OPIS PRZYPADKU / CASE REPORT
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Metamizole-induced hypersensitivity – a case report and literature review

Reakcja nadwrażliwości po metamizolu – opis przypadku i przegląd piśmiennictwa

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Streszczenie

Wstęp. Metamizol to pochodna pirazolonowa, nieopioidowy prolek, mający właściowści przeciwbólowe, przeciwgorączkowe i spazmolityczne. Jest on wskazany w leczeniu ostrego, silnego bólu po urazie lub zabiegu chirurgicznym, bolesnej kolki, bólu nowotworowego, ostrego lub przewlekłego bólu, jeśli inne środki terapeutyczne są przeciwwskazane, oraz wysokiej gorączki, nie reagującej na inne środki. Do najważniejszych działań niepożądanych metamizolu należą agranulocytoza, niedokrwistość, reakcje skórne, zaburzenia skórne oraz skurcz oskrzeli. **Materiał i metody**. Przedstawiamy przypadek 48-letniego pacjenta, u którego kilka minut po podaniu metamizolu w dawce 2,5 g drogą dożylną wystąpiły wysypka skórna, kaszel i duszność. **Wyniki.** Odstawienie leku i podawanie deksametazonu, antazoliny i wapnia doprowadziło do złagodzenia objawów. **Wnioski.** Metamizol jest silnym lekiem przeciwbólowym o działaniu spazmolitycznym. Reakcje anafilaktyczne związane z metamizolem są poważnymi powikłaniami i mogą być wywołane mechanizmem zależnym od IgE. Szczegółowy wywiad dotyczący wcześniejszych reakcji alergicznych na metamizol oraz obserwacja pacjenta po podaniu leku są kluczowymi elementami poprawy bezpieczeństwa i skuteczności leczenia pacjenta. *(Farm Współ 2021; 14: 146-148) doi: 10.53139/FW.20211418*

Słowa kluczowe: metamizol, reakcja nadwrażliwości

Abstract

Introduction. Metamizole is a pyrazolone derivative, a non-opioid prodrug with analgesic, antipyretic and spasmolytic properties. It is indicated for the treatment of acute severe pain after trauma or surgery, painful colic, tumour pain, other acute or chronic pain, if other therapeutic measures are contraindicated, and high fever, not responding to other measures. The most important adverse reactions of metamizole include agranulocytosis, anemia, skin disorders and bronchospasm. **Material and methods.** We report a case of 48-year-old patient, who developed skin rash, cough and dyspnea a few minutes after receiving metamizole 2.5 g *iv*. **Results.** Drug was immediately halted while dexamethasone, antazoline and calcium were administered which led to relieving the patient's symptoms. **Conclusions**. Metamizole is a strong analgesic drug with a spasmolytic effect. Anaphylactic reactions associated with metamizole are serious complications and may be driven by IgE-mediated mechanism. Conclusions. A detailed medical history regarding any previous allergic reactions to metamizole and observation of the patient after administration of the drug are crucial elements of improving the safety and effectiveness of patient's treatment. *(Farm Współ 2021; 14: 146-148) doi: 10.53139/FW.20211418*

Keywords: metamizole, hypersensitivity

Introduction

Metamizole is a pyrazolone derivative, a non-opioid prodrug with analgesic, antipyretic and spasmolytic properties [1]. Its analgesic and antipyretic effect includes the inhibition of cyclooxygenase (COX) enzyme (predominantly type 2) while the spasmolytic

effect may be associated with a decreased release of Ca^{2+} due to reduced synthesis of inositol phosphate [1,2]. Metamizole is also assumed to inhibit COX-3 enzyme thus reducing the prostaglandin synthesis. It can also stimulate opioid receptor as naloxone was found to counteract the analgesic effect of metamizole [2]. According to EMA, current indications for metamizole include acute severe pain after trauma or surgery, painful colic, tumour pain, other acute or chronic pain, if other therapeutic measures are contraindicated, and high fever, not responding to other measures [3]. Metamizole is available in various pharmaceutical forms (oral, parenteral). The injection should only be used when oral administration is contraindicated [4].

The most important adverse reaction to metamizole is agranulocytosis. It is diagnosed when no neutrophils are found in the peripheral blood or there are less than 200-500 /µl [5]. In many countries, agranulocytosis caused by metamizole led to its withdrawal from the market or introduction of restrictions to its use [2,6]. Other serious adverse reactions induced by metamizole include aplastic anemia, skin and subcutaneous disorders (such as skin rash, urticaria, morbilliform, scarlatiniform, erythematous, bullous, purpuric, exudative or fixed drug eruption, pemphigus vulgaris and toxic epidermal necrolysis) and bronchospasm [2]. The report presents a case of skin rash, cough and dyspnea observed after metamizole administered iv.

Case description

A 48-year-old patient was admitted to the otolaryngology department for the endoscopic reoperation of the paranasal sinuses due to the nasal congestion and difficulties with breathing through the nose. The previous surgery of paranasal sinuses was carried out 30 months ago. The patient had a history of asthma and no previous hypersensitivity reactions to drugs. On admission, the patient was using the following drugs: rupatadine (10 mg daily), salmeterol (100 µg daily) and fluticasone (1000 µg daily). Blood morphology was correct except for slightly elevated eosinophil count (0.52×10^3 per µl; reference values: $0.02 – 0.50 \times 10^3$ per µl). INR and prothrombin index were valid, while prothrombin time was shortened (10.8 s; reference values: 12.0 – 16.0 s). APTT, creatinine, eGFR, glucose, sodium and potassium were within reference range. The course of the reoperation was uneventful. After the surgery, the patient was administered metamizole (2.5 g iv) as an analgesic which resulted in skin rash, cough and dyspnea a few minutes later. Metamizole was immediately halted while dexamethasone (8 mg iv), antazoline (100 mg im) and calcium were administered which led to relieving the patient's symptoms. The analgesic was switched to paracetamol (1 g daily).

Discussion

Metamizole is a drug that often shows a stronger analgesic effect than paracetamol or NSAIDs [7]. It also has a spasmolytic effect and helps relieve visceral pain. After oral administration, it has quick absorption, high bioavailability and similar efficacy as administered *iv* [8]. As a result, it is readily used to treat pain associated that has visceral or spastic component [9]. Anaphylactic reactions after metamizole are serious complications, clinically manifested by edema of the laryngeal mucosa, angioneurotic edema, bronchospasm, urticaria, edema and anaphylactic shock [9]. According to the study of Blanca-López et al., the most frequent hypersensitivity reaction to metamizole manifested within 24 hours and included anaphylaxis followed by urticarial, angioedema, exanthema and glottis edema. Moreover, adverse reactions were more severe and occurred faster in patients who received the drug via the intravenous route, compared to oral administration [10]. A recent restrospective study on a group of 239 patients revealed that observed hypersensitivity reactions included anaphylaxis, non-allergic immediate hypersensitivity and delayed reactions [11]. Immediate hypersensitivity is most probably driven by IgE-mediated mechanism leading to cutaneous, respiratory, cardiovascular and gastrointestinal symptoms [12]. As such, it could be assessed using skin prick tests – an efficient method for *in vivo* detection of IgE-mediated reactions. In a case report by Arslan et al., a skin prick test of hypersensitive patient resulted in positive result (even in case of 1/10 metamizole dilution) with irritant reactions excluded. However, the authors underlined that metamizole was not purified [11]. Another study on 16 subjects with confirmed immediate hypersensitivity to metamizole revealed that not only metamizole but also its metabolites can induce specific basophil activation leading to allergic reaction. As a result, introducing pyrazolone metabolites to basophil activation tests significantly improved the diagnosis of metamizole hypersensitivity [13].

Conclusion

Metamizole is a commonly used analgesic and antipyretic drug, available in Poland as an OTC oral preparation. Its toxicity is associated primarily with agranulocytosis, while allergic reactions may be another serious adverse effect. The literature data indicate that this complication may appear after the first dose of the drug, but may also occur during long-term treatment. Therefore, a detailed medical history regarding any previous allergic reactions to drugs and observation of the patient after administration of the drug are crucial elements of improving the safety and effectiveness of patient's treatment.

Conflict of interest
None

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