

The Anaphylactic Reaction Due to Diclofenac Sodium: Case Report

Diklofenak Sodyuma Bağlı Anaflaktik Reaksiyon

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Geliş Tarihi/Received: 20.01.2012
Kabul Tarihi/Accepted: 25.04.2012

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ABSTRACT Of nonsteroidal antiinflammatory drugs (NSAID) often preferred to opioids in pain therapy especially after one-day (ambulatory) surgery, diclofenac provides effective analgesia. However, NSAID might lead to certain side effects. NSAID are most frequently used agents that may cause hypersensitivity reaction. Anaphylaxis associated with NSAID is rarely seen. It's impossible to know whether a simple allergic reaction or life-threatening anaphylactic shock will develop against these drugs. This creates a great risk for the patient. Our case report presents the anaphylaxis developing in a patient who received IM diclofenac sodium for postoperative analgesia after mastopexy surgery, what was performed to establish its diagnosis and successful therapy.

Key Words: Anaphylaxis; diclofenac; pain, postoperative

ÖZET Özellikle gününbirlik cerrahi sonrası ağrı tedavisinde opioidlere alternatif olarak sık tercih edilen nonsteroid antiinflatuar ilaçlar (NSAİİ) arasından diklofenak etkin analjezi sağlamaktadır. Ancak NSAİİ da belli yan etkilere yol açabilmektedirler. NSAİİ en sık kullanılan ilaçlar arasındadır, hipersensivite reaksiyonuna neden olabilirler. NSAİİ ile ilişkili anaflaksi nadir görülür. Bu ilaçlara karşı basit bir allerjik reaksiyondan hayatı tehdit eden anaflaktik şoka kadar ilerleyebilecek tablonun hangisinin gelişeceği önceden bilinemez. Bu durum hasta için risk oluşturmaktadır. Olgu raporumuzda, mastopeksi ameliyatı sonrası postoperatif analjezi amacıyla İM diklofenak sodyum uygulanan hastada gelişen anaflaksi, anaflaksi tanısının konulması için yapılanlar ve başarılı tedavisi sunulmuştur.

Anahtar Kelimeler: Anaflaksi; diklofenak; ağrı, postoperatif

Türkiye Klinikleri J Anest Reanim 2013;11(2):88-93

An appropriate drug selection for pain therapy following one-day surgery may be necessary, since opioid analgesics can cause respiratory depression, addiction, intense sedation, alteration in psychological activity, sleep disturbance, urinary and gastrointestinal side effects, thus prolonging the duration of hospitalization.

Among the NSAIDs used as a good alternative to opioids due to the above-mentioned side effects in one-day surgery, the diclofenac sodium provides an effective analgesia. However, this does not mean that it has no side effects. Nonsteroidal antiinflammatory drugs have been reported to lead to side effects because of inherent acidic molecules.¹ Hypersensitivity reactions vary widely, from benign urticaria and short episodes of shaking

chills or fever, to potentially fatal bronchial spasms, angioneurotic edema and anaphylactic shock.² More serious drug-hypersensitivity reactions associated with diclofenac sodium can occur as a sudden and unpredictable allergic reaction with Type I clinical appearance and may proceed to anaphylactic shock. There are two mechanisms involving hypersensitivity reactions that develop due to nonsteroidal antiinflammatory drugs; one of which is thought to be pharmacokinetic disorders associated with non-selective cyclo-oxygenase inhibition that leads to alterations of prostaglandin and leucotriene levels; and the other is a mechanism in which immune system plays a role.¹ Although this type of reactions occur rarely and are treated appropriately, 3.5-10% can result in death.³

We aim to present the conditions under which the clinical findings occurred, therapeutic responsiveness, diagnostic features in the subject in whom anaphylactic reaction developed following administration of diclofenac sodium, and to discuss anaphylaxis which can be a fatal complication, under the light of literature.

CASE REPORT

A 32-year-old, (64 kg, 167 cm) female was referred to the clinic of plastic and reconstructive surgery for mastopexy surgery due to mastoptosis. The patient whose mother had a history of legume allergy did not have a history of allergy herself on the preoperative evaluation at all. Her medical history included mastoplasty operation and abdominoplasty 8 years and 5 years ago, respectively, both of which had been performed under general anesthesia without problems peroperatively. No pathological evidence was found on the examination of other body systems of the case whose findings of head-neck, cardiovascular and respiratory systems were normal. In addition, her laboratory data were within normal levels.

In the operating room, noninvasive arterial blood pressure (NIABP), electrocardiogram (ECG) and peripheral oxygen saturation (SpO₂) were monitored. Before induction of anesthesia, blood

pressure was 130/75 mmHg, heart rate (HR) was 92 beat/min and SpO₂ was 99%. General anesthesia consisted of induction with atropine 0.5 mg, lidocain 1 mg/kg, propofol 2.5 mg/kg, fentanyl 2 µg/kg and rocuronium 0.6 mg/kg followed by intubation and maintained with sevofluran of 1-2% and remifentanyl infusion of 0.25 µg/kg/min in 50% oxygen-air mixture. By the end of the 2.5-hour surgery, paracetamol 1 g IV and tramadol 100 mg were administered for postoperative analgesia and the patient was recovered without any complication.

The patient was transferred in to Postoperative Care Unit (PACU) and diclofenac sodium 75 mg was administered IM since her VAS score was reported to be 8. The development of numbness on her lips and tingling on her tongue forty minutes after injection, but failing to report them believing that they might be normal after general anesthesia, the case complained of these abnormalities when she had swollen tongue and experienced difficulty in breathing and informed the PACU nurse 20 minutes later. Physical examination showed that she was conscious, had full cooperation with normoisochoic pupils, angioedema at periorbital region, lips and tongue (Figure 1) and a dark-red cutaneous reaction in the form of a simultaneously developing widespread erythema at the upper extremities and on the front wall of body (Figure 2). Her pulmonary auscultation was normal, blood pressure was 80/40 mmHg, HR was 105 beat/min and sinus rhythm and SpO₂ were 96%. At PACU (while receiving nasal O₂ 2-3 L/min), in the blood gas analysis, pH was 7.41; pO₂, 85 mmHg; pCO₂, 35 mmHg; HCO₃, 21.4 mmol/L; BE, -1.3 mmol/L and SpO₂ 98%. Adrenalin 100 µgr, feniramin hydrogen maleat 45.5 mg and metilprednizolon 80 mg were given IV. Because her blood pressure was measured as 80/40 mmHg despite drug therapy, colloid solution 500 ml and crystalloid solution 1500 ml were infused. Posttreatment hemodynamic stability ensured, although the edema of her tongue regressed compared to that on the initial examination, she was not completely restored; since widespread erythema on her body continued after two hours, the second adrenalin (0.3 mg IM)



FIGURE 1: Angioedema at periorbital region, lips and tongue.
(See color figure at <http://anestezi.turkiyeklinikleri.com/>)



FIGURE 2: Erythema developed at the upper extremities.
(See color figure at <http://anestezi.turkiyeklinikleri.com/>)

was applied. No other complications were found in the patient whose vital functions were stabilized and clinical signs remitted eight hours later.

Because the serum tryptase value cannot be measured in Turkey, we collected blood samples to examine the serum tryptase levels at the 1st and 24th hours after anaphylactic reaction developed. They

were sent to Cerba Laboratories in Paris. 7 days later, serum tryptase levels were studied on the blood samples stored at -80°C. The serum tryptase level of the blood sample taken within the 1st hour was 24.7 µg/L (reference interval <11.4 µg/L), but the one taken at 24th hour was found to be 1.3 µg/L (reference interval <11.4 µg/L).

DISCUSSION

Anaphylactic reaction is a significantly life-threatening, general or systemic hypersensitivity reaction which occurs within minutes when individual has subjected to a specific antigen. NSAIDs are amongst the most frequently used drugs that may cause hypersensitivity reaction. Anaphylaxis to diclofenac is an idiosyncratic reaction and is a rare event.⁴

In postoperative analgesia applications, side effects such as urticaria, angioedema, laryngospasm, bronchospasm or anaphylaxis may occur with diclofenac sodium and other NSAIDs. It is known that side effects such as bronco-spasm, urticaria or angioedema occur more frequently in atopic individuals who use NSAIDs, compared to general population. Patients who display allergy-like reactions to aspirin and NSAIDs have been reported to develop both tolerance and intolerance against selective COX-2 inhibitors.⁵ Risk groups for allergic reactions are patients with allergy, atopy, history of asthma and latex allergy. Characteristics of genetic predisposition such as atopic individual, family history, female gender also increase risk for allergic reactions. Our patient had no specific medical history, whereas her mother's leguma allergy and her female gender indicate that the patient might have genetic predisposition for anaphylactic reactions.

The prevalence of NSAID-induced severe anaphylaxis has been reported by Allergy Vigilance Network to be 13 % in 2003-2004.⁶ In a study carried out by Puijenbroek et al. between 1985 and 2000, it was reported that the risk for anaphylactic reaction increased with diclofenac sodium, naproxen and ibuprofen, with anaphylaxis occurring most often with diclofenac sodium.⁷

NSAIDs may lead to cardiovascular side effects anaphylaxis as well as.⁸ Myocardial infarction with ST-segment elevation is a rare complication of anaphylactic reaction; however, it should be noted that it may accompany anaphylactic reaction even in patients with normal coronary angiography.⁹ Groot et al. emphasized that in a 48 year-old patient, acute myocardial infarction developed during diclofenac-induced anaphylaxis, care should be taken for anaphylactic reaction and appropriate therapy methods should be employed by making early diagnosis.⁹

Hadar et al. reported that a 39 year-old patient who had no history of allergy and who underwent caesarean operation received IM diclofenac sodium injection due to additional analgesia requirement 6 hours later and severe angioedema and marked hemodynamic shock developed 10 minutes after the injection.¹⁰

Indu et al. reported that a 9 year-old girl operated on for synovitis was prescribed oral diclofenac of 25 mg twice daily at discharge, upon intake of the first dose; itching, widespread rashes developed and her body temperature increased; after second dose fatal allergic reactions developed and she died because of delayed referral to hospital.¹¹

Anaphylactic hypersensitivity may be initiated when any antigen increases IgE production. When hypersensitized patient comes into contact with any antigen, histamine, leucotriene, tryptase and prostaglandins are released. Although anaphylactoid reactions have almost the same clinical table as that of anaphylactic reactions, neither antigens nor susceptible IgE are present in the mechanism of anaphylactic reactions.¹²

Just as in anaphylactic reactions, the mast cells in hypersensitivity reactions also become activated and release vasoactive mediators. Tryptase is one of these mediators. The measurements of serum tryptase concentration in anaphylactic reactions occurring during anesthesia are helpful in making the diagnosis. Measurement of serum tryptase and specific IgE levels should be undertaken for possible anaphylaxis.² Tryptase is elevated 1 hour

after the reaction takes place and decreases within 10 hours. The sensitivity and specificity of serum tryptase test was specified as 75% and 51% respectively.¹³ Since its biologic half-life is 2 hours, serum tryptase level should be checked in 1-6 hours. In postmortem studies, the increased tryptase concentration suggest systemic anaphylaxis as the cause of death.¹⁴ Since we were not able to measure the serum tryptase levels of our patients who developed anaphylactic reaction in our university hospital, blood samples were studied in Cerba Laboratories in France. The serum tryptase levels in blood samples taken at first hour were found to be 24.7 µg/L (reference interval <11.4 µg/L); and in those taken within 24 hours as 1.3 µg/L (reference interval <11.4 µg/L). The increase in serum tryptase levels at the first hour was two- fold higher than the reference value and reverted to normal at 24 hours, indicating that the reaction developing in our case is consistent with anaphylaxis. The fact that although the clinical findings of the patient, as well as the elevated levels of tryptase confirm the diagnosis of anaphylaxis, the increase is not so severe might be related to the stabilization of basophil and mast cell with early intervention. We believe that we prevented a probable cardiovascular collapse which is likely to develop due to mediators, because our patient was under the supervision of doctor and nurse during postoperative care, was conscious and necessary intervention was practiced timely by identifying symptoms early. Careful clinical assessment is important so that appropriate treatment can be instituted promptly to avoid further morbidity and mortality. Epinephrine is the first and most important treatment for anaphylaxis; considering its relative safety, when in doubt, epinephrine should be administered.¹⁵ The recommended treatment guidelines for anaphylaxis, inside and outside the operating room, are all based on firstline treatment with epinephrine.¹⁶⁻¹⁸

Not surprisingly, a recent Cochrane review could find no randomized or quasirandomized trials of the use of epinephrine in anaphylaxis.¹⁵

As a result of consultation requested from Immunology and Allergy Section of Internal

Diseases Department in order to clarify specific diagnosis for the agent which causes anaphylactic reaction, the skin test to be performed with diclofenac has a higher false negative rate therefore it is not useful in making the diagnosis; an oral provocation test should be performed to confirm the diagnosis even if the result is positive; however, this application is not recommended because it might be highly risky for the patient who experienced a serious reaction such as angioedema or anaphylaxis.

Pazo et al. in their own unit performed skin test on 12 non-atopic patients with diclofenac hypersensitivity.¹⁹ The results were negative in 10 patients and severe symptoms related to urticaria and respiratory system developed in two patients. Pazo et al. concluded that skin test with diclofenac is not helpful in establishing the diagnosis.¹⁹

Aksoy et al. described anaphylactic reaction 15 minutes following oral intake of lansoprazole 30 mg capsule.²⁰ They did not perform a challenge test with lansoprazole in their patient because there was a clear temporal relationship between lansoprazole use and anaphylaxis. They did not want to take any risk of harm to their patient.

Kowalski et al. stated that the skin test with NSAID is not indicated, and that the serious risks of oral provocation test in patients with history of

severe reaction (angioedema and/or anaphylactic shock) should be weighed when making the diagnosis.²¹ Yet they emphasized that different protocols should standardize it in their practices.

Recently a number of medications have been used in daily practice during anesthesia applications and postoperative pain therapies. Not knowing in advanced which clinical picture will appear such as a simple allergic reaction to life-threatening anaphylactic shock increases the risk. The ambulatory surgery and postoperative drug selection to shorten the hospitalization may decrease the duration of patient monitoring in PACU. Patients may be rapidly discharged considering that analgesia is provided and reactions not under observation might be more life-threatening. This situation might be an important factor that increases the risk when treatment of patients is delayed. Fortunately, in this case we presented, early detection and treatment of anaphylactic reaction that appeared while she was under observation in PACU, may have enabled clinical table not to become more exacerbated. The result we want to underline or the important result to be inferred with this case presentation is that patients should not be discharged earlier than at least one hour after the last medication was administered, even following an ambulatory surgery.

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