

Allergic and nonallergic reactions to nitroglycerin

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ABSTRACT

Allergic and nonallergic reactions to nitroglycerin occur. The aims of this study were to review the different manifestations of nitroglycerin allergy, to explain how to evaluate for it, and to discuss its treatment. We reviewed relevant literature in peer-reviewed journals, computerized databases, and references identified from relevant bibliographics. Nitroglycerin's most common side effects are headache, facial flushing, head throbbing, fainting, hypotension, tachycardia, and syncope. The majority of reported skin reactions to topical and transdermal nitroglycerin products are irritant contact dermatitis, allergic contact dermatitis, and urticaria. Five cases of presumed allergic reactions to oral, sublingual, intravenous, or perianal nitroglycerin products have been described. Patch testing may be helpful in subjects with skin reactions to topical or transdermal nitroglycerin. In subjects with positive patch tests to nitroglycerin (allergic contact dermatitis), transdermal nitroglycerin patches and other topical nitroglycerin products should be avoided. Most patients with contact dermatitis to nitroglycerin have tolerated oral nitroglycerin, sublingual nitroglycerin, or oral isosorbide challenges.

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Nitroglycerin was discovered in 1847 by Sobrero.¹ In 1867, Alfred Nobel used nitroglycerin as an explosive in dynamite; the proceeds from this invention fund the Nobel prize.¹ Nitroglycerin was first used in 1879 for the treatment of angina² and was introduced in 1955 as a topical ointment.³

In 1898, nitroglycerin's effect on chemical workers was described.⁴ Some workers developed headaches, nausea, and vomiting while handling nitroglycerin, and some of the workers' wives experienced the same symptoms while washing their spouses' contaminated clothing. The author observed that it was "... not safe for one of these men to carry his infant in his arms for any length of time; he is sure to have a sick baby."⁴ He actually described the first case of skin manifestation to nitroglycerin as "... an eruption over the body like that from poison ivy. After three or four attacks he was compelled to abandon ... " working with nitroglycerin. A case report in 1949 described some pharmaceutical workers who developed rashes of variable severity from handling nitroglycerin.¹ The first contact skin reaction to topical nitroglycerin was reported in 1978.⁵

CASE

A 57-year-old white man presents with a history of a rash secondary to nitroglycerin. Seven years ago, he developed substernal chest pain that resulted in a myocardial infarction. During a 1-week hospitalization, he underwent angioplasty and received intravenous (i.v.),

and sublingual nitroglycerin, atenolol, ticlopidine, famotidine, aspirin, metoprolol, niacin, temazepam, heparin, and abciximab. At discharge, he was placed on a transdermal nitroglycerin patch, ticlopidine, atenolol, simvastatin, aspirin, and vitamin E. After wearing transdermal nitroglycerin for approximately 24 hours, he developed diffuse itchy "hives" without any local reaction around the nitroglycerin patch. He removed the patch, and the rash resolved within 12 hours.

Six years after the initial rash, he again developed substernal chest pain. He took two sublingual tablets of nitroglycerin. One hour later, he developed diffuse pruritus with generalized erythema that lasted 4 hours. He denied any other symptoms. The pruritus and erythema resolved without any further treatment.

METHODS

The patient underwent skin testing prepared from nitroglycerin (5 mg/mL) i.v. solution (Table 1). Each milliliter of the nitroglycerin solution contains 5 mg of nitroglycerin, 30% alcohol, and 30% propylene glycol. Both prick and intradermal skin testing were performed. A control subject who had never used nitroglycerin products also was skin tested. The subject and control had a positive prick puncture test to histamine, but the skin tests to nitroglycerin were negative in both.

The patient then underwent patch testing with Nitro-Bid ointment (nitroglycerin 2%, Fougere, Melville, NY), which contains glyceryl trinitrate 2%, lactose in lanolin, white petrolatum, and a purified water base. Full strength of the Nitro-Bid ointment was applied to the patient's skin. The patient had no reaction to the negative control or the Nitro-Bid ointment at 48 and 96 hours.

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Table 1 Prick and intradermal skin tests results

Nitroglycerin Concentration	Results for Subject	Results for Control
Saline control	Negative	Negative
Histamine control	4+	4+
200 µg/mL Prick	Negative	Negative
0.02 µg/mL Intradermal	Negative	Negative
0.2 µg/mL Intradermal	Negative	Negative
2 µg/mL Intradermal	Negative	Negative
20 µg/mL Intradermal	Negative	Negative
200 µg/mL Intradermal	Negative	Negative

Because both patch and skin testing were negative, it was impossible to definitively conclude that nitroglycerin caused the patient's reaction. The patient had also taken multiple new medications before both reactions. Skin testing in patients with a suspected IgE reaction to nitroglycerin may or may not be helpful especially because nitroglycerin may act as a hapten, therefore making skin testing impractical. This is the first article to describe skin testing with nitroglycerin.

TYPES OF NITROGLYCERIN REACTIONS

Nitroglycerin's most common side effects are headache, facial flushing, head throbbing, fainting, hypotension, tachycardia, and syncope. Various skin reactions have been described to topical or transdermal nitroglycerin preparations. Some studies report a transient erythema with first application of a nitroglycerin patch⁶⁻⁸ and a reactive hyperemia with its removal.⁹ Burns have been reported at the sites of nitroglycerin patches after close contact with a microwave and after use of a defibrillator.^{10,11} Irritant contact dermatitis, allergic contact dermatitis, and urticaria also have been described.¹²⁻¹⁶ Irritant contact dermatitis is an inflammatory reaction to any substance where inflammatory and immunologic mediators are activated, but no memory T lymphocytes or antigen-specific immunoglobulins are produced.⁹ Allergic contact dermatitis is an example of a type IV T-lymphocyte-mediated reaction in which the subject will have a positive patch test to the offending substance.

Components of the nitroglycerin patch, which include nitroglycerin, silicone adhesive, glycerin, and lanolin, can cause allergic contact dermatitis.^{17,18} Glycerin can be converted by skin bacteria into acrylic aldehyde, a known cause of irritant contact dermatitis.¹⁹ Allergic contact dermatitis also can occur after occupational exposure to nitroglycerin in explosives.²⁰

Enhancers such as ethyl oleate, glyceryl monolaurate, and sorbitan monooleate are found in some nitroglycerin patches²¹ and have been shown to cause skin sensitization in subjects with cutaneous ulcers.²² These

additives increase the risk of sensitization through epidermal maceration and alteration in the skin's bacterial flora.^{22,23} Enhancers still are not known to cause allergic contact dermatitis in nitroglycerin patch users. Newer generation patches, which liberate nitroglycerin by changing from a lipophilic to a hydrophilic state during perspiration, have been developed to rid the system of enhancers.²¹

DESCRIPTION OF NITROGLYCERIN PATCHES

Minitran (3M), Nitro-Dur (Key), and Nitrek (Bertek) are the three brand-named nitroglycerin patches used in the United States whereas Nitroderm, Transderm-Nitro, Deponit, Diafusor, *Trans*-Nitro Disk, and Nitradisc are no longer available. Generic nitroglycerin patches are also available. Minitran (3M) is composed of nitroglycerin, organic nitrates, methyl alcohol, acrylate copolymer, glycerol monolaurate, and ethyl oleate. Nitro-Dur (Key) is made of nitroglycerin, glycerin, water, lactose, polyvinyl alcohol, povidone, and sodium citrate. The manufacturer of Nitrek (Bertek) would only reveal that its product contained nitroglycerin and an acrylic-based polymer adhesive.

SKIN REACTIONS TO NITROGLYCERIN PATCHES

Skin reactions to transdermal or topical nitroglycerin products vary widely in the literature. One study reported no cutaneous reactions to Nitroderm after 3 years of use in over 3000 patients.²⁴ The pharmaceutical firm which manufactures Nitrol described 25 cases of "nonspecific" skin reactions over a 12-year period.⁵ Only seven patients reported skin reactions in a study that used 600,000 tubes of Nitro-Bid ointment.⁵ Valliant reported that 15% of patients using transdermal nitroglycerin experience irritant contact dermatitis²⁵ whereas others have reported rates of cutaneous reactions ranging from 10% to 75%.^{7,26} The onset of contact dermatitis from the first application of the patch has ranged from 6 hours to 13 months.^{27,28}

Table 2 Case reports of skin reactions to NTG ointment

Year	Reference	Preparation	Amount of Time before Reaction Occurred	Patch Testing	Oral Challenge	Previous Exposure to NTG	Type of Reaction
1978	5	Nitrol (NTG ointment)	3 mos	+NTG	Tolerates SL and p.o. NTG	?	ACD
1979	32	NTG ointment	Several days	+NTG	Tolerates SL and p.o. NTG	SL NTG and peritrate	ACD; previous reaction to ointment 2 years earlier
1979	32	NTG ointment	Several days	+NTG	Tolerates SL and p.o. NTG	Erythrityl tetranitrate, SL NTG, NTG ointment and isosorbide	ACD; previous reaction to ointment 9 months earlier
1979	31	Nitro-Bid (NTG ointment)	9 mos	+NTG	Tolerates SL and p.o. NTG	p.o. NTG and SL NTG	ACD
1979	27	NTG ointment	3 days	-Tape and application ruler	None	Isosorbide and SL NTG	Diffuse reaction
1979	27	NTG ointment	4 mos	+NTG; -tape and application ruler	Tolerates isosorbide and SL NTG	Isosorbide and SL NTG	ACD
1979	27	NTG ointment	3 wks	-Tape and application ruler	None	SL Isosorbide and SL NTG	Local reaction
1979	27	NTG ointment	6 mos	-Tape and application ruler	None	?	Local and diffuse reaction
1979	27	NTG ointment	6 hrs	None	None	?	Generalized rash, swelling of left eye and mucus membrane

ACD = allergic contact dermatitis; i.v. = intravenous; NTG = nitroglycerin; p.o. = oral; SL = sublingual; + = positive patch test to NTG solution or ointment; - = no reaction to patch test; - tape and application ruler = this nitroglycerin ointment uses a special application ruler and tape. The subjects had negative patch tests to the application ruler and tape.

Table 3 Allergic contact dermatitis to transdermal NTG products

Year	Reference	Preparation	Amount of Time before Reaction Occurred	Patch Testing	Oral Challenge	Previous Exposure to NTG
1984	33	Transderm-Nitro	4 mos	+NTG	Tolerates p.o. isosorbide and SL NTG	Isosorbide
1987	24	Nitroderm	3 mos	+NTG; +placebo patch	Tolerates p.o. NTG	?
1987	19	Nitroderm	1 mos	+NTG	Tolerates p.o. long acting nitrates	?
1987	19	Nitroderm	1 mos	+NTG	?	?
1988	45	NTG patch	?	+NTG	?	?
1989	34	Nitroderm and Deponit	1 mos	+NTG	Tolerates SL NTG and p.o. isosorbide	Isosorbide and SL NTG
1994	14	Nitroderm	96 hrs	+NTG	None	Isosorbide and SL NTG
1994	14	Nitradisc	15–20 days	+NTG	Tolerates p.o. and SL NTG	?
1992	36	Nitradisc	Few weeks	+NTG	Tolerates SL NTG and p.o. Isosorbide	Isosorbide
1999	40	Nitroderm Diafusor	5 mons	+NTG	None	p.o. NTG
2002	37	Nitroderm	12 mons	+NTG	Tolerates SL nitroglycerin	None
2003	15	Transdermal NTG	12 hrs	+NTG	Tolerates SL isosorbide	i.v. Isosorbide

i.v. = Intravenous; NTG = nitroglycerin; p.o. = oral; SL = sublingual; + = positive reaction to patch test; – = no reaction to patch test; ? = no information given in article. Nitroderm, Nitradisc, Diafusor, Transderm-Nitro, Nitro-Dur, and Deponit are different manufacturers' transdermal products. A positive reaction to NTG means that patient was patch test positive to NTG solution or ointment.

A prospective study in 320 subjects with angina investigated reactions to different manufacturers' nitroglycerin patches.¹⁸ Approximately 5% (17/320) of patients developed a localized reaction confined to the area of application, and 1.2% (4/320) developed a localized and diffuse skin reaction. Patch testing was performed in patients with a localized reaction, and 76.4% (13/17) had a positive test to silicone adhesive, 17.6% (3/17) had a positive test to nitroglycerin ointment and solution, and 5.9% (1/17) had a positive test to glycerin. Seventy-five percent (3/4) of the patients with a generalized skin reaction were patch test positive to both nitroglycerin ointment and solution. Fifty-nine percent (10/17) of patients with localized skin reactions tolerated a different manufacturer's nitroglycerin patch. No patch test results were provided,

making it impossible to determine why these 10 patients with allergic contact dermatitis to either silicon adhesive, nitroglycerin, or glycerin, tolerated a different product.

Schrader studied 30 patients with chronic stable angina and their reactions to three different manufacturers' nitroglycerin patches.²⁹ He found that 70%, 43%, and 57% of patients had some type of skin reaction to Nitro-Dur, Transderm-Nitro, and Nitrodisc, respectively. He also reported that 30%, 7%, and 10% had severe skin reactions that necessitated discontinuation to Nitro-Dur, Transderm-Nitro, and Nitrodisc, respectively. These reactions included exfoliative reactions, hyperpigmentation, or vesiculopapular reactions. No patch testing was done to determine causation. However, 83% of patients with severe skin reactions were

Table 4 Skin reactions to transdermal NTG

Year	Reference	Preparation	Amount of Time before Reaction Occurred	Patch Testing	Oral Challenge	Previous Exposure to NTG	Type of Reaction
1984	38	Transderm-Nitro	7 wks	+ Placebo patch	None	p.o. NTG and ointment	Local reaction
1985	39	Nitro-Dur	3 wks	None	None	SL NTG	Local reaction
1985	39	Transderm-Nitro	9 mos	None	None	Isosorbide and SL NTG	Local reaction
1987	13	NTG patch	?	None	None	?	Lichen planus
1989	28	Nitroderm	13 mos	+ NTG patch; - NTG solution	Tolerates p.o. isosorbide	p.o. Nitrates	Diffuse reaction
1989	35	NTG patch	?	None	Tolerates challenge	?	Chronic pigmented purpura
2001	16	Nitradisc 10	15 days	+ NTG	None	None	Erythema multiform
2003	15	i.v. Isosorbide	12 hrs	+ NTG	Tolerates SL isosorbide	i.v. Isosorbide	Diffuse reaction with facial swelling to isosorbide

i.v. = Intravenous; NTG = nitroglycerin; p.o. = oral; SL = sublingual; + = positive reaction to patch test; - = no reaction to patch test; ? = no information given in article. Nitroderm, Nitradisc, Diafusor, Transderm-Nitro, Nitro-Dur, and Deponit are different manufacturers' transdermal products. A positive reaction to NTG means that patient was patch test positive to NTG solution or ointment.

able to tolerate another manufacturer's patch. These patients were not allergic to nitroglycerin but most likely allergic to another patch component.

Rayment compared the acceptance of three different transdermal nitroglycerin patches: Transderm-Nitro, Nitro-Dur, and Nitrodisc.³⁰ The most common side effects were local erythema, pruritus, and rash. Transderm-Nitro (16/81 subjects) had significantly less skin irritation than Nitro-Dur (40/80 subjects) or Nitrodisc (44/81 subjects). Fewer subjects stopped taking Transderm-Nitro (3/81 subjects) than Nitro-Dur (9/80 subjects) or Nitrodisc (15/81 subjects) because of the irritation. The authors did not state whether this skin irritation was an immediate or delayed reaction.

In contrast to the three previously mentioned studies, most of the case reports describe allergic contact dermatitis to nitroglycerin rather than to the other patch components (Tables 2–4). The majority of cases had positive patch tests to nitroglycerin solution or ointment, but were able to tolerate oral nitroglycerin, sublingual nitroglycerin, or oral isosorbide challenges.^{5,14,15,19,24,27,28,31–37} The low cross-reactivity between oral and topical nitroglycerin may be explained by their differences in duration of action. For example, sublingual nitroglycerin lasts approximately 1 hour, and transdermally applied nitroglycerin has a duration of action of 24 hours.

Skin sensitization may occur by previous use of oral nitroglycerin products. Most cases of allergic contact dermatitis used oral nitroglycerin products for months to years before having a reaction to the transdermal nitroglycerin.^{14,15,27,28,31–34,36,38–40} Camarasa took 22 patients who had been on oral nitroglycerin products for at least 10 years and patch tested them to nitroglycerin to determine if oral nitroglycerin causes skin sensitization.⁴¹ Only 1 out of 21 patients had a positive response; this subject had never been exposed to a topical nitroglycerin. The authors concluded that sub-clinical sensitization may occur through oral treatment.

REACTIONS TO INTRAVENOUS, SUBLINGUAL, ORAL, AND PERIANAL NITROGLYCERIN PRODUCTS

Reactions to nitroglycerin products other than transdermal delivery systems are rare (Table 5). Five cases of reactions to nitroglycerin products that were not transdermally delivered have been described. The only report of oral nitroglycerin causing an allergic reaction was described in 1972.¹² A patient who had been on oral peritrate (a nitroglycerin derivative not available in the United States) and nitroglycerin developed a diffuse erythematous rash on four different occasions when exposed to these products. The authors did not state how long it took for the rash to develop after nitroglycerin administration or whether the nitroglyc-

Table 5 Skin reactions to other preparations of NTG

Year	Reference	Preparation	Patch testing	Oral Challenge	Time after Starting Preparation	Previous Exposure to NTG	Type of Reaction
1955	46	p.o. Trinitrin	None	None	7 mos	None	Thrombocytopenic skin purpura
1972	12	p.o. Peritrate and glyceryl trinitrate	None	Erythroderma with p.o. peritrate and glyceryl trinitrate	8 yrs	Peritrate and NTG	Diffuse rash
1999	42	Perianal 0.2% NTG	None	None	2 doses	Nitrofurantoin	Anaphylaxis
2000	17	Perianal 0.2% NTG	+NTG & lanolin	None	Few weeks	None	Eczema of the left fingers and rectum
2003	15	Transdermal NTG and i.v. Isosorbide	+NTG	Tolerates SL isosorbide	24 hrs	i.v. Isosorbide	Local reaction to transdermal; Diffuse reaction with facial swelling to Isosorbide

i.v. = Intravenous; NTG = nitroglycerin; p.o. = oral; SL = sublingual; + = positive reaction to patch test; ? = no information given in the article.

erin product was given sublingually. No patch or skin testing was done.

A patient was reported to react to i.v. isosorbide.¹⁵ During a seven-day hospitalization, the subject tolerated i.v. isosorbide. The patient was discharged on transdermal nitroglycerin and developed a local contact dermatitis. Ten days later, the patient was admitted with chest pain, which required i.v. isosorbide. After only a few hours, she developed "a severe generalized and very pruritic, erythematous maculopapular rash associated with facial swelling." The rash resolved slowly with discontinuation of the isosorbide and treatment with i.v. antihistamine and hydrocortisone. No skin testing was performed to confirm an IgE-mediated event secondary to the isosorbide; however, the patient did have a positive patch test to nitroglycerin.

Two reactions to perianal preparations of nitroglycerin have been described.^{17,42} A woman with a chronic anal fissure developed diffuse itching, dyspnea, and hypotension shortly after her second application of perianal nitroglycerin.⁴² No further testing was done to document an IgE-mediated reaction. This same patient had had an "anaphylactic" reaction to nitrofurantoin 20 years earlier. Another case involved a man with pruritus ani who had been using 0.2% nitroglycerin perianally for 3 months.¹⁷ The patient developed marked perianal eczema and was patch test positive to nitroglycerin and lanolin.

PATCH TESTING

Patch testing may be helpful in patients with skin reactions to topical or transdermal nitroglycerin (Table 6).^{9,43,44} It is important to contact the patch's manufacturer to identify the components to be used in patch testing. A placebo patch without nitroglycerin also may be obtained from the manufacturer to determine if the subject is allergic to the nitroglycerin versus the patch; however, this strategy does not determine what patch component caused the reaction.

TREATMENT

In subjects with positive patch tests to nitroglycerin (allergic contact dermatitis), transdermal nitroglycerin patches and other topical nitroglycerin products should be avoided. However, two subjects with allergic contact dermatitis to nitroglycerin continued wearing nitroglycerin patches with premedication of 0.05% fluocinonide cream to the same site as the patch.³²

If the subject has a positive patch test to another component other than nitroglycerin, then another manufacturer's transdermal nitroglycerin product could be tried to see if it is tolerated. Before using a different patch, a list of patch components should be obtained to confirm that the new patch does not contain the of-

Table 6 Common components used in patch testing for nitroglycerin-induced allergic contact dermatitis

Offending transdermal patch
Transdermal placebo patch without nitroglycerin (may be obtained from the manufacturer)
Nitroglycerin, 0.2 mg/mL of water
2% Nitroglycerin ointment
100% Glycerin
100% Lanolin
100% Lactose
White petrolatum
Saline placebo
Silicon adhesive

fending agent. If unable to tolerate a different manufacturer's patch, then topical or transdermal nitroglycerin products should be avoided.

CONCLUSIONS

Allergic and irritant contact dermatitis can occur in subjects using nitroglycerin ointment or transdermal nitroglycerin patches. Patch testing may be helpful in these individuals. In subjects with positive patch tests to nitroglycerin (allergic contact dermatitis), transdermal nitroglycerin patches and other topical nitroglycerin products should be avoided. Most patients with contact dermatitis to nitroglycerin patches have tolerated oral nitroglycerin, sublingual nitroglycerin, or oral isosorbide challenges.

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