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Original article

Milk transfer of cyanide and thiocyanate: Cyanide exposure by lactation in goats

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Abstract – The present work was aimed at evaluating the effects of maternal exposure to potassium cyanide (KCN) during lactation in goats. Twenty-seven lactating female goats were orally dosed with 0 (control), 1.0, 2.0, or 3.0 mg KCN/kg body weight/day from lactation days 0 to 90. After this period, all male kids and one mother from each group were killed for a pathological study. Cyanide treatment promoted the clinical signs of maternal toxicity in the highest KCN group but did not affect body weight. Both cyanide and thiocyanate presented increased levels in both dams and kids from the treated groups. Microscopic lesions, but without alterations on the biochemical panel, were found in the brain, thyroid, liver, and kidneys of both dams and kids from the treated groups. These findings suggest that lactating offspring can be indirectly intoxicated by maternal exposure to cyanide.

cyanide / thiocyanate / milk / goat

1. INTRODUCTION

Several plant toxins are known to be transferred through milk, having an important impact on animal production, food safety and public health. Some examples include indolizidine [14], piperidine [17], pyrrolizidine [7, 19, 30], and quinolizidine alkaloids [23], glucosinolates [10, 11, 28, 38], sesquiterpene lactones [13], and ptaquilosides [1, 9]. Although excretion of plant toxins through the mammary gland reduces the toxicity to lactating animals, it is an important source of such toxins to the consumer. Moreover, neonates are usually more sensitive to the toxins than adults [24]. The toxicological hazard of this route of elimination is more significant in cases of repetitive exposure rather than single exposure.

A number of plants used in animal feeding are cyanogenic, such as cassava, sorghum, and Cynodon grasses [3]. Long-term cyanide ingestion, which occurs when cyanogenic plants are part of the diet, has been associated to hypothyroidism, pancreatic diabetes, and several neuropathies in both humans and animals [16, 26]. The major route of detoxification of cyanide is

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through the transformation to thiocyanate, which is eliminated mainly via the urine but also via the milk and saliva [2]. In the cellular membrane of the cells from thyroid follicles, the protein responsible for iodide capture from the bloodstream was identified as $Na^{+}I^{-}$ symporter (NIS) [6]. NIS has also been discovered in the mammary gland [35], probably with the function of passing iodide to milk in order to supply the suckling's needs. Thiocyanate anion possesses a high affinity for NIS being a competitive inhibitor in the iodide capture [8], and may be eliminated in the milk through NIS in the mammary epithelial cells. In addition, thiocyanate is a normal component in low amounts of the milk participating in the lactoperoxidase system, an unspecific antimicrobial [27]. Nonetheless, no work was found in the literature aimed at understanding the effects of exposure to cyanogenic plants or to cyanide on lactation in ruminants.

Thus, the objective of the present work was to evaluate the effects on both the dams and litter of the maternal exposure to potassium cyanide (KCN) during the lactation period in goats. A previous study showed that this species is an excellent animal model for studies on the chronic toxicity of cyanogenic plants [31]. An experimental model to study the transfer of plant toxins through milk in ruminants is proposed.

2. MATERIALS AND METHODS

Twenty-eight mixed bred female goats, 1–3 years old, were bred to one Alpine buck. At the day of birth, the dams were divided into 4 equal groups and were dosed with 0, 1.0, 2.0, or 3.0 mg KCN (Merck, Darmstadt, Germany)/kg body weight/day administered orally, with tap water, for 3 months. The experimental animals received KCN twice a day, between 7:30 and 8:00 and between 16:30 and 17:00. All the goats were fed 100 g concentrate and Napier grass (*Pennisetum purpureum* Schumach) ad libitum. Body weights from all goats (dams and kids) were recorded weekly for the whole experimental period.

Blood samples were collected from the jugular vein of every dam and kid. Whole blood cyanide and plasma thiocyanate levels were measured on the 30th, 60th, and 90th days of the experiment, and a biochemical panel (glucose, cholesterol, plasma urea nitrogen-PUN, creatinine, thyroxin-T4, and triiodotironin-T3 concentrations and aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transferase-γGT activities) was determined on the 90th day. Plasma samples were held at −10 °C until analysis, whereas whole blood samples for cyanide determination were used immediately after collection.

Plasma thiocyanate concentrations were determined spectrophotometrically by the method of Pettigrew and Fell [25] with minor modifications. Plasma samples (200 μL) were added to 1.8 mL trichloroacetic acid, centrifuged for 15 min at 350 *g*. One milliliter of the supernatant was used for the colorimetric procedure with 500 μL 1 M HCl and 100 μL bromine saturated water. The solution was shaken for 30 s, then 200 μL arsenous trioxide (20 g in 0.1 M NaOH) was added and the solution was shaken for 30 s, and 1.8 mL pyridine (10 mL 12 N HCl, 60 mL pyridine, 40 mL deionised water) - p-phenylenedianize (2 g / 1 L 0.5 M HCl) solution (3:1) was added. The absorbance was measured after 30 min at 505 nm. All the reagents used in the assay were of reagent grade and the solutions were prepared with deionised water.

Immediately after collection, blood cyanide concentrations were measured by the procedure of Holzbecher and Ellenberger [12] as modified by us. In this methodology, glass headspace vials (30 mm × 49 mm o.d., inner chamber) with special tubes inside (14 mm × 30 mm o.d., inner chamber) were used. One milliliter of whole blood plus one drop of 10% EDTA followed by 1 mL of 50% H_2SO_4 was put into the external portion of the microdiffusion chamber containing 2 mL of 0.1 M

Table I. Body weight gain (in kg) from dams treated with KCN for 90 days of lactation and in their kids. Data are presented as mean ± SEM.

	Control	KCN (mg/kg/day)		
		1.0	2.0	3.0
Dams	–5.39 ± 2.6	–7.0 ± 1.3	–1.78 ± 0.8	–5.75 ± 2.3
Male kids	12.7 ± 1.6	10.2 ± 1.2	7.65 ± 0.9	12.5 ± 1.4
Female kids	9.56 ± 1.3	7.63 ± 0.9	7.17 ± 1.6	9.79 ± 0.6

NaOH in the internal chamber. After 2 h at room temperature, 0.5 mL of the solution in the internal portion of the chamber was transferred to a tube containing 1.5 mL of 0.1 M NaH_2PO_4 and then 0.5 mL 0.1% Chloramin T was added. After two minutes, 1.5 mL of pyridine-barbituric acid solution (21 mL deionised water, 10 mL pyridine, 2 mL 12 N HCl, and 2 g barbituric acid) were mixed. Spectrophotometric measurement of the colour complex at 584 nm occurred 2 min after addition of the latter solution.

At the end of the experimental period, one doe from each group and every male goat from every litter was killed. The pancreas, thyroid glands, liver, kidneys, and the whole central nervous system were collected for histological examination and the fragments were fixed and stored in 10% buffered formalin. All the fragments were embedded in paraffin blocks, and 5 μm sections were stained with haematoxylin and eosin (H&E).

Data are reported as mean ± SEM and were analysed statistically by two-way and one-way analysis of variance, followed by the Dunnett test. The level of significance was set at $p < 0.05$.

3. RESULTS

No clinical signs of toxicity were seen in any goat from any group. However, a dam from the 3.0 mg/kg/day group died on the 55th day of lactation. There were no differences between the weights of the goats receiving cyanide and the controls. The body weights from the dams had no interaction between KCN doses and the period of lactation and were not affected by the KCN doses, but were significantly affected by the period of lactation. The comparison between the male and female kids showed that males were heavier than females, but this parameter was not affected by the treatment. Furthermore, the body weight gain of the dams and kids from all experimental groups did not differ significantly from the controls (Tab. I).

The whole blood cyanide and plasma thiocyanate concentrations in the dams and kids are presented in Figures 1 and 2, respectively. Both thiocyanate and cyanide levels presented a dose and time-dependent increase in all experimental mothers. In the kids, the thiocyanate levels were increased dose-dependently, with a peak on the 30th day. The concentrations of cyanide in the treated offspring were increased only on the 30th day, detectable but not quantifiable on the 60th, and undetectable on the 90th day. No control animal presented detectable cyanide in the blood. Table II presents the results of the biochemical panel from both mothers and kids. None of the evaluated plasma parameters (glucose, cholesterol, AST, ALT, γGT, PUN, creatinine, T3, and T4) were affected by the KCN treatment.

The histopathological study in the dams treated with cyanide revealed an increased number of reabsorption vacuoles on the colloid of thyroidal follicles, moderate hepatocellular vacuolisation and degeneration,

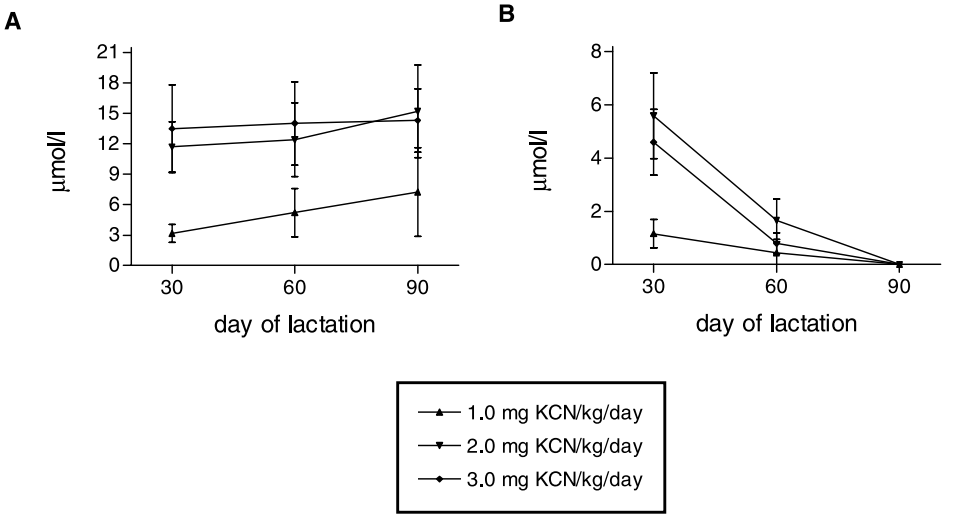

Figure 1. Blood cyanide (in µmol/mL) levels from dams treated with KCN for lactation (A) and in their kids (B).

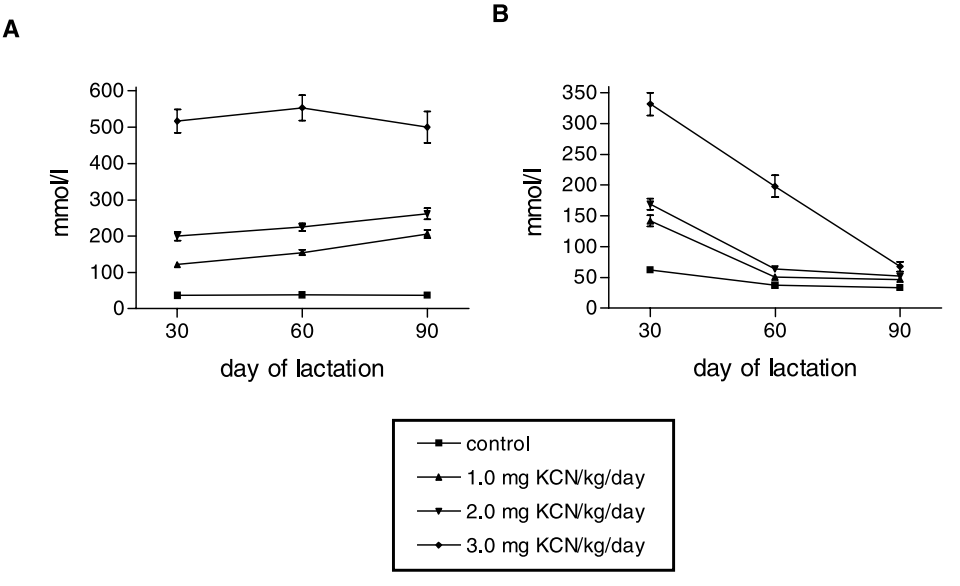

Figure 2. Plama thiocyanate (in mmol/mL) concentrations from dams treated with KCN for lactation (A) and in their kids (B).

and mild cytoplasmic vacuolisation of the tubular epithelial cells, but not in the glomerular cells, of the kidneys. The observed histological changes in the kids from the treated groups included an increased number of reabsorption vacuoles on the colloid of thyroidal follicles with cytoplasmic vacuoles in the epithelial cells

Table II. Plasma glucose, cholesterol, plasma urea nitrogen (PUN), creatinine (in mg/dL), triiodothyronine (T3, in ng/dL), and thyroxine (T4, in μg/dL) concentrations and aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase (γGT) (in U/L) activities from dams treated with KCN for 90 days of lactation and in their kids. Data are presented as mean ± SEM.

Plasma Substance	Control	KCN (mg/kg/day)		
		1.0	2.0	3.0
		Dams[a]		
Glucose	46.9 ± 4.7	41.2 ± 2.4	44.9 ± 5.1	34.0 ± 2.2
Cholesterol	139.0 ± 25.0	117.8 ± 14.4	135.9 ± 13.4	130.6 ± 5.4
AST	39.2 ± 1.0	36.7 ± 1.6	40.4 ± 2.3	43.3 ± 1.9
ALT	11.6 ± 0.6	11.8 ± 0.7	12.3 ± 0.8	12.7 ± 0.6
γGT	28.4 ± 1.3	25.3 ± 1.8	26.8 ± 1.7	33.0 ± 2.9
PUN	20.7 ± 0.4	18.5 ± 1.7	14.0 ± 1.0	19.7 ± 2.6
Creatinine	0.74 ± 0.02	0.80 ± 0.02	0.82 ± 0.03	0.69 ± 0.04
T3	85.6 ± 3.1	71.4 ± 5.8	105 ± 15.1	122 ± 17.9
T4	2.93 ± 0.11	2.62 ± 0.29	3.16 ± 0.36	3.54 ± 0.13
		Kids[b]		
Glucose	73.2 ± 5.7	74.7 ± 4.9	59.3 ± 5.6	67.5 ± 8.5
Cholesterol	208.8 ± 11.4	178.9 ± 9.3	170.2 ± 13.3	184.3 ± 12.8
AST	37.5 ± 0.9	41.9 ± 2.7	46.1 ± 1.9	47.2 ± 4.5
ALT	14.8 ± 2.0	12.8 ± 0.8	13.1 ± 0.7	12.9 ± 1.2
γGT	27.0 ± 1.0	27.5 ± 1.6	27.2 ± 0.9	28.5 ± 0.9
PUN	20.5 ± 2.2	24.5 ± 2.3	24.6 ± 1.2	23.7 ± 1.6
Creatinine	0.73 ± 0.04	0.80 ± 0.03	0.80 ± 0.04	0.77 ± 0.04
T3	125 ± 14.4	97.1 ± 17.6	94.1 ± 12.3	137 ± 9.3
T4	3.00 ± 0.20	2.80 ± 0.14	3.02 ± 0.26	3.40 ± 0.11

[a] Were used 7 samples in each group.
[b] Were used 9 samples in each group, except in the group 2.0 mg/kg KCN, where was used 11 samples.

of these follicles, mild cytoplasmic vacuolisation of the tubular epithelial cells of the kidneys, and moderate but more severe than in the mothers, hepatocellular vacuolisation and degeneration with loss of acinar architecture, nuclear picnosis in some hepatocytes, and fibrinoid deposition in the periportal region. All the observed lesions were more intense in the group that received the largest KCN dose. On the contrary, the pancreas and central nervous system sections (including the cortex, hippocampus, brainstem, cerebellum, and spinal cord) were unaffected by the cyanide treatment. No lesions were found in any tissues from the controls.

4. DISCUSSION

The presence of cyanide and increased thiocyanate levels in the blood of the suckling kids from the experimental groups found in the present study demonstrates that both substances are transferred from the maternal bloodstream through the

milk. In fact, it is well known that thiocyanate is an ubiquitous substance in milk, and its concentration is influenced by the diet [10, 11, 28, 36]. Furthermore, cyanide has been detected in milk from cows [4], but it is possible that it could be generated from thiocyanate. The amount of this substance in the blood of the kids suggests that the transfer of cyanide occurs at low levels, whereas thiocyanate was found to be largely transmitted to the offspring by lactation. However, the conversion of thiocyanate back to cyanide could not be excluded. The decrease in the levels of both cyanide and thiocyanate in the offspring is probably due to a relative reduction of milk consumption concomitant with an increase of other foods (grass and ration).

Glucosinolates, also known as thioglucosides, are toxins that produce goiter and are present in plants of the Cruciferae, Capparaceae, Limnanthaceae, and Resedaceae families. Glucosinolate hydrolysis generates thiocyanate, isothiocyanate, organic nitrites, and goitrin (5-vinyl-oxazolidine-2-thione) [37]. Thyroid disturbances are found in goats and rabbits fed with milk from goats consuming glucosinolates containing plants [38]. Furthermore, increased thiocyanate levels are found in the milk of cows fed meals with different glucosinolate concentrations; however, isothiocyanate, goitrin and 1-cyano-2-hydroxy-3-butene are not present in detectable levels [36]. Thus, it is probable that thiocyanate is responsible for the impaired thyroid function present in milk. Furthermore, thiocyanate, but not cyanide itself, was probably the most responsible for the effects observed in suckling goats; this could also be true for chronic cyanide toxicity.

A toxin can be present in any of the three fractions of milk (water, lipids and proteins), depending on its physical and chemical properties [24]. There is strong evidence that thiocyanate would form a complex with milk proteins, since it occurs in blood [2] and this anion has been found to be retained in dairy products rich in milk components [29].

Tropical pancreatic diabetes, also known as “J diabetes”, has been linked to chronic cyanide exposure through the consumption of cassava [18]. In the present work, no alterations were found in the plasma glucose levels and the histological morphology of the pancreas from goats (both dams and kids) of all groups. This result agreed with earlier studies conducted with rats, rabbits, pigs, and goats [21, 32], reinforcing the hypothesis that cyanide itself does not induce a pancreatic disturbance.

Long-term cyanogenic plant consumption by both men and animals has been associated to the development of hypothyroidism and goiter. Thiocyanate, the main cyanide metabolite is probably responsible because this ion competes with iodide in its capture by the thyroid gland [26]. Previous work with rats [34] and goats [31] has verified that the prolonged administration of KCN causes an increase in the number of resorption vacuoles in the follicles of the thyroid and reduced T3 levels in goats. In the present work, an increased number of these vacuoles was also observed in both dams and kids, but the levels of the thyroid hormones were unaffected, suggesting a slight disturbance on thyroid homeostasia.

The liver and kidney changes were observed in several animal species and humans exposed to cyanide [5, 15, 20, 22, 34]. These changes were also present in both dams and kids in the present experiment, showing that they also occur in the suckling offspring of treated goats. Furthermore, the higher severity of liver changes in the kids than in the mothers is probably related to a greater susceptibility of younger animals to toxins. The absence a disturbance in the liver and kidney functions assessed by the plasma biochemical exploration is compatible with the lack of tissue necrosis observed in the histological exploration.

Long-term exposure to cyanide is responsible for several degenerations in the central nervous system in both humans [39] and animals [33]. In goats, it is responsible for spheroids on the medulla spinal, spongiosis and gliosis on the medulla oblongata, gliosis on the pons, and damaged Purkinje cells in the cerebellum [33]. However, no lesion was found in any portion of this system from any animal in the present study. The absence of neuronal lesions can be attributed to cyanide and thiocyanate elimination by lactation and thus protecting the lactating animals, whereas the levels of these substances were not sufficient to promote lesions in the kids.

In summary, sucking goats from mothers exposed to cyanide can be affected. Thiocyanate and probably cyanide can be transferred from the maternal bloodstream to the offspring through milk. From this, lactating kids can be indirectly intoxicated by cyanogenic plants.

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