# Neurotoxicidade aguda em dois cães da raça yorkshire, após o uso de ciclosporina- relato de caso

*Acute neurotoxicity in two yorkshire terriers after use of cyclosporine  case report*

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## Abstract

Cyclosporine is widely used in small animal veterinary medicine, particularly in dermatology. A similar efficacy to corticosteroids and the absence of significant side effects when used chronically, turns cyclosporine an excellent choice for the canine atopic dermatitis treatment. The most frequent side effects are diarrhea, vomiting and anorexia, which usually occur in the first weeks and do not preclude the continuation of treatment. Neurotoxicity is rare in dogs, unlike humans, in which it´s observed in 40% of patients. The purpose of this study was to report two cases of acute neurotoxicity in two Yorkshire terrier dogs, few hours after cyclosporine administration.

**Keywords:** Drug hypersensitivity, allergy, treatment.

## Introduction

Cyclosporine is isolated from the fungus Tolypocladium inflatum, and presents immunomodulatory and immunossupressive effects. It is used in human medicine to prevent organ transplant rejection (1,2). In veterinary medicine it is widely used to treat diverse inflammatory and immune-mediated skin diseases (3). In the last two decades it has been considered an excellent alternative to control perianal fistulas, sebaceous adenitis and pruritus in canine atopic dermatitis (4,5,6).

It is quite safe for dogs even in chronic use (7,8,9), and acts by blocking the calcineurin activity, an essential enzyme for activation of T lymphocytes. Therefore the expression of proinflammatory cytokines is reduced. Cyclosporine also inhibits the action of various cells involved in allergic and inflammatory processes, such as Langerhans cells, keratinocytes, mast cells and eosinophils (2,6).

Cyclosporine is metabolized by cytochrome P450 3a (CIP450 3a) and is influenced by P-glycoprotein, which acts as a transmembrane efflux pump, transporting substances from the inside to outside the cell and direct influence on the pharmacodynamics and pharmacokinetics of many drugs (10). This protein is expressed in many mammalian tissues, including the gastrointestinal tract, renal tubular cells, bile canaliculi, besides being an important component of the protective blood-brain barrier (11,12).

The main side effects are related to the gastrointestinal tract. Vomiting and diarrhea are observed in about, 20-46% of canine patients, (5,9). However, these gastrointestinal disorders usually occur in the first weeks and are self-limiting, so do not preclude the treatment (5). Other less common side effects, related with chronic use, are gingival hyperpasia, hirsutism, and predisposition to papilomatosis and bacterial pyoderma (7).

There is no strong evidences of hepato, nephro or myelotoxicity, even when high doses are used (13). Neurotoxicity is also considered a rare side

effect, observed in just six (0,8%) of 769 dogs treated with cyclosporine in one study (9). By the other hand, in humans, nephropathy and neurotoxicity, occur in about 40% of the transplant patients after chronic use of cyclosporine, and are considered the main side effects (14,15). It is believed that those side effects are related to hypertension, hypomagnesemia, hipolesterolemia and the release of a harmful factor to the vascular endothelium (14).

This article aims to report two cases of acute neurotoxicity after cyclosporine administration, represented by behavioral changes such as hyperexcitability, tremors and drooling, which have not been reported yet.

## Case report

Two female Yorkshire Terrier, 6 and 8 years of age, weight average of 2.5 kg, received 5mg/kg once daily of cyclosporine (Sandimunn Neoral®) oral solution, for pruritus control after the diagnosis of atopic dermatitis. In the two cases, diagnosis was made by the observation of typical clinical features of atopic dermatits, as proposed by Favrot et al. (2010) and after exclusion of other pruritic diseases such as food hypersensibility. As adjuvant treatment, the dogs had been receiving therapy for cutaneous hydration with topic ceramides and free fatty acids (Allerderm spot-on®) for about a month. Within hours of the first administration of cyclosporine, hiperexcitability, tremors and drooling were observed and persisted for some hours. The owners were asked to perform a new exposure to confirm the adverse side effects were due to cyclosporine usage. After rechallenge, the same clinical signs were observed. As these clinical signs in dogs have not been reported, and are not tolerated by the owners and patients, it was decided to withdraw the drug and establish other methods for control pruritus in both patients.

## Discussion

Cyclosporine is widely used in veterinary medicine, mostly for the treatment of skin diseases (17). Lately, it has been considered the drug of choice for the treatment of canine atopic dermatitis, since its efficiency is similar to glucocorticoids, with minimum side effects (7).

The currently recommended dosage of cyclosporine for treatment of canine atopic dermatitis is 5mg/kg every 24 hours (3,8). Despite the occurrence of some adverse side effects, mainly related to the gastrointestinal tract, withdrawal of medication is not necessary, since in most cases are self-limiting. The neurotoxicity reported in a retrospective study of dogs treated chronically with cyclosporine, was extremely low, being observed in only 6 of 759 dogs (9). Among the neurological disorders, seizures were observed in four patients, but all of them were later diagnosed with a concomitant neurological disease (8). So, it cannot be asserted that chronic use of the drug resulted in seizures or if this was a result of a pre-existing neurological disease. In another study, neurological sings were observed in only 1 of 25 dogs that were in chronic use of cyclosporine, however the study does not specify the clinical sings nor the existence of concomitant disease (18). Acute adverse reactions observed in this study, such as hyperexcitability, tremors and salivation, have not been reported in dogs, although this is described in the bula of the veterinary formulation that has similar properties to human cyclosporine (Sandimmun Neoral®) used in both patients (2,19). In humans, neurotoxicity is one of the major side effects observed with the chronic use of cyclosporine in post-transplant. Clinical signs as headache, seizures, tremors and altered mental status have been observed (14). Some factors such as hypertension, hypomagnesemia, hypocholesterolemia and ischemic cerebral disorders by the action of endothelin-1, substance harmful to the vascular endothelium, predisposes to drug toxicity (14,19). Some intoxication observed in small animals are related to changes in the MDR-1 gene, decoding an abnormal P-glycoprotein, which allows the accumulation of substances in the brain (6). This mutation is well recognized in Collies, Shetland Sheepdog and Old English Sheepdog, that are sensible to ivermectin, one of the drugs excreted by the P-glycoprotein (10). Some others P-glycoprotein substrate agents, such as the doxorrubicin, vincristin and vinblastin, were reported to cause side effects in these breeds (12). Although cyclosporine is metabolically influenced by P-glycoprotein, there is no information about the relationship of mutation of MDR-1 gene with sensibility to cyclosporine, such as there in the ivermectin sensitive breeds (10), or even if Yorkshire Terrier could have any defi-

ciency in the MDR-1 gene. It is also unknown that factors that predispose human intoxication by this drug could be the cause of the neurotoxicity in these animals. As this is an unpublished report, as far as concerned, there are no studies correlating breed sensitivity to this drug. However, both observations have been made in Yorkshire, and so, further investigation is required.

A plausible association can be made between the use of cyclosporine and the observed adverse side effects, since they occurred acutely and resolved with withdrawal of the drug. However, the mechanism by which this drug caused neurological signs acutely is still uncertain.

## Final considerations

The report of two cases of cyclosporine neurotoxicity is extremely important to the scientific literature, as it addresses issues that have not yet been disclosed. Despite being a very effective and safe in the treatment of some dermatological disorders, attention in the early phase of drug administration should be given to patients in order to avoid any major harm. Further studies are needed to elucidate the causes of intoxication with cyclosporine.

## References

1- Robson D. Review of the pharmacokinetics, interactions and adverse reactions of cyclosporine in people, dogs and cats. Vet Record, v.152, n. 24, p.739-748, 2003.

2- Marsella R. Calcineurin inhibitors: a novel approach to canine atopic dermatites. J Am Anim Hosp Assoc, v.41, p-92-97, 2005.

3- Palmeiro BS. Cyclosporine in Veterinary Dermatology. Vet Clin Small Anim, v.43, p.153-171, 2013.

4- Linek M, Boss C, Haemmerling R, Hewicker-Trautwein M, Mecklenburg L. Effects of cyclosporine A on clinical and histologic abnormalities in dogs with sebaceous adenitis. JAVMA, v. 226, n.1, p. 59-64, 2005.

5- Steffan J, Favrot C, Mueller R. A systematic review and meta-analysis of the efficacy and safety of cyclosporin for the treatment of atopic dermatitis in dogs. Vet Dermatol, v. 17, p.3-16, 2006.

6- Forshythe P, Paterson S. Ciclosporin 10 years on: indications and efficacy. Vet Records, 174, p.13-21, 2014.

7- Olivry T, Rivierre C, Jackson HA, Murphy KM, Davidson G, Sousa CA. Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial. Vet Dermatol, v.13, p.77-87, 2002.

8- Steffan J, Parks C, Seewald W. Clinical trial evaluating the efficacy and safety of cyclosporine in dogs with atopic dermatites. J Am Vet Med Assoc, v.226, n.11, p.1855-1863, 2005.

9- Nuttal T, Reece D, Roberts E. Life-long diseases need life-long treatment: long-term safety of cyclosporin in canine atopic dermatitis. Vet Records, v. 174, p.3-12, 2014.

10- Dowling, P. Pharmacogenetics: It´s not just about ivermectin in collies. Can Vet J, v.47, n.12, p.1165-1168, 2006.

11- Sakaeda T, Nakamura T, Okumura K. MDR1 genotype-related pharmacokinetics and pharmacodynamics. Biol Pharm Bull, v.25, n.11, p.1391-1400, 2002.

12- Mealey KL, Northrup NC, Bentjen SA. Increased toxicity of P-glycoprotein-substrate chemotherapeutic agentes in a dog with the MDR1 deletion mutation associated with ivermectin sensitivity. JAVMA, v.223, n.10, p.1453-1455, 2003.

13- Riffel B, Donatsch P, Madorin M, Matter BE, Ruttimann G, Schon H et al. Toxicological evaluation of cyclosporin A. Arch Toxicol, v.53, n.2, p.107-141, 1983.

14- Gijtenbeek JMM, Van den Bent MJ, Vecht ChJ. Cyclosporine neurotoxicity: a review. J Neurol, v.246, n.5, p.339-346, 1999.

15- Derici U, Arinsoy T, Sindel S, Tali T, Leventoglu A, Sert S. Cyclosporine-A induced neurotoxicity after renal transplantation. Acta Neurolo bel, v.101, p.124-127, 2001

16- Favrot C, Steffan J, Seewald W, Picco F. A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. Vet Dermatol, v.21, p.23-31, 2010.

17- Kovalik M, Thoday KL, Van den Broek AHM. The use of ciclosporin A in veterinary dermatology. Vet J, v.193, n.2, p.317-325, 2012.

18- Thelen A, Mueller RS, Linek M, Peters S, Stechmann K, Steffan J. Influence of food intake on the clinical response to cyclosporin A in canine atopic dermatitis. Vet Records, v.159, p.854-856, 2006.

19- Novartis. Freedom of information summary. Greensboro (NC): Novartis Animal Health; 2003. Atopica, NADA 141–218.

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