
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 In consultation with the doctor, nicorandil was withdrawn.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. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011;112:754-759)

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 France^{6,7} and subsequent reports from other European countries^{1-5,8-19} 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 literature²¹⁻³⁰; however, most reports of nicorandil-induced oral ulceration in Japanese patients have been published in Japanese^{20-25,27-29}; 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 × 10 mm 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 22 months for angina pectoris; therefore, ulceration caused by nicorandil was suspected. In consultation with his doctor, nicorandil was withdrawn a week after the first visit. After the cessation of nicorandil, the ulcer decreased in size and had completely disappeared by 5 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 × 4 mm 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

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Fig. 1. Clinical manifestation of case 1. **A**, An oval ulcer of 15×10 mm was observed at the right border of the tongue. **B**, After healing.



Fig. 2. Clinical manifestation of case 2. **A**, A flat oval ulcer of 10×4 mm was observed at the right border of the tongue. **B**, After healing.

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.²⁻⁴ 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.^{1,5,15} Other less frequent adverse events include flushing, nausea, dizziness, hypotension, and tachycardia.^{1,5} 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.³¹ 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.¹⁷ 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 $\sim 5\%$ 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

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