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IgE-Mediated Reaction to Metamizole: Evaluation of a Patient with Severe Anaphylaxis

Metamizole Karşı IgE Aracılı Reaksiyon: Ağır Anafilaksili Bir Hastanın Değerlendirilmesi

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Abstract

Metamizole, a non-steroidal anti-inflammatory drug with weak anti-inflammatory and spasmolytic effects, is used as an analgesic and antipyretic agent. Many adverse reactions to metamizole, such as early or late-onset systemic reactions and bone marrow suppression, have been identified. In this report, we present a case of systemic reaction after the application of parenteral metamizole (Novalgin® ampoule; Sanofi Aventis, İstanbul, Turkey) and discuss the mechanism underlying the reaction.

Keywords: Abdominal pain, metamizole, systemic reactions

Öz

Metamizol, temel olarak analjezik ve antipiretik etkili, ayrıca kısmen antiinflamatuvar ve spazmolitik etkileri de olan bir ilaçtır. Metamizole bağlı birçok istenmeyen etki tanımlanmıştı. Erken ya da geç başlangıçlı sistemik reaksiyonlara ve kemik iliği baskılanması ile ilişkili reaksiyonlara neden olabilir. Bu makalede, parenteral metamizol (Novalgin® ampul; Sanofi aventis, İstanbul, Türkiye) uygulanmasını takiben sistemik reaksiyon gelişen bir hastada reaksiyonun mekanizmasına yönelik araştırmalar sunularak tartışılmaktadır.

Anahtar Kelimeler: Karın ağrısı, metamizol, sistemik reaksiyon

Introduction

Metamizole is an analgesic and antipyretic drug with weak anti-inflammatory and spasmolytic effects. Metamizole, a pyrazolone derivative, is classified in the non-steroidal anti-inflammatory drug (NSAIDs) group, and is used widely in Turkey because of its low cost and broad availability in a pharmacy without prescription [1].

Many adverse effects of metamizole have been identified, including early or late onset systemic reactions and bone marrow suppression. Early onset reactions are usually non-IgE-mediated anaphylactoid reactions, but they are clinically indistinguishable from IgE-mediated reactions. IgE-mediated allergic reactions are found in only a small proportion of patients suffering from early onset reactions [1-4]. Here, we present a case of a patient with systemic reaction after application of parenteral metamizole and discuss the mechanism underlying the reaction.

Case Report

History of the Reaction in the Emergency Department

A 36-year-old female patient was admitted to the emergency department because of bilateral lumbar and abdominal pain. Initial examination revealed consciousness and normal orientation with respect to time and location. Her blood pressure was 120/70 mmHg, heart rate was rhythmic at 100 beats/min. and respiratory rate was 16/min. Clinical and laboratory evaluation for abdominal pain revealed no surgical or internal pathology requiring further intervention. After a period of observation, the physical examination was repeated, and other investigations found no emergent situation. Therefore, the patient received symptomatic treatment.

Isotonic sodium chloride (0.9%) infusion was started, and an ampoule of metamizole (Novalgin® ampoule) (1 g/2 mL) was administered intravenously (IV) as an analgesic. Immediately after the delivery, the patient developed flushing, generalized urticaria and angioedema. The reaction progressed rapidly, and the patient developed hoarseness and the inability to swallow saliva (pharyngeal/laryngeal angioedema). Physical examination revealed the blood pressure as 60/40 mmHg, heart rate as 156 beats/min and respiratory rate as 26/min. Her clinical symptoms were evaluated as anaphylactic, and epinephrine 0.3 mg intramuscular (IM) and diphenhydramine 10 mg IV were administered. Oxygen therapy was started with the support of oropharyngeal air-

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Figure 1. *Epidermal prick test was positive with undiluted metamizole, the negative control was negative, and histamine was 4 mm.*

way cannula, and IV methylprednisolone 1 mg/kg was given. The general condition of the patient was stabilized due to the rapid response with the correct approach. After 24 h of intensive care follow-up, she was monitored in-service for 24 h, discharged with a detailed epicrisis report, and referred to the outpatient immunology and allergy clinic.

Etiological Assessment in the Immunology and Allergy Clinic

The patient was admitted to our clinic 3 months after the reaction, and the electronic hospital records and epicrisis were investigated. The diagnosis of anaphylaxis in the emergency department was confirmed after the evaluation of the clinical course of reaction and response to appropriate treatment.

The reaction began immediately after the 4th administration of metamizole, and included a rash on the neck, followed by a prickle in the throat, cough and dyspnoea, and memory lapse. The patient identified no precipitating factors such as drug use or consumption of different foods prior to the reaction. After providing a detailed history, the patient underwent an epidermal skin prick test with inhalant and food allergens. A skin prick test was performed in an asymptomatic period (3 months after the anaphylactic attack) and at least 7 days after discontinuation of antihistamines. Inhalant and food allergen tests were performed on separate days. Histamine (1%) was used as a positive control, while 0.9% saline and 0.4% phenol solution served as a negative control. The skin test panels were negative when evaluated 15 min after the application.

After receiving verbal and written informed consent, an epidermal prick test was performed with metamizole. The epidermal prick test was positive with undiluted metamizole (oedema 6 mm in diameter, with surrounding erythema, the negative control was negative, and histamine was 4 mm, Figure 1). Metamizole diluted 1/10 was evaluated to exclude an irritant reaction, and this dilution showed positivity (Figure 2). No intradermal tests were performed due to the positive skin test with 1/10 dilution metamizole and previous anaphylactic reaction. A control group of 10 healthy volunteers was tested with the 1/10 diluted metamizole using the same protocol to verify the positive response and to exclude an irritant response. Epidermal prick tests were negative in the control group.

Discussion

Anaphylaxis is a life-threatening, sudden-onset systemic hypersensitivity reaction caused by the release of various mediators from mast cells and basophils via immunological or non-immunological mechanisms [5]. Immunological mechanisms may be allergic (IgE-mediated) or non-allergenic. Acute allergic reaction develops as a result of interactions between allergen and allergen-specific IgEs bound to high-affinity IgE receptors on the surface of mast cells, inducing the release of histamine and other mediators such as leukotrienes, tryptase, prostaglandins and tumour necrosis factor-alpha [6-8].

IgE-mediated drug reactions are usually preceded by a history of exposure to the offending drug or structurally similar drugs. Cutaneous, respiratory, cardiovascular and gastrointestinal systems are frequently involved in anaphylaxis. Anaphylaxis is a serious emergency that can be fatal; therefore, identifying the etiology of anaphylaxis is critical for preventing possible future anaphylactic reactions. Drugs

Figure 2. *Metamizole diluted 1/10 showed positivity.*

are the leading cause of anaphylaxis in adults, whereas food induced-anaphylaxis is more common in children [9, 10]. Although drug-induced anaphylaxis can occur with any drug type, beta-lactam antibiotics and NSAIDs are the most frequently reported inducers [11, 12].

Chemical compounds smaller than 1000 Da are not immunogenic, and are metabolized and eliminated in the body without causing an immune response. Some drugs may form reactive metabolic intermediates during the elimination step, which may bind covalently to proteins such as albumin or integrins on the cell membrane and intracellular enzymes. After forming such interactions between the reactive intermediate and proteins, proteins rapidly undergo haptenization and form multivalent complexes. These complexes activate antigen-presenting cells and initiate specific IgE production. Drug-specific IgE molecules bound to high-affinity IgE receptors on mast cells initiate type 1 hypersensitivity reaction.

The course of drug related IgE-mediated reactions could range in severity due to haptenization. Haptens facilitate IgE cross-linking, which could result in rapid mast cell degranulation and anaphylaxis. Haptenization might induce conformational changes, and new epitopes could develop. Haptens alone can initiate the reaction after repeated exposure to the drug [13].

Metamizole was first introduced in the 1950s for analgesia, and drug-related toxicity has been reported [14]. Metamizole remains in use as an antipyretic and analgesic agent in Europe and Turkey; however, it was withdrawn in the US due to bone marrow suppression and agranulocytosis [15].

In a case of metamizole-associated anaphylaxis, metamizole 1 g was injected into a 48-year-old female patient for pain prophylaxis before elective tympanoplasty surgery. Shortly after, skin erythema, laryngeal oedema and bronchospasm, and cardiopulmonary arrest developed. After successful cardiopulmonary resuscitation, the reaction was found subsequently to be associated with type 1 sensitization to metamizole [4].

The epidermal skin prick test is an efficient, rapid, inexpensive, and practical diagnostic method of demonstrating IgE-mediated reactions in vivo. The test shows high sensitivity and reproducibility with standardized antigens. However, epidermal and intradermal allergy tests with drugs are limited because of irritant reactions and lack of standardized antigens. Therefore, careful interpretation of results is important for allergy tests with drugs.

In our case, the skin prick test showed positivity with undiluted drug and when repeated with 1/10 dilution. To eliminate the possibility of an irritant reaction, the test was administered in healthy volunteers with no history of reaction using a 1/10 dilution. The control tests were negative, whereas the skin test of the patient was interpreted as positive due to an IgE-mediated reaction. However, the skin test was performed with metamizole ampoule, not purified metamizole. Thus, the culprit agent is likely to be metamizole and the excipient in the preparation. Therefore, the results obtained from the IgE-mediated drug allergy tests should be interpreted as Novalgin® ampoule allergy.

In conclusion, it is important for clinicians to be aware that metamizole, an antipyretic and analgesic frequently used in emergency departments and clinics, might cause anaphylaxis in patients. A detailed medical history and period of careful observation after administration of medicine are critical in recognizing adverse reactions in patients. The use of adrenaline is essential, as mortality in anaphylaxis cases is related to a delay in, or lack of, application of adrenaline.

Informed Consent: Written informed consent was obtained from the patient.

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