

Single nonsteroidal anti-inflammatory drug induced serum sickness-like reaction to naproxen in a patient able to tolerate both aspirin and ibuprofen



Rebecca Koransky, MD^a, Denisa Ferastraoaru, MD, MSc^b, and Elina Jerschow, MD, MSc^b

Clinical Implications

- This case is a unique presentation of a serum sickness-like reaction to a single nonsteroidal anti-inflammatory drug (NSAID). After reaction, patients may still be able to safely tolerate other NSAIDs.

TO THE EDITOR:

Serum sickness is a hypersensitivity condition characterized as a type III, or immune complex-mediated, reaction. This reaction was initially described in patients who received heterologous proteins as treatment for diphtheria. After treatment, patients developed a syndrome of fever, rash, and arthralgias.¹

Serum sickness-like reaction is a related condition that presents with similar clinical symptoms in response to medication administration. These symptoms usually arise 7 to 10 days after the medication is started, but can occur earlier in sensitized patients.^{2,3} Common laboratory findings include neutropenia, thrombocytopenia, elevated inflammatory markers like C-reactive protein (CRP), and an elevation in transaminases.^{1,2} Symptoms usually resolve after discontinuation of the medication, but some patients may also need a short treatment with oral corticosteroids.² This reaction has been described for many different medications, including antibiotics like cefaclor and penicillin.

Less is known about serum sickness-like reactions to nonsteroidal anti-inflammatory drugs (NSAIDs), and to our knowledge, NSAID-induced serum sickness-like reactions have not been reported. We present a case of a patient who was able to tolerate aspirin and ibuprofen, but developed a serum sickness-like reaction to naproxen.

The patient is a 61-year-old woman with hypertension, diabetes, and cervical radiculopathy who was prescribed naproxen and cyclobenzaprine for pain control. Seven days after starting the new medications, the patient developed an urticarial rash, and 3 days later, she developed severe polyarthritides, fever, and myalgias. Laboratory results showed an elevated CRP of 7.98 mg/dL from a baseline of 0.2 mg/dL (normal < 0.1 mg/dL). The patient was diagnosed with serum sickness-like reaction to either naproxen or cyclobenzaprine and was instructed to avoid both medications and all NSAIDs in the future.

Three years after the initial presentation, the patient presented to our clinic wanting to know if she could tolerate other NSAIDs. She underwent successful aspirin and ibuprofen challenges in our office in separate visits 3 weeks apart and then continued aspirin 81 mg daily and ibuprofen 400 mg as needed. Complement levels, CRP, basic metabolic panel, complete blood

count, and aspartate (AST) and alanine transaminases (ALT) were normal at each follow-up appointment.

Two months after it was established that the patient could safely tolerate aspirin and ibuprofen the patient requested a naproxen challenge. The naproxen challenge was initiated, and she tolerated 100 mg of naproxen daily for 7 days. Laboratory values while on 100 mg of naproxen included white blood cell count of 5.8 k/ μ L, platelets of 187 k/ μ L, AST of 20 U/L, and ALT of 35 U/L. Her dose of naproxen was increased to 250 mg at the subsequent visit to our office, and 3 days later she developed stiff neck, headache, myalgias, arthralgias, and a low-grade fever. Urticarial rash was not noted. Laboratory results 1 week after starting the 250 mg dose were significant for an elevated CRP to 1.6 mg/dL from a previous baseline of 0.1 mg/dL (normal < 0.8), lymphocytopenia (WBC 3.6 k/ μ L), thrombocytopenia (platelets 130 k/ μ L), and a mild transaminitis (AST 47 U/L, ALT 62 U/L). These findings resolved after naproxen discontinuation and a short steroid course of prednisone 60 mg for 4 days (Figure 1). The patient was advised to avoid naproxen in the future. She has been able to safely tolerate both aspirin and ibuprofen as needed since the challenge.

This case illustrates the clinical symptoms of a serum sickness-like reaction, and is a unique presentation of a patient who reacted to a single NSAID.

Type III reactions are mediated by immune complexes. When in excess, immune complexes deposit in tissues and joints and trigger an inflammatory response, leading to the clinical symptom of arthralgias and an associated increase in acute phase reactants.^{2,4}

A serum sickness-like reaction produces a similar clinical presentation as serum sickness, but the mechanism is likely different. It is thought that a serum sickness-like reaction is caused not by immune complexes, but by altered metabolism of the offending drug, resulting in toxic reactive intermediates.⁵

Little is known about NSAID-induced serum sickness-like reactions. Better known NSAID reactions include IgE-mediated, aspirin-exacerbated respiratory disease, and exacerbations of urticaria in chronic urticaria. These reactions vary in cross-reactivity between NSAID class members; IgE-mediated reactions are drug specific, whereas aspirin-exacerbated respiratory disease and urticaria exacerbation have COX-1 inhibitor cross-reactivity.⁴

No data are available about the existence or absence of cross-reactivity between NSAIDs in serum sickness-like reactions. It is interesting to note that nabumetone has a structurally similar active metabolite to naproxen: 6-methoxy-2-naphthyl-acetic acid.⁷ Perez-Ezquerria et al described a patient who tolerated aspirin but developed angioedema to both nabumetone and naproxen. The authors hypothesized that this reaction was drug-specific and not secondary to COX-1 inhibition. It is likely that nabumetone would produce similar symptoms of a serum sickness-like reaction in this patient.⁶

Naproxen is metabolized by undergoing demethylation and/or esterification with glucuronide.⁷ Approximately 70% is metabolized to the active metabolite naproxen glucuronide. This metabolite was found to cause immune thrombocytopenia in patients taking naproxen. Assays for platelet binding antibodies

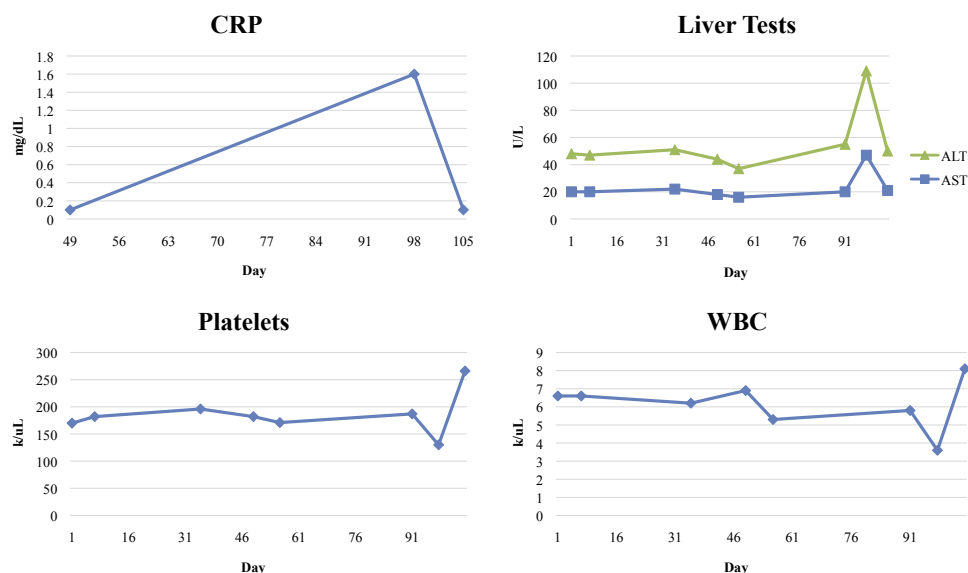


FIGURE 1. Laboratory values. Laboratory results from the first visit to our office through the follow-up visit after naproxen challenge. The 250 mg dose was given on day 91.

were negative with patient serum and naproxen, but positive with naproxen glucuronide.⁷

In the reported case, the different chemical structures and active metabolites of naproxen, ibuprofen, and aspirin likely influence the specific immune response, and may explain the sensitization to naproxen but not to aspirin or ibuprofen.

Another interesting aspect of this case is the possibility that the reaction was dose dependent. The patient developed symptoms after the dose was increased. She reacted on the tenth day after starting naproxen, which was the third day after the dose was increased. In studies of a cefaclor-induced serum sickness-like reaction, the onset of symptoms appeared after a mean time period of 7.4 days.⁵ This was the time necessary for accumulation of reactive cefaclor metabolites to produce the exposure needed for a reaction.⁵

To our knowledge, this is the first reported case of a single NSAID-induced serum sickness-like reaction. With this case report we would like to emphasize the fact that patients who previously developed a NSAID-induced serum sickness-like reaction may still be able to safely tolerate other NSAIDs following a thorough drug allergy evaluation.

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Corresponding author: Rebecca Koransky, MD, Department of Internal Medicine, Montefiore Medical Center, 111 East 210th St, Bronx, New York 10467. E-mail: rkoransk@montefiore.org.

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^aDepartment of Medicine, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

^bAllergy/Immunology Division, Department of Medicine, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

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