

Cutaneous and ocular adverse reactions in a dog following meloxicam administration

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What is known about the topic of this paper

- Meloxicam is a nonsteroidal anti-inflammatory drug indicated for the control of inflammation and pain in acute and chronic musculoskeletal disorders in dogs.
- In dogs, the most common side-effects reported in the literature are gastrointestinal signs and less frequently nephrotoxicity.
- Meloxicam has frequently associated to dermatological adverse drug reactions (ADR) in humans.

What this paper adds to the field of veterinary dermatology

- The paper documents a case of cutaneous and ocular ADR to meloxicam in a dog.
- To the authors' knowledge, this is the first report of such ADR in a dog.
- The paper alerts the practitioners for the eventual occurrence of ADRs to meloxicam.

Abstract

The present report addresses the development of cutaneous and ocular reactions possibly related to meloxicam administration in a dog.

Based on clinical signs and absence of laboratory data compatible with the other differential diagnoses considered, the possibility of an adverse drug reaction (ADR) due to meloxicam was considered. Skin biopsy revealed haemorrhage of the superficial and deep dermis, associated with hyperplasia of endothelial cells and epidermal sloughing. Vasculitis in the deep dermis was also noted. Such lesions were considered compatible with an ADR. Although the owner was not aware of any previous allergic reaction to drugs, the animal had a clinical history of atopic dermatitis.

Meloxicam is a nonsteroid anti-inflammatory drug (NSAID) in the oxicam family, indicated for the control of inflammation and pain in acute and chronic musculoskeletal disorders in dogs. Although meloxicam is usually well tolerated, the present clinical case represents an alert to practitioners about the potential role of NSAIDs in ADRs in dogs with a history of allergic cutaneous diseases.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used classes of drugs used in human and veterinary medicine. Their analgesic, anti-inflammatory and antipyretic properties render them very useful for symptomatic relief in a number of inflammatory conditions.^{1,2} The major side-effects of NSAIDs noted in humans are gastrointestinal.³ Other side-effects are bleeding tendencies because of decreased platelet adhesion, renal damage^{4,5} and allergic reactions including cutaneous reactions and asthma-like attacks.^{6,7} In dogs the most common side-effects are gastrointestinal signs⁸ and less frequently nephrotoxicity.⁹

In humans, a growing number of adverse drug reactions (ADR) related to NSAIDs have been reported.¹⁰ An ADR is any response to a drug that is noxious and unintended that occurs at doses used for prophylaxis, diagnosis or therapy.¹¹ Dermatological clinical signs due to NSAIDs of the oxicam class range from photosensitivity reactions¹² to toxic epidermal necrosis (TEN) and Stevens Johnson syndrome (SJS).^{13,14} The increased number of TEN cases induced by NSAIDs in humans has been attributed to the introduction of oxicam derivatives.^{15,16} Although meloxicam was recommended in humans with cutaneous hypersensitivity to NSAIDs,¹⁷ this drug was recently identified among the NSAID class as a culprit in dermatological reactions.¹⁰

NSAIDs inhibit the enzyme cyclo-oxygenase (COX) and subsequent prostaglandin formation. Two distinct COX isoforms have been identified. The COX-1 enzyme is constitutive and associated with physiological functions of prostaglandins. COX-2 enzyme, the inducible isoform, is mainly responsible for the production of prostaglandins causing pain and inflammation.¹⁸ Meloxicam is an NSAID of the oxicam family that preferentially inhibits COX-2¹⁹ and is indicated for the control of inflammation and pain in acute and chronic musculoskeletal disorders in dogs.^{20,21} To the authors' knowledge this is the first description of cutaneous and ocular ADRs to meloxicam in the dog.

Case history

A 10-year-old, 25 kg mongrel intact male dog was referred for orthopaedic consultation at the Teaching Hospital of the Faculty of Veterinary Medicine of Lisbon, with a 3-week history of weakness and bilateral lameness of the hind limbs. The dog had been adequately dewormed and vaccinated 8 months before, and the owner was not aware of any previous allergic reaction to drugs. However, the dog had a history of recurrent pruritus, mainly involving the face, axillae, groin and pinnae, associated with recurrent otitis,



Figure 1. Presence of intact and ruptured vesicles with suppurative discharge between digits and footpad.

which had been diagnosed as atopic dermatitis. Neither intradermal nor serological tests were performed and diagnosis was based only on clinical evidence and remission of clinical signs after prednisolone and clemastine administration.

Clinical examination revealed bilateral hind limb muscular atrophy and pain, and cranial drawer sign on manipulation of both stifles. The dog did not have any other clinical signs and the neurological examination was unremarkable. Radiographs showed changes compatible with cranial cruciate rupture in both stifles, with a synovial effusion and osteophytes on the distal part of patella. Surgery for both knees was scheduled for 5 days later, and the dog was orally medicated with meloxicam (Metacam, Boehringer Ingelheim, Germany) 0.1 mg kg^{-1} , once a day, until surgery. Previous laboratory analysis did not show any abnormalities in blood count and biochemistry (blood urea nitrogen, creatinine, alanine aminotransferase, alkaline phosphatase, albumin, total protein and glucose).

Three days after discharge, the dog was returned to the Teaching Hospital with an owner complaint of anorexia, depression and reluctance to move. According to the owner, 1 day after the first administration of meloxicam, the dog started licking the hind limbs and, the following day, developed oedema distally to the right anterior limb carpus and pruritus to all four limbs. Physical examination revealed that the dog was febrile (39.8°C) and presented with painful skin lesions. Lesions were mainly located between the digits and footpads of both thoracic limbs, on the lateral and cranial portion of the fifth digit of the left rear limb, internal surface of the right tarsal and metatarsal area in the same pelvic limb, with others being dispersed through the inguinal, medial face of the rear limbs and axillae. Lesions consisted of erythema, erosions, ulcers, and 5–13-mm diameter vesicles, some being ruptured and showing suppurative discharge (Fig. 1). Skin biopsy was not performed at presentation because of the owner's economical constraints. Ophthalmic examination revealed mild blepharoeidema and bilateral conjunctivitis with chemosis, conjunctival hyperaemia and a mucoid ocular discharge. A mild bilateral corneal oedema was present. Fluorescein test was negative and fundoscopic examination was unremarkable.

The main differential diagnoses considered were ADR, including erythema multiforme, TEN and SJS, bacterial infection, vasculitis, pemphigus, systemic lupus erythematosus and leishmaniasis. Laboratory studies revealed moderate neutrophilia, mild thrombocytopenia, slight decrease



Figure 2. Granulation tissue over the metatarsus, tarsus and distal tibia at 2 weeks of evolution.

in serum albumin level and mildly elevated globulins. Kidney and liver function parameters were normal and antinuclear antibodies and rheumatoid factor titres were negative. Urine analysis showed mild proteinuria. Skin bacterial culture and leishmaniasis serology were negative.

Symptomatic treatment was initiated on admission, consisted of intravenous fluid with Ringer's Lactate, intramuscular amoxycillin/clavulanate (Synulox, Pfizer, Seixal, Portugal) at 8.75 mg kg^{-1} every 24 h and oral prednisolone (Lepicortinolo, Decomed, Massama, Portugal) at 2 mg kg^{-1} every 12 h. A topical ointment of prednisolone and chloramphenicol (Predniftalmína, Dávi Farmacêutica, Mem Martins, Portugal) was applied every 8 h in both eyes. Ruptured skin vesicles started to coalesce within 2 days, evolving to ulcers several centimetres diameter and, 2 days later, the surrounding skin became necrotic. Lesions were thoroughly cleaned with sterile saline, necrotic tissue was removed and wet-to-dry sterile dressings were applied every 12 h. Gradually, lesions started to heal and granulation tissue became evident (Fig. 2). Prednisolone was reduced to 1 mg kg^{-1} every 12 h and dressings were daily changed.

Five days after admission, skin lesions were healing, but the dog still showed erythema and pruritus in the surrounding areas. Despite the economical constraints, the owner then agreed to have a skin biopsy performed. Histopathology revealed superficial and deep dermal haemorrhage associated with hyperplasia of the endothelium of superficial capillaries and epidermal sloughing (Fig. 3).

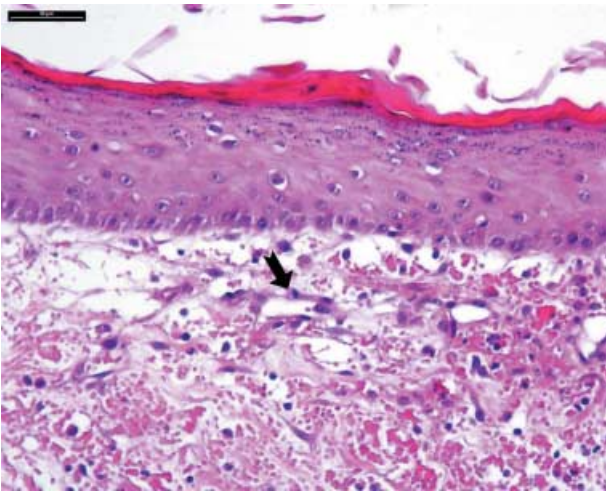


Figure 3. Superficial dermis haemorrhage and endothelial hyperplasia. A mitotic endothelial cell can be seen in a capillary (arrow). Small vesicles are forming underneath the epithelium (haematoxylin & eosin, bar = 50 μ m).

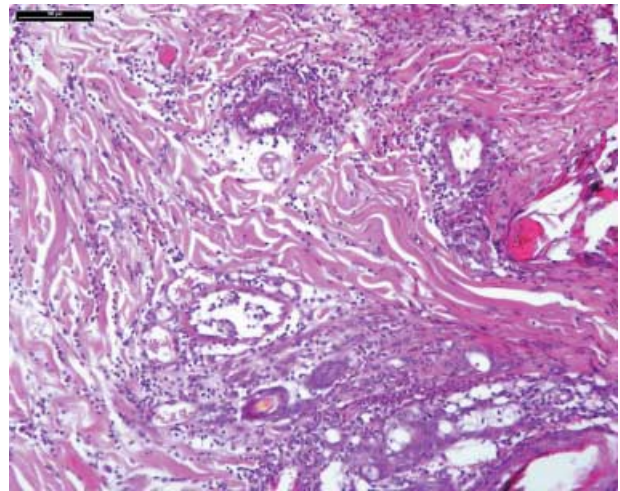


Figure 4. Vasculitis without leukocytoclasia is present in the deep dermis, with neutrophils swarming around the median size vessels, migrating through the wall. Neutrophils surround hair follicles in the vicinity of vasculitis. A free hair shaft is seen on the right in an area of deep dermal necrosis (haematoxylin & eosin, bar = 100 μ m).

Neutrophilic vasculitis in the deep dermis without leukocytoclasia was also noted, together with a neutrophil-rich perifollicular inflammatory infiltrate (Fig. 4). The most affected area that was biopsied also showed deep skin destruction, with release of hair shafts, amidst necrotic material. Oedema of the superficial dermis was also present. The described lesions, particularly haemorrhage, endothelial hyperplasia, epidermal sloughing and vasculitis were considered compatible with an ADR.

Based on the case history, clinical signs developing immediately after the initiation of meloxicam administration, histopathological findings and the absence of laboratory data compatible with the other differential diagnoses considered, a cutaneous ADR caused by meloxicam was diagnosed. The patient was discharged 7 days after admission, medicated with amoxycillin/clavulanate and the same eye ointment, and dressings were changed every other day. The dog fully recovered in 6 weeks, although a corneal opacification because of stromal corneal degeneration of the right eye remained as a sequel.

Discussion

The present report describes the development of cutaneous and ocular reactions in a dog, following meloxicam administration. Meloxicam is an NSAID indicated for the control of inflammation and pain in acute and chronic musculoskeletal disorders in dogs.^{20,21} Reports of ADRs are important to make the scientific community aware of possible undesirable consequences of medication.

Adverse drug reactions, often referred to as type B or idiosyncratic drug reactions, designate reactions that do not occur in most patients at any dose and in which the mechanism does not involve the known pharmacological properties of the drug.^{22,23} A diagnosis of ADR is often difficult, especially in the presence of cutaneous manifestations, because drug reactions can mimic different dermatoses^{24,25} and the clinical presentation may vary greatly.¹⁴ Therefore, it is essential to assess the complete

historical review, including previous reactions to the suspected drug, data from the patient, concurrent diseases, all the administered drugs at the time of the event, the time, appearance and course of the event and response to treatment.^{26,27}

In the case here presented, symptoms began 24 h after meloxicam administration and differential diagnostic procedures ruled out other diagnoses. The patient also presented with acute ocular manifestations, namely conjunctivitis, keratitis and late corneal opacities. In humans, ocular involvement is common in ADR²⁸ and corneal scarring is a common late sequel.²⁹ Currently, in veterinary medicine, the only reliable test for a definitive ADR diagnosis to NSAIDs is the animal re-exposure to the suspected drug.^{25,30} This last criterion is often difficult to fulfil, because of the understandable owner's reluctance to subject the animal to further discomfort and because of the possibility that a recurrence of the ADR may be life-threatening.²⁴ Besides, this procedure is questionable under an ethical perspective of animal welfare.

Skin biopsy was not performed at presentation, when ulcers, vesicles and erosions were present, because of owner's economical constraints. However, 5 days after admission, and although skin lesions were healing, the dog still showed erythema and pruritus in the surrounding areas. Therefore, a skin biopsy was performed. In fact, the skin biopsy should have been done earlier, when lesions appeared and before other drugs, namely glucocorticoids, were administered, because these drugs can change the histological pattern. However, the histopathology of skin lesions was considered compatible with ADR because of the presence of areas of dermal haemorrhage and oedema that, associated with endothelial hyperplasia, could explain the basement membrane fragility and the epidermal-dermal split formation. Sub-epidermal bullous eruption or bullous pemphigoid-like drug eruption lesions associated to ADR are described.²⁴ In these cases, proliferation of vascular endothelial cells is referred to, similarly to the present case. Sub-epidermal microvesicles are suggestive

of SLE associated with vasculitis.³¹ However, lupus erythematosus and vasculopathies have been described in cases of cutaneous drug eruptions responsible for foot pad and pressure points ulceration, as those described in this case.²⁴ Neutrophilic immunological vasculitis triggered by drug reaction has also been described.³² The presence of neutrophilic folliculitis in areas of vasculitis shows that follicles were being targeted, possibly because of necrosis as a result of deficient blood supply. Follicle necrosis could also explain the free hair shafts, which were seen in association with deep dermal necrosis.

The exact mechanism of ADRs induced by NSAIDs is still under investigation. In humans, a strong association between atopy and other allergic diseases and intolerance to NSAIDs has been demonstrated.^{33,34} However, this association is poorly understood, because no pathological mechanism linking NSAIDs sensitivity to allergic immunoglobulin E (IgE)-mediated diseases has been identified.³⁵ Genetic predisposition is a recognized factor in atopy in humans associated with an increased production of IgE antibodies and allergic diseases,^{36,37} but in canines, such an association has yet to be shown. Similarly, a common genetic control has been suggested for the development of both atopy and NSAID sensitivity.³⁵ In human medicine, specialized tests for drug hypersensitivity diagnosis are available.²² In the case here presented, the dog had a clinical diagnosis of atopic dermatitis, although the dog was never tested either intradermally or serologically to ascertain which allergens were involved. Similarly to humans, the hypothesis of an eventual relation between cutaneous allergic disease and the development of an ADR could be considered. Nevertheless, a direct relation between ADR and atopic dermatitis cannot be inferred from this case.

To our knowledge, this is the first report of probable cutaneous and ocular manifestations related to meloxicam administration in a dog. Re-challenge tests are required to assess the possible link between the use of NSAIDs administration and an ADR. Because of the generalized use of NSAIDs in different conditions, the present clinical case represents an alert to practitioners about the potential role of NSAIDs in the occurrence of ADRs.

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Résumé Cet article décrit l'apparition de réactions cutanées et oculaires peut être reliées à l'administration de méloxicam chez un chien.

La possibilité d'une réaction à un médicament (ADR) a été suspectée sur la base des signes cliniques et de l'absence de données de laboratoire compatibles avec un autre diagnostic. Les biopsies cutanées ont montré des hémorragies dans le derme superficiel et profond associées à une hyperplasie des cellules endothéliales et un décollement épidermique. Une vasculite était également notée dans le derme profond. Ces lésions étaient compatibles avec une ADR. Bien que les propriétaires n'aient pas remarqué une réaction préalable à l'administration de médicaments, l'animal avait un passé d'atopique.

Le méloxicam est un AINS de la famille des oxicam, indiqué pour le traitement de l'inflammation et de la douleur dans les affections musculosquelettiques du chien. Bien qu'il soit généralement bien toléré, le cas clinique présenté ici doit alerter les cliniciens sur le rôle potentiel des AINS dans les réactions aux médicaments chez les chiens présentant un historique de terrain allergique.

Resumen El presente artículo analiza el desarrollo de reacciones cutáneas y oculares en posible relación a la administración de meloxicam en un perro. Basado en los signos clínicos y en la ausencia de datos laboratoriales compatibles con otros diagnósticos diferenciales considerados, se debe tener en consideración la posibilidad de una reacción farmacológica adversa. La biopsia de la piel reveló hemorragias en la dermis superficial y profunda, asociadas con hiperplasia de celular endoteliales y separación de la epidermis. También observamos vasculitis en la dermis profunda. Estas lesiones se consideraron compatibles con una reacción farmacológica adversa. Aunque el dueño no era consciente de ninguna previa reacción alérgica a fármacos, este animal tenía una historia clínica de dermatitis atópica.

Meloxicam es un fármaco antiinflamatorio no esteroideo en la familia de los compuestos oxicam, y esta indicado para el control de inflamación y dolor en enfermedades musculoesqueleticas agudas y crónicas en perros. Aunque es normalmente bien tolerado, el presente caso clínico subraya la necesidad de estar alerta sobre el posible potencial de fármacos antiinflamatorios no esteroideos para producir reacciones farmacológicas adversas en perros con historia de enfermedades alérgicas cutáneas.

Zusammenfassung Der vorliegende Bericht beschäftigt sich mit der Entstehung von kutanen und okulären Reaktionen im Zusammenhang mit Meloxicamverabreichung bei einem Hund.

Basierend auf den klinischen Veränderungen und der Abwesenheit von Laborergebnissen, die mit den anderen erwogenen Differentialdiagnosen kompatibel gewesen wären, wurde die Möglichkeit einer Arzneimittelnebenwirkung (ADR) aufgrund von Meloxicam in Betracht gezogen. Die Hautbiopsie zeigte eine Blutung der oberflächlichen und der tiefen Dermis, die zusammen mit einer Hyperplasie der Endothelzellen und epidermaler Verschorfung auftrat. Vaskulitis in der tiefen Dermis wurde ebenso festgestellt. Derartige Läsionen wurden als vereinbar mit einer ADR betrachtet. Wenn auch der Besitzer von keinen früheren allergischen Reaktionen auf Medikamente wusste, so hatte das Tier eine klinische Anamnese von atopischer Dermatitis.

Meloxicam ist ein nicht-steroidales entzündungshemmendes Medikament der Oxicam Familie, welches eingesetzt wird, um die Entzündung und den Schmerz bei akuten und chronischen muskuloskeletalen Erkrankungen des Hundes unter Kontrolle zu halten. Obwohl Meloxicam normalerweise sehr gut toleriert wird, repräsentiert der beschriebene klinische Fall eine Warnung an praktizierende Tierärzte über die mögliche Rolle der nicht-steroidalen entzündungshemmenden Medikamente (NSAIDs) bei ADR bei Hunden mit einer Geschichte von allergischen Hauterkrankungen.