











An outbreak of systemic intoxication with irritant contact dermatitis due cypermethrin in dairy cows – case report

[Surto de intoxicação sistêmica com dermatite de contato irritante devido à cipermetrina em vacas leiteiras - relato de caso]

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ABSTRACT

Pyrethroids are ectoparasiticides safe for mammals and widely used in farm animals. An outbreak of systemic intoxication with irritant contact dermatitis resulting from the use of cypermethrin pour on in dairy cows is reported in the state of Pernambuco. Eight adult animals were affected, three died on the property and five were referred to the *Clínica de Bovinos, Universidade Federal Rural de Pernambuco, Campus Garanhuns*. These received 100 mL of pour on Cypermethrin (Ectonil[®], Cipermetrina, Labgard, Brasil). Apathy, hyperexcitability, muscle tremors, sialorrhea, bradycardia and crusted lesions were observed on the dorsum of the neck, scapula, ears and ulcerations in the oral and vaginal mucosa. There was hyperfibrinogenemia and leukocytosis due to neutrophilia with a regenerative left shift. Histopathology showed areas of erosion and ulceration of the epidermis and perivascular lymphohistiocytic and neutrophilic infiltrate in the superficial dermis. Supportive treatment was done with improvement of systemic signs and skin lesions, however, in one animal (with 19 days hospitalized), there was no complete regression of neurological alterations of bradycardia and muscle tremors, even so, it was possible to return to productive activity. High doses of pour on cypermethrin may cause systemic intoxication in cattle and result in bradycardia, hyperexcitability, muscle tremors and sialorrhea with irritant contact dermatitis, and death in severe cases.

Keywords: systemic intoxication, outbreak, pyrethroids, dairy cattle, Brazil

RESUMO

Os piretroides são ectoparasiticidas com grande segurança para mamíferos, utilizados amplamente em animais de produção. Relata-se um surto de intoxicação sistêmica com dermatite irritante por contato, resultante do uso de Cipermetrina Pour-On em bovinos, no estado de Pernambuco. Oito animais adultos foram acometidos: três deles morreram na propriedade e cinco foram recebidos na Clínica de Bovinos da Universidade Federal Rural de Pernambuco, Campus Garanhuns. Todos haviam recebido 100mL de Cipermetrina Pour-On (Ectonil[®], Cipermetrina, Labgard, Brasil). Observou-se apatia, hiperexcitabilidade, tremores musculares, sialorreia, bradicardia e lesões crostosas no dorso da região de pescoço, na escápula, nas orelhas, bem como ulcerações em mucosa oral e vaginal. No hemograma, verificou-se hiperfibrinogenemia e leucocitose por neutrofilia com desvio à esquerda regenerativo. Na histopatologia, foram constatadas áreas de erosão e ulceração da epiderme e infiltrado linfocitário e neutrofílico perivascular na derme superficial. O tratamento de suporte gerou melhora dos sinais sistêmicos e das lesões cutâneas, porém, em um dos animais (que esteve internado por 19 dias), não houve regressão completa das alterações neurológicas de bradicardia e de tremores musculares; mesmo assim, foi possível o retorno à atividade produtiva. Doses elevadas de Cipermetrina Pour-On podem causar intoxicação sistêmica em bovinos e resultarem em bradicardia, hiperexcitabilidade, tremores musculares e sialorreia com dermatite irritante por contato, bem como morte em casos severos.

Palavras-chave: intoxicação sistêmica, surto, piretroides, vacas leiteiras, Brasil

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INTRODUCTION

Cypermethrin is a compound part of the pyrethroid group used as ectoparasiticide, especially against arthropods and it has selective toxicity to insects in comparison to mammals (Casida *et al.*, 1983, Sartor and Santarém, 2017). Despite low toxicity, intoxication may occur, causing vomit, diarrhea, tremors, hyperexcitability or depression (Tiwari and Sinha, 2010). Systemic effects are consequent of its interaction with Gamma aminobutyric acid (GABA) receptors, an inhibitory neurotransmitter, blocking its activity and resulting in hyperexcitation, and change cellular membrane sodium channels (Montanha and Pimpão, 2012; Rehman *et al.*, 2014). Skin contact may result in tegumentar irritation, paresthesia, pruritus, and erythema, as reported in human beings, and, are exacerbated by solar light (Christofoletti and Mamprim, 2020; Flannigan and Tucker, 1985; Sharma *et al.*, 2018).

Irritant contact dermatitis is a tegumentar nonspecific inflammatory response, consequent of contact with chemical or physical agents that cause direct or indirect tissue damage; and it may occur in any animal species, mostly horses, cattle, and dogs (Ho *et al.*, 2015; Tan *et al.*, 2014). Observed lesions of irritant contact dermatitis are relationated with the caustic nature of the agent; and the diagnosis is dependent on the history, clinical signs and mainly, the distribution (Mauldin and Peters-Kennedy, 2016). There are no antidotes for pyrethroid intoxication; clinical support and early decontamination are mandatory (Christofoletti and Mamprim, 2020). The present work aims to report an outbreak of pour on cypermethrin causing systemic intoxication with irritant contact dermatitis in dairy cows.

CASE REPORT

Were referred to the *Clínica de Bovinos de Garanhuns, campus Garanhuns, Universidade Federal Rural de Pernambuco* (CBG/UFRPE) five adults mixed breed dairy cows from Lagoa do Ouro - Pernambuco (9° 7' 28" South 36° 27' 35" West) in February 2021, with history of pour on cypermethrin based medication (Ectonil®) application one day after; and that before use animals showed sialorrhea, incoordination, blindness, and anorexia. Moreover, application was done around 1:00 pm and utilized volume was about 100mL per animal, applied at the dorsal regions, caudal to atlanto-occipital joint to the scapular caudal region. At the farm, animals were medicated with fluid therapy, vitamins and atropine, and water to clean the affected areas, but without improvement. Three animals died at the farm with similar signs after the application and no further necropsy were done.

On physical examination, well defined raised areas and shedding of skin with crusts were observed in the dorsal region of the scapula, neck and ears that progressed ventrally over the thorax, resulting in an appearance of "drained liquid" (Fig.1 and 2).

These were painful to palpation. In addition, whitish and/or blackened, poorly-defined, multifocal to coalescent areas of epithelial shedding in the vulvar mucosa and dorsal region of the tongue (Fig. 3), also showing detachment and painful sensitivity to palpation, probably resulting from licking the region where the application was done.

Animal 1 had severe tegumentar lesions, with 8% dehydration, mild apathy, sialorrhea, anorexia, hyperexcitability, resulting in generalized muscle tremors when stimulated and bradycardia.



Figure 1-2: Irritant dermatitis due to cypermethrin Pour on in dairy cattle. Animal 1, Well-defined and raised area with crusts in the dorsal region of the scapula, neck and ears that progressed ventrally resulting in an appearance of “drained liquid”. CBG/PE.



Figure 3. Irritant dermatitis due to cypermethrin Pour on in dairy cattle. Animal 1, poorly-defined, multifocal to coalescent areas of epithelial shedding in the tongue. CBG/PE.

The blood count (Table 1) showed a slightly elevated total plasma protein and an expressive increase in plasma fibrinogen, indicating an active inflammatory process (Wood; Quiroz-Rocha, 2010). On white blood cell count, mild neutrophilia with regenerative left shift (Table 2). Considering the clinical and laboratory findings, a systemic protocol was started with antibiotic (ceftiofur hydrochloride 50mg, 1mL/50kg PC, IM, SID, 7 applications), non-steroidal anti-inflammatory drug (flunixin meglumine, 1.1mg/kg PV, IV, SID, 5 applications) and topical treatment with potassium permanganate solution (KMnO₄ 1mg/mL, topical, SID) on the vulvar mucosa and tongue, followed by application of triamcinolone acetonide on tongue lesions and sunflower oil in skin lesions, daily. In addition to pasty diet, adjuvant therapy with 5% glucose serum and rumen fluid when considered necessary.

Table 1. Erythrogram values from cows 1 and 2, with systemic intoxication due to cypermethrin, on the first and seventh day of treatment

Parameters	Cow 1	Cow 2	Cow 1	Reference (Jain, 1993)
	Day 1	Day 1	Day 8	
Erythrocytes (x 10 ³ /μL)	8.31	8.03	6.18	5.0-10.0
Hematocrit (%)	40	33	32	24-46
Hemoglobin (g/dL)	12.34	10.54	10.64	8.0-15.0
MCV (fL)	48.13	41.09	51.77	40-60
MCHC (%)	30.85	31.93	33.25	30-36
TPP (g/dL)	8.6	8.5	7.2	7.0-8.5
PF (mg/dL)	1.100	900	600	300-700

MCV- Mean corpuscular volume. MCHC- Mean corpuscular hemoglobin concentration. TPP- Total plasma protein. PF- Plasmatic fibrinogen.

Table 2. White blood cell count from cows 1 and 2, affected with systemic intoxication due to cypermethrin on the first and seventh day of treatment

Parameters	Cow 1	Cow 2	Cow 1	Reference (Jain, 1993)
	Day 1	Day 1	Day 8	
Leucocytes (x 10 ³ /μL)	8.100	7.800	3.875	4.0-12.0
Band neutrophils (cells/μL)	162	234	0	0-120
Segmented neutrophils (cells/μL)	4.860	2.184	1.395	600-4.000
Lymphocytes (cells/μL)	2.754	4.446	2.402	2.500-7.500
Monocytes (cells/μL)	0	0	39	25-840
Eosinophils (cells/μL)	324	936	39	0-2.400
Basophils (cells/μL)	0	0	0	0-200

A second blood count (Table 1) was performed 7 days after the treatment began, showing a positive evolution in the parameters, with fibrinogen value drop and white blood count with the total count slightly below the reference values (Jain, 1993) (Table 2). The animal responded satisfactorily to therapy, the skin and mucosal lesions were in process of repair and appetite returned. Some alterations did not completely regress, such as sialorrhea, bradycardia and muscle tremors; however, it remained in a lesser degree when compared to arrival. The animal was discharged after 19 days of hospitalization.

Animal 2, in addition to moderate skin lesions, had mild apathy, 8% dehydration and hypomotility of the gastrointestinal tract. The blood count (Table 1) revealed high fibrinogen, white blood cell count within normal limits, but in the differential count, a high value of rods (Table 2). A protocol similar to animal 1 was done, with positive clinical evolution, reduction of mucosal, sialorrhea and skin lesions, as well as improvement in gastrointestinal dynamics, being discharged after 8 days of hospitalization.

It was possible to contact the owner 8 months after the last animal was discharged, reporting that both had responded satisfactorily.

A skin biopsy was performed from animal 1 on the seventh day of hospitalization and a focally extensive area of erosion and ulceration was observed in the epidermis with an extensive crust composed of keratin interspersed with a large number of degenerated neutrophils, red blood cells and mild amount of brownish pigment and

hairs. In the superficial dermis, moderate perivascular lymphohistiocytic and neutrophilic infiltrate with moderate dilatation of paratrichial glands (Fig. 4).

DISCUSSION

This is the first description of systemic intoxication with irritant contact dermatitis caused by pour on cypermethrin in dairy cows and the diagnosis was made based on application history of a product containing the active agent, as well as clinical findings similar to those reported in animals and humans (Mendonça *et al.*, 2010, Christofoletti and Mamprim, 2020). One report of cattle intoxicated by ectoparasiticide containing cypermethrin had dichlorophos too, hence due to the association of the two compounds, it is impossible to affirm which signs are related to each (Mendonça *et al.*, 2010). Moreover, in cattle, the only report of irritant contact dermatitis was done by Onda *et al.*, 2008, but it differs from our case, as it was a non-veterinary product used in the environment that remained in the skin of the animals.

Animals in this case received cypermethrin 1:00pm, which is contraindicated by the drug insert (Ectonil[®], Cipermetrina, Labgard, Brasil), as well as the dosage used (100mL per animal), which was many times higher to that indicated by the manufacturer (10mL/100kg PV) (Ectonil Pour On, 1997). This was certainly the cause of the clinical signs and tegumentar lesions, in addition, literature confirms the irritating action of cypermethrin on the skin may occur in animals and humans (Environmental..., 1989, Sharma *et al.*, 2018).

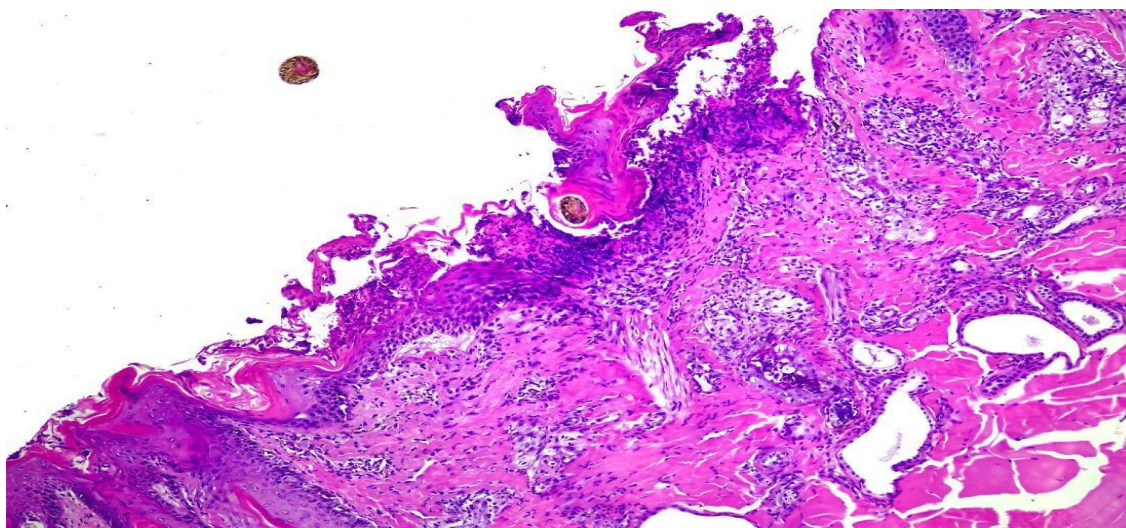


Figure 4. Microscopic alterations observed in the epithelial tissue of an animal with contact dermatitis due to cypermethrin. Animal 1, microscopic image of ulceration in the epidermis with keratin crust interspersed with degenerated neutrophils and lymphohistiocytic superficial dermatitis. Skin. HE. obj. 10X CBG/PE, 2021.

There were observed also symptoms similar to those already described in the literature, including apathy, hyperexcitability, muscle tremors and incoordination, the latter not found in the physical examination, however, it was reported by the owner in animals that died on the farm (Segundo *et al.*, 2018, Tiwari and Sinha, 2010). These effects were probably due to the cypermethrin action on the inhibitory neurotransmitter Gamma-aminobutyric acid (GABA), resulting in excessive excitation and on sodium channels, changing the action potentials of neurons (Montanha and Pimpão, 2012; Rehman *et al.*, 2014). In addition to bradycardia that can occur in cypermethrin intoxication, in cattle it can be caused by a disturbance in the conduction of the heart, with the opening of sodium channels being an essential point for the functioning of the cardiac pacemaker (Dirksen *et al.*, 1993, Montanha and Pimpão, 2012, Klein, 2014, Christofolletti and Mamprim, 2020). This mechanism justifies the non-use of atropin in the present cases, which is indicated for organophosphorated compounds intoxication and has parasympatholytic effect (Vital and Acco, 2017).

In both animals in the present case, erythrogram showed no changes, however, in experimental cypermethrin intoxication in rats, reduction in the total red cell count and globular volume and hemoglobin were reported, indicating reduced erythropoiesis (Nair *et al.*, 2010). While the

occurrence of an active inflammatory process in the animals in the present case resulted in elevated fibrinogen (Wood and Quiroz-Rocha, 2010), reduced in the second evaluation of animal 1, indicating a positive response to the treatment. The total leukocyte count was in the normal range, however, animal 1 had neutrophilia with regenerative left shift in the first exam, indicating that there was granulopoiesis stimulus (Jain, 1986).

The histopathological findings of tegumentar ulceration in the present case are different from those described in the literature on irritant contact dermatitis in cows, which include visualization of spongiosis, epidermal hyperplasia and hyperkeratosis (Onda *et al.*, 2008). This difference is probably the result of an acute and more intense aggression in our case. However, there were similarities in the visualization of epidermal ulceration, superficial perivascular dermatitis and lymphohistiocytic infiltrate (Ho *et al.*, 2015).

Systemic treatment was effective with antimicrobial therapy being indicated in cases of tegumentar deep or widely distributed lesions, as well as topical corticosteroids, used in the affected mucosa (Ho *et al.*, 2015); in addition to the application of sunflower oil on the wounds, responsible for accelerating the repair process, as already observed in sheep and horses (Marques *et al.*, 2004, Oliveira Jr. *et al.*, 2012).

CONCLUSIONS

In conclusion, tegumentar (pour on) high dosage of cypermethrin may cause irritant contact dermatitis, as well as nervous alterations of hyperexcitability, muscle tremors and apathy and death in dairy cows. Although there is no specific antidote for pyrethroid intoxication, supportive treatment was effective in this outbreak to resolve the skin lesions; using systemic antimicrobial and topical anti-inflammatory therapy, however, the nervous signs of bradycardia and muscle tremors were not fully reversible until the moment of clinical discharge.

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An outbreak of systemic...

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