OPIS PRZYPADKU / CASE REPORT
Otrzymano/Submitted: 08.06.2022 • Zaakceptowano/Accepted: 21.06.2022

Ketoprofen hypersensibility – a case report and literature review


Katarzyna Malesza

Katarzyna Korzeniowska, Katarzyna Malesza
Zakład Farmakologii Klinicznej, Katedra Kardiologii, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu

Abstract

Background. Ketoprofen, a nonsteroidal anti-inflammatory drug (NSAID), is a potent inhibitor of cyclooxygenase that inhibits the synthesis of prostaglandins. It is widely used as an analgesic, anti-inflammatory, and antipyretic drug. However, there have been reports of a steady increase of allergic reactions to this medication. ***Material and methods.*** We describe a case report of a 27-year-old patient who experienced adverse reactions of dyspnea and skin lesions a few minutes after intravenously administered ketoprofen due to pain after FESS (Functional Endoscopic Sinus Surgery). ***Results***. The patient was administered dexamethasone and hydroxyzine, which resulted in clinical improvement. Instead of ketoprofen, the patient was treated with paracetamol (i.v.) in a dose of up to 2 g/day without complications. ***Conclusions.*** The described case confirms the risk of allergic reaction following the administration of ketoprofen. This adverse effect is especially dangerous for patients with concomitant respiratory diseases (e.g. asthma), therefore the administration of NSAIDs should be avoided in these patients, and paracetamol should be preferred. *Anestezjologia i Ratownictwo 2022; 16: 67-71. doi:10.53139/AIR.20221610*

Keywords: ketoprofen, NSAIDs, adverse drug reactions, allergic reaction

Introduction

The standard procedure for most paranasal sinus diseases is endonasal endoscopic sinus surgery. Functional Endoscopic Sinus Surgery (FESS) has emerged as treatment of choice for nasal polyposis and chronic rhinosinusitis (not responsive to aggressive medical treatment). Nasal polyps are tear-drop shaped benign inflammatory outgrowths in the nose or paranasal sinuses. They can developed in about 25% of patients with chronic rhinosinusitis (CRS) [1-2]. Polyps can develop in the area of sinonasal tissue in all paranasal sinuses but most likely in the region of the middle meatus and osteomeatal complex. This ailment is often linked to allergies and long term infections, especially fungal sinusitis. Rhinorrhoea, sneezing, anosmia or hyposmia and post-nasal drip are some of the symptoms affecting most people with nasal polyps. Moreover, deviated nasal septum (DNS), enlarged turbinates or atopies may appear [1, 3]. Generally, these symptoms can be relieved by applying topical nasal steroid drops with oral antihistamine; in some cases, short-term systemic steroid courses can benefit the patient. However, severe, refractory cases require surgical treatment such as Functional Endoscopic Sinus Surgery. FESS has been proven to improve patients' quality of life significantly - Damm et al. have demonstrated that this surgical approach was helpful in 85% of patients (after a mean postoperative follow-up of 31.7 months) [4]. As with any surgical procedure, FESS is associated with immediate postoperative pain (during the first 24 hours), requiring appropriate analgesic support [5]. Commonly prescribed pain medication after FESS are acetaminophen, hydrocodone-acetaminophen, ibuprofen, oxycodone-acetaminophen, acetaminophen-codeine, oxycodone, tramadol. It should be noted that opioids are generally overprescribed [6].

Nevertheless, there has been a growing reluctance to prescribe opioids to treat postoperative pain due to the risk of potential abuse. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce or even eliminate the need for opioid analgesics following otolaryngologic surgery [7]. Ketoprofen is a phenylpropionic acid derivative that has been in clinical use since 1973. It is a nonsteroidal anti-rheumatic drug with anti-inflammatory, analgesic and antipyretic properties. It can be applied orally, rectally, topically in the form of an ointment, gel or cream, and as a solution for injection (i.v. formulation is routinely administered to treat mild to moderate postoperative pain) [8-10]. Ketoprofen is clinically administered as a racemic mixture. The S-isomer possesses cyclooxygenase inhibiting activity, while the R-isomer is much less potent. The bioavailability of the drug is 90%. After oral administration, ketoprofen is almost completely absorbed by the gastrointestinal tract (90-99%) and bound to plasma proteins, mainly albumin, with peak plasma concentration reached after 15 min [8, 11-12]. The mean plasma concentration of ketoprofen, 5 minutes after the intravenous infusion and 4 minutes after administration, is 26.4 ± 5.4 μg/ml. The volume of distribution is 0.1-0.2 l/kg. Ketoprofen can be detected in serum and cerebrospinal fluid 15 minutes following intramuscular administration of a single 100 mg dose. The drug reaches peak plasma concentrations (1.3 μg/ml) within 2 hours after dosing. Ketoprofen is extensively metabolized by hepatic microsomal enzymes. It binds to glucuronic acid and is removed from the body in conjugated form. After oral administration, the plasma clearance of ketoprofen is 1.16 ml/min/kg. Due to the fast metabolism, its half-life is only 2 hours. Up to 80% of a dose is excreted in the urine, mainly (over 90%) as ketoprofen glucuronide. About 10% is excreted in the faeces. In patients with renal insufficiency, ketoprofen is eliminated more slowly, and its half-life is prolonged by one hour. In patients with hepatic insufficiency, ketoprofen may accumulate in the tissues. The metabolism and elimination of the drug are slower in the elderly, but this is of clinical significance only in patients with renal impairment [8, 13]. Ketoprofen is a nonspecific cyclooxygenase inhibitor. It has been shown to inhibit prostaglandin and leukotriene synthesis by blocking the enzyme cyclooxygenase (at least two of its isoenzymes: cyclooxygenase-1 (COX) 1 and cyclooxygenase-2 (COX 2), which catalyzses prostaglandin synthesis via the arachidonic acid pathway. It results in decreased levels of prostaglandins that mediate pain, fever and inflammation. Moreover, ketoprofen stabilizes lysosomal membranes *in vitro* and *in vivo* and inhibits the activity of bradykinins. The mechanism of the antipyretic activity of ketoprofen is not entirely known. It may be due to inhibition of the synthesis of prostaglandins in the central nervous system, most likely in the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. In some individuals, ketoprofen alleviates the symptoms of spontaneous dysmenorrhea, possibly due to inhibition of prostaglandin synthesis and/or its activity. However, inhibition of COX-1 is thought to confer some of the ketoprofen's adverse effects, such as gastrointestinal upset and ulceration [8, 14]. The other adverse effects of ketoprofen include asthenia, malaise, fatigue, headache, drowsiness, cardiovascular reactions (peripheral edema), gastrointestinal problems- increased liver enzymes, indigestion, nausea, abdominal pain, vomiting, diarrhea, ulcers, gastritis, and bleedings, skin sensitization and photosensitization (after topical use) and allergic reactions [8, 15]. In the article, we describe a case of a patient who developed an allergic reaction to ketoprofen.

Case report

A 27-year-old female patient underwent an endoscopic surgery of the paranasal sinuses without complications. Due to pain complaints reported by the patient after the procedure, intravenous ketoprofen in a dose of 100 mg was administered. A few minutes after the injection, the patient reported dyspnea and skin lesions appearing on the body. The patient was administered intravenous dexamethasone in a dose of 8 mg and orally hydroxyzine in a dose of 30 mg, which resulted in clinical improvement. The analgesic therapy was modified - intravenous administration of paracetamol in a dose of up to 2 g/day - without complications. A preoperative interview indicated that the patient has bronchial asthma which is treated with the combination of an inhaled corticosteroid and a long-acting β2-adrenomimetic. When selecting an analgesic, it was necessary to consider the reactions reported by the patient, similar to those described after using metamizole and ibuprofen in the past.

Discussion

Postoperative pain (determined by the type of surgery) may be a great discomfort for patients as it delays the return to normal daily activities and work after surgery. Moreover, it may increase the risk of other complications (e.g. cardiovascular, pulmonary), leading to chronic pain [16]. Usually, it may take around two weeks to recover after endoscopic endonasal surgery [17]. Furthermore, after discharge following day-case nasal surgery, patients need to take care of their pain management individually and postoperative pain is an important cause for their readmission. Hence, it is essential to provide adequate postoperative analgesic care. However, despite recent advances in the anesthetic and surgical fields, it remains a challenge after laryngological (ENT- ear, nose, and throat) surgeries [18]. Functional endoscopic sinus surgery (FESS) is a common procedure; however, the knowledge about precise pain management after this procedure remains incomplete. Laryngological surgeries are subsumed under head and neck surgery, which is a broad field covering variable surgical procedures. Thus, pain management during and after FESS is not specific. In a prospective case study by Finkensieper et al., the objective was to evaluate pain, its influencing factors and its management on the first postoperative day following FESS in a group of 101 patients. The patients were examined within the Quality Improvement in Postoperative Pain Management (QUIPS) project, which allowed a standardized assessment of patients' characteristics, pain, outcome and process parameters. Statistical analysis revealed that pain was moderate during the first postoperative day after FESS, and younger patients reported significantly more pain than older ones. Nine percent of patients reported not having received a preoperative counseling on pain management after surgery and this group demanded for more pain medication in comparison with the group that received general and specific pain management counseling. Patients in need of pain medication predominantly received acetaminophen (non-opioid) and piritramide (opioid), but this pain management was insufficient for those individuals. It occurred that specific counseling about postoperative pain management prior to surgery resulted in fewer postoperative pain reports in patients. However, only about 17% reported having received specific pain management counseling [19]. Gill et al. aimed to quantify pain after routine FESS and determine the most commonly used pain management regimen (assessment of the narcotic use). One hundred patients who underwent FESS from Oct 2017 to May 2019 were reviewed. They were categorized into groups: narcotics ect., non-narcotics, combination, or none based on the type of analgesic used and asked to prospectively complete a daily pain diary and report pain levels that were categorized into no pain (0), mild (1-3), moderate (4-7), or severe (8-10), up to six postoperative days (PODs). Sixty-nine patients were included. On POD1, 37% of patients used opioids (n = 37), 32% used non-opioids (n = 32), 22% used a combination (n = 22), and 9% used no analgesics (n = 9). Within the first 5 PODs, the mean number of narcotic pills used was two on any given day. During the first 5 PODs (even on POD1), the majority of individuals reported either mild (39%) or no pain (28%); the mean POD1 pain score was 3.98, which decreased with each subsequent POD. In conclusion, reported pain scores were inconsistent with the decision to use narcotics over acetaminophen for postoperative pain management [20]. However, NSAIDs are considered the primary elicitors of drug hypersensitivity reactions (classified according to the time of onset and the clinical manifestations into acute and delayed). The risk among the general population is 0.5%-6%, but it increases up to 20% in asthmatics with nasal polyps and to 40% in chronic spontaneous urticaria (CSU) patients. Clinical manifestations of hypersensitivity to NSAIDs include urticaria, angioedema, laryngeal edema, anaphylaxis, generalized pruritus, allergic rhinitis or bronchospasm [21-22]. Araujo described a case of a 43-years-old man diagnosed with renal colic, who was initially treated with 100 mg of tramadol (IV), followed by 4 mg of thiocolchicoside (IM) which caused no relief. Following the administration of 100 mg of ketoprofen (IV), the patient developed hypersensitivity reaction type I, characterized by intense coughing, rhinitis, angioedema, periorbital edema, rash, and scleral jaundice [22]. According to allergic standards proposed by Sánchez-Borges et al. [23], this reaction can be classified either as a cross allergic reaction (the patient has a history of hypersensitivity to other NSAIDs) and a mixed reaction (the patient presented respiratory symptoms and urticaria, which was triggered by nonspecific immune mechanisms related to arachidonic acid and the COX-1 enzyme). The suggested culprit of this kind of reaction is inhibition of COX-1 and subsequent activation of mast cells and

eosinophils with the release of inflammatory mediators, overproduction of leukotrienes associated with overexpression of 5-lipoxygenase and related enzymes and a decrease in the production of prostaglandin E2 (modulator of inflammatory cells mediators) [22]. Some patients with asthma may experience bronchospasm, rhinorrhea, and nasal obstruction after exposure to NSAIDs. The inhibition of COX-1 by NSAID triggers the synthesis of cysteinyl leukotrienes (Cys-LT) that causes bronchospasm and nasal obstruction [24]. To induce a reaction, NSAIDs or their metabolites (due to their low molecular weight) need to be conjugated with proteins. These drug-protein adducts are processed by dendritic cells and presented to Th2 lymphocytes. Then these lymphocytes interact with B cells, which differentiate into plasma cells that produce drug-specific IgE antibodies. IgE antibodies bind to specific receptors on basophil and mast cell membranes. When there is a further contact with the drug, the drug-protein complexes are recognized by two molecules of adjacent IgEs, and then intracellular pathways that head basophil/mast cell degranulation are activated. A repercussion of this process is a release of the pro-inflammatory preformed (histamine, chymase and tryptase) and de novo synthesized mediators- prostaglandin D2 (PGD2) and the cysteinyl leukotrienes (CysLTs) [21]. The non-allergic hypersensitivity reactions caused by NSAIDs depend on the power of COX inhibition. Besides, the beginning and the intensity of these manifestations may be directly associated with the route of administration of ketoprofen. Additionally, the activation of basophils and monocytes can be significantly more potent in individuals who present immediate and quite severe reactions. Also, genetic factors have a role in the development of cross hypersensitivity reactions- a mutation in the preliminary diamine oxidase gene is suggested to impact the development of hypersensitivity to NSAIDs [22].

Conclusion

The hypersensitivity reactions to NSAIDs have different mechanisms associated with each of them, and thus, multiple clinical manifestations may appear, and there are also variations according to the administered drug and the distinctive responses of individuals. The described case confirms the risk of the allergic reaction in the form of dyspnea and skin lesions a few minutes after administration of ketoprofen (i.v.) in a patient with previous reaction to other NSAIDs who undergone FESS. Despite advances in the anesthetic and surgical fields, postoperative pain management after laryngological surgeries still remains a challenge. It is essential to provide an adequate postoperative analgesic care with regard to patients' medical history, to avoid complications during and after surgical treatment.

Konflikt interesów / Conflict of interest
Brak / None

Adres do korespondencji / Correspondence address
Katarzyna Korzeniowska
Zakład Farmakologii Klinicznej
Katedra Kardiologii
Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu
ul. Św. Marii Magdaleny 14, 61-861 Poznań
☎ (+48 61) 853 31 61
katakorz@wp.pl

Piśmiennictwo/References

1. Gohar MS, Niazi SA, Niazi SB. Functional Endoscopic Sinus Surgery as a primary modality of treatment for primary and recurrent nasal polyposis. Pak J Med Sci. 2017;33(2):380-382. doi:10.12669/pjms.332.11800.
2. Stevens WW, Schleimer RP, Kern RC. Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol Pract. 2016;4(4):565-72. doi:10.1016/j.jaip.2016.04.012.
3. del Toro E, Portela J. Nasal Polyps. [Updated 2021 Aug 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Available from: https://www.ncbi.nlm.nih.gov/books/NBK560746/.
4. Damm M, Quante G, Jungehuelsing M, et al. Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. Laryngoscope. 2002;112(2):310-5. doi: 10.1097/00005537-200202000-00020. PMID: 11889389.
5. Patrocínio LG, Rangel Mde O, Marques Miziara GS, et al. A comparative study between ketorolac and ketoprofen in postoperative pain after uvulopalatopharyngoplasty. Braz J Otorhinolaryngol. 2007;73(3):339-42. doi: 10.1016/s1808-8694(15)30077-x. PMID: 17684654.
6. Gray ML, Fan CJ, Kappauf C, et al. Postoperative pain management after sinus surgery: a survey of the American Rhinologic Society.

Int Forum Allergy Rhinol. 2018;8(10):1199-203. doi: 10.1002/alr.22181. Epub 2018 Jul 18. PMID: 30019397.

7. Saini AT, Jiang ZY, Starr NC, et al. Are nonsteroidal anti-inflammatory drugs effective enough for postoperative pain control after functional endoscopic sinus surgery and septoplasty? A randomized, controlled study. Int Forum Allergy Rhinol. 2021. doi: 10.1002/alr.22941. Epub ahead of print. PMID: 34936232.
8. www.urpl.gov.pl.
9. Oberhofer D, Skok J, Nesek-Adam V. Intravenous ketoprofen in postoperative pain treatment after major abdominal surgery. World J Surg. 2005;29(4):446-9. doi: 10.1007/s00268-004-7612-0. PMID: 15776297.
10. Porażka J, Szałek E, Żółtaszek W, et al. Influence of obesity on pharmacokinetics and analgesic effect of ketoprofen administered intravenously to patients after laparoscopic cholecystectomy. Pharmacol Rep. 2020;72(3):763-68. doi: 10.1007/s43440-019-00042-9. Epub 2020 Jan 8. PMID: 32048255.
11. Lorier M, Magallanes L, Ibarra M, et al. Stereoselective Pharmacokinetics of Ketoprofen After Oral Administration of Modified-Release Formulations in Caucasian Healthy Subjects. Eur J Drug Metab Pharmacokinet. 2016;41(6):787-93. doi: 10.1007/s13318-015-0313-2. PMID: 26590950.
12. Atzeni F, Masala IF, Bagnasco M, et al. Comparison of Efficacy of Ketoprofen and Ibuprofen in Treating Pain in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Pain Ther. 2021;10(1):577-88. doi: 10.1007/s40122-021-00250-3. Epub 2021 Mar 5. PMID: 33674957; PMCID: PMC8119581.
13. Siepsiak-Połom M, Szałek E, Porażka J, et al. Ketoprofen and tramadol pharmacokinetics in patients with chronic pancreatitis. Eur Rev Med Pharmacol Sci. 2019;23(9):4044-51. doi: 10.26355/eurrev_201905_17835. PMID: 31115034.
14. https://go.drugbank.com/drugs/DB01009.
15. Carbone C, Rende P, Comberiati P, et al. The safety of ketoprofen in different ages. J Pharmacol Pharmacother. 2013;4(Suppl 1):S99-S103. doi:10.4103/0976-500X.120967.
16. Sommer M, Geurts JW, Stessel B, et al. Prevalence and predictors of postoperative pain after ear, nose, and throat surgery. Arch Otolaryngol Head Neck Surg. 2009;135(2):124-30. doi: 10.1001/archoto.2009.3. PMID: 19221238.
17. Mehta U, Huber TC, Sindwani R. Patient expectations and recovery following endoscopic sinus surgery. Otolaryngol Head Neck Surg 2006;134:483-7.
18. Kemppainen TP, Tuomilehto H, Kokki H, et al. Pain treatment and recovery after endoscopic sinus surgery. Laryngoscope. 2007;117(8):1434-8. doi: 10.1097/MLG.0b013e3180600a16. PMID: 17572643.
19. Finkensieper M, Poller K, Wittekindt C, et al. Postoperative pain assessment after functional endoscopic sinus surgery (FESS) for chronic pansinusitis. Eur Arch Otorhinolaryngol. 2013;270(1):157-66. doi: 10.1007/s00405-012-2015-6. Epub 2012 Apr 13. PMID: 22526577.
20. Gill KS, Chitguppi C, Haggerty M, et al. Assessment of narcotic use in management of post-op pain after functional endoscopic sinus surgery. Laryngoscope Investig Otolaryngol. 2021;6(1):42-8. doi: 10.1002/lio2.519. PMID: 33614928; PMCID: PMC7883617.
21. Doña I, Pérez-Sánchez N, Eguiluz-Gracia I, et al. Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. Allergy. 2020;75(3):561-75. doi: 10.1111/all.14032. Epub 2019 Oct 28. PMID: 31469167.
22. Araujo MAR. Ketoprofen hypersensibility and idiosyncratic response - a case report. Immunopharmacol Immunotoxicol. 2020;42(2):174-7. doi: 10.1080/08923973.2020.1728764. Epub 2020 Feb 21. PMID: 32079429.
23. Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A, et al. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs: an update. Pharmaceuticals. 2010;3(1):10-18.
24. Picado C. The role of cyclooxygenase in acetylsalicylic acid sensitivity. Allergy Clin Immunol Int J World Allergy Org. 2006;18(04):154-7.