

Anaphylactoid reaction after injection of ketorolac in a loading dose for patient-controlled analgesia

-A case report-

Hyun Sik Chung, Eun Sung Kim, Young June You, and Chul Soo Park

Department of Anesthesiology and Pain Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Anaphylaxis is a severe and life-threatening systemic hypersensitivity reaction. Ketorolac is a popular drug used for patient-controlled analgesia. Although anaphylactic reaction to ketorolac has not been frequently reported, it can develop by way of several mechanisms. A 41-year-old male patient was scheduled for laparoscopic correction of a perforated gastric ulcer. Emergency surgery was performed under general anesthesia with no complications. Near the end of anesthesia administration, ketorolac in a loading dose was administered intravenously in order to launch patient-controlled analgesia. Following injection, urticaria-like skin lesions, including rashes and wheals appeared systemically; tachycardia and breathing difficulty with oxygen desaturation also developed. Through additional inquiry into the patient's drug history, past experience with ibuprofen allergy was identified. Antihistamine, steroid, and aminophylline were administered, and continuous positive airway pressure by full facial mask was applied to relieve bronchospastic symptoms. The patient recovered without further complications. (Korean J Anesthesiol 2010; 58: 565-568)

Key Words: Anaphylaxis, Ketorolac, Patient-controlled analgesia.

Nowadays, most anesthesiologists not only administer anesthesia for surgery, but have also extended their role to the area of postoperative pain relief. After surgery, drugs and pain relief methods are used in a variety of ways; the most common drugs are narcotic analgesics and nonsteroidal antiinflammatory drug (NSAIDs), which are commonly mixed with a patient-controlled analgesia (PCA) device via intravenous line. Reduction of the side effects of narcotic analgesics while at the same time maintaining optimal conditions for the

purpose of a pain relief drug as a secondary is an advantage of using PCA with NSAIDs [1,2]. Ketorolac is the most commonly used drug for intravenous injection, and ketorolac can cause anaphylaxis associated with anesthetic complications. NSAIDs-induced anaphylaxis can be triggered by both the immune system and the non-immune system. Therefore, if the reaction is anaphylactoid via a non-immune mechanism, anaphylaxis can occur regardless of the structure of the NSAIDs. Therefore, patients who have shown hypersensitivity to NSAIDs require

Received: August 12, 2009. Revised: 1st, August 18, 2009; 2nd, September 3, 2009. Accepted: December 7, 2009.

Corresponding author: Chul Soo Park, M.D., Department of Anesthesiology and Pain Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, 505, Banpo-dong, Seocho-gu, Seoul 137-701, Korea. Tel: 82-2-2258-2235, Fax: 82-2-537-1951, E-mail: p6c8s17@catholic.ac.kr

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special care in with regard to use of NSAIDs [3].

In this case, we report on a case of anaphylactoid reaction that developed after ketorolac injection in a loading dose for PCA, along with a review of the literature.

Case Report

A 41-year-old patient visited the emergency center with a complaint of acute abdominal pain. The height of the patient was 175 cm, and his weight was 71 kg. He was diagnosed with acute gastric ulcer perforation, and underwent emergency surgery for laparoscopic repair. Other than drinking one bottle of distilled liquor daily, the patient's past medical history revealed no unusual findings. Premedication was not administered. Meperidine and nalbupine were injected in an intravenous loading dose, followed by intravenous administration of Meperidine 200 mg mixed with a normal saline drip for the purpose of pain control during the patient's entry into the operation room. After preoxygenation, the original anaesthetic consisted of thiopental and succinylcholine administered intravenously for induction. This was followed by administration of sevoflurane and vecuronium for maintenance of anaesthesia. Before administration of anaesthesia, the patient's vital signs included a blood pressure of 119/82 mmHg, regular sinus rhythm of pulse rate 91 beats/min, and peripheral oxygen saturation of 100%. Surgery was performed without unusual findings. For control of postoperative pain, fentanyl 1,000 µg and ketorolac 180 mg in the saline solution were made by mixing 100 ml total, of which the loading dose of 10 ml and the remaining 90 ml prepared as a PCA device (Accufuser plus 1008M, Wooyoung medical, Korea) and were mounted inside. Following surgery of 1 hour 40 minutes duration, the loading dose of 9 ml of 10 ml (fentanyl 90 µg, ketorolac 16.2 mg) for PCA was administered intravenously for control of postoperative pain. PCA was then connected to the intravenous line by 1 ml/hr basal continuous infusion. Neuromuscular blocker was then reversed by pyridostigmine and glycopyrrolate. Extubation was performed without complications, and the patient was transported to the postanesthetic care unit (PACU). At that time, his vital signs included blood pressure of 122/83 mmHg, regular sinus rhythm of pulse rate 80 beats/min, and normal peripheral oxygen saturation. Skin examination showed no unusual finding.

After 30 minutes in PACU, erythematous rashes developed on the neck. Therefore, chlorpheniramine 4 mg and dexamethasone 5 mg were administered intravenously. After 10 minutes, wheals with erythematous rashes developed on the neck and upper limbs. Therefore, chlorpheniramine 4 mg and hydrocortisone 100 mg were administered intravenously. After 5 minutes, angioedema of the face was newly observed, with

no relief from any symptoms; both erythematous rashes and wheals spread over the entire body, including both extremities. At that time, body temperature indicated mild hyperthermia at 37.4°C. His vital signs showed low normal borderline blood pressure; however, his pulse rate increased gradually, up to 120 beats per minute. Oxygen saturation decreased 92% by peripheral oxygen saturation. Findings from arterial blood gas analysis were pH 7.38, PCO₂ 41.6 mmHg, PO₂ 55.9 mmHg, and oxygen saturation 89.1%. Findings from examination with auscultation included wheezing, stridor on both lung fields, and a decreased breathing sound on both lower lung fields. Further inquiry into the patient's past medical history revealed hypersensitivity to ibuprofen, one of the NSAIDs. Therefore, anaphylaxis was suspected. Consequently, the PCA device was removed from the patient's intravenous line. In addition, aminophylline 250 mg and hydrocortisone 200 mg mixed in 100 ml normal saline respectively were administered intravenously during intravenous fluid challenge. A full face mask (Mirage Quattro, ResMed, Australia) was applied with FiO₂ 1.0 and continuous positive airway pressure (CPAP) for improvement of oxygen saturation. After 5 minutes, his oxygen saturation improved. After 15 minutes, his oxygen saturation was maintained at 100% by FiO₂ 0.6. Therefore, the full face mask was replaced with a re-breathing oxygen mask (Medium concentration oxygen mask, Telflex Medical, USA) as 5 L/minute oxygen. His symptoms showed no further worsening. After an hour, his general condition showed significant improvement with reduced erythematous rashes and wheals; however, he was transferred to the surgical intensive care unit due to the need for continuous monitoring. The next day, he was transferred to the general ward, and was discharged without further complications.

Discussion

The European academy of allergy and clinical immunology (EAACI) nomenclature committee proposed a broad definition of anaphylaxis as a severe, life-threatening, generalized or systemic hypersensitivity reaction [4]. Therefore minor, localized or non-systemic reactions, such as erythematous rashes or wheals are not included in the definition of anaphylaxis. Clinical features of anaphylaxis may be identical; however, anaphylaxis may be divided into allergic anaphylaxis and non-allergic anaphylaxis. Allergic anaphylaxis is further subdivided into an immunoglobulin E mediated reaction and an immunological mechanism (such as IgG, complement activation) mediated reaction, with the exception of IgE [3]. A general example of an IgE mediated allergic anaphylaxis is an allergic reaction to peanut ingestion, and blood transfusion reactions are an example of a non-IgE mediated allergic

anaphylaxis [5]. Exact etiology for non-allergic anaphylaxis is unknown; however, potential pathogenic mechanisms include idiosyncratic events, non-specific complementary activation, activation of humoral proteolytic systems, such as the clotting cascade, and direct histamine release [6]. Therefore, allergic anaphylaxis can be elucidated by skin test or drug-specific testing for IgE; however, non-allergic anaphylaxis cannot be explained by testing for specific sensitivity. The more important point is that the one is often more severe with subsequent administration of the causal drug, but the other tends to be similar with repeat administration of the causal drug. The other is more likely dose-dependent [5]. Clinical signs and symptoms can occur within seconds, but usually start within 5–10 minutes after intravenous administration of the responsible agent. Anaphylaxis usually resolves in 2–8 hours [3,7].

Prevalence of anaphylaxis during anesthesia administration has never been reported in Korea. Estimated overall frequency between 1 in 3,500 and 1 in 25,000 has been reported in studies from France and Australia [5]. Mortality from these reactions ranges from 3% to 6%, and an additional 2% of patients experience significant residual brain damage [7].

The exact diagnosis of anaphylaxis during anesthesia is difficult to ascertain. Because a number of drugs are administered simultaneously under anesthesia, these drugs can be implicated in allergic reactions, even if there is disparity between these drugs [7]. Major causal agents of anesthesia-related anaphylaxis include muscle relaxants (60%), latex (20%), antibiotics (15%), and colloids (4%), in that order. Outside of that, anesthesia-related anaphylaxis rarely occurs with NSAIDs, opioids, and local anesthetics [3,8]

Even if NSAIDs rarely cause anesthesia-related anaphylaxis, NSAIDs induced anesthesia-related anaphylaxis has been reported in Korea [9]. Mechanisms of NSAIDs induced anaphylaxis include inhibition of cyclo-oxygenase (COX)-1 iso-enzyme with subsequent depletion of prostaglandin E₂, unstrained synthesis of cysteinyl leukotrienes (cys-LT), and release of mediators from mast cells and eosinophils [10]. Therefore, anaphylaxis rarely occurs with weak COX-1 inhibitors, such as paracetamol and partial inhibitors of both COX-1 and COX-2, such as nimesulide and meloxicam, and selective COX-2 inhibitors at usual drug doses; it generally occurs only at high drug doses [11]. Currently, diagnosis of ASA and NSAID-induced hypersensitivity reactions can only be established with provocative drug testing [10]. As previously mentioned, because of non-IgE mediated mechanisms, there are currently no available sIgE assays for ASA or NSAID. The experimental diagnostic value of histamine and cys-LT release assays and flow-assisted quantification of in vitro activated basophils remains to be established [7].

In this case, when the patient received preoperative intra-

venous administration of meperidine for control of pain, he did not develop symptoms or signs associated with meperidine. Therefore, opioids can be excluded as a cause of anaphylaxis. Also, drugs administered between the period following surgery and PACU before anaphylaxis were drugs for PCA and pyridostigmine and glycopyrrolate for reversal of neuromuscular blocker. Through further inquiry into his past medical history, hypersensitivity to ibuprofen and a hypersensitivity reaction were found to have occurred after injection of an intravenous loading dose for PCA. Hence, comprehensively, ketorolac was more suspicious than fentanyl as the PCA's that caused anaphylaxis. Also, anaphylaxis occurred 30 minutes after injection of ketorolac, and the patient had experienced hypersensitivity reactions to other NSAIDs. Therefore, in this case, anaphylaxis can be presumed anaphylactoid reaction as non-allergic anaphylaxis less than IgE-mediated allergic anaphylaxis reaction definitely.

When anaphylaxis is diagnosed, rapid management is critical. Immediate treatment of allergic anaphylaxis and non-allergic anaphylaxis are identical. The major immediate treatments consist of epinephrine, oxygen 100%, intravenous fluid challenge, and intubation for airway maintenance [3,12,13]. Epinephrine should be administered as early as possible. An initial dose of 50 µg (0.5 ml, 1 : 10,000 solution) intravenously or 300–500 µg (0.3–0.5 ml, 1 : 1000 solution) intramuscularly is recommended [6]. Epinephrine has alpha-agonist activity, which reverses vasodilation. In addition to having a beta-agonist, which is inotropic, and also a bronchodilator, it reduces further release of mediators, such as histamine and leukotrienes [14]. Epinephrine is metabolized in liver and its half-life is 15 minutes. Therefore, epinephrine should be given repeatedly or infused continuously if necessary. Intravenous injection of chlorpheniramine 10 mg as an anti-histamine agent and hydrocortisone 200 mg (0.25–1.0 g) as a steroid are recommended. In case of severe bronchospasm, aminophylline, salbutamol, and magnesium sulphate can be given, and a beta-2 agonist may be inhaled using a metered-dose inhaler [3,6]. Hypotension leads to systemic vasodilation. Therefore, 0.9% normal saline or lactated Ringer's solution are given rapidly, and the patient should be placed in the supine position. Hypotensive patients must avoid a sitting or elevated upper body position. Symptoms of dizziness and loss of consciousness can be induced by hypotension. At that time, the patient should be placed in the supine position, and venous return can be increased by elevation of both legs if necessary [3,15].

In this case, the patient showed a mild hypersensitivity reaction. Therefore, only anti-histamine and steroid were administered intravenously. When the hypersensitivity reaction became systemic, tachycardia and de-saturation developed. However, hypotension requiring adrenaline did not occur. To

relieve bronchospasms, administration of aminophylline and establishment of CPAP with full face mask were attempted. At that time, the patient was mentally alert and had no severe bronchospasm. Hence, improvement of arterial oxygenation by use of a non-invasive full face mask, without intubation was attempted. Application of a full face mask was effective for improvement of arterial oxygenation, even though he had a naso-gastric Levin tube.

Even if anesthesia-related anaphylaxis is uncommon, anaphylaxis is fatal. A number of drugs are administered simultaneously during the peri-operative period, and the patient can come in contact with causal agents directly through the site of the operation. Therefore, in the event of anesthesia-related anaphylaxis, identification of the causes of anaphylaxis is difficult. Hence, standardized methods for selection of high risk patients must be established through reported cases of anaphylaxis and close examination of the patient. In addition, we must be fully aware of differential diagnosis and appropriate treatment for anaphylaxis. In so doing, diagnosis and management of anaphylaxis must be rapid and exact.

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