantas A.F.M., Colegate S.M. & Riet-Correa F. 2013. Natural and experimental poisoning of goats with the pyrrolizidine alkaloid-producing plant *Crotalaria retusa* L. J. Vet. Diagn. Invest. 25(5):592-595. <https://dx.doi.org/10.1177/1040638713495544> <PMid:23847092>

Meerdink G.L. 1989. Organophosphorus and carbamate insecticide poisoning in large animals. Vet. Clin. N. Am., Food Anim. Pract. 5(2):375-389. <https://dx.doi.org/10.1016/S0749-0720(15)30982-8> <PMid:2667712>

Melo D.B., Simões S.V.D., Dantas A.F.M., Galiza G.J.N., Matos R.A.T., Medeiros R.M.T. & Riet-Correa F. 2014. Intoxicação crônica por *Amaranthus spinosus* em bovino no semiárido paraibano. Ciência Rural 44(5):861-864. <https://dx.doi.org/10.1590/S0103-84782014000500017>

Mendonça F.S., Freitas S.H., Dória R.G.S., Camargo L.M. & Evêncio-Neto J. 2010. Intoxicação por diclorvós e cipermetrina em bovinos em Mato Grosso - relato de caso. Ciênc. Anim. Bras. 11(3):743-749. <https://dx.doi.org/10.5216/cab.v11i3.1029>

Meuten D. 2015. Avaliação e interpretação laboratorial do sistema urinário, p.689-806. In: Thrall M.A., Weiser G., Allison R.B. & Campbell T.W. (Eds), Hematologia e Bioquímica Clínica Veterinária. 2ª ed. Roca, São Paulo.

Mosier D.A. 2017. Vascular disorders and thrombosis, p.44-72. In: Zachary J.F. (Ed.), Pathologic Basis of Veterinary Disease. 6ª ed. Elsevier, St. Louis, Missouri.

Osweiler G.D. 1998. Toxicologia Veterinária. Artes Médicas, Porto Alegre. 526p.

Peixoto P.V., Brust L.C., Duarte M.D., Franca T.N., Duarte V.C. & Barros C.S. 2000. *Cestrum laevigatum* poisoning in goats in southeastern Brazil. Vet. Hum. Toxicol. 42(1):13-14. <PMid:10670079>

Penumarthy L., Frederich W.O. & Monty J.M. 1975. Investigations of therapeutic measures for disophenol toxicosis in dogs. Am. J. Vet. Res. 36(8):1259-1262. <PMid:1155844>

Philip J.R. & Shone D.K. 1967. Anthelmintic and toxicity studies with tetramisol. II. Toxicity studies in sheep and goats. J. S. Afr. Vet. Assoc. 38(3):287-293. <https://dx.doi.org/10520/AJA00382809_4234>

Rahman M.M., Kabir A., Ahmed S., Islam M.K., Rahman M.S., Alam S., Mubeen M.A.A., Yasmin M.S., Hossain M.S., Haque M.W.U. & Mia M.T. 2017. Nitroxynil uncouples oxidative phosphorylation in the cell mitochondria and a drug wherever injectables are preferred over drenches. Bangl. J. Vet. Med. 15(1):45-49. <https://dx.doi.org/10.3329/bjvm.v15i1.34054>

Reece W.O. 2006. Respiração nos mamíferos, p.462-475. In: Reece W.O. (Ed.), Fisiologia dos Animais Domésticos. 12ª ed. Guanabara Koogan, Rio de Janeiro.

Robertshaw D. 2006. Regulação da temperatura e o ambiente térmico, p.897-909. In: Reece W.O. (Ed.), Fisiologia dos Animais Domésticos. 12ª ed. Guanabara Koogan, Rio de Janeiro.

Seixas J.N., Peixoto P.V., Armién A.G., Jabour F.F. & Brito M.F. 2006. Aspectos clínicos e patogenéticos da intoxicação por abamectina em bezerros. Pesq. Vet. Bras. 26(3):161-166. <https://dx.doi.org/10.1590/S0100-736X2006000300006>

Soares M.P., Karam F.S.C. & Andrade G.B. 2001. Intoxicação por Disofenol em caprinos. Ciência Rural 31(1):155-157. <https://dx.doi.org/10.1590/S0103-84782001000100026>