http://dx.doi.org/10.1590/1678-4162-12961

(cc) BY

Arq. Bras. Med. Vet. Zootec., v.75, n.5, p.936-940, 2023

Hypersensitivity reaction after intravenous administration of meloxicam in dogs – case report

[*Reação de hipersensibilidade após administração intravenosa de meloxicam em cães – relato de casos*]

S.L. *Beier*, M.P.A. *Lima*, R.A. *Silva*, O.H.R. *Ladeira*, E.H. *Bitencourt*, S.E.M.T. *Branco*, F.G. *Sousa**

Escola de Veterinária, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil

ABSTRACT

Although rarely reported in veterinary medicine, this article shows three cases of dogs that presented anaphylactic reactions after intravenous administration of meloxicam at therapeutic doses. Three dogs of different breeds and ages were submitted to anesthesia for surgical procedures of ovariohysterectomy and repair of patellar luxation. The animals were classified as ASA I and did not present changes in clinical and laboratory tests. All dogs were anesthetized and monitored by anesthesiologists, with careful multiparametric evaluation. Near the end of the procedures, meloxicam was administered intravenously in all dogs, and the drug used had the same commercial presentation and concentration, but with different lot numbers and with different months. For less than a minute, the animals showed significant hypotension, with pressure values close to 30 mmHg or inaudible by Doppler. The animals had no skin signs, only hypotension and a decrease in heart rate in one of them. All dogs were immediately treated with intravenous ephedrine and atropine in the bradycardic patient. After the emergency treatment, the dogs showed stabilized vital signs, with no complications or need for additional intervention. After the event, the three dogs showed no signs of clinical, behavioral or laboratory changes.

Keywords: anaphylactic reaction, anaphylaxis, hypersensitivity reaction, veterinary emergency

RESUMO

Este artigo apresenta três casos de cães que apresentaram reações anafiláticas após administração intravenosa de meloxicam em doses terapêuticas, ocorrência menos frequente na medicina veterinária. Três cães de raças e idades distintas foram submetidos à anestesia para realização de procedimentos cirúrgicos de ovário-histerectomia e reparação de luxação patelar. Os animais foram classificados como ASA I, e não manifestaram alterações nos exames clínico e laboratoriais. Todos os cães foram anestesiados e monitorados por anestesiologistas, com avaliação multiparamétrica criteriosa. Próximo ao término dos procedimentos, foi administrado meloxicam pela via intravenosa em todos os cães, sendo usado fármaco com a mesma apresentação comercial e concentração, porém com números de lotes e validade diferentes. Cerca de menos de um minuto, os animais apresentaram hipotensão significativa, com valores pressóricos próximos a 30mmHg ou inaudível pelo Doppler. Não apareceram sinais cutâneos, apenas hipotensão e queda de frequência cardíaca em um deles. Todos os cães foram tratados imediatamente com efedrina intravenosa, e o paciente bradicárdico com atropina. Após o tratamento emergencial, os cães apresentaram sinais vitais estabilizados, sem complicações ou necessidade de intervenção adicional. Após o evento, os três cães não apresentaram sinais de alterações clínicas, comportamentais ou laboratoriais.

Palavras-chave: reação anafilática, anafilaxia, reação de hipersensibilidade, emergência veterinária

*Corresponding author: fgaias@outlook.com
Submitted: December 31, 2022. Accepted: April 26, 2023.

INTRODUCTION

Adverse drug reactions and their collateral effects are usually expected, and while they are dose-dependent, they can occur with therapeutic doses (Patton and Borshoff, 2018; Ferner and Pucci, 2020). Immediate hypersensitivity reactions (a subgroup of adverse drug reactions), characterized by anaphylactic and anaphylactoid responses, are unexpected regardless of the dose administered, and can happen even on the first exposure to drugs used in anesthesia (Aun *et al.*, 2014; Ferner and Pucci, 2020). Anaphylactic reactions are life threatening conditions that must be effectively controlled. The use of meloxicam in anesthetic procedures can promote anaphylaxis, even with therapeutic doses. During anesthesia, patients are exposed to a mixture of drugs (antibiotics, sedatives, anesthetics, anti-inflammatory and analgesic drugs, among others) (Brown *et al.*, 2018; Del Prete and Scarabelli, 2021) that can potentially cause these immediate hypersensitivity reactions, culminating in serious and life-threatening complications (Aun *et al.*, 2014).

The incidence of allergic reactions in human medicine is widely variable, ranging from around 1:1250 to 1:18.600 (Mertes *et al.*, 2016), leading to a mortality rate between 3.5% and 10% (Dippenaar and Naidoo, 2015). However, veterinary medicine data is still scarce, with no direct determination of the incidence in different species, and only a few case reports of anaphylactic and anaphylactoid reactions due to the use of opioids, anesthetics, sedatives and antioxidants in dogs and cats (Onuma *et al.*, 2017; Del Prete and Scarabelli, 2021; Gregory and Binagia, 2022).

Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in humans has a high incidence when compared to other pharmacological classes, representing 48.7% of anaphylaxis (Aun *et al.*, 2014). Among patients who are hypersensitive to NSAIDs, meloxicam has shown lower reaction rates (5%) (Dworzynski *et al.*, 2014). On the other hand, in veterinary medicine there is only one case report of a possible anaphylactoid reaction due to intravenous administration of meloxicam in a cow (Okushima *et al.*, 2013), and one case report of cutaneous and ocular reaction possibly related to the oral administration of meloxicam in a dog (Niza *et al.*, 2007). The aim of this paper is to present three cases of severe and immediate hypersensitivity after intravenous administration of meloxicam in dogs.

CASUISTRY

This is a descriptive case report study with the purpose of describing three cases of anaphylactoid reaction in dogs after the use of meloxicam. The present case report was not submitted to the Ethics Committee because it deals with routine surgical procedures at the institution, however, the term of free and informed consent of the tutors was obtained for the description of the cases.

Three canine patients, two presented at the Veterinary Hospital of Federal University of Minas Gerais and one at a private veterinary clinic in Belo Horizonte, underwent anesthetic/surgical procedures. They were classified as ASA I patients, with no abnormalities in their laboratory tests (complete blood count and biochemistry panel) and physical exams. Two of them were females submitted to ovariohysterectomy (OH), and the other was a male submitted to an orthopedic surgery to repair a patellar luxation. They were a 9-month-old French Bulldog, a 1-year-old Chow Chow, and a 1.5-year-old mixed-breed dog. All patients were properly assessed by anesthesiologists, and the anesthetic protocols were determined (Table 1). Anesthesia monitoring consisted of electrocardiography, esophageal temperature, pulse oximetry, capnography, and arterial blood pressure assessment (invasive in two of the patients and monitoring by Doppler in one case).

Meloxicam was administered (Table 1) near the end of the surgical procedures. In all three cases, the same meloxicam commercial presentation and concentration was used, however they had different lot numbers. They were not diluted and were all administered intravenously in the same venous access used for crystalloid administration (RL). Less than one minute after the intravenous administration of the NSAID, all three animals developed significant hypotension. The three cases of anaphylaxis caused by intravenous meloxicam occurred within months of each other.

Table 1. Anesthetic protocol (drugs and doses) used in three patients with different breeds and ages

Breed	Age	Pre-Med	Induction	Maintenance	Analgesia	Meloxicam
French Bulldog	9 Months	Dexmedetomidine 0.002 mg/kg Methadone 0.3 mg/kg	Propofol 2 mg/kg Midazolam 0.3 mg/kg	Isoflurane	Fentanil	0.1 mg/kg
Chow Chow	1.5 Years	Acepromazine 0.01 mg/kg Morphine 0.5 mg/kg	Propofol 3 mg/kg Midazolam 0.3 mg/kg	Sevoflurane	Fentanil	0.1 mg/kg
Mixed-Breed	1 Year	Acepromazine 0.01 mg/kg Morphine 0.5 mg/kg	Propofol 3 mg/kg Midazolam 0.3 mg/kg	Sevoflurane	Fentanil	0.05 mg/kg

Consider: Pre Med – pre-anesthetic medications; mg/kg – milligrams per kilogram

The dogs monitored by invasive measurement had a decrease in the mean arterial blood pressure from 70-85mmHg to lower than 30 mmHg, while in the patient monitored by Doppler the pulse sound became inaudible. One of the animals had a decrease in heart rate from 100 bpm to 45 bpm. An irregular, rapid and shallow respiratory pattern, with hypercapnia, was observed in one of the dogs. This patient also had a prolonged anesthesia recovery time, with a reduced level of consciousness, and little response to stimuli. No cutaneous signs such as erythema, redness or angioedema were seen.

All patients were promptly treated with intravenous ephedrine at a dose of 0.2mg/kg, and 0.03mg/kg of atropine was given intravenously to the one that presented bradycardia. The dog that showed an altered breathing pattern received 2mg/kg of intramuscular dexamethasone, and dexmedetomidine effects were reversed by atipamezole (20μ/kg). After emergency treatment, all vital signs were stabilized, with no subsequent complications or need of additional interventions.

The anesthesia recovery was monitored by anesthesiologists. Oxygen supplementation by facial masks was given when judged necessary, while evaluating the level of consciousness, and monitoring and stabilizing arterial blood pressure. Blood gas analysis was not performed in these patients due to difficulties in catheter placing and proper blood collection, along with financial restrictions. In all three patients, meloxicam was administered near the end of the surgical procedure and no other drug was administered at that moment. Anesthesia was ending and the surgical procedure occurred with no bleeding intercurrences. Another limitation in these cases was the lack of ultrasonography/ AFAST exams and biochemistry assessment of alanine aminotransferase (ALT) for the analysis of possible delayed reaction effects.

All the dog's owners were informed of the reactions and that for future interventions it will be necessary to register in the medical history that these animals had a hypersensitivity reaction after the use of meloxicam. All animals were evaluated 10 days after the incident to assess the quality of the surgical procedure, healing phase and presence of any deterioration. Approximately 3 months after the event, the legal guardians of all three animals contacted the hospital staff where the procedures were performed and informed that since their last visit (10 days after the incident), the animals showed no physical, behavioral, or laboratorial changes.

DISCUSSION

Anaphylaxis during anesthesia is rare, but it can result in fatal consequences when it is not promptly treated. Hypersensitivity reactions, like anaphylactic and anaphylactoid reactions, are potentially dangerous situations for many reasons, since anesthesiologists are only aware of this event when it becomes serious enough to cause rapid and significant cardiovascular and respiratory compromise, with only a short amount of time to intervene. In the description of the three cases, an emergency intervention was performed with the administration of drugs such

as ephedrine, atropine, corticosteroids, and reversers. Certainly, if the anaphylactic reactions in the three cases had not been observed with caution and in time, the aid in the emergency care would not have been enough and the animals could have died. The precocious and mild signs, characteristic of allergic reactions, remain virtually unrecognizable and its severity can be underestimated when it is masked by the pharmacological effects of other anesthetics being used, such as hypotension and respiratory depression (Dippenaar and Naidoo, 2015).

Okushima *et al.* (2013) reported the first veterinary case of hypersensitivity reaction after intravenous meloxicam administration, specifically in a cow. The patient of the referred case report received meloxicam once and manifested, after a few minutes, dyspnea, cyanosis, tachycardia, and circulatory collapse. Due to the severity of the established anaphylactic reaction, euthanasia was performed. In the reports described above, patients showed signs of a significant decrease in blood pressure and bradycardia after meloxicam was administered intravenously, which were observed with the invasive method and vascular Doppler.

Characterization of anaphylactic responses can be described based on the manifestation of one or more symptoms such as erythema, dyspnea, and circulatory collapse (Del Prete and Scarabelli, 2021; Gregory and Binagia, 2022). According to Lee and Vadas (2011), acute episodes of hypotension associated to dyspnea, syncope and depression, or events with only severe hypotension, related to exposure to the possible allergen, can determine its occurrence. In the present report, the animals showed some of the clinical signs described by Lee and Vadas (2011) and Onuma *et al.* (2017), such as arterial hypotension and respiratory depression. Cutaneous changes are absent in approximately 20% of hypersensitivity reactions cases, particularly when it begins during surgery, and are usually absent in severe and fatal cases of anaphylaxis (Lee and Vadas, 2011). In the present reports, cutaneous changes such as erythema, redness or angioedema were not observed, in partial accordance with Lee and Vadas' (2011) description. For Onuma *et al.* (2017), cutaneous manifestations may not be perceived in fur-covered animals, which can mask skin changes.

Most of the reactions with NSAIDs are associated to cyclooxygenase (COX)-1 inhibition, along with changes of lipoxygenase function, causing mast cells and basophils degranulation, and this probably explains why hypersensitivity reactions to COX-2 are extremely rare. Meloxicam is a COX-2 selective anti-inflammatory drug used for various situations such as post-surgical procedures, and therefore, these drugs preferential COX-2 inhibitors can cause IgE-mediated anaphylactic reactions, and this path can lead to more intense responses (Okushima *et al.*, 2013). The anaphylactic reaction of the described animals occurred shortly after intravenous administration of meloxicam. The route of administration of meloxicam for the three patients may have been a possible cause for the appearance of the hypotensive event, given that the anaphylactic reaction could not have occurred if meloxicam had been applied subcutaneously. Availability, concentration, and clearance of drugs, as well as adverse effects, may vary depending on the route of application.

The systems most affected by anaphylactic reactions include cutaneous (90%), respiratory (70%), gastrointestinal (30-45%), cardiovascular (10-45%) and central nervous system (10-15%) (Lee and Vadas, 2011). Another interesting phenomenon that can occasionally occur is the Bezold-Jarisch reflex, causing paradoxical bradycardia with profound hypovolemia (Del Prete and Scarabelli, 2021), present in approximately 10% of all anaphylactic patients (Lee and Vadas, 2011). After anaphylaxis is identified, treatment consists of three main actions: remove or cease provision of the possible allergen; interrupt the effects of released mediators; prevent more mediators from being released. Supportive treatment comprises 100% oxygen administration and, when necessary, airway access, adrenaline (Onuma *et al.*, 2017) to provide sympathetic activation of alfa and beta-adrenergic receptors, shock infusion rates of intravenous crystalloids (20ml/kg in 20 minutes to reestablish blood pressure), H1 antagonists such as promethazine (0.3-1mg/kg), corticosteroids such as hydrocortisone (50mg/kg), and beta-blockers in severe bronchospasm cases (Lee and Vadas, 2011;

Dippenaar and Naidoo, 2015). The aim is to restore and maintain vital functions, like adequate oxygenation and tissue perfusion, while the effects of the allergen substance are eliminated or blocked. In the present report, the animals were given emergency assistance with ephedrine and intravenous atropine for bradycardia correction and normalization. The only animal that presented with respiratory depression was treated with corticosteroids and dexmedetomidine reversal with atipamezole. After emergency treatment, vital parameters were reestablished in all three patients.

The easiest and most effective way to avoid recurrence of these reactions is through complete medical history that relates changes in previous procedures or that shows that the patient is allergic to other substances and/or food. Therefore, as a form of security and prevention of future situations, the occurrence and description of complications observed in the respective patients were recorded in the medical and anesthetic records. In addition, all dog owners were informed about hypersensitivity reactions to intravenous meloxicam, as a means of warning, in case the same animals needed to be exposed to new surgical procedures.

CONCLUSION

This is the first case report of hypersensitivity due to the use of intravenous meloxicam in dogs, with efficient treatment and resolution. More studies are necessary to evaluate the use of intravenous or subcutaneous meloxicam in anesthetized patients. Awareness of the possibility of this complication occurring when this medication is used is essential so that newer and safer protocols can be established.

REFERENCES

AUN, M.V.; BLANCA, M.; GARRO, L.S.; RIBEIRO, M.R. *et al.* Nonsteroidal Anti-Inflammatory Drugs are Major Causes of Drug-Induced Anaphylaxis. *J. Allergy Clin. Immunol.*, v.2, p.414-420, 2014.

BROWN, E.N.; PAVONE, K.J.; NARANJO, M. Multimodal general anesthesia: theory and practice. *Anesth. Analg.*, v.127, p.1246-1258, 2018.

DEL PRETE, T.; SCARABELLI, S. A suspected anaphylactoid reaction to propofol in a dog. *Top. Companion Anim. Med.*, v.44, p.100536, 2021.

DIPPENAAR, J.M.; NAIDOO, S. Allergic reactions and anaphylaxis during anaesthesia. *Curr. Allergy Clin. Immunol.*, v.28, p.18-22, 2015.

DWORZYNSKI, K.A.; JONES, M.A.; NASSER, S. Diagnosis and management of drug allergy in adults, children and young people: summary of NICE guidance. *BMJ*, v.349, p.4852, 2014.

FERNER, R.; PUCCI, M. Adverse drug reactions. *Medicine*, v.48, p.443-449, 2020.

GREGORY, E.A.; BINAGIA, E.M. Anaphylaxis due to First-Time Intravenous Infusion of N-Acetylcysteine in a Dog. *Top. Companion Anim. Med.*, v.51, p.100734, 2022.

LEE, J.K.; VADAS, P. Anaphylaxis: mechanisms and management. *Clin. Exp. Allergy*, v.41, p.923-938, 2011.

MERTES, P.M.; VOLCHECK, G.W.; GARVEY, L.H.; TAKAZAWA, T. *et al*. Epidemiology of perioperative anaphylaxis. *Presse Med.*, v.45, p.758-767, 2016.

NIZA, M.M.; FELIX, N.; VILELA, C.L.; PELETEIRO, M.C. *et al*. Cutaneous and ocular adverse reactions in a dog following meloxicam administration. *Vet. Dermatol.*, v.18, p.45-49, 2007.

OKUSHIMA, S.; CHESNEL, M.A.; CLUTTON, R.E. A possible anaphylactoid reaction in a cow after intravenous meloxicam. *Vet. Anaesth. Analg.*, v.40, p.333-338, 2013.

ONUMA, M.; TERADA, M.; ONO, S. *et al*. Incidence of anaphylactic reactions after propofol administration in dogs. *J. Vet. Med. Sci.*, v.79, p.1446-1452, 2017.

PATTON, K.; BORSHOFF, D.C. Adverse drug reactions. *Anaesthesia*, v.73, Suppl.1, p.76-84, 2018.