

Nitrate allergy and desensitization in a patient with refractory angina

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Clinical Implications

- Allergic reactions to nontransdermal formulations of nitrates are rare. To our knowledge, this is the first report of a successful isosorbide mononitrate desensitization protocol in a patient with refractory angina who experienced generalized maculopapular rash to multiple forms of nitrates.

TO THE EDITOR:

Approximately 3.4 million adults with coronary artery disease (CAD) experience angina each year.¹ Most patients can be adequately treated with a combination of beta blockers, calcium channel blockers, long-acting nitrates, or ranolazine.^{2,3} Short-acting nitroglycerin is indicated for all patients to provide rapid relief of anginal symptoms.^{2,3} Long-acting nitrates are often added on to beta blockers or calcium channel blockers when initial therapy with these agents is not effective or is poorly tolerated.^{2,3}

Refractory angina is significant in patients with advanced disease who are not candidates for further revascularization or who continue to experience debilitating symptoms despite optimal pharmacologic treatment. For patients with a nitrate allergy, acute and chronic management of angina can be limited. Although desensitization protocols for drugs such as penicillin exist, there is currently no accepted protocol for the desensitization of nitrates.

We report a case describing the development and successful implementation of a nitrate desensitization protocol for oral nitrates in a patient with severe refractory angina who experienced generalized morbilliform skin rash with nitroglycerin. Contact dermatitis or erythema to topical and transdermal nitroglycerin products are more common and have been described in the literature.^{4,5} Reactions to other nontransdermal nitrate formulations are rare but can result in more serious systemic reactions in some patients.^{5,6}

A 69-year-old man with significant CAD was admitted to the intensive care unit (ICU) to undergo nitroglycerin desensitization. The patient's past medical history included type 2 diabetes mellitus, hyperlipidemia, hypothyroidism, hypertension, and CAD with persistent, refractory angina requiring multiple prior admissions. His surgical history included a 4-vessel coronary artery bypass surgery. A documented allergy in the medical record of generalized pruritic maculopapular rash to multiple forms of nitrates including oral isosorbide mononitrate (ISMN), sublingual form, and transdermal patch prevented nitrate use. Despite receiving maximally tolerated doses of antianginal medications including metoprolol 100 mg twice daily, amlodipine 10 mg daily, and ranolazine 1000 mg twice daily, the

patient continued to experience significant angina affecting his quality of life.

The patient reported initial exposure to nitrate therapy during hospitalization for angina 9 years ago. He received sublingual nitroglycerin, and nitroglycerin paste was applied on his left shoulder. The next day, the patient complained of itching and burning on his left shoulder and back. There was erythematous maculopapular rash on the left shoulder at and around the site of the nitroglycerin patch as well as on his back, which lasted for 2 to 3 days. He did not experience angioedema or any other anaphylactic symptoms. This resulted in discontinuation of therapy and the patient was advised to avoid nitrates in the future. Six years later, he was started on ISMN 30 mg daily after onset of angina, resulting in the placement of a coronary artery stent at a different hospital. Approximately 12 hours later, the patient developed itching, rash, and redness over his chin, chest, abdomen, and back extending down to his waist area. There were no associated angioedema or anaphylactic symptoms. He was later evaluated by dermatology and noted to have a pink morbilliform rash on his flanks and abdomen. The rash resolved with the discontinuation of ISMN and treatment with Sarna lotion and oral diphenhydramine. The patient was again advised to avoid nitrate therapy. He continued to suffer with daily angina that resulted in frequent emergency department visits and hospitalizations and placement of 3 stents. To further optimize treatment, his cardiologist requested nitrate desensitization after the patient had been admitted for unstable angina that led to the placement of a fifth coronary artery stent.

A review of the medical literature did not reveal any published protocol, and therefore one was developed to assist with nitrate desensitization. The protocol would proceed as follows: on the day of desensitization, skin prick testing would be performed, followed by intradermal testing to determine whether an IgE-mediated allergy to nitroglycerin existed (Figure 1). If the prick test is negative, intradermal testing would begin with serial dilutions (0.2, 2, 20, and 200 mcg/mL) made from intravenous nitroglycerin 200 mcg/mL manufactured by Baxter (Orting, Wash). Dilutions were to be mixed with dextrose 5% in water to obtain 1:10, 1:100, and 1:1000 concentrations.

Intradermal testing would start with the injection of a control (normal saline with human serum albumin; Greer Laboratories, Lenoir, NC) and 0.2 mcg/mL of nitroglycerin followed by subsequent injections of nitroglycerin administered at concentrations of 2, 20, and 200 mcg/mL at 15-minute intervals. The patient would then begin desensitization with isosorbide dinitrate (ISDN) and ISMN. Administration of ISDN would be initiated with a 1 mg orally compounded dose, proceeding to 2, 5, 10, and 20 mg at 30-minute intervals. Successful titration of ISDN without any reaction would then allow the administration of ISMN 30 mg, followed by 60 mg 24 hours later (Figure 2).

Our patient was admitted to the ICU for nitrate desensitization. A crash cart was maintained at bedside in case of a severe reaction. On the day of desensitization, the patient underwent skin prick testing and was found to have a negative reaction to nitroglycerin 200 mcg/mL with a negative control and a positive histamine response (9 mm wheal and 30 mm flare). The patient was then

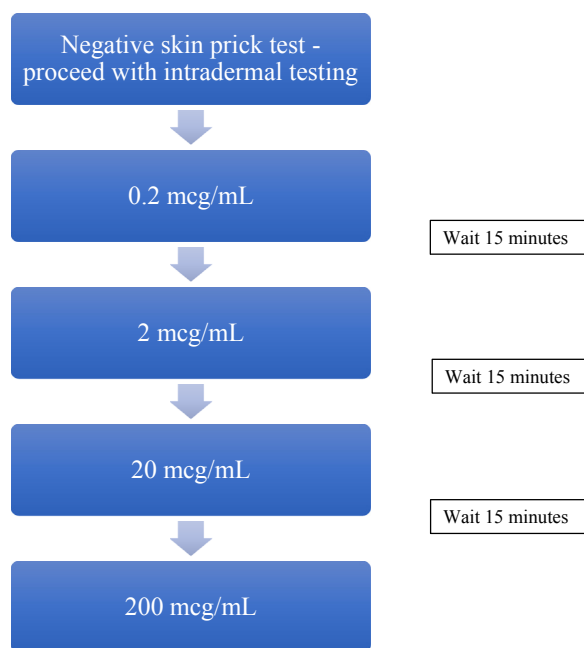


FIGURE 1. Phase 1: intradermal testing with nitroglycerin 200 mcg/mL.

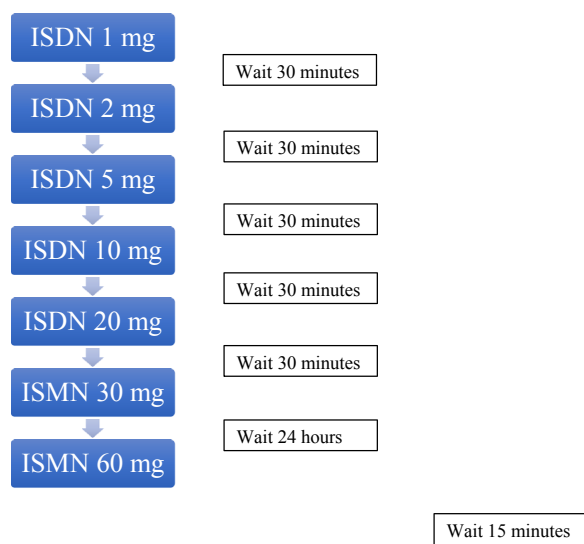


FIGURE 2. Phase 2: oral desensitization protocol. *ISDN*, Isosorbide dinitrate; *ISMN*, isosorbide mononitrate.

advanced for intradermal testing as previously described. Both the control and nitroglycerin concentration of 0.2 mcg/mL were injected intradermally. The patient developed a 6 mm wheal with no flare to the 0.2 mcg/mL nitroglycerin concentration and no reaction to the control after 15-minute intervals. No further intradermal testing was performed. There was no delayed intradermal reaction observed even up to 24- to 48-hour period after intradermal testing. The immediate reaction could be an irritant and/or local vasodilatory effect of nitroglycerin as there is no

standardized testing for nitroglycerin. Given the history of repeated maculopapular reactions, a delayed hypersensitive reaction to nitroglycerin was strongly suspected and decision to proceed with desensitization was made. The patient underwent desensitization according to the developed protocol and was able to tolerate ISMN ER 30 mg. The patient was transferred to the floor for 24 hours of observation. On day 2 of desensitization, ISMN 60 mg was initiated and he was able to tolerate it without any adverse events. He was discharged on ISMN 60 mg/day. Before discharge, the patient was counseled on the importance of uninterrupted therapy to ensure continued desensitization. To date, the patient continues to tolerate ISMN 60 mg/day.

Contact dermatitis to transdermal nitroglycerin is common, but allergic reactions to nontransdermal nitroglycerin formulations are extremely rare.⁵ This report demonstrates the successful desensitization of ISDN in a patient with a history of generalized maculopapular reactions to oral nitrates. Under the direction of allergy and immunology specialists in conjunction with clinical pharmacists, it is possible to safely perform nitroglycerin desensitization in patients with a history of nitroglycerin-induced allergic reactions.

The patient has not been readmitted for angina since desensitization 22 months prior, indicating that the addition of ISMN has improved his quality of life. The development of a nitrate desensitization protocol allows for standardization and improved safety for future use. Extrapolation of these results to more severe allergies such as anaphylaxis cannot be determined based on this case report.

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