

Meloxicam-Associated Anaphylactic Reaction

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Abstract. Anaphylactic reaction to meloxicam has never been reported to date. We report 2 cases of meloxicam-induced anaphylactic reaction with no sensitivity to another selective cyclooxygenase 2 inhibitor. A thorough drug allergy work-up should be done before other cyclooxygenase inhibitors are prescribed.

Key words: Anaphylactic reaction. Meloxicam.

Resumen. Hasta la fecha, no se ha informado sobre reacciones anafiláticas al meloxicam. Confirmamos 2 casos de reacción anafilática inducida por meloxicam sin sensibilidad a otro inhibidor selectivo de la ciclooxigenasa 2. Se recomiendan pruebas minuciosas de alergia a medicamentos antes de prescribir otros inhibidores de ciclooxigenasa.

Palabras clave: Reacción Anafilática. Meloxicam.

Introduction

The anti-inflammatory action of acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) is ascribed to the inhibition of cyclooxygenase (COX) 2, whereas adverse events such as respiratory reactions are mediated through inhibition of COX-1. Therefore, a new class of COX-2 selective drugs may be well tolerated in patients with ASA intolerance [1]. A number of studies have already demonstrated the safety of COX-2 selective inhibitors (rofecoxib, celecoxib, valdecoxib) in patients with ASA-sensitive asthma, suggesting a lack of cross reactivity between COX-1 and COX-2 inhibitors in these patients [2-4]. There have been reports of skin reactions with these drugs in the patients with such reactions to ASA and other NSAIDs [2-5]. Although quite rare, systemic reaction to COX-2 selective inhibitors has also been observed. To date, 5 adverse reactions suggestive of anaphylactic shock associated with the use of celecoxib have been reported [6-10].

The preferential COX-2 inhibitors meloxicam and nimesulide have also been implicated in respiratory and/or urticaria/angioedema type hypersensitivity reactions [2, 11-14]. Additionally, anaphylactic type systemic reaction following nimesulide intake has been demonstrated in one case [13]. However, thus far, no anaphylactic reaction to meloxicam has been reported. We report 2 cases of meloxicam-induced grade 3 anaphylactic reactions with

evidence of sensitivity to ASA but no sensitivity to other selective COX-2 inhibitors.

Case Descriptions

Case 1

A 26-year-old woman was admitted to our clinic with a runny nose, nasal blockage, sneezing, and ocular watering, itching, and redness in March 2004. These complaints had been continuing for 4 years and were more frequent between April and September. When the patient was further questioned, she defined 3 episodes of allergic reactions following drug intake. The first reaction had occurred 4 years earlier after use of levofloxacin (Cravit, 500 mg, Daiichi-Fako, Istanbul, Turkey). Ten minutes after taking a dose of levofloxacin, numbness developed in her tongue and lips, followed by facial and body swelling. She said that she could not swallow or breathe because of the swelling in her throat. She went immediately to an emergency service and was given oxygen treatment and medications, the names of which she could not recall. Her dyspnea was relieved within 15 minutes, but she had to use antihistamines for a week for the facial and body swelling. The second and third drug reactions occurred with antibiotic use 3 years and 1 year earlier, but the patient could not recall the names of the 2

drugs involved. As in the first reaction, those episodes were also marked by facial and body swelling and throat swelling. After 10 to 15 minutes, she had difficulty swallowing and was short of breath. Emergency care was required.

She had never experienced angioedema or dyspnea apart from these episodes and the only known medical disease was migraine. However, she was afraid of taking analgesics because of the drug reactions.

On physical examination, the patient appeared healthy and well nourished. The findings of physical examination were unremarkable. Skin prick tests were positive to pollen and cockroach. Pulmonary function tests were normal. A nonspecific bronchial provocation test to methacholine was negative.

Taking into account the patient's need for analgesics to treat migraine attacks and also a possible need for antibiotic treatment, oral provocation tests (OPTs) were performed with celecoxib (Celebrex 100 mg; Pfizer; Istanbul, Turkey) and clarithromycin (Klacid 500 mg; Abbott; Istanbul, Turkey) according to the single-blind, placebo-controlled method used in our previous study [2]. The challenge protocol consisted of oral administration of drug in increasing doses. On two separate days, placebo (lactose) and one-quarter and three-quarter doses of the active drug (celecoxib or clarithromycin) were given at 2-hour intervals, and there was a washout period of at least 3 days between the two drugs. If no reaction developed the tests were considered negative. The patient was informed of drug allergies and the use of these drugs.

A year later, in March 2005, the patient was referred to our clinic again for an alternative analgesic since Celebrex had been withdrawn from use in our country. She had used Celebrex 5 times in the past year without any symptoms but she had had no occasion for antibiotic use.

This time OPT with meloxicam (Melox 7.5 mg; Nobel; Düzce, Turkey) was planned according to the same method [2]. During the first day no reaction developed with placebo. On the second day, blood pressure was 110/70 mmHg, pulse rate was 72 beats/min, and forced expiratory volume in 1 second (FEV₁) was 2.95 L (87% of predicted) prior to the OPT. These values were consistent with the findings of the first test day. Twenty minutes after the first drug dose (a quarter of the usual dose), the patient developed nausea, shivering, dizziness, itching on palms, erythema on arms, and the feeling of something being stuck in her throat. Blood pressure was measured as 150/90 mm Hg, the pulse rate was 76 beats/min, and her temperature was 36.5°C. The only abnormal finding on physical examination was cyanosis of the finger tips. FEV₁ was 2.16 L (26% decrease from baseline). The patient was treated with 40 mg of intravenous methyl prednisolone, 45.5 mg of intramuscular pheniramine maleate and 2.5 mg of salbutamol via nebulizer. Fifteen minutes later, she still felt as if something was stuck in her throat, though the sensation had decreased; when 0.2 mg of subcutaneous adrenalin was administered, blood

pressure was 130/80 mm Hg, pulse rate was 76 beats/min, and FEV₁ had increased to 2.88 L. All symptoms completely disappeared within an hour, and she was discharged after 24 hours of observation.

Case 2

A 26-year-old female diagnosed with bilateral nasal polyps and nonatopic asthma has been treated at our clinic since 1998. She was on regular treatment with inhaled and nasal corticosteroids. She described two episodes of asthma attack after taking ASA and metamizol. Her first reaction to ASA was in 1996. One hour after taking 500 mg of ASA, she developed a severe asthma attack associated with rhinoconjunctivitis. She was admitted to the emergency service and recovered fully after systemic administration of steroids, bronchodilators, and antihistamines. To confirm ASA intolerance, an OPT was performed according to the method described by Szczeklik et al [15]. During the OPT, bronchospasm occurred at a 188 mg cumulative dose of ASA, and the concentration provoking a 20% decrease in FEV₁ was calculated to be 130 mg. The patient's total score for extrabronchial symptoms such as rhinorrhea, nasal congestion, ocular itching and congestion and sneezing reached 10 when each was scored on a scale of 0 to 4 (0, no symptom; 1, symptom of slight intensity; 2, moderate intensity; 3, strong intensity; 4, very strong intensity). A second OPT was performed with rofecoxib (Vioxx 12.5 mg; Merck, Sharp & Dohme; Istanbul, Turkey) to find a safe alternative analgesic according to the method used in our previous study [2]. No symptoms occurred with the drug, a diagnosis of ASA allergy was recorded, and Vioxx was prescribed.

During a follow-up visit in March 2005, since Vioxx had been withdrawn from the use, an OPT with meloxicam (Melox 7.5 mg; Nobel; Düzce, Turkey) was carried out. She had used Vioxx many times without any symptoms. On the first test day, no reaction developed with placebo. On the second day, blood pressure was 100/90 mm Hg, pulse rate was 78 beats/min, and FEV₁ was 2.76 L (85% of predicted) when the meloxicam started. Those values were consistent with those observed a day earlier. An hour after the first dose, the pulse rate was 76 beats/min and FEV₁ was 2.65 L. The second dose was given, and 20 minutes later, the patient developed progressive dyspnea and generalized flushing. Blood pressure was 100/80 mm Hg, pulse was 84 beats/min, and FEV₁ was 1.86 L (33% reduction from the baseline). Bilateral rhonchi were present during the physical examination. We administered 40 mg of intravenous methyl prednisolone, 45.5 mg of intramuscular pheniramine maleate and 2.5 mg of salbutamol via nebulizer. Her symptoms disappeared and FEV₁ increased to 3.01 L within 60 minutes. The patient was discharged with recommendations after 24 hours of observation in the hospital.

Discussion

COX-2 inhibitor-related anaphylaxis is a difficult problem. It is possible that the COX-2 inhibition-induced cutaneous or systemic reaction in patients with or without ASA or NSAID sensitivity is different from that of the ASA-sensitive asthma in which respiratory reactions are triggered by COX-1 inhibitors [16].

We made some important observations from these cases. First, we could not attribute the reaction to the drugs' COX-2 inhibitory activity, because the patients could tolerate the selective COX-2 inhibitors celecoxib and rofecoxib without showing any difficulty of any sort. Second, it is considered that single NSAID-induced reactions are probably IgE-mediated and require prior sensitization [16]. If a patient does not have any underlying disease such as ASA-induced asthma or chronic idiopathic urticaria, the patient is more likely to experience a single-drug IgE-mediated reaction [1, 16]. Sensitization to selective COX-2 inhibitors has occurred during re-exposure, and later doses of the drugs have caused urticaria and anaphylaxis, indicating a role for IgE mediated reaction [5, 8, 10]. The preferential COX-2 inhibitors meloxicam and nimesulide are known to have the capacity to induce IgE-mediated hypersensitivity reactions [1]. Our patients had never been exposed to the meloxicam previously and therefore could not have been sensitized de novo before this challenge. However, unrecognized prior exposure to similar chemical structures can not be ruled out. We did not perform skin testing or immunoassays for IgE antibodies to meloxicam because no standardized kits or skin test reagents are available for this drug. Skin prick and intradermal tests done according to the general principles of the European Network for Drug Allergy could have been useful to evaluate such patients [17], however. Accordingly, skin prick tests with celecoxib and rofecoxib were performed on a patient who developed generalized urticaria and angioedema following oral intake of rofecoxib, and negative results were reported [5].

Nor can we explain the reactions as vasovagal ones due to the fear of the challenge procedure, because the first patient had had drug challenge experiences twice prior to the meloxicam challenge and she was quite familiar with the procedure. Moreover, she had hypertension during the systemic reaction. The second patient had also been challenged with rofecoxib and ASA prior to the meloxicam challenge. Subsequent rechallenge with rofecoxib or celecoxib to validate the results of the first challenge has been suggested in case of urticaria and angioedema induced by these drugs [18], but considering the severity of the 2 reactions, we did not rechallenge either patient with meloxicam.

Finally, the COX-1 inhibitor activity of meloxicam is the mechanism that best explains the cases we report. The drug preferentially inhibits COX-2 at lower doses, but a high enough concentration of it inhibits the COX-1 enzyme. Theoretically, the induction of an anaphylactic

reaction to the first exposure to a COX-2 inhibitor is possible if there is ASA intolerance [1]. Our second patient had such ASA intolerance, but the first patient was quite reluctant to accept a challenge with ASA. She reported 3 episodes of anaphylaxis with antibiotics. Recent studies have demonstrated that atopy and a history of allergic reactions to antimicrobial drugs increase the likelihood of intolerance of NSAIDs [19, 20]. Considering the first patient's history, we may speculate that she may also have ASA intolerance although we were not able to conduct an OPT for ASA.

In conclusion, these cases demonstrated that selective inhibition of the COX-2 enzyme can not rule out the possibility of adverse reactions, including severe systemic reaction. Therefore, a thorough drug allergy work-up should be done before prescribing other coxibs.

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