

Celecoxib-Associated Anaphylaxis

Kevin W Chamberlin and Adam R Silverman

Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) are well described in the literature as producing anaphylactoid reactions.¹ Such reactions are not considered to be due to immunoglobulin E (IgE) mechanisms and can produce symptoms including pruritus, bronchospasm, and angioedema.²

Literature reports of cyclooxygenase 2 (COX-2) inhibitor-associated anaphylactoid reactions are rare, in comparison with its COX-1 inhibitor counterparts.³⁻⁷ Celecoxib is a COX-2 receptor inhibitor commonly used to treat inflammatory-related pain symptoms and various other diagnoses.⁸ We report a case of anaphylaxis associated with celecoxib in a young patient with no history of allergy to aspirin, NSAIDs, or sulfa-containing compounds.

Case Report

A 27-year-old white man with significant medical history for a bicuspid aortic valve, seasonal rhinitis, and symptomatic, intermittent low back and right hip pain was referred to a proctologist for relief of a pilonidal cyst. Magnetic resonance imaging (MRI) incidentally revealed a disc protrusion at L5/S1, which was considered to be the likely cause of the periodic lower back and hip pain. Allergies to penicillin (anaphylaxis at age

OBJECTIVE: To report and discuss a case of anaphylaxis in a young, healthy white male taking celecoxib for intermittent lower back pain.

CASE SUMMARY: A healthy 27-year-old man with a documented history of anaphylaxis to penicillins and macrolides presented to the emergency department (ED) in anaphylactic shock after ingesting a 200-mg capsule of celecoxib and a cup of orange juice. The patient had been taking celecoxib over the past 6 months, for 1–2 weeks at a time, for low back pain secondary to a pilonidal cyst and an L5/S1 bulging disc. The day of admission was the seventh day of the most recent course of twice-daily celecoxib. The patient initially self-treated the reaction with diphenhydramine and subcutaneous epinephrine that he had at home due to his history of drug- and bee sting-induced anaphylaxis; neither intervention improved his symptoms. He became profoundly diaphoretic and developed systemic swelling, shortness of breath, bradycardia, and hypotension. Emergency medical services transported the patient to the ED, where he was treated appropriately and the symptoms resolved. However, 4 hours later, at time of discharge from the ED, the symptoms recurred. He was admitted to the intensive care unit and monitored for 3 days. Supportive care, steroids, and histamine blockade provided resolution of the symptoms. Cardiac workup was initiated because of the recurrence and severity of bradycardia and hypotension; results of the workup were unremarkable. The patient was discharged in stable condition.

DISCUSSION: This case demonstrates rare anaphylaxis to celecoxib in a patient who had previously taken the drug and who had documented tolerance to sulfonamide antibiotics. Despite this history, our patient developed type V immunoglobulin E-mediated anaphylaxis secondary to the sulfonamide component of celecoxib. This reaction was considered probable according to the Naranjo probability scale. A review of published case reports and related allergy literature for celecoxib allergenicity revealed that such reactions are rare. This is the first case report with great detail of a patient with anaphylaxis to celecoxib after having previously tolerated the medication.

CONCLUSIONS: Celecoxib can produce an anaphylactic reaction in patients who have previously tolerated sulfonamide antibiotics and who have previously tolerated celecoxib. This case also reviews the potentially biphasic presentation of anaphylaxis. Clinicians need to be aware of this biphasic anaphylactic response to ensure optimal duration of evaluation.

KEY WORDS: anaphylaxis, celecoxib, cyclooxygenase-2 inhibitor.

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Author information provided at the end of the text.

7), macrolides (anaphylaxis at age 13), and bee stings were reviewed with the patient and a 1-month prescription, with refills, for celecoxib 200 mg twice daily as needed was written for reduction of the inflammation related to both the pilonidal cyst and the herniated disc.

The patient used celecoxib continuously for 6 months. Additionally, he reported having taken celecoxib intermittently over the next 6 months for 1–2 weeks duration over the course of a year because of several recurrences of symptoms. Concurrent medications included aspirin 81 mg once daily and fexofenadine/pseudoephedrine 60 mg/120 mg once or twice daily during spring and summer. The patient's community pharmacy record showed evidence of past use of trimethoprim/sulfamethoxazole for an upper respiratory infection. This was apparently taken without incident. Approximately 12 months after the original celecoxib prescription was dispensed, the final refill was dispensed for a flare of the back symptoms. Seven days prior to picking up the final celecoxib refill, the patient reported having discontinued use of fexofenadine/pseudoephedrine secondary to the start of autumn.

On the seventh day of the most current use of celecoxib, the patient arose at approximately 0900 hours and reported taking one celecoxib 200-mg capsule with a cup of orange juice and placed a new, unworn baseball cap on his head. Ten minutes later, the patient complained to his spouse of intense pruritus, erythema, and swelling of his hands and feet. He took 25 mg of liquid diphenhydramine without effect. As the symptoms persisted, he became worried of possible topical exposure to an irritant and subsequently took a shower. Within 30 seconds of being exposed to the warm water, the patient developed worsening whole-body swelling, including his tongue and lips. He left the shower and self-administered subcutaneous epinephrine while his wife called emergency medical services (EMS). In the subsequent 7 minutes it took for paramedics to arrive, the patient's symptoms worsened and throat swelling minimized his ability to talk. He subsequently became profoundly weak and diaphoretic.

Upon arrival, EMS found a conscious, diaphoretic, dyspneic male with swollen extremities and facial features, having difficulty talking. As paramedics began examining him, the patient's heart rate dropped to 40 beats/min and his blood pressure was 60/40 mm Hg. EMS administered 50 mg of intravenous diphenhydramine, placed the patient on a heart monitor, and transferred him to an acute care medical facility. In the emergency department, his blood pressure was 80/40 mm Hg and he received intravenous doses of epinephrine 0.3 mg, diphenhydramine 25 mg, methylprednisolone 125 mg, and famotidine 20 mg. Ten minutes later, his blood pressure dropped lower and his heart rate was in the low 40s. The patient was pale and was having near-syncopal symptoms. He was administered 1 L of intravenous fluid and recovered after 3 minutes. Four hours later, as the attending physician was discussing dis-

charge instructions with the patient, a similar cardiac response was noted as the patient became hypotensive, bradycardic, pale, and diaphoretic. He also vomited. He was subsequently admitted to the intensive care unit for 3 days for further observation and a cardiac workup. The results of this workup were essentially negative, with the exception of an echocardiogram that showed mild aortic stenosis, which was felt to be nonetiologic in this patient's presentation. He was discharged on a slow tapering regimen of prednisone, with diphenhydramine and fexofenadine to be taken as needed. The patient then followed up with an outpatient allergy practice that confirmed via skin and systemic methods no allergenicity of aspirin, NSAIDs, oranges, or the baseball cap.

A causal relationship assessment between celecoxib therapy and the occurrence of anaphylaxis, assessed using the Naranjo probability scale, was scored as probable.⁹

Discussion

Anaphylaxis, a severe systemic hypersensitivity reaction, is characterized by multisystem involvement that may include hypotension or airway compromise and can be life-threatening. Anaphylaxis is a cascade of events resulting from the release of mediators from mast cells and basophils in an IgE-dependent fashion.¹⁰ Anaphylaxis to sulfa-containing medications is well described throughout the literature; however, not all compounds with a sulfa moiety precipitate anaphylaxis.

Many drugs contain a sulfonamide moiety; however, several structural differences exist among the sulfonamides. One major difference between sulfonamide antimicrobials (eg, sulfamethoxazole) and other sulfonamide-containing agents (eg, furosemide, hydrochlorothiazide) is the presence of an aromatic amine (arylamine) group at the N4 position.^{11,12} This structural difference is the basis for classification of the sulfonamides into either aromatic or nonaromatic amines.

Celecoxib is a nonarylamine benzenesulfonamide derivative and does not contain a heterocyclic ring attached to the sulfonamide-N1 position, nor does it contain an N4 aromatic amine group.⁸ Research on celecoxib debates the incidence of celecoxib-induced allergic reactions in patients with or without a history of hypersensitivity to sulfonamides.^{13–17} Verdel et al.¹⁸ suggest that sulfonamide antibiotics probably do not cross-react with sulfonamide nonantibiotics, which confirms the findings of Johnson et al.¹⁹ in their extensive literature review, including COX-2 inferred sulfonamide reactions. Of note, our patient had past evidence of tolerance to sulfonamide antibiotics; however, the package insert of celecoxib describes the drug as a sulfonamide with the potential for skin reactions that can occur without warning in patients with no history of a sulfa allergy.⁸

Despite a history of tolerance to sulfonamide antibiotics in the past, it appears that our patient had a type V IgE-mediated anaphylaxis secondary to the sulfonamide component of celecoxib. IgE-mediated reactions require previous sensitization. Our patient's exposure to celecoxib, hiatus from use, and subsequent restart likely resulted in his being sensitized, as we know it was not from previous NSAID exposure, because cross-reactivity to NSAIDs with chemically distinct structures does not occur.^{20,21} Our patient's reaction was likely not type I, II, or III, because those reactions exhibit cross-reactivity to other NSAIDs. While type IV and type V reactions do not require cross-reactivity between NSAIDs, our patient developed anaphylaxis, which is a type V reaction.

Celecoxib is metabolized through the CYP2C9 pathway. The orange juice that the patient consumed for breakfast is a mild inhibitor of that enzyme. While doubtful, given the mild inhibition of the CYP2C9 isoenzyme by the orange juice and the small quantity ingested, the orange juice could have reduced the amount of drug that was metabolized and subsequently increased circulating concentrations of celecoxib.²²

Levy and Fink⁶ described the case of a 55-year-old woman who experienced an anaphylactic reaction after ingesting a single dose of celecoxib. This case was similar to our own in that the patient ingested the single dose after a 3-month hiatus of celecoxib therapy. The authors went on to report that the patient had taken a 1-month course of celecoxib approximately 6 months prior to the reported event. The authors stated that within 15 minutes of ingesting the medication, the patient developed palmar itching and edema, with subsequent erythema, pruritic rash, shortness of breath, throat tightness, and nausea. She then became lightheaded and collapsed. She was profoundly hypotensive, with a measured blood pressure of 70/0 mm Hg. Laboratory test results showed a low potassium level of 2.8 mEq/L. The patient is said to have responded to epinephrine, steroids, and fluid resuscitation with potassium corrections. Enzyme-linked immunoassay was performed to attempt to demonstrate an IgE mechanism, but the authors stated, without explanation, that the method was unsuccessful. Skin testing to inhalants and foods were negative, and oral rechallenge was considered too risky to the patient.

Shapiro et al.¹² evaluated cross-reactivity between sulfonamide antimicrobials and celecoxib in a small pilot study. Of 28 immunocompetent patients enrolled (26 women, mean age 60 y), 6 proved to be positive to skin prick or in vitro testing to sulfamethoxazole sensitivity. All 28 patients had a reported allergy to sulfonamide antimicrobials and all tolerated celecoxib 10 mg orally followed by 100 mg orally 60 minutes later without adverse effects. While the study was small, the results do lend support to the hypothesis that the aromatic amine group in sulfonamide antimicrobials, which is not pre-

sent in celecoxib, indicates that cross-reactivity would be rare.

Also of clinical interest is our patient's profound bradycardia at presentation and persistence of bradycardia despite therapeutic adrenergic stimulation. Although atypical, bradycardia in the face of a profound anaphylactic response has been described and is most likely due to a marked increase in vagal tone.²³ Lastly, our case demonstrates the potential biphasic nature of anaphylactic reactions: recurrence of anaphylactic symptoms can develop from 4 to 72 hours after the resolution of presenting symptoms, in up to 20% of cases.²⁴

Several questions remain unanswered in this case. What role could the recent discontinuation of fexofenadine have had in this patient's presentation? Could discontinuation of this second-generation antihistamine have unmasked a smoldering, subclinical allergic response? We failed to identify a causal relationship between the presence of this patient's environmental allergies (as evidenced by his use of fexofenadine) and a direct increased risk of drug allergies. Was this patient simply more prone to allergic reactions secondary to his reported multiple antibiotic allergies? Strom et al.²⁵ suggested this in their study looking at the association between prior penicillin allergy and subsequent reaction to nonantibiotic sulfonamides (celecoxib was not specifically studied). Multiple antibiotic allergy syndrome was also considered for our patient. While there is the belief that multiple drug allergies increase a patient's risk for developing other drug allergies, Macy²⁶ suggests that this cannot be definitively confirmed or refuted because of poor data collection and lack of prospective studies on the topic, as well as overall poor allergy testing. Additional literature review suggests some possible association between different drug classes, but fails to conclusively support that our patient's anaphylactic reaction to celecoxib could have been predicted with any certainty.^{27,28}

After a hiatus between scheduled, daily use, and subsequent as needed dosing of celecoxib, a 27-year-old otherwise healthy male had a probable serious anaphylactic reaction to the nonantibiotic sulfonamide, celecoxib. This case outlines the importance for clinicians to be aware that such serious reactions can occur in patients who might otherwise be considered nonrisk and that the duration of the reaction can vary greatly among individuals.

Kevin W Chamberlin PharmD, Assistant Clinical Professor of Pharmacy Practice, School of Pharmacy, University of Connecticut and Department of Pharmacy, University of Connecticut Health Center, Farmington, CT

Adam R Silverman MD FACP, Chief, Division of General Internal Medicine, University of Connecticut Health Center; Associate Professor of Medicine, School of Medicine, University of Connecticut

Reprints: Dr. Chamberlin, Department of Pharmacy, MC2205, University of Connecticut Health Center, 263 Farmington Ave., Farmington, CT 06030, fax 860/679-1231, chamberlin@uchc.edu

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Hipersensibilidad a Celecoxib

KW Chamberlin y AR Silverman

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EXTRACTO

OBJETIVO: Describir y analizar un caso de choque anafiláctico en un paciente joven de raza blanca bajo tratamiento con celecoxib para una lumbalgia intermitente.

RESUMEN DEL CASO: Un hombre sano de 27 años con antecedentes documentados de hipersensibilidad a penicilinas y macrólidos se presentó en el servicio de urgencias con un choque anafiláctico tras haber ingerido una cápsula de 200 mg de celecoxib y un vaso de zumo de naranja. El paciente había estado tomando celecoxib durante los últimos 6 meses en períodos de 1 a 2 semanas por una lumbalgia secundaria a un quiste pilonidal y a una hernia discal en L5/S1. El día de ingreso constituía el séptimo día de la última tanda del tratamiento con celecoxib, cuya pauta posológica era de 2 comprimidos diarios. El paciente se medicó inicialmente con difenhidramina y una epi-pen (auto inyección de epinefrina) que tenía en casa de medicaciones anteriores por haber sufrido en el pasado un choque anafiláctico inducido por una picadura de avispa, pero esta medicación no resultó efectiva. El paciente comenzó a sudar de forma excesiva, a presentar inflamación sistémica, disnea, bradicardia, e hipotensión. Los servicios médicos de urgencias transportaron al paciente hasta el hospital donde fue tratado adecuadamente y los síntomas remitieron. No obstante, 4 horas después de abandonar el servicio de urgencias, los síntomas reaparecieron. Posteriormente, el paciente ingresó en la unidad de cuidados intensivos donde fue vigilado durante 3 días. Los síntomas remitieron con esteroides, antihistamínicos y cuidados adicionales. Se realizó un estudio diagnóstico del corazón debido a la recurrencia y la gravedad de la bradicardia y la hipotensión, pero no se encontró nada destacable. El paciente recibió el alta estando estable.

DISCUSIÓN: Este caso demuestra una hipersensibilidad rara al celecoxib en un paciente que había tomado previamente el fármaco y que había demostrado una tolerancia documentada a las sulfonamidas. A pesar de estos antecedentes, el paciente sufrió un choque anafiláctico mediado por IgE tipo V, provocado por el componente sulfonamida de celecoxib. Esta reacción se consideró probable según la escala de probabilidad de Naranjo. El análisis de los casos publicados y de la literatura relacionada sobre la alergenidad de celecoxib reveló que dichas reacciones son raras. Se trata del primer caso clínico descrito con gran detalle de un paciente con hipersensibilidad a celecoxib después de haber tolerado previamente la medicación.

CONCLUSIONES: Celecoxib puede producir una reacción de hipersensibilidad en pacientes que han tolerado previamente antibióticos con sulfonamidas y que han tolerado previamente celecoxib. Este caso también analiza la presentación bifásica potencial de la hipersensibilidad. Los médicos deben conocer esta respuesta bifásica de la hipersensibilidad para garantizar una duración óptima de la evaluación.

Traducido por Violeta Lopez Sanchez

Anaphylaxie Associée au Célécoxib

KW Chamberlin et AR Silverman

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RÉSUMÉ

OBJECTIF: Signaler et discuter d'un cas d'anaphylaxie survenue chez un jeune caucasien en santé prenant du célécoxib pour soulager une douleur intermittente dans le bas du dos.

PRÉSENTATION SOMMAIRE DU CAS: Un homme âgé de 27 ans ayant déjà présenté une anaphylaxie aux pénicillines et aux macrolides se présente à l'urgence en choc anaphylactique après avoir ingéré une capsule de 200 mg de célécoxib et une tasse de jus d'orange. Durant les 6 derniers mois, le patient a ingéré du célécoxib à différentes reprises pendant 1 à 2 semaines pour soulager une douleur dans le bas du dos associée à un kyste pilonidal et à une hernie discale L5/S1. Le jour de l'admission, le patient en est à sa septième journée de prise de célécoxib 2 fois par jour. Le patient s'est traité lui-même avec de la diphenhydramine et de l'épinéphrine en injection qu'il conservait chez lui étant donné ses antécédents d'anaphylaxie associée à la médication et aux piqûres d'abeille. Aucune des 2 interventions n'a amélioré ses symptômes. Il présente une diaphorèse importante, un œdème généralisé, un souffle court, de la bradycardie, et de l'hypotension. Les ambulanciers le transportent à l'urgence où il reçoit les soins appropriés conduisant à une résolution des symptômes. Cependant, 4 heures plus tard, alors que l'on s'apprête à libérer le patient de l'urgence, les symptômes réapparaissent. Le patient est alors admis à l'unité des soins intensifs et est surveillé pendant 3 jours. Des soins de support, des corticostéroïdes, et des antihistaminiques réussissent à enrayer les symptômes. Une évaluation de la fonction cardiaque est initiée étant donné la récurrence et la gravité de la bradycardie et de l'hypotension; aucun problème n'est détecté. Le patient est libéré lorsque sa condition est stabilisée.

DISCUSSION: Ce cas illustre la survenue rare d'une anaphylaxie associée au célécoxib chez un patient qui a déjà pris le médicament et qui n'a pas d'histoire de non tolérance aux antibiotiques de type sulfamidé. Malgré tout, le patient présente une anaphylaxie (impliquant des IgE) associée à la composante sulfamidé du célécoxib. Avec l'échelle de Naranjo, on obtient un lien probable entre cette réaction et le célécoxib. La révision des rapports de cas et de la documentation traitant de l'allergénicité du célécoxib révèle que de telles réactions sont rares. Il s'agit du premier cas signalé d'un patient ayant présenté une anaphylaxie associée au célécoxib après avoir précédemment toléré cette médication.

CONCLUSIONS: Le célécoxib peut produire une réaction de type anaphylactique chez des patients qui ont précédemment toléré des antibiotiques de type sulfamidé et qui ont aussi précédemment toléré le célécoxib. Ce cas rappelle aussi la présentation bi phasique potentielle de l'anaphylaxie. Les cliniciens doivent être conscients de cette réponse anaphylactique bi phasique possible pour assurer un suivi d'une durée optimale.

Traduit par Marie Larouche

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