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Hyponatremia in sheep in Northeastern Brazil[1]

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ABSTRACT.- Cunha W.R.X., Silva Filho G.B., Bom H.A.S.C., Fonseca S.M.C., Wicpolt N.S., Pontes R.M., Oliveira Filho E.F., Soares P.C. Almeida V.M. & Mendonça F.S. 2022. **Hyponatremia in sheep in Northeastern Brazil**. *Pesquisa Veterinária Brasileira 42:e07023, 2022*. Laboratório de Diagnóstico Animal, Universidade Federal Rural de Pernambuco, Rua Dom Manoel de Medeiros, s/n, Dois Irmãos, Recife, PE 52171-900, Brazil. E-mail: fabio.mendonca@ufrpe.br

Mineral deficiencies are important causes of productive losses in ruminant farming, especially in semiarid regions. This study aimed to determine Na, K, and Cl serum concentrations, plus the salivary concentrations of Na and K in sheep raised in a semiarid region of Northeastern Brazil, and to report the epidemiology, clinical and the pathological aspects of an outbreak of hyponatremia in sheep. For this, serum and salivary samples of 55 sheep were collected in 6 different farms in the region. Na, K, and Cl concentrations were determined by colorimetric test, using commercial kits in a semi-automatic biochemical analyzer. The mean serum concentrations ranged from 131.5±13.1mEq/L to 172.4±9.3mEq/L for Na, 6.28±1.3mEq/L to 13.9±1.4mEq/L for K, and 91.6±54.8mEq/L to 113.6±1.5mEq/L for Cl. The mean salivary concentrations ranged from 119.4±9.5mEq/L to 161.8±15.2mEq/L for Na, 10.1±3.1mEq/L to 22.3±2.3mEq/L for K, and the ratio Na:K ranged from 6.0±1.3mEq/L to 11.8±4.1mEq/L. These results revealed that most sheep raised in the farms in this region are marginally depleted in sodium. In one farm, sheep had severe clinical signs of Na deficiency consisting of haggard appearance, craving for salt, polydipsia, polyuria, dry cough, inappetence, pica, weakness, difficulty to rise and move, severe emaciation, and dehydration. On autopsy, the ruminal content was generally impacted, giving to the content an aspect of clay balls. Four sheep presented hypertrophy of the adrenal glands. Histopathologically, the width of the zona glomerulosa was expanded, there was loss of the architecture and loss of adrenocortical cell cords. The epithelial cells in the zona glomerulosa and fasciculata were pyramidal, and contained hypereosinophilic cytoplasm and hyperchromatic nuclei. These data demonstrate the occurrence of Na deficiency in different degrees in sheep farms in the State of Pernambuco and highlight the importance of providing NaCl to avoid outbreaks of hyponatremia.

INDEX TERMS: Hyponatremia, sheep, Brazil, mineral deficiency, hypokalemia, hypochloremia, ruminants.

RESUMO.- [**Hiponatremia em ovinos no Nordeste do Brasil.**] Deficiências minerais são importantes causas de perdas produtivas em criações de ruminantes, sobretudo em regiões semiáridas. Este trabalho teve como objetivo determinar as concentrações séricas de Na, K e Cl, além das concentrações salivares de Na e K em ovinos criados em uma região semiárida do Nordeste do Brasil e relatar a epidemiologia e os aspectos clínicos e patológicos de um surto de hiponatremia severa em ovinos. Para isso, amostras de soro e saliva de 55 ovinos foram coletadas em 6 diferentes fazendas da região. As concentrações de Na, K e Cl foram determinadas por teste colorimétrico, utilizando kits comerciais em analisador bioquímico semiautomático. As concentrações séricas médias variaram de 131,5±13,1mEq/L a 172,4±9,3mEq/L para Na, 6,28±1,3mEq/L a 13,9±1,4mEq/L para K e 91,6±54,8mEq/L

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a 113,6±1,5mEq/L para Cl. As concentrações salivares médias variaram de 119,4±9,5mEq/L a 161,8±15,2mEq/L para Na, 10,1±3,1mEq/L a 22,3±2,3mEq/L para K, e a razão Na: K variou de 6,0±1,3mEq/L a 11,8±4,1mEq/L. Esses resultados revelaram que a maioria dos ovinos criados nas fazendas desta região são marginalmente sódio deficientes. Em uma fazenda, os ovinos apresentavam um quadro clínico grave de deficiência de Na. Os principais sinais clínicos consistiam em apatia, avidez por sal, polidipsia, poliúria, tosse seca, inapetência, pica, fraqueza, dificuldade de se levantar e se locomover, emagrecimento e desidratação. À necropsia, o conteúdo ruminal estava geralmente compactado, dando ao conteúdo um aspecto de bolas de argila. Quatro ovelhas apresentaram hipertrofia das glândulas adrenais. Histopatologicamente, a zona glomerulosa apresentava-se espessa, com perda da arquitetura e desarranjo dos cordões celulares. As células epiteliais da zona glomerulosa e fasciculada eram piramidais, apresentavam citoplasma hipereosinofílico e continham núcleos hipercromáticos. Esses dados demonstram a ocorrência de deficiência de Na em diferentes graus em criações de ovinos no Estado de Pernambuco e evidencia a importância do fornecimento de NaCl para a prevenção de surtos de hiponatremia.

TERMOS DE INDEXAÇÃO: Hiponatremia, ovinos, Brasil, deficiência mineral, hipocalemia, hipocloremia, ruminantes.

INTRODUCTION

Minerals are inorganic nutrients that perform three types of essential functions in the organism of animals: they participate as structural components of body tissues; act on tissues and body fluids as electrolytes to maintain the acid-base balance, osmotic pressure and permeability of cell membranes, and osmotic balance; and play a role as activators of enzymatic processes or as components of the structure of metalloenzymes and vitamins. To perform these functions, the organism needs certain amounts of each essential mineral. Concentrations of minerals below the minimum required by each species can change the metabolic dynamics and compromise several organic activities (Riet-Correa 2007, Soetan et al. 2010, Suttle 2010).

Amongst major minerals considered essential for animal health, sodium (Na) stands out for being the main intracellular cation, which, in combination with chlorine (Cl), maintains the osmotic pressure, regulates the acid-base balance, and controls water metabolism in the body (Russell & Roussel 2007, Sykes 2007, Suttle 2010, Tokarnia et al. 2010). Na metabolism is greatly disturbed in ruminants when mineral salt supplies are interrupted or not provided, causing hyponatremia (Tokarnia et al. 2000, 2010, Russell & Roussel 2007, Sykes 2007).

Ruminant species fed tropical grasses may present hyponatremia because these grasses generally have low levels of Na (Suttle 2010). In different regions of Brazil, the majority of grasslands are deficient in Na throughout the year (Tokarnia et al. 1999, 2000, 2010, Conti et al. 2015). Hyponatremia also results from excessive loss of Na-rich fluids, as in case of diarrhea, renal failure, or an obstructed or ruptured urinary tract (Russell & Roussel 2007). Other factors, including lactation, fast growth, excessive sweating in tropical climates, and fertilization of grazing areas with excess K favor Na deficiency (Riet-Correa 2007, Tokarnia et al. 2010). Disorders in which Na is lost tend to produce hypokalemia and hypochloremia (Russell & Roussel 2007). Hyponatremia, hypokalemia, and hypochloremia are frequent findings in obstructive gastrointestinal diseases, including displaced abomasum, abomasal volvulus, intussusception, and cecal torsion (Russell & Roussel 2007).

The clinical signs presented by sheep and goats affected by hyponatremia are notably a marked craving for salt, weight loss or lesser weight gain than normal, slower growth, decreased meat and milk production, and allotriophagy, with a tendency for animals to ingest soil or wood and lick the sweat of other animals, and in the case of confined sheep and goats, lick the walls (Riet-Correa 2007, Tokarnia et al. 2010). However, despite being the second most common mineral deficiency in the world, only behind phosphorus (P) deficiency (Tokarnia et al. 2010), Na deficiency in small ruminants is poorly understood and knowledge about this condition is scarce, especially in sheep. Additionally, levels of Na, K and Cl in serum or saliva of sheep raised in semiarid conditions, such as observed in northeastern Brazil are lacking. In the present study, we aimed to determine Na, potassium (K), and Cl serum concentrations, plus the salivary concentrations of Na and K in sheep raised in a semiarid region of Northeastern Brazil and report the epidemiology, clinical and pathological aspects of an outbreak of severe hyponatremia in sheep occurred in this region.

MATERIALS AND METHODS

Five sheep breeding farms located in the semiarid region of Pernambuco were evaluated. Clinical and epidemiological data were obtained by veterinarians in the properties. During technical visits, ten adult sheep were randomly chosen from each herd for clinical evaluation according to Radostits (2000) and blood samples were collected by jugular venipuncture in silicone tubes with and without anticoagulant. A complete blood count was performed to determine the packed cell volume using the microhematocrit technique. The hemoglobin level was assessed by the cyanmethemoglobin method and the red blood cell (RBC) count was performed using a Neubauer chamber. To determine the plasma protein level, blood samples were collected with EDTA at 10%, heated at 57°C for 3 minutes, centrifuged, and analyzed by refraction. To obtain the serum, the blood samples without anticoagulant remained at rest at room temperature for clot retraction and then were centrifuged for 15 minutes at 500G. Serum samples were stored in Eppendorf tubes at -20°C for further mineral analysis.

Saliva samples were obtained by suction of mixed saliva from the oral cavity in the lateral region of the lower molar teeth using a 30-cm plastic cannula coupled to a clinical aspirator (aspira max, Omron Healthcare Brasil Indústria and Commerce of Medical Products LTDA). The cannula was washed with distilled water and the syringe exchanged for a new one between samplings in order to avoid saliva contamination. After sampling, each saliva sample was placed in a sterile 15mL Falcon tube, packed in polystyrene boxes with recyclable ice until arrival at the laboratory where they were centrifuged at 2000 rpm for 10 minutes for separation and removal of residues, and then pipetted and placed in 2mL Eppendorf microtubes and frozen at -80°C until processing.

Serum and salivary concentrations of Na, K and Cl were determined using an automated biochemical analyzer (Labmax 240®), with commercial kits from Labtest®. The Na:K ratio was obtained by dividing the value of total calcium by the value of potassium. These data were evaluated according to measures of

central tendency (mean, median, range, minimum and maximum values, and standard deviation).

Additionally, the rumen content of selected sheep was collected using a gastric tube and used to evaluate pH, color, odor, appearance, flotation-sedimentation, methylene blue reduction, and protozoan activity. Five sheep were necropsied after presenting severe clinical signs of sodium deficiency and spontaneous death. The following tissues were collected and fixed in 10% neutral buffered formalin, pH 7.2, for 24 hours: brain, spinal cord, lung, heart, liver, pancreas, kidney, adrenal gland, thyroid, spleen, rumen, reticulum, omasum, and abomasum. All samples were processed routinely for the production of 4-µm thick hematoxylin and eosin (HE) sections.

RESULTS

The study was carried out in the semiarid region of the state of Pernambuco at the municipalities of Limoeiro (Farm 1), Custódia (Farm 2), São José do Egito (Farm 3), Sertânia (Farm 4), Venturosa (Farm 5), and Belo Jardim (Farm 6) during the dry season (Fig.1). The weather in this region is semiarid, with high mean temperatures and scarce and irregularly distributed rainfall throughout the year. This region is located within the Brazilian biome Caatinga, which is predominantly composed of xerophytic, woody, thorny, and deciduous vegetation. The farms were small to medium size and the main source of income is family farming. The management adopted was semi-extensive, and protein and mineral supplementation was barely provided with exception of Farm 6, where commercial pelleted feed containing ground whole corn, soybean meal, cottonseed meal, wheat bran, and vitamin A, vitamin D3, and vitamin E supplement was provided.

The mean serum concentrations of Na, K, and Cl and salivary concentrations of Na, K and the Na:K ratio in sheep of different farms are summarized in Table 1. The serum concentrations of Na, K, and Cl remained within normal ranges in sheep from Farms 1 to 5. Sheep from farm 6 presented serum values of Na of 131.5±13.1mEq/L, while K remained within normal values. The values of Na in the saliva of sheep from all farms were below reference values and the lowest value was 119.5±9.5mEq/L, in sheep from Farm 6. In this farm, average values of K also remained below the reference values. The Na:K ratio in saliva of sheep from Farms 1 to 6 remained below reference values.

No clinical signs of Na deficiency were noted in sheep from Farms 1 to 5. Unspecific clinical signs consisting of pale mucosa, mild inappetence, haggard appearance because of a rough coat, and salt craving were noted in a general manner. No significant changes were noted in hematological parameters or in the ruminal fluid in sheep from the Farms 1 to 5.

In farm 6, an outbreak of Na deficiency affected 42 out of a total of 212 sheep. The morbidity was 19.81% (42/212), mortality 3.30% (7/212), and lethality 16.6% (7/42). The clinical signs were variable in this group, ranging from mild to severe alterations, mainly affecting pregnant or lactating

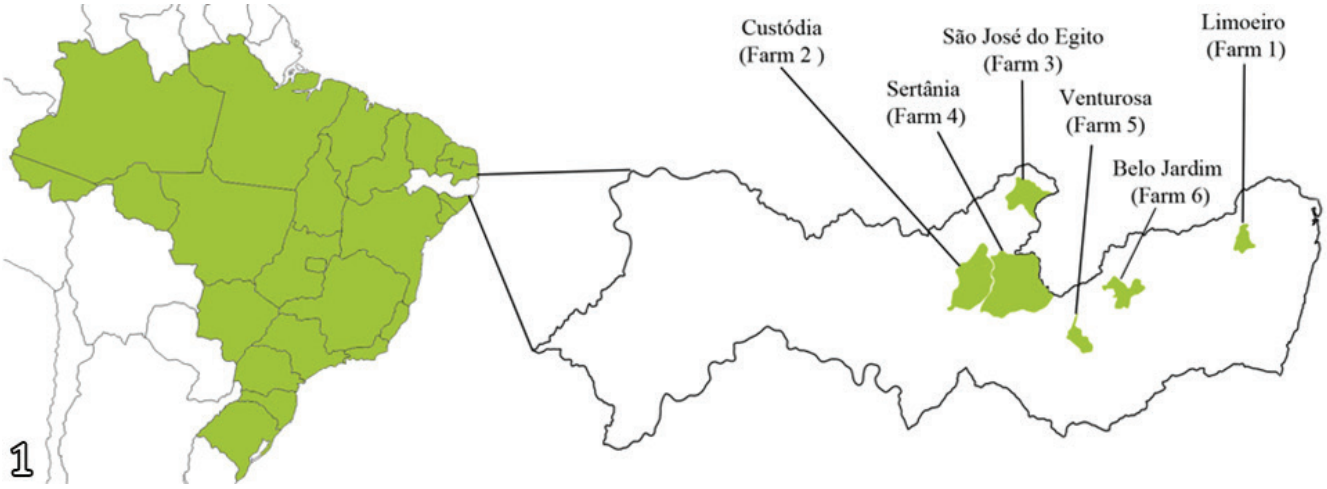

Fig.1. Geographic map of Brazil highlighting the Northeast region, the State of Pernambuco and, in the high magnification, the municipalities studied.

Table 1. Average and standard deviation of Na, K, and Cl concentrations in serum and salivary samples of sheep

Minerals (mEq/L)	Farms						Reference values*
	1	2	3	4	5	6	
Serum							
Na	156.8±4.5	172.4±9.3	170.2±8.4	165.4±8.8	181.5±16.5	131.5±13.1	145-152
K	8.0 2±0.7	8.2±0.6	12.26±1.3	13.9±1.4	15.5±1.6	6.28± 1.3	4-6.5
Cl	107.2±1.2	91.6±54.8	103.6±31.2	112.5±3.0	113.6±1.5	-	102-113
Saliva							
Na	145.2±23.5	129.1±22.4	142.7±28.7	161.8±15.2	163.6±2.4	119.4 ±9.5	~160
K	19.5±19.5	22.3±2.3	19.9±1.8	21.8±1.7	22.6±2.5	10.1 ±3.1	~10
Na:K	7.5±1.6	6.0±1.3	7.2±1.9	7.5±1.2	7.3±1.4	11.8 ±4.1	~ 20:1

* Radostits et al. (2000), Denton (1956).

ewes. Thirty-nine sheep (92.8%; 39/42) presented mild to moderate clinical signs that consisted of haggard appearance because of a rough coat, salt craving (Fig.2) and pica, which was manifested mainly by avid craving for soil (Fig.3 and 4) and the stall walls (Fig.5). Other manifestations included polydipsia, polyuria, dry cough, inappetence, weakness and difficulty to stand. As the deficiency progressed, from four to seven weeks after the observation of the first clinical signs, five sheep became emaciated, dehydrated and died suddenly. During the inspection of mineral supply, it was noted that the shepherd was not giving adequate mineral salt for this group of sheep (i.e. intermittent supply, inadequate amount for the number or animals or the mineral salt remained wet for a long time).

Hematological analysis revealed an increase of 60% to 65% in the hematocrit in five sheep. No other alterations were noted. The results of the analysis of the ruminal fluid revealed a decrease in methylene blue reduction activity and the density and motility of protozoa were decreased by 70-80% in five sheep. In two of them, the color of the ruminal fluid was brownish. No other alteration was noted.

On autopsy, the ruminal content was generally compacted and brownish, forming round masses composed of grass and clay or sand, sometimes giving it an aspect of clay balls (Fig.6). In two sheep, the content was also compacted, but had a green color and contained a grayish sand content. Four of the five sheep presented enlarged adrenal glands (Fig.7), nearly double in size, and on the cut surface they were swollen and had thick edges. In two sheep, the cranioventral lobes of the lungs were focally dark red, condensed, and had a bright appearance. No other gross lesions were observed. Histopathologically, the main changes were observed in the cortex of the adrenal gland. The width of the zona glomerulosa was expanded and occupied at least a double proportion of the cortex. Additionally, a marked disorganization of the adrenal cortex was noted, characterized by thickening of the zona glomerulosa, loss of cell cords in the zona fasciculata, and pooling of RBCs in the fibrovascular stroma (Fig.8). These same alterations were observed in the zona fasciculata. Adjacent cortical cells in both zones were pyramidal in shape, condensed, with hypereosinophilic cytoplasm and hyperchromatic nuclei, and were coated by abundant proteinaceous fibrillar material. The epithelial cells of the zona fasciculata had a similar appearance but were larger and lighter than glomerulosa cells. The cells from the zona reticularis were similar to those of the zona glomerulosa in shape and were also condensed, with hypereosinophilic cytoplasm and hyperchromatic nuclei. No alterations were noted in the cells of the medulla (Fig.9).

Fig.2-5. Hyponatremia in sheep. (**2**) Several sheep exhibiting a craving for salt. (**3**, **4**) Sheep presenting pica, mainly manifested by avid craving for soil. Note there are several holes in the ravines. (**5**) Sheep presenting pica, charachterized by liking the walls of stalls in an area of confinement. Note holes in the sheep trough due to constantly liking.

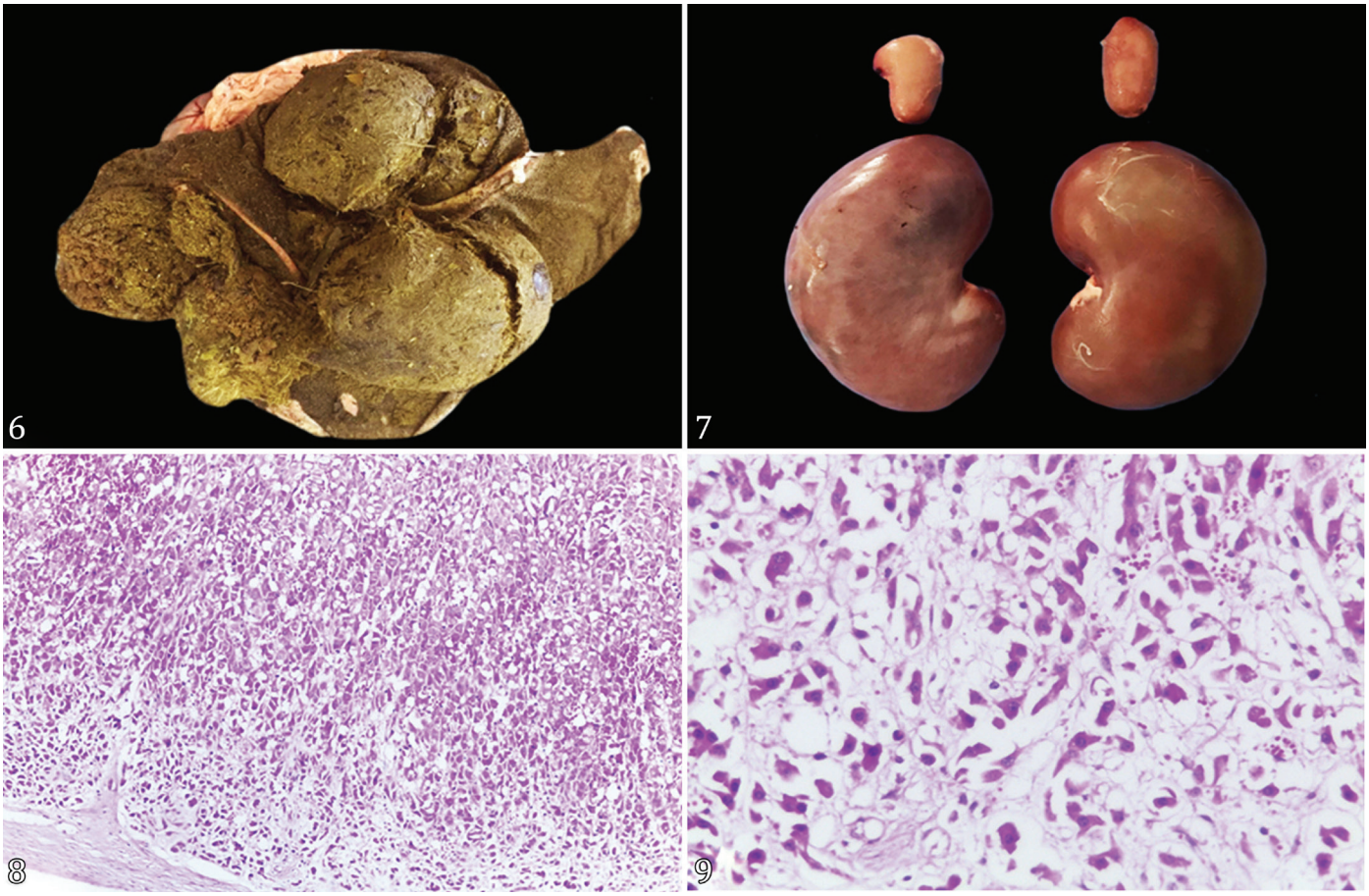

Fig.6-9. Hyponatremia in sheep. (**6**) Ruminal content is impacted, brownish, forming round masses composed of grass and clay with an aspect of clay balls. (**7**) Hypertrophy of adrenal glands, which are approximately double in size. (**8**) Hypertrophy of adrenal gland in a Na-depleted sheep. The width of the zona glomerulosa is expanded and occupies at least a double proportion of the adrenal cortex. Loss of the architecture and loss of cortical cell cords is noted. HE, obj.10x. (**9**) Glomerulosa cells are pyramidal in shape, condensed, with hypereosinophilic cytoplasm and containing hyperchromatic nuclei, and are lined by abundant proteinaceous fibrillar material. HE, obj.40x.

DISCUSSION

The diagnosis of hyponatremia described here was based on epidemiological and clinical findings and confirmed by low salivary Na concentration in sheep from four farms (1, 2, 3, and 6) and low Na:K ratios, ranging from 6.0-11.8mEq/L, in sheep from all farms. These rates indicate marginal levels for Na deficiency in all sheep examined. When Na concentration is approximately 160mEq/L and the K concentration is 10mEq/L (Na:K ratio = 20), with a normal diet, and adequate replacement of Na, the sheep remained in good condition indefinitely (Denton 1956, Suttle 2010). Values between 4.0 and 10.0mEq/L indicate a marginal Na deficiency, while values less than 4.0mEq/L indicate deficiency. However, Na:K ratios of in Na-depleted sheep are known to present a wide variation, ranging from 40.0 to 114mEq/L for Na and from 7.8 to 16mEq/L for K (Denton 1956), also reaching negative proportions, such ratios as 0.4-0.5 (Sykes 2007, Suttle 2010). Additionally, narrow salivary Na:K ratios (less than 10:1) may be associated with responses to supplemental Na because in depleted animals, the adrenal cortex responds rapidly by increasing the secretion of aldosterone, which acts directly on the parotid salivary gland, causing a reduction in Na and elevation of K concentration in the saliva (Morris 1980). Maybe this was the reason why we found higher levels of salivary K in sheep from Farms 1-5.

The concentration of Na in the blood plasma is not considered an adequate parameter for the diagnosis of hyponatremia and caution is recommended when interpreting the analyses of animal pastures, as the Na concentration in the forage can present seasonal variation (Morris 1980). In chronically Na-deficient cattle, little or no change is usually found in serum concentrations of Na even in severely affected animals. In the present study, serum levels of Na in sheep from Farms 1 to 5 remained within normal values, and only sheep from Farm 6 had low values. The average serum K levels were higher than 8mEq/L, above the reference value adopted, 24-6.5mEq/L. However, the animals did not show signs of hyperkalemia. Therefore, salivary Na:K ratio and adrenal histology are the most sensitive indices of Na inadequacy (Morris 1980, Suttle 2010) and the surest indicator of Na deprivation remains a positive response in appetite, appearance, and productivity to salt supplementation (Sykes 2007). Other laboratory findings in Na deficiency include low urinary, ruminal and fecal Na concentrations, concurrent increased ruminal and

fecal K concentrations, and increased serum aldosterone concentration (Olson et al. 1989). However, these parameters were not analyzed in our study.

Sheep from Farms 1 to 5 did not show clinical signs that indicated Na deficiency, while sheep from farm 6 presented severe clinical signs. In this last case, the deficiency affected mostly pregnant and lactating ewes, a well-known factor that precipitates Na deficiency (Michell et al. 1988, Sykes 2007, Suttle 2010, Tokarnia et al. 2010). The remaining flocks were formed by meat sheep, which were younger and did not stay long on the farms because they were quickly sent to slaughterhouses. It is noteworthy, also, that sheep from farm 6 presented deficiency because mineral salt was not being provided for a long period and the climate in the region is semiarid. When one or more of these conditions persist continuously, Na deprivation is inevitable (Suttle 2010).

The most obvious sign of Na depletion, which is craving for salt, does not provide a definitive diagnosis of Na deprivation because some healthy individuals eat salt avidly (Denton 1956) and salt craving characterizes several disorders. Other manifestations of Na deprivation such as polydipsia and polyuria (Whitlock et al. 1975) are also non-specific. For this reason, parasitic diseases causing malnutrition such as coccidiosis, phosphorus and copper deficiency and several other diseases where anorexia, emaciation, opaque and brittle hair, low growth and less weight gain, and low milk production must be remembered when a differential diagnosis of Na deprivation is performed.

Similarly to the observed in sheep in the present study, chronic Na deficiency has been shown to result in enlargement of the zona glomerulosa of the adrenal in several species, such as rats (Wardlaw & Pike 1963), rabbits and kangaroos (Myers 1967, Blair-West et al. 1968), and cattle (Morris & Gartner 1975). However, in addition to this, we described here changes in glomerulosa and fasciculata cells. These alterations are probably related to hyperaldosteronism induced by chronic low levels of Na. In this situation, cells of the zona glomerulosa look small and markedly stained with eosin because of the presence of increased mitochondria, whereas fasciculata cells look large and light because of the great abundance of lipid droplets, while cells from the zona reticulata are similar to those of the zona glomerulosa, appearing as dark grey cells (Gioco et al. 2015). These lesions herein described are very useful to diagnose Na deprivation in sheep.

Agricultural farming in semiarid regions is practiced on a small scale due to the scanty and uncertain rainfall and limited water irrigation. Rangeland grazing instead prevails in these regions. However, due to the increasing rate of rangeland degradation and economic instability, livestock feeding generally faces serious difficulties related to quantitative and qualitative provision of nutrients and minerals, which is exacerbated by the continuous increase of feedstuff prices (Salem 2010). Especially in northeastern Brazil, ruminants raised under these conditions generally graze on degraded rangelands and do not receive adequate mineral provision. This is the major cause of mineral deficiencies in livestock in this region.

The management of mineral supplies for sheep in the studied region is so unbalanced that the provision of complements is necessary for maintenance and production. Regarding Na concentration in the diet for sheep, a daily consumption of 0.7-0.9g of Na is recommended and, in general, a dietary NaCl supply at the level of 0.25% -0.5% is considered adequate for ruminants (Riet-Correa 2007). For lactating ewes in extensive or semi-extensive rearing systems, loose or block salt should be continuously provided. In general, this is usually sufficient, but it is necessary to highlight that the physical form of the salt affects voluntary consumption. Ewes at pasture consume significantly more loose than block salt, but intakes of block salt are still sufficient to meet the Na needs of lactation.

CONCLUSION

Sodium deficiency in sheep occurs in the state of Pernambuco and the inadequate mineral supplementation of Na is a potential risk for the occurrence of outbreaks in the region. Oral prophylactic supplementation with NaCl is the best strategy to prevent and treat this deficiency in sheep.

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

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