Nicorandil-induced oral ulceration: report of 3 cases and review of the Japanese literature

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Nicorandil-induced oral ulceration in 3 Japanese patients is reported. The patients were men aged 86, 81, and 91 years. Ulcers of 15, 10, and 12 mm in diameter, respectively, were observed at the border of all of the patients’ tongues. These were painful and persistent but not indurated. Irritation by the teeth or dentures was not evident. They had been administered nicorandil at a dose of 15 mg for 22, 54, and 90 months, respectively; therefore, ulceration induced by nicorandil was suspected. In consultation with the doctor, nicorandil was withdrawn. The ulcers disappeared 5, 8, and 9 weeks, respectively, after the cessation of nicorandil. No relapse of the ulcer was noted. The findings suggest that these were the examples of nicorandil-induced oral ulceration.


Nicorandil, a nicotinamide ester, is a potassium channel blocker used in the prevention and long-term treatment of angina pectoris.1 The drug was developed and has been used in Japan for over 2 decades and was introduced in Europe in 1994.2-4 It has been described as a hybrid between nitrates and potassium channel activators.5 It opens the potassium channel, causing sustained dilation of both peripheral and coronary arteries, this reducing cardiac afterload. The nitrate moiety dilates venous capacitance vessels to reduce cardiac preload.4 It is not currently a first-line agent in the management of angina but is sometimes used in combination with other antianginal drugs for refractory stable and unstable angina.1

Oral ulceration is known as an adverse effect of nicorandil, since initial reports from France6,7 and subsequent reports from other European countries1,5,8-19 suggested a link between oral ulceration and the use of nicorandil. In Japan, the first case of nicorandil-induced oral ulceration was reported in 2001.20 Since then, several reports have appeared in the literature;21-30 however, most reports of nicorandil-induced oral ulceration in Japanese patients have been published in Japanese20-25,27-29; therefore, information as to the prevalence of such adverse effects of the drug in Japanese patients is not available outside of Japan, although the drug has been used for >2 decades.

In the present paper, we present 3 cases of nicorandil-induced oral ulceration experienced in our clinic and review the Japanese literature.

CASE REPORTS

Case 1
The patient was an 86-year-old man who consulted us with the chief complaint of an ulcer on the right side of the tongue. The ulcer had developed 5 months before and had not responded to treatment. On examination, an oval ulcer of 15 mm in diameter was observed on the right border of the tongue (Fig. 1, A). The ulcer was painful but not indurated. Irritation by the teeth or dentures was not evident. The patient had been treated with 15 mg/d nicorandil for 34 months; therefore, ulceration caused by nicorandil was suspected. In consultation with his doctor, nicorandil was withdrawn. The ulcer decreased in size 10 days after reduction of the dose and had completely disappeared by 8 weeks (Fig. 1, B). For >6 months, no relapse of the ulcer was noted.

Case 2
The patient was an 81-year-old man who consulted us with the chief complaint of an ulcer on the right side of the tongue. The ulcer had developed 2 months before and had not healed at all. A flat oval ulcer of 10 mm in diameter was observed on the right border of the tongue (Fig. 2, A). The ulcer was painful but not indurated. Irritation by the teeth or dentures was not evident. Because the patient had been treated with 15 mg/d nicorandil for 54 months for angina pectoris, ulceration caused by nicorandil was suspected. In consultation with his doctor, the dose of nicorandil was reduced and terminated within 2 weeks. The ulcer decreased in size 10 days after reduction of the dose and had disappeared completely by 8 weeks.
weeks after cessation of nicorandil (Fig. 2, B). For ≥7 months, no relapse of ulcer was noted.

Case 3

The patient was a 91-year-old man who consulted us with the chief complaint of an ulcer on the left side of the tongue. The ulcer had developed a month before and had not healed at all. An oval ulcer of 12 × 9 mm was observed on the left border of the tongue (Fig. 3, A). The ulcer was painful but not indurated. Irritation by the teeth or dentures was not evident. The patient had been treated with 15 mg/d nicorandil for 90 months for angina pectoris; therefore, ulceration caused by nicorandil was suspected. Nicorandil was withdrawn in consultation with his doctor on the day of the first visit. The ulcer decreased in size within 6 weeks and had completely disappeared by 9 weeks (Fig. 3, B). For >4 months, no relapse of the ulcer was noted.

DISCUSSION

Nicorandil is a widely prescribed and well tolerated drug that has been available in Japan for ≥2 decades. Its well recognized side effect is mild to moderate headache, which occurs in one-third of patients, particularly during the first few days of treatment, and diminishes with continued treatment. Other less frequent adverse events include flushing, nausea, dizziness, hypotension, and tachycardia. Oral ulceration induced by nicorandil is now recognized as an adverse effect; however, the incidence of this phenomenon is not well known yet. Marquart-Elbaz et al. prospectively investigated the prevalence of nicorandil-induced ulceration and found unusual oral ulceration in 5 of 100 patients taking nicorandil and no ulceration in a group of 100 patients taking other antianginal drugs. Jang et al. reviewed 140 consecutive patients receiving nicorandil for ≥1 month and found recurrent oral ulceration in 3 of them. From these studies, the incidence of oral ulceration associated with nicorandil therapy may be estimated at ~5% or less.

Clinically, oral ulceration induced by nicorandil may be single or multiple, and isolated or in association with ulceration elsewhere in the mucosa or on the skin. The ulcers develop most frequently on the tongue and are
sometimes seen at the buccal mucosa or other oral sites.\textsuperscript{15} These ulcers are usually large, deep, and persistent with a well circumscribed and punched-out appearance.\textsuperscript{32} These are intensely painful and may interfere with eating and speaking and have a negative impact on the quality of life, such as weight loss,\textsuperscript{2,12} and even depression in some cases.\textsuperscript{31} Histologically, these are nonspecific ulcers, excluding malignancy, infection, and immunoallergic reaction.\textsuperscript{2,8,18,32} Oral ulceration, which can arise in many systemic disorders or be induced by other drugs,\textsuperscript{17} should be excluded. Nicorandil-induced ulceration does not respond to any form of treatment, but usually resolves itself by stopping nicorandil or reducing the dose.\textsuperscript{1} An oral provocation test with nicorandil can confirm the diagnosis but is rarely performed.\textsuperscript{17,26}

Eighteen cases of nicorandil-induced oral ulceration, including the 3 present cases, were found in the Japanese literature.\textsuperscript{20-30} 14 in case reports\textsuperscript{20,21,25-28,30} and 4 in abstracts\textsuperscript{22-24,29} (Table I), although it is considered that there have been more cases not reported in the literature. The patients were 7 men and 11 women, and their age ranged from 65 to 91 years old with an average of 78.9 years. The tongue was commonly involved in 17 patients, including 2 patients with ulcers in other sites. The lower lip was involved in 2 patients, including 1 patient with tongue ulcer. The size of the ulcer was 2-30 mm. The dose of nicorandil was 5-30 mg/d, which was lower than in the reports from Europe.\textsuperscript{30} The duration of taking nicorandil ranged from 2 to 148 months. Most of the patients had several diseases and had taken other drugs together with nicorandil. All ulcers disappeared within 1-15 weeks after cessation of the drug. These features are basically similar to those in reports from European countries.\textsuperscript{3}

Nicorandil-induced ulcerations have been reported at other sites of the body since anal ulceration was firstly described by Watson in 2002.\textsuperscript{33} Ulcerations have been observed in the gastrointestinal tract,\textsuperscript{34-36} anal or perianal region,\textsuperscript{35,37-40} peristomal region,\textsuperscript{41} penis,\textsuperscript{42} vulvovaginal region,\textsuperscript{40,43,44} skin,\textsuperscript{40,45} and sometimes involve multiple sites.\textsuperscript{35,40} Although the prevalence of ulcerations at these sites is not well known, nicorandil seems to induce ulceration primarily at mucocutaneous interface zones of the body.\textsuperscript{44} It is believed that these cases are still widely underestimated, because of the lack of awareness of this phenomenon.\textsuperscript{41}

The mechanism by which nicorandil produces oral ulceration is poorly understood, and several hypotheses have been described: 1) A direct local effect induced by electrolyte disturbance by nicorandil of the oral mucosa\textsuperscript{38}; nicorandil or a metabolite may be secreted in saliva and produces a similar toxic effect; 2) manifestation of a hypersensitivity reaction to nicorandil, which is associated with similar nonkeratinized squamous epithelium lining a specific area\textsuperscript{1,38}; 3) a vascular steal phenomenon, a perfusion deficiency caused by redistribution of the arterial and venous flow, which makes the mucosa potentially more susceptible to ulceration\textsuperscript{37}; 4) accumulation and abnormal distribution of nicotinic acid from nicorandil outside the endogenous pool of nicotinamide adenine dinucleotide phosphate, which makes the mucous membrane more susceptible to physical aggression or local flora\textsuperscript{46}; and 5) an inhibitory effect of type 1 plasminogen activator inhibitor activity, which may reduce antiinflammatory action.\textsuperscript{28} The predominant occurrence on the tongue also suggests the involvement of local anatomic and/or physiologic factors for the development of ulcer.

Initially, it was considered that nicorandil-induced ulceration occurred at high doses and required a minimum dose of 30 mg/d\textsuperscript{19}; however, oral ulceration has been reported even at the low dose of 5 mg/d.\textsuperscript{17} There may be a threshold dose for the development of oral ulcers that is related to the physiologic reserve of the
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AF, Atrial fibrillation; AP, angina pectoris; AR, arrhythmia; BA, bronchial asthma; BT, brain tumor; CC, colon cancer; CI, cerebral infarction; DM, diabetes mellitus; GU, gastric ulcer; HL, hyperlipidemia; HT, hypertension; HU, hyperuricemia; HY, hypothyroidism; LC, liver cirrhosis; MI, myocardial infarction; ND, not described; PH, prostate hypertrophy; RA, rheumatoid arthritis; VZ, varicella zoster.
(a) Famotidine, dried aluminum hydroxide gel, magnesium oxide, furosemide, dipyridamole, allopurinol, triazolam; (b) aspirin, atorvastatin calcium hydrate; (c) amlodipine besilate, isosorbide dinitrate, Nitroglycerin, famotidine, cetaxate hydrochloride, simvastatin; (d) mecobalamin, brotizolam, teprenone,loxoprofen sodium, sennoside; (e) diltiazem hydrochloride, methotrexate, risedronate sodium hydrate, prednisolone,loxoprofen sodium,alfacalcidol, potassium l-aspartate; (f) omeprazole, aspirin, ticlopidine hydrochloride, candesartan cilexetil, carvedilol, voglibose, glibenclamide, simvastatin, sodium ferrous citrate; (g) warfarin potassium, aspirin, ticlopidine hydrochloride, varsartan, bisoprolol fumarate, furosemide, atorvastatin calcium hydrate, azosemide, lansoprazole; (h) insulin, pioglitazone hydrochloride, diltiazem hydrochloride, warfarin potassium, aspirin, trichlormethiazide; (i) usrodeoxycholic acid, lisinopril, nifedipine; (j) proctacrol hydrochloride inhalation, aspirin; (k) aspirin, clopidogrel sulfate, isosorbide dinitrate, timaprost alfadex, silodosin, imidafenacine, magnesium oxide; (l) telmisartan, aspirin dialuminate, clopidogrel sulfate, diltiazem hydrochloride, enalapril maleate, isosorbide dinitrate, pravastatin sodium, famotidine, furosemide, naftopidil, allopurinol; (m) ubidecarenone, dilazep dihydrochloride, riboflavin butyrate, silodosin, aliskiren fumarate, chloromadinone acetate, eviprostat, senna extract.
patients. The age-related physiologic change, the presence of other diseases, and an interaction with other drugs taken together may affect the threshold dose of the toxicity. For some patients, the threshold dose required to induce ulceration may be below the minimum therapeutic dose, especially those >75 years old. A possible threshold dose-effect is also suggested from the findings that ulceration occurs frequently after an increase in dose rather than the initiation of the drug. If this is so, reduction of the dose instead of stopping it could also be effective to promote healing and prevent the recurrence of ulceration. This is beneficial for patients with severe coronary disease, because it may not be possible to stop it completely without the recurrence of anginal symptoms.

In conclusion, three cases of nicorandil-induced oral ulceration have been reported along with a review of the Japanese literature. Oral ulceration is now recognized as an adverse effect of nicorandil. There is a need to increase awareness among general physicians, dental practitioners, and cardiologists of the link between nicorandil and persistent ulceration.

REFERENCES

30. Tera H, Yamanishi H, Shimahara M. Nicorandil-induced tongue ulceration with or without fungal infection. Odontolology 2011. [Epub head of print.]

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