

Off-Label Drug Uses

Nitroglycerin (Topical): Raynaud Phenomenon

Joyce A. Generali, RPh, MS, FASHP,* and Dennis J. Cada, PharmD, FASHP, FASCP (Editor)[†]

This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a quarterly publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature will enable the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. A summary of the most relevant data is provided, including background, study design, patient population, dosage information, therapy duration, results, safety, and therapeutic considerations. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to hospitalpharmacy@drugfacts.com.

BACKGROUND

Raynaud phenomenon, a vasospastic disorder, is characterized by sensitivity to cold temperatures and triggers the release of vasoconstrictors, including catecholamines, endothelin-1, or 5-hydroxytryptamine. Clinically, vasospasm or vasoconstriction may be associated with a change in color of the fingers or toes, starting with 1 or several digits and spreading symmetrically to all fingers or toes. Attacks usually end with a sudden reflow of blood to the area, creating reactive hyperemia. Criteria for primary Raynaud phenomenon are symmetric attacks without necrosis, ulceration, or gangrene and no evidence of secondary causes. Typical onset of primary Raynaud phenomenon occurs in the early to middle teens and sometimes after age 40 with a possibility of milder symptoms. In contrast, criteria of secondary Raynaud phenom-

non are associated with severe episodic attacks, usually asymmetric, or with ulcerations. Patients also may have other manifestations of connective tissue disease (eg, arthritis, systemic sclerosis).

Although it is thought that the primary cause is a local fault in digital microcirculation, Raynaud phenomenon actually may be a systemic disease with a multifactorial etiology. Vasospasms in the digits also may be accompanied by similar effects in other major organs (eg, lungs, kidneys). Repeated vasospasm attacks can cause ischemic reperfusion endothelial injury, resulting in further vasospasms. The continuing cycle may result in further endothelial damage, particularly in severe cases. Calcium channel blockers are potent vasodilators and are typically first-line treatment. However, local vasodilation may provide some benefit in the treatment of this disorder.¹

PATIENT POPULATION

Adults with primary or secondary Raynaud phenomenon.

DOSAGE AND DURATION

Administered as ointment (1% or 2%). Used clinically as 1% ointment for 6 weeks.

RESULTS

The use of topical nitroglycerin in the treatment of Raynaud phenomenon has been evaluated in a limited number of controlled trials with some therapeutic clinical effects.

Controlled Trials

Digital vascular response was determined via laser Doppler imaging in a controlled trial that enrolled 10 adults with Raynaud phenomenon, 13 adults with systemic sclerosis, and 10 healthy adults. After the nondominant hand was exposed to 23°C for 20 minutes, the skin microvascular blood flow of the dorsum of the middle 3 fingers (index, middle, and ring) was measured at baseline and again after topical application of treatment at 0, 10, and 20 minutes. Nitroglycerin 2% ointment was applied on the dorsum of the first finger for 1 minute. Placebo was applied in the same manner on the second finger, and the third finger received no treatment. Significant increases in blood flow response were observed with placebo compared with no treatment ($P < 0.001$), and with

*Director, Drug Information Center, Kansas University Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160, e-mail: jgeneral@kumc.edu; [†]Editor-in-Chief, *Hospital Pharmacy*, and Executive Editor, *The Formulary*, e-mail: Dennis.Cada@wolterskluwer.com.

nitroglycerin compared with placebo ($P = 0.004$). In addition, the change in blood flow over time differed significantly between placebo and nitroglycerin ($P < 0.001$) but not between placebo-treated fingers and no-treatment fingers. In contrast to nitroglycerin, which increased blood flow response at 10 and 20 minutes after application, both the placebo-treated fingers and no-treatment fingers demonstrated decreases in blood flow.²

In a small, double-blind, placebo-controlled, crossover trial, 17 adults with bilateral Raynaud phenomenon received 6 weeks of treatment with nitroglycerin 1% ointment and placebo. Most patients were allowed to continue concurrent therapy with sympatholytic medications (eg, methyl dopa, guanethidine). Therapy was applied to only 1 hand 3 times daily and during acute vasospastic attacks. All patients were instructed to apply the ointment in a thin layer without massaging or rubbing. The total amount did not exceed 4 inches,

and the dose was reduced if headache occurred. There was no washout period between treatment phases. When compared with placebo, topical nitroglycerin significantly reduced the frequency and severity of attacks. None of the patients in the nitroglycerin group experienced more-frequent attacks during treatment. Eleven patients also experienced less numbness, less pain, or both during the nitroglycerin phase. Of the 9 patients with ulcerations, improvement in ulcer size was noted in 7 patients during nitroglycerin treatment, compared with 1 patient in the placebo group.³

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Adverse effects noted in patients taking nitroglycerin for Raynaud phenomenon do not appear to significantly differ from the drug's

adverse effect profile for cardiac uses. Limited data are available regarding the safety profile of this drug when used locally at concentrations of 1% or 2%.

THERAPY CONSIDERATIONS

Evidence from a limited number of controlled studies suggests that topical nitroglycerin may be of benefit for the treatment of Raynaud phenomenon. However, larger, controlled trials are needed to confirm these results.

REFERENCES

1. Wigley FM. Clinical practice. Raynaud's phenomenon. *N Engl J Med.* 2002;347(13):1001-1008.
2. Anderson ME, Moore TL, Hollis S, Jayson MI, King TA, Herrick AL. Digital vascular response to topical glyceryl trinitrate, as measured by laser Doppler imaging, in primary Raynaud's phenomenon and systemic sclerosis. *Rheumatology.* 2002;41(3):324-328.
3. Franks AG. Topical glyceryl trinitrate as adjunctive treatment in Raynaud's disease. *Lancet.* 1982;1(8263):76-77. ■