

Nicorandil Induced Oral Ulceration in Indian Patient

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ABSTRACT

Systemic medications are known to have potential adverse side effects on the oral mucosa. Oral adverse effects commonly manifested are either gingival hyperplasia due to phenytoin and nifedipine or xerostomia in patients on anti-depressants and antihypertensives. Oral ulceration is a well recognized but under-appreciated adverse drug reaction produced by or implicated in a number of prescribed and over-the-counter medications. The anti-anginal drug Nicorandil is becoming increasingly recognised as a causative factor for oral ulceration. Several case reports pertaining to the same have been reported in western literature but sparsely reported in Indian literature. The aim of this case report is to increase awareness among clinicians that nicorandil can induce extensive oral ulceration and thus should be included in the differential diagnosis when presented with patients complaining of long standing oral ulceration. Nicorandil's association with oral, anal, gastrointestinal ulceration, and more recently parastomal ulceration has also been reported.

KEYWORDS: Nicorandil, oral ulceration

INTRODUCTION

Nicorandil is a nicotinamide ester, a potassium channel activator used in the prevention and long term treatment of angina pectoris.¹ It is generally given in a maximum dose of 30 mg twice daily.² Nicorandil's well recognized side effects are mild to moderate headache, flushing, nausea, dizziness, hypotension, and tachycardia whereas oral ulceration being a rare one.³

The incidence of oral ulceration associated with nicorandil therapy may be estimated at 5% or less. Since, the first case of "giant buccal aphthosis" induced by nicorandil was published in 1996, a plethora of reports of nicorandil associated oral ulceration have been reported in different countries like Europe, Japan, France but literature is sparse in Indian scenario.⁴

These ulcerations cause considerable discomfort interfering with eating, speaking and even cause weight loss and depression leading to negative impact on quality of life.⁵

So, here we report one such case of nicorandil induced oral ulceration which healed completely by withdrawing nicorandil in a time span of 15 days.

CASE REPORT

A 69 year old male patient reported to the dental clinic in Navi Mumbai with chief complaint of pain and burning sensation in relation to right buccal mucosa since 1 month. Pain was succeeded by ulcer on right buccal mucosa which was persistent even after application of topical medications. No history of previous oral ulcerations. His medical history revealed hypertension,

ischaemic heart disease, and type II diabetes mellitus since 12 years for which he was taking aspirin 75 mg once daily, Losartan 40 mg once daily and glipizide 5 mg twice daily orally. Nicorandil (Avcor) 20 mg twice daily was started 1 month back due to persistent chest pain.

On clinical examination; solitary ulcer was present on right buccal mucosa and vestibule opposite 14,15 which was roughly oval in shape about 3 X 2 cm with sloping edge and well defined borders covered by yellowish slough on floor surrounded by mild erythematous halo. (Figure 1) On palpation ulcer was tender, non indurated. No ulcerations present elsewhere in oral cavity.



Figure 1 : ulcer seen in relation to right buccal mucosa and vestibule.

Thus, in view of provisional diagnosis of Nicorandil induced oral ulceration nicorandil was withheld and doxycycline

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(choline salicylate 8.7% + benzylnonium 0.01% + lignocaine hydrochloride 2%) was given. On follow up after 15 days ulcer healed completely with no recurrence.

DISCUSSION

Nicorandil belongs to the class of compounds known as potassium channel activators which are characterised by their arteriovenous dilating properties, and represents a novel type of compound for use in the treatment of angina pectoris.⁶ Apart from oral ulceration nicorandil was associated with ulceration of anus⁷, gastrointestinal tract⁸, terminal ileum⁹ and para-stomally.¹⁰

Some reports have shown oral ulceration from 10–80 mg (across the recommended dose range)¹¹ but occurs usually at high doses ie 40 mg per day¹². This is consistent with our case where patient was receiving a dose of 40 mg/day. The wide variation in incriminated dose could be because of age-related physiological change, presence of other diseases, and an interaction with other drugs taken together that may affect the threshold dose of the toxicity. For some patients especially those 75 years old, ulceration may occur with sub-minimal therapeutic dose.⁴

Latency in the development of ulcer with nicorandil is 15 days to 24 months (generally 2 months). Cure is obtained in all cases after 1 to 12 weeks.¹³ This patient developed ulcer within 4 weeks of nicorandil therapy. Nicorandil-induced oral ulceration seems to have a predilection for the tongue though other sites e.g. buccal mucosa, labial mucosa, gingiva may also be affected.¹⁴

It has been suggested that a previous history of aphthous ulceration may predispose to the development of nicorandil-induced ulcers.^{13,15} Recurrent oral ulceration history was negative in our case. Oral ulceration can also occur with aspirin (chemical burn, if left to dissolve whilst in contact with the oral mucosa), captopril, gold salts, penicillamine, non steroidal analgesics and cytokine inhibitors.¹⁴ Though this patient was also taking aspirin it was not thought of as a causative factor as the patient improved despite continuing it. But it could be a possibility that it contributed in development of nicorandil induced ulcer.

These painful ulcers are usually large, deep, and persistent with a well circumscribed and punched-out appearance. Histologically, these are nonspecific ulcers, excluding malignancy, infection, and immunoallergic reaction.⁴ Clinically they are larger than minor aphthous ulcers and have an irregular outline. Furthermore they appear on keratinized mucosa (tongue) whilst major aphthae have fewer predilections for this site. Nicorandil-induced oral ulcers are painful from the outset while oral squamous cell carcinoma may be painful in the late stage of the disease and presents as an indurated, exophytic lesion or as a red, white or speckled patch.¹⁴ The screening of differential diagnosis of these ulcerations paves a way to appropriate treatment modality.

The recently postulated mechanism of this adverse effect might be that nicorandil, in a dose-dependent manner,

dephosphorylates myosin and so hinders the actin filament contraction that is necessary for cell migration, as would be required to repair mucosal microtrauma and surgical wounds. This pathophysiology could be implicated in a case reported by Riddell et al where nicorandil could be responsible for non healing of a surgical wound.^{16,17}

The causality assessment in this case suggest a probable association of nicorandil in causing oral ulceration as per the WHO causality assessment scale as the lesion healed completely on discontinuation of nicorandil. So de-challenge was positive confirming the causality as Probable.

Discontinuing the nicorandil (which may exacerbate angina), decreases the pain associated with the ulcer rapidly (within weeks) and complete healing ensues; depending on the original size of the wound, this usually takes between 2–6 months.¹⁶ As, in our case the lesion healed completely without recurrence in 15 days.

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.⁴ Thus a high index of suspicion is necessary in diagnosis to prevent morbidity in such cases and optimise pharmacotherapy of angina patients.

CONCLUSION

Nicorandil at high dosage 40 mg/day can cause chronic oral ulcers which heal on stoppage of the medication. Nicorandil induced oral ulceration should be considered in differential diagnosis when patient on nicorandil therapy presents with chronic oral ulcer.

REFERENCES

1. Agbo-Godeau S, Joly P, Lauret P, Szpirglas R, Szpirglas H. Association of major aphthous ulcers and nicorandil. *Lancet* 1998;352(9140):1598–9.
2. Frampton J, Buckley MM, Fitton A. Nicorandil. A review of its pharmacology and therapeutic efficacy in angina pectoris. *Drugs* 1992;44:625–55.
3. Farah CS, Carey LM, Savage NW. Nicorandil induced severe oral ulceration. *Aust Fam Physician* 2003;32:452-3.
4. Yamamoto K, Matsusue Y, Horita S, Minamiguchi M, Komatsu Y, Kirita T. Nicorandil-induced oral ulceration: report of 3 cases and review of the Japanese literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011;112(6):754-9.
5. Cribier B, Marquart-Elbaz C, Lipsker D, Alt M, Grosshans E. Chronic buccal ulceration induced by nicorandil. *Br J Dermatol* 1998;138(2):372–3.
6. Udaykumar P, Adhikari P, Periera P. Safety and Efficacy of Nicorandil in Chronic Stable Angina – A Double Blind Comparative Randomised Trial with Isosorbide Mononitrate. *JACM* 2003;4(3):205-9.
7. Watson A, Suttie S, Fraser A, O’Kelly T, Loudon M. Nicorandil associated anal ulceration. *Colorectal Dis* 2004;6(5):330-1.

8. Egred M, Andron M, Morrison WL. Nicorandil may be associated with gastrointestinal ulceration. *BMJ* 2006;332(7546):889.
9. King PM, Suttie SA, Jansen JO, Watson AJ. Perforation of the terminal ileum: a possible complication of nicorandil therapy. *Surgeon* 2004;2:56-7.
10. Abdelraseq AS, Owen CM, Smith L, McAdam JG, Pearson HJ, Leveson SH. Nicorandil-associated parastomal ulceration: case series. *Eur J Gastroenterol Hepatol* 2006;18(12):1293-5.
11. Webster K, Godbold P. Nicorandil induced oral ulceration. *Br Dent J* 2005;198(10):619-21.
12. Healy CM, Smyth Y, Flint SR. Persistent nicorandil induced oral ulceration. *Heart*. 2004;90(7):e38.
13. Boulinguez, Bonnetblanc JM. Aphthae or painful ulcers induced by nicorandil. *Presse Med* 2000;29(33):1828-32.
14. Ciantar M, Gibson J. Nicorandil-induced oral ulceration. *Malta Medical Journal* 2008;20(1):30-33.
15. O'Sullivan EM. Nicorandil-induced severe oral ulceration. *J Ir Dent Assoc*. 2004 inter;50(4):157-9.
16. Patel GK, Harding KG. Nicorandil ulcer: moves beyond the mucosa. *Ann R Coll Surg Engl* 2010;92(6):451-2.
17. Riddell AD, Minhas U, Williams GL, Harding KG. The role of nicorandil in non healing surgical wounds. *Ann R Coll Surg Engl* 2010; 92.

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