Case Series

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Ketorolac-induced anaphylaxis following oral administration: a case series

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Background: Ketorolac is a commonly used non-steroidal anti-inflammatory drug for reducing pain and inflammation. Anaphylaxis is a medical emergency that occurs after exposure to an allergen, with a varied clinical presentation requiring prompt and appropriate measures to prevent or manage it. Although uncommon, ketorolac can cause anaphylaxis requiring immediate medical care. The authors present two cases of anaphylaxis in females induced after oral intake of ketorolac with successful outcomes.

Case presentations: The cases involve two adult women who experienced an allergic reaction to ketorolac. The first woman, aged 36, and the second woman, aged 26, on her second postpartum day, both developed similar types of symptoms like periorbital swelling, itching, and difficulty breathing after taking oral ketorolac. The second woman had a history of allergic rashes. They received immediate treatment with epinephrine, oxygen therapy, intravenous fluids, and other medications. They showed a rapid improvement and were discharged after observation.

Clinical discussion: Anaphylactic reactions to ketorolac, a commonly used pain management drug, have been reported. Symptoms include swelling, difficulty breathing, and hypotension. Treatment involves medications like epinephrine, hydrocortisone, and pheniramine. A detailed medical history, laboratory investigations, appropriate medication, oxygen therapy, and follow-up care are important in managing anaphylactic reactions, which can be life-threatening.

Conclusion: Although rare, ketorolac can cause anaphylactic reactions in patients with or without a history of drug allergy. Immediate recognition and management are essential, along with a detailed medical history and follow-up care.

Keywords: anaphylaxis, case series, cyclooxygenase, drug allergy, epinephrine, ketorolac

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, antipyretic, and immune-modulating properties. They work by inhibiting the cyclooxygenase enzyme, which is responsible for the production of prostaglandins that play a crucial role in inflammatory and immune responses[1]. NSAID hypersensitivity is a major health concern, ranking second after antibiotics as a cause of drug hypersensitivity reactions (DHRs). Prevalence ranges from 0.6 to 2.5% in the general population, with higher rates among females and patients with chronic urticaria or asthma[2].

Ketorolac is a commonly used NSAID that inhibits the action of the cyclooxygenase enzymes (COX-1 and COX-2), blocking the formation of prostaglandins and thromboxane A2. It is effective for prostaglandin-mediated pathologies causing pain and inflammation, including trauma. It is particularly useful for colicky pain and also for the short-term management of moderate-to-severe acute postoperative pain[3]. Although generally safe and effective, rare anaphylactic reactions to ketorolac have been reported[4,5]. Anaphylaxis is a severe and potentially life-threatening allergic reaction that requires immediate medical attention[6]. Clinicians should be aware of this medical emergency and take prompt measures to prevent or manage ketorolac-induced anaphylaxis.

Here, we present two cases of anaphylaxis in females induced after oral intake of ketorolac that were successfully managed after

HIGHLIGHTS

- Ketorolac-induced anaphylaxis is a rare but serious side effect that can occur within minutes to hours after taking the medication.
- Symptoms of anaphylaxis may include difficulty breathing, swelling of the face or throat, hives or rash, and low blood pressure.
- Patients who have a history of allergies or asthma may be at a higher risk of developing anaphylaxis after taking ketorolac.
- Treatment for anaphylaxis typically involves administering epinephrine and other medications to manage symptoms and stabilize the patient's condition.
- If a patient experiences symptoms of anaphylaxis after taking ketorolac, they should seek immediate medical attention and inform their healthcare provider of their symptoms and medical history.

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being promptly diagnosed in two different settings. The work has been reported in line with the PROCESS (Preferred Reporting Of CasE Series in Surgery) 2020 criteria[7].

Case presentation

Case 1

A 36-year-old female with no known history of drug or substance allergy presented to the emergency department with abrupt onset of shortness of breath, periorbital swelling (as shown in Fig. 1), and itching in her left arm and forearm (as shown in Fig. 2). She had a history of colicky abdominal pain since the morning and was administered oral ketorolac 10 mg in a local clinic 4 h before her presentation at our hospital. At presentation, the patient's oxygen saturation was 80%, respiratory rate was 25 breaths per minute, blood pressure was 90/60 mmHg, and pulse rate was 136 beats per minute. The physical examination revealed respiratory distress with bilateral wheezing, an inflamed and non-tender left arm (as shown in Fig. 2), and periorbital swelling of the left eye, which had partially subsided during transit to the emergency department according to the patient. Lab investigations showed normal results except for an elevated eosinophil count (12% of total leukocyte count) (reference value: <5%) and raised serum tryptase level (20 ng/ml) (reference value: 3–5 ng/ml). Treatment included oxygen therapy via a face mask (8 l/min), intravenous (i.v.) hydrocortisone 200 mg thrice daily, i.v. fluids (normal saline), and intramuscular epinephrine (0.5 mg). The patient was observed in the emergency department for 24 h without any further episodes of anaphylaxis. She was discharged with a prescription for oral antihistamines to be taken at bedtime for 5 days. At her first follow-up appointment after a week, she was asymptomatic and had no complaints.

Case 2

A 26-year-old female primipara, on the second postpartum day, complained of gross swelling of lips and the periorbital region. She also complained of difficulty in breathing and rashes along with itching over the flexural surface of her forearms. The complaints were noticed just 5–10 min after the oral administration of ketorolac 10 mg, which was prescribed for pain following episiotomy. On gross examination, she had swollen lips and the periorbital region as shown in Figure 3.

Before conception, she had a history of multiple episodes of allergic rashes over her body, after being exposed to agricultural fields during work, which used to subside on their own or after the intake of fexofenadine 180 mg OD (once daily) for 1–2 days. She underwent normal vaginal delivery after being induced with two doses of misoprostol 25 μg given 4 h apart for pre-labor premature rupture of membranes without chorioamnionitis, and the delivery was uneventful.

The mother had mild rashes on her right forearm and complained of persistent abdominal pain, so she was admitted to the Maternal and Child Healthcare (MCH) ward. She was advised to take Fe and Ca tablets for 6 weeks, a tablet of rabeprazole per oral twice daily for 5 days, a tablet of metronidazole 400 mg per oral three times a day for 5 days, a tablet of ampicillin 500 mg per oral twice daily for 5 days for treatment, and a tablet of ketorolac 10 mg per oral three times a day for 3 days; then SOS (use as needed) was prescribed for pain management.

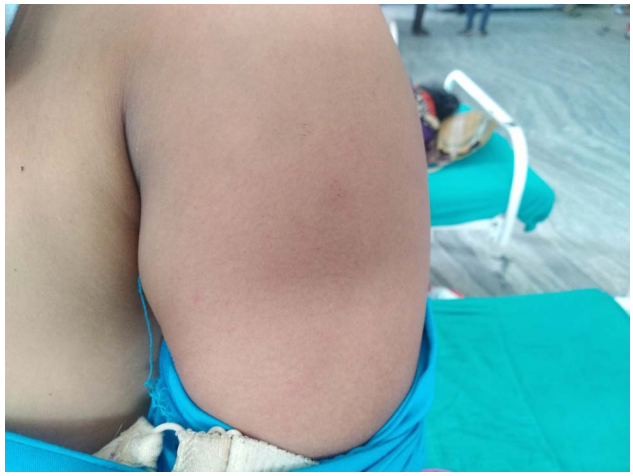

Figure 2. Rashes over the left arm after intense itching.

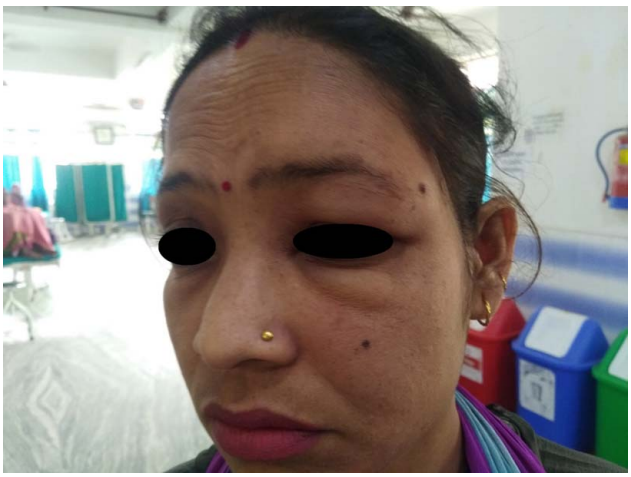

Figure 1. Periorbital swelling.

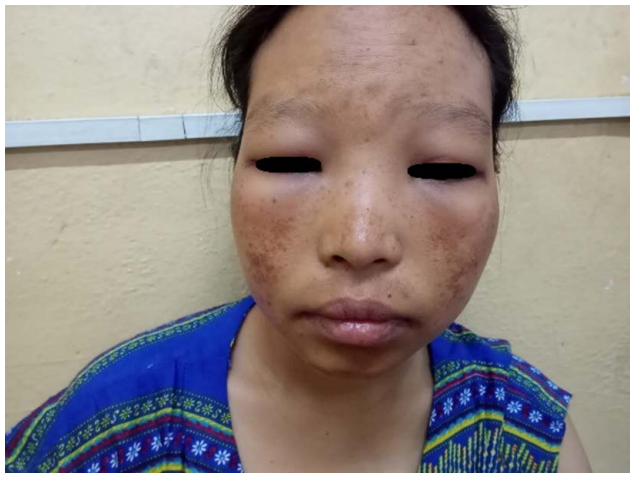

Figure 3. Gross swelling of the periorbital regions and lips.

All other drugs were started in the postnatal ward, but ketorolac was started only after admission to the MCH ward, after which she developed symptoms and signs suggesting the clinical diagnosis of anaphylaxis. Her laboratory investigations were normal except for the raised eosinophil count (10% of the total leukocyte count) (reference value: <5%) and raised serum tryptase level (16 ng/ml) (reference value: 3–5 ng/ml).

All i.v. medications were immediately stopped. Vitals were assessed, which came out to be normal, aside from mild tachypnea. Other systemic examinations were also found to be normal. The patient was advised to be placed on oxygen therapy via a face mask at the rate of 4 l/min along with the following medications: an injection of ranitidine 50 mg i.v. immediately, an injection of hydrocortisone 100 mg i.v. STAT, and an injection of pheniramine 25 mg immediately.

Rashes and itching in the forearm, along with shortness of breath, gradually subsided. Periorbital and lip swelling persisted till the following day, after which it reduced. She was discharged on oral antihistamines.

Based on the Adverse Drug Reaction (ADR) Probability Scale (Naranjo), both cases were scored at 9 individually after evaluating them, which showed that anaphylaxis was induced by ketorolac in both the cases[8].

Discussion

The presented case series highlights two cases of anaphylaxis following the administration of ketorolac, a commonly used NSAID for pain management. Both patients were young females presenting with signs and symptoms suggestive of anaphylaxis. The first case highlights the importance of considering ketorolac as a potential cause of anaphylaxis in patients presenting with respiratory distress, skin symptoms, and peripheral swelling, even if they have no history of drug or substance allergy. The second case raises concerns about using ketorolac in postpartum women with a known history of allergies who developed anaphylaxis following its administration. Both the cases involve the oral administration of ketorolac. Timely interventions prevented the further complications.

Yousefi *et al.*[4] described a 51-year-old man who presented to the emergency department with worsening flank pain that had spread to his abdomen. He was diagnosed with urolithiasis and given i.v. ketorolac, which caused an anaphylactic reaction with symptoms such as itching, redness, urticaria, angioedema, hypotension, cyanosis, and dyspnea. The patient's condition was immediately managed, and he recovered completely after an hour. He was discharged after 8 h with i.v. paracetamol used to control the pain[4]. Similarly, Karki *et al.*[9] described a case of a 26-year-old male who presented to the emergency room with left flank pain and was diagnosed with mild left hydroureteronephrosis with ureteric calculi. After receiving a rapid bolus of i.v. ketorolac, the patient developed an anaphylactic reaction characterized by generalized swelling and erythema. The anaphylactic reaction was managed with oxygen supplementation, i.v. normal saline, epinephrine, hydrocortisone, and pheniramine. The patient was discharged after 24 h of observation in the emergency room.

All patients experienced symptoms such as swelling, erythema, difficulty breathing, itching, and/or hypotension, suggestive of anaphylactic reactions triggered by the administration of ketorolac and were managed with medications such as epinephrine, hydrocortisone, and pheniramine. They had elevated eosinophil counts and raised serum tryptase levels, which are common indicators of anaphylaxis. The primary differences among these cases are age, gender, clinical presentation, duration of observation, and anaphylaxis triggered by different modes of administration of ketorolac. Overall, when compared to our reports, they highlight the importance of taking a detailed medical history, conducting laboratory investigations, and providing appropriate medication, oxygen therapy, and follow-up care to manage anaphylactic reactions effectively. Unlike the previous literatures, our cases suggest the potentiality of ketorolac causing anaphylaxis following its oral administration.

Anaphylaxis is an acute, serious, and severe life-threatening systemic or generalized hypersensitivity reaction with varied clinical presentations and mechanisms resulting from the sudden release of mediators from mast cells and basophils that might even cause death[10]. The pathophysiology behind anaphylaxis includes the release of different cell mediators due to mast cell degranulation that may be through either IgE-mediated or non-IgE-mediated mechanism causing several pathophysiological changes in the body like systemic vasodilation leading to extravasation of fluid, edema and hypotension, coronary vasoconstriction, tachycardia, rashes, and cardio-respiratory failure[11].

Various risk factors for moderate-to-severe anaphylaxis include food allergy, previous history of biphasic anaphylactic reactions, mast cell diseases, insect bites, medications, and so on, among which medications like antimicrobials, antivirals, and NSAIDs are the common triggers after penicillin group of drugs. However, anaphylaxis triggered by NSAIDs is medication-specific within its pharmacological class[12,13]. Ketorolac, although uncommonly, can cause hypersensitivity reactions, which may result in acute or delayed systemic allergic reactions when taken through enteral or para-enteral routes. Previous studies have consistently reported that the leading causes of medication-induced anaphylaxis are antibiotics and NSAIDs, especially when these medications are administered via parenteral routes[14]. However, we report anaphylaxis with ketorolac after its oral administration. NSAIDs, such as ketorolac, can inhibit both COX-1 and COX-2 but are relatively more selective for COX-1. NSAID-induced anaphylaxis occurs through the inhibition of COX-1, leading to the depletion of prostaglandin E2 and the shunting of arachidonic acid metabolism toward the 5-lipoxygenase pathway, resulting in increased cysteinyl leukotriene synthesis. This process can lead to the release of mediators from mast cells and eosinophils, causing anaphylactic reactions[15,16]. These anaphylactic reactions can occur in patients with or without a known history of allergy, which can be fatal[17].

Detailed history-taking and examination are crucial for clinically diagnosing anaphylaxis characterized by sudden onset of signs and symptoms, which primarily contributes to establishing an effective treatment plan. Skin and mucosal symptoms are present in 80–90% of the patients with variable target organ involvement[12]. NSAID-induced anaphylactic reactions express four clinical patterns, which are respiratory, cutaneous, mixed, and systemic. Case 1 expresses a systemic pattern of reaction, which is more severe, whereas case 2 expresses a mixed type of reaction, both produced by the oral administration of ketorolac. As described, periorbital edema is the commonest presentation with NSAID-induced anaphylaxis, which corresponds to our cases[18].

Focused history and examination support the diagnosis of ketorolac (NSAIDs)-induced anaphylaxis as supported by the algorithm in the previous literature by Castillo-Zamora et al [17]. However, for the confirmation of the diagnosis, of anaphylaxis in-vitro testing and oral provocation may be required when history remains insufficient[19]. In either of the cases, the tests were not performed as most of the information from the history itself indicated ketorolac as the cause of anaphylaxis. Moreover, in-vitro testing and oral provocation testing may not necessarily confirm the diagnosis but rather can exacerbate the situation[17].

The works of the literature suggest that laboratory parameters may not be necessarily helpful in the diagnosis of anaphylaxis due to limitations like being time-consuming, universal unavailability, not being performed routinely on an emergency basis, and being non-specific for anaphylaxis. However, a rise in certain biological markers like total leukocyte count (TLC), serum tryptase, platelet-activating factor, and histamine levels supports the diagnosis and correlates with the severity of anaphylaxis, serum tryptase being elevated in only 60% of adults with anaphylaxis who are clinically confirmed, but their unavailability does not pose a barrier to prompt clinical diagnosis. Eosinophilia is a common feature of allergic reactions, and elevated tryptase levels are indicative of mast cell activation, which is a key feature of anaphylaxis[10,12]. The presented case reported a rise in the level of TLC (eosinophilia) and serum tryptase, which supported the diagnosis of anaphylaxis.

Anaphylaxis is characterized by its acute onset with its initial course occurring within minutes to 1 h, followed by a second phase reaction occurring within 1–8 h of onset and as lately as up to 34 h. Most of the symptoms will resolve within the first hour of treatment whereas nearly 20% of them will follow a biphasic course which requires continuous monitoring to prevent any complications[20]. Both the presented cases responded well to immediate treatment and were discharged the following day after continuous monitoring. Prompt diagnosis and immediate treatment are critically important as anaphylaxis is a medical emergency. Immediate treatment involves the administration of epinephrine, high-flow oxygen, i.v. fluids, removal of triggers, airway management, etc. The clinical practice guidelines for the management of anaphylaxis, such as those developed by the National Institute for Health and Care Excellence (NICE), recommend the prompt administration of epinephrine as the first-line treatment for anaphylaxis. The guidelines also recommend the use of antihistamines and corticosteroids as adjunctive therapy. The management of anaphylaxis should be tailored to the individual patient, and treatment should be guided by the severity of the reaction[21].

Epinephrine is a life-saving first-line medication in the initial treatment. It is a potent vasoconstrictor that prevents and relieves airway obstruction, hypotension, and shock as it acts on alpha-1-adrenergic receptors. Its B-1-adrenergic agonist properties increase the force and rate of cardiac contraction, while its B-2-adrenergic agonist property leads to decreased mediator release, bronchodilation, and relief of urticaria. It is administered intramuscularly to a maximum dose of 0.5 mg (1:1000 dilutions) in adults, which is considered safe and effective. If required, the doses can be repeated and continuously infused i.v. (1:100 000 dilution; i.v.)[10,12].

Intramuscular or slow i.v. administration of antihistamines like pheniramine 10 mg and hydrocortisone 200 mg is recommended in adults. Along with leg elevation and placing a patient in the supine position to increase venous return. Anaphylaxis leads to vasodilation and extravasation of fluid, therefore rapid i.v. fluid challenge with crystalloids (0.9% normal saline or ringer lactate) is required with timely monitoring to prevent fluid overload[22]. Observation and monitoring are required for 6–8 h or longer in case of severe respiratory distress than those with mild anaphylaxis, which contributes to the effective management of the patient[10].

In the above presented initial case report, the patient presented with systemic anaphylactic reactions involving hypotension, tachycardia, and respiratory distress with a fall in SpO_2 level for which she was rapidly treated with intramuscular administration of epinephrine, high-flow oxygen, and i.v. hydrocortisone. She was discharged with an antihistamine for 5 days after being observed for 24 h. She was fine with no complaints after 1 week of follow-up visits. Similarly, the latter case developed mild hypersensitivity reactions, which were acute in onset with normal vitals except for mild tachypnea and shortness of breath and were therefore managed by cessation of all i.v. medication, 100% oxygen, i.v. administration of pheniramine, and i.v. hydrocortisone, after which her symptoms subsided and she was discharged on oral antihistamines the following day after being closely observed and monitored for 12 h.

It is required to make a prompt diagnosis and provide immediate management of anaphylaxis, as delayed treatment can lead to several complications like hypoxia, ischemia, encephalopathy, and death[4].

The study describes two cases of anaphylaxis following ketorolac administration, including patient history, symptom onset, and management. It may be relevant to various clinicians and researchers studying anaphylaxis. Limitations include a small sample size, a lack of information on specific triggering components, and no information on long-term outcomes. Patients with a history of allergy to ketorolac or other potential anaphylaxis-causing medications should be monitored closely, and prompt treatment is necessary in cases of anaphylaxis.

Conclusion

This case report series highlights the potential for ketorolac to induce anaphylactic reactions when administered orally, even in patients without a history of drug or substance allergy. The prompt recognition and management of these reactions with epinephrine, oxygen therapy, corticosteroids, i.v. fluids, and antihistamines can be effective in controlling acute symptoms and preventing further complications. These cases also highlight the importance of taking a detailed medical history, conducting laboratory investigations, and providing appropriate medication and follow-up care to manage anaphylactic reactions effectively. Healthcare providers should consider the possibility of drug allergy as a potential cause of anaphylaxis in patients presenting with symptoms such as respiratory distress, skin symptoms, and peripheral swelling. Finally, further studies are warranted to understand the underlying mechanisms of anaphylaxis induced by ketorolac and the potential risk factors involved.

Ethical approval

The study is exempt/waived from ethical approval in our institution.

Consent

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

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Author contribution

T.N.Y., A.B., R.K., S.L., and S.P.: literature review, follow-up of the patient, writing the manuscript, and final approval of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

Not done (no new surgical technique or new equipment/ technology used).

Guarantor

Mr Tek Nath Yogi.

Data availability statement

Not applicable.

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References

[1] Bosch DJ, Nieuwenhuijs-Moeke GJ, van Meurs M, *et al*. Immune modulatory effects of nonsteroidal anti-inflammatory drugs in the perioperative period and their consequence on postoperative outcome. Anesthesiology 2022;136:843–60.

[2] Bonadonna P, Olivieri F, Jarkvist J, *et al*. Non-steroidal anti-inflammatory drug-induced anaphylaxis infrequent in 388 patients with mastocytosis: a two-center retrospective cohort study. Front Allergy 2022;3: 1071807.

[3] Mallinson TE. A review of ketorolac as a prehospital analgesic. J Paramed Pract 2017;9.

[4] Yousefi H, Sahebi A, Farahani M, *et al*. Anaphylaxis as a rare side effect of ketorolac; a case report. Arch Acad Emerg Med 2020;8:e22.

[5] Chung HS, Kim ES, You YJ, *et al*. Anaphylactoid reaction after injection of ketorolac in a loading dose for patient-controlled analgesia– a case report. Korean J Anesthesiol 2010;58:565–8.

[6] Sampson HA, Muñoz-Furlong A, Campbell RL, *et al*. Second symposium on the definition and management of anaphylaxis: summary report — Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391.

[7] Agha RA, Sohrabi C, Mathew G, *et al*. The PROCESS 2020 Guideline : Updating Consensus Preferred Reporting of CasESeries in Surgery (PROCESS) Guidelines. Int J Surg 2020;84:231–5.

[8] Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30: 239–45.

[9] Karki S, Shrestha G, Yadav S, *et al*, Anaphylactic reaction after intravenous injection of ketorolac for colicky pain: a case report and review of literature. Authorea Preprints, no. Iv,2022;1–14.

[10] Simons FER, Ardusso L, Bilò MB, *et al*. International consensus on (ICON) anaphylaxis. World Allergy Organ J 2014;7:9.

[11] Ben-Shoshan M, Clarke AE. Anaphylaxis : past, present and future. Allergy 2011;66:1–14.

[12] Simons FER, Ardusso LRF, Bilò MB, *et al*. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J 2011;4:13–37.

[13] Campbell RL, Li JTC, Nicklas RA, *et al*. Emergency department diagnosis and treatment of anaphylaxis : a practice parameter. Ann Allergy Asthma Immunol 2014;113:599–608.

[14] Lee Y-S, Sun W-Z. Epidemiology of anaphylaxis : a retrospective cohort study in Taiwan. Asian J Anesthesiol 2017;55:9–12.

[15] Mastalerz L, Setkowicz M, Sanak M. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. J Allergy Clin Immunol 2004;113:771–5.

[16] Waterbury LD, Silliman D, Jolas T. Comparison of cyclooxygenase inhibitory activity and ocular anti-inflammatory effects of ketorolac tromethamine and bromfenac sodium. Curr Med Res Opin 2006;22: 1133–40.

[17] Castillo-Zamora C, Castillo-Peralta LA, Nava-Ocampo AA. Report of an anaphylactoid and an anaphylactic reaction to ketorolac in two pediatric surgical patients. Ther Drug Monit 2006;28:458–62.

[18] Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. The multiple faces of nonsteroidal antiinflammatory drug hypersensitivity. J Investig Allergol Clin Immunol 2004;14:329–4.

[19] Kowalski ML, Makowska JS. Seven steps to the diagnosis of NSAIDs hypersensitivity: how to apply a new classification in real practice ? Allergy Asthma Immunol Res 2015;7:312–20.

[20] Ellis AK, Day JH. Diagnosis and management of anaphylaxis. CMAJ 2003;169:307–12.

[21] Center for Clinical Practice at NICE (UK), Anaphylaxis: Assessment to Confirm an Anaphylactic Episode and the Decision to Refer After Emergency Treatment for a Suspected Anaphylactic Episode. National Institute for Health and Clinical Excellence (UK); December 2011.

[22] El-Shanawany T, Williams PE, Jolles S. Clinical immunology review series: an approach to the patient with anaphylaxis. Clin Exp Immunol 2008;153:1–9.