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Marcio Antonio Rodrigues Araujo

To cite this article: Marcio Antonio Rodrigues Araujo (2020): Ketoprofen hypersensitivity and idiosyncratic response – a case report, Immunopharmacology and Immunotoxicology, DOI: [10.1080/08923973.2020.1728764](https://doi.org/10.1080/08923973.2020.1728764)

To link to this article: <https://doi.org/10.1080/08923973.2020.1728764>



Published online: 21 Feb 2020.



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CLINICAL NOTES



Ketoprofen hypersensitivity and idiosyncratic response – a case report

Marcio Antonio Rodrigues Araujo 

Pharmacology, Department of Physiological Sciences, Federal University of Maranhão, UFMA, São Luís, Brazil

ABSTRACT

Context: Ketoprofen is widely used to remove pain. A steady increase on allergic reactions and photo-allergic contact dermatitis related to ketoprofen has been reported when there is topical use. However, there are few documented cases of hypersensitivity when it is administered systemically.

Objective: Present a case of hypersensitivity reaction after systemic administration of ketoprofen for pain control in nephritis crisis.

Case description: A 43-years-old Caucasian man diagnosed with renal colic (kidney lithiasis), who was initially treated with 100 mg of tramadol (IV), followed by 4 mg of thiocolchicoside (IM) which caused no relief. Then 100 mg of ketoprofen was administered (IV). Right after the patient began to show hypersensitivity reaction type I characterized by intense coughing, rhinitis, angioedema, periorbital edema, rash, and scleral jaundice.

Discussion and conclusion: Maybe it was a case of drug-induced liver disease, however therapeutic dosages of all administered drugs only once. The mechanisms involved were not investigated, but may be the result of allergic and immunologic aspects caused by ketoprofen and facilitated by a history of hypersensitivity to other NSAIDs as reported by the patient. As for jaundice can be attributed to drug toxicity since laboratory parameters did not reveal any evidence of liver disease.

ARTICLE HISTORY

Received 23 September 2019
Accepted 2 February 2020

KEYWORDS

Ketoprofen; hypersensitivity; jaundice; NSAIDs; side effects

Introduction

Analgesic and anti-inflammatory medications are widely used in all age groups for the treatment of pain, inflammation and fevers of diverse etiologies. Thus, a large proportion of the population is exposed to these drugs, what makes them the second cause of untoward reactions, after β lactam antibiotics [1].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for 21–25% of reported adverse drug events which include immunological and non-immunological hypersensitivity reactions [2].

Ketoprofen is a propionic acid derivative that belongs to the group of nonsteroidal anti-inflammatory drugs which inhibits prostaglandin synthesis and is widely used to remove pain [3]. It is one of the most powerful inhibitors of cyclooxygenase at concentrations well within the range of therapeutic plasma concentrations [4]. However, there have been reports of a steady increase on allergic reactions and photoallergic contact dermatitis related to ketoprofen when there is topical use [5]. The photoallergic reactions are well documented [6–7] and ketoprofen is considered one of the most frequent photoallergic drugs [8].

The objective here is to present a case of hypersensitivity reaction after systemic administration of ketoprofen for pain control in nephritis crisis.

Case report

A 43-years-old Caucasian man was admitted to the emergency department of a private hospital (at 12:50 pm) in

severe pain, located in the retrosternal region which radiated into the dorsal lumbar region. The pain was characterized as diffuse, of sudden onset, not being related to any cause identified by the patient, who characterized the pain as severe, with EVA = 9. The urinary tract computed tomography revealed distal ureterolithiasis and mild hydronephrosis on the left.

Diagnosed as suffering from renal colic (kidney lithiasis), the patient was initially treated with 100 mg of tramadol intravenous (IV) (at 01:00 am), followed by 4 mg of thiocolchicoside intramuscular (IM) (at 01:32 am) which caused no relief. Then 20 mg of scopolamine (IV) (at 02:00 am) and 200 mg of acetaminophen oral solution (at 02:03 am) were administered, but they did not provide pain relief either. Finally, 100 mg of ketoprofen was administered (IV) (at 02:19 am). About 20 min after the injection, the patient began to show hypersensitivity reaction type I characterized by intense coughing, rhinitis, angioedema, periorbital edema, rash, and scleral jaundice (Figures 1 and 2). To control the hypersensitivity reaction, 50 mg of promethazine (IM) (at 04:10 am) and 500 mg of glucocorticoid methylprednisolone (IV) (at 04:20 am) were administered. As the administration of ketoprofen had no effect, relief of pain was achieved after administration of 10 mg of morphine (IV) (at 05:25 am). In his history the patient had had mild hypersensitivity reactions to other NSAIDs as dipyrene and piroxicam several years before, reporting no use of NSAIDs except for acetaminophen, which was occasionally used, only when really necessary. It has been evidenced in blood parameters performed low levels of



Figure 1. A 43-years-old male NSAID-sensitive, 20 min after administration of 100 mg ketoprofen intravascularly.

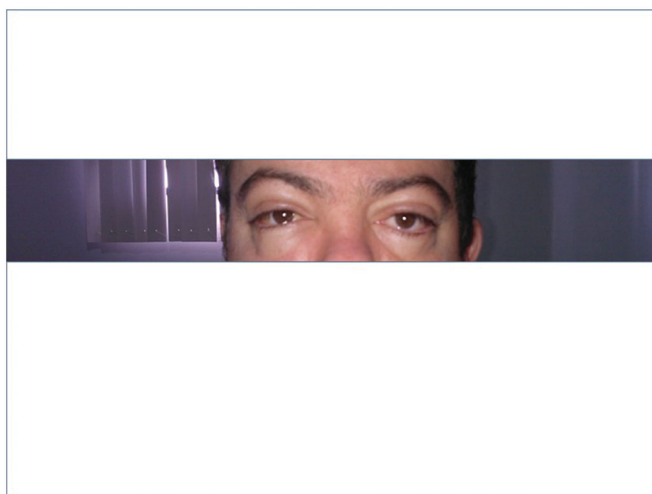


Figure 2. A 43-years-old male NSAID-sensitive, 12 h after administration of 100 mg ketoprofen intravascularly.

eosinophils ($18.6/\text{mm}^3$), a reduction on basophils ($9.3/\text{mm}^3$) and monocytes values were $688.2/\text{mm}^3$.

Discussion

The prevalence of NSAIDs hypersensitivity can reach 6% of the general population, increasing up to 20% in asthmatic patients and up to 40% in chronic urticaria. Clinical manifestations range from rhinoconjunctivitis, asthma and urticaria to anaphylaxis [9].

Hypersensitivity to NSAIDs can be classified according to the time of onset and the clinical manifestations into acute and delayed. Acute reactions start immediately to several hours after drug administration and may be associated with administration of one or more NSAIDs. Clinical manifestations include urticaria, angioedema, laryngeal edema, anaphylaxis, generalized pruritus, allergic rhinitis or bronchospasm [10].

Five major clinical syndromes involved in NSAID hypersensitivity can be distinguished in phenotypes: aspirin-exacerbated respiratory disease (AERD), aspirin-exacerbated

cutaneous disease (AECD), multiple NSAID-induced urticaria/angioedema (MNSAID-UA), single NSAID-IgE reactions and single NSAID T cell responses [11].

A review article have classified patients experiencing NSAID-induced urticaria/angioedema into different categories, including single reactors, multiple reactors, and multiple reactors with underlying chronic urticaria, and Ketoprofen has been pointed out as single and multiple reactors [12].

According to allergic standards proposed by Sánchez-Borges et al. [13], the case presented here can be pharmacologically classified as a cross allergic reaction, once the patient has a history of hypersensitivity to other NSAIDs, and clinically, it can be classified as a mixed reaction, since the patient presented respiratory symptoms and angioedema, which was triggered by nonspecific immune mechanisms related to arachidonic acid and the COX-1 enzyme. The frequency of this mixed hypersensitivity reactions to NSAIDs, or did not meet the classification, has been reported as low (1.6%) in the population [14]. Unclassified reactions in childhood according to European Network for Drug Allergy (ENDA) classification system revealed to occur in about 10.8%, of which 8% were associated with NSAIDs derived from propionic acid [15], as well as the manifestation of allergic reactions due to concomitant drug usage it was 20% [14].

The mechanisms involved in these hypersensitivity reactions have not been fully elucidated. There may be variations according to the administered drug and the individual response of each. Facial angioedema is the most frequent clinical manifestation [16] and it has been associated with A444-C allele of LTC₄ synthase [17], a protein involved the production of leukotrienes. Other reactions suggest immediate-type responses, mediated by IgE, produced in the skin, in the respiratory tract and in the cardiovascular system, but also delayed responses, such as contact dermatitis, erythema multiforme, and Stevens-Johnson syndrome [18].

The fact that the hypersensitivity reactions to NSAIDs have multiple clinical manifestations, the mechanisms associated with each of them are different. The mechanism of the reaction has been associated with inhibition of COX-1 and subsequent activation of mast cells and eosinophils with release of inflammatory mediators. Overproduction of leukotrienes (LTs) is associated with overexpression of 5-lipoxygenase (5-LO) and related enzymes [19]. Besides, it seems to be a decrease in the production of PGE₂, which is a modulator of mast cells release and other inflammatory cells mediators as well [20].

Due to their low molecular weight, NSAIDs or their metabolites need to be conjugated with proteins to induce a reaction, which requires a previous exposition (sensitization). During sensitization dendritic cells process and present drug-protein adducts to Th2 lymphocytes. Such lymphocytes interact with B cells, which differentiate to plasma cells that produce drug-specific IgE antibodies. These antibodies bind to specific receptors on basophil and mast cell membranes. A further contact (re-exposition) to the culprit drug leads to the recognition of drug-protein complexes by two molecules of adjacent IgEs, activating intracellular pathways that head



Figure 3. A 43-years-old male NSAID-sensitive, 36 h after administration of 100 mg ketoprofen intravascularly, with scleral jaundice.

basophil/mast cell degranulation. This process leads to the release of pro-inflammatory preformed (histamine, chymase and tryptase) and *de novo* synthesized mediators (PGD₂ and CysLTs) [21].

NSAIDs can cause non-allergic hypersensitivity reactions depending on the power of inhibition of COX. The inhibitory effect on COX isoenzymes attributed to ketoprofen is around 91% [12]. Moreover, the beginning and the intensity with which these manifestations happen may be directly associated with the route of administration as in the case of this patient, who received ketoprofen through intravascular administration.

It is intriguing that chemically unrelated NSAIDs can cause cross-hypersensitivity reactions. Data accumulated so far suggest the involvement of peptidyl leukotrienes and other mediators including histamine, as factors involved in the clinical development of these hypersensitivity responses [22–23]. In addition, the activation of basophils and monocytes can be significantly stronger in patients who present immediate and quite severe reactions [24].

Genetic factors have also been related to the mechanisms by which cross hypersensitivity reactions are developed. It has been suggested that a mutation in the preliminary diamine oxidase gene is related to the development of hypersensitivity to NSAIDs [22]. The presence of gene variations cannot explain, by itself, the development of most cases of drug hypersensitivity reaction yet. However, the single nucleotide polymorphism (SNP) of the vitamin D point to mechanisms involved and add novel information that can be used as a proof of mechanism [25].

The group of delayed NSAID-specific reactions involves exanthems, pustular and bullous reactions, and organ-specific reactions, including hepatitis. T lymphocytes play a key role in the pathogenesis with drug specificity the hallmark of these reactions [26], but in this case the demonstration was right after the drug administered. The prevalence of NSAIDs-induced delayed reactions is not known [19].

NSAIDs can rarely induce allergic hepatitis [27], unless the patient receives multiple medications as in this case. Even so, there are reports of hepatitis induced by ketoprofen [28–29]. Thus, several possible molecular mechanisms of liver damage induced by NSAIDs have been reported, including reactive metabolite, metabolic idiosyncrasy, impairment of ATP synthesis, and hyper-sensitivity [30–32]. It was suggested inhibition of mitochondrial function, fat and reactive oxygen species accumulation and lipid peroxidation [33]. A recent study revealed that farnesoid X receptor (FXR), a master regulator of hepatic triglyceride, is a possible off-target protein mediating NSAID-induced liver injury. Furthermore, yeast two-hybrid and mammalian transactivation assays show that at least some NSAIDs (e.g. ibuprofen) are potential FXR antagonists [34].

In this patient, hepatitis could be suggested by the clinical manifestation of scleral jaundice which remained for five days (Figure 3). However liver enzymes rates investigated about 24 h after the allergic reaction showed normal values [aspartate aminotransferase (AST) = 35 U/L; alanine aminotransferase (ALT) = 34 U/L; gamma glutamyl transferase (GGT) = 22 U/L; alpha amylase = 53 U/L]. Bilirubin values were regular (negative) and urobilinogen also. What is intriguing once clinical presentation of jaundice as scleral icterus is best appreciated only when the levels of bilirubin reach more than 3 mg/dl. Sclerae have a high affinity for bilirubin due to their high elastin content [35] and if AST and ALT levels are normal then the jaundice is not due to liver or bile duct injury. The cause must probably be pre-hepatic: inherited disorders of liver conjugation or blood disorders or defect in hepatic excretion [36]. Furthermore, there was no history of alcohol consumption as well as drugs nor herbal medications or intake of squash, carrots or orange melons. The patient had not been taking any medication beforehand. In medical history there is no immunodeficiency, only mild evidence of fatty liver of family origin but not overweight nor a family history of atopy. No other signs of liver disease were observed. Histological examination of the liver was not possible. Also, there are no reports of similar reactions associated with other drugs administered (Tramadol, Thiocolchicoside, Scopolamine, Acetaminophen) alone and in therapeutic doses. So this is a rare case of NSAIDs acute toxicity with scleral icterus manifestation after single dose administration, which is quite intriguing. Certainly genetic aspects must to be considered for its elucidation. Maybe it was a case of drug-induced liver disease, however therapeutic dosages of all administered drugs only once and in such a short time could rule out this possibility.

The mechanisms involved in such hypersensitivity reactions were not investigated, but may be the result of allergic and immunologic aspects caused by ketoprofen and facilitated by a history of hypersensitivity, albeit softly, to other NSAIDs as reported by the patient. As for jaundice can be attributed to drug toxicity since laboratory parameters did not reveal any evidence of liver disease.

On the other hand, diagnosing single NSAID reactors is challenging. It is of critical importance to identify patients who are the single NSAID reactor so as to not indiscriminately eliminate all future use of innocent NSAIDs. So with the exception of pyrazolones, there are no standardized skin tests of *in vitro* assays available to diagnose NSAID hypersensitivity [26]. Moreover, a number of factors should also be considered, such as the natural evolution of the phenotypes of NSAIDs hypersensitivity and their potential interconversion, the development of tolerance over time or the role of atopy [37].

It should be considered that it is important to document adverse drug reactions such as this one, as a way to encourage research on the mechanisms involved in this type of hypersensitivity reaction, in order to elucidate how these mechanisms are processed and disseminate the risks involved in its use.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Disclosure statement

The author declares that he has no conflicts of interest.

ORCID

Marcio Antonio Rodrigues Araujo  <http://orcid.org/0000-0003-2755-1251>

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