IN BRIEF

- Nicorandil is a common anti anginal drug.
- It can cause large ulcers that may be debilitating to the patient.
- Ulcers may resemble Major Aphthous Stomatitis or Squamous Cell Carcinoma.
- Any ulcer which becomes increasingly painful or is persistent should be seen by a specialist.

Nicorandil induced oral ulceration

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Oral ulceration has many different causes. The association between Nicorandil and oral ulceration is not a new phenomenon. There have been several previous case reports regarding a possible association although none in publications for general dental practice. In this report we have a case series of seven patients and we compared our findings with those in the current literature.

Nicorandil (Ikorel, Rhône-Poulenc Rorer Ltd) is a potassium channel activator used in the treatment of Angina pectoris.[1] On the whole Nicorandil is a widely prescribed and well tolerated anti anginal drug. It has been available in Japan for more than 10 years and was introduced into the UK and the rest of Europe in 1994. Initial adverse reactions include headaches, nausea and cutaneous erythema. The first reports of Nicorandil induced oral ulceration came from France in 1997.[2] Interestingly, there have been no reports of Nicorandil induced oral ulceration from Japan.

To date in the UK the Medicines and Healthcare products Regulatory Agency (MHRA) have received 66 reports of patients with ulcerative stomatitis and nine patients with tongue ulceration associated with Nicorandil. A prospective case control study has been performed for patients taking Nicorandil which showed that 5% of the patients in the Nicorandil group developed mouth ulcers from the start of treatment. The authors of that study stated that it is not rare for ulcers to occur with Nicorandil treatment[8] although a Prescription Event Monitoring Study assessing the overall safety of Nicorandil in everyday practice came up with a much lower incidence of ulcers; of the 13,260 patients taking Nicorandil 49 (0.4%) developed mouth ulcers.[9]

Nicorandil induced oral ulceration may cause severe symptoms for the sufferer, including weight loss as a consequence of anorexia due to discomfort and dysphagia.[3,5] There have even been reports of depression.[8] It is important that clinicians elsewhere be made aware that Nicorandil can be a potential inducer of ulcers that may mimic major aphthous ulcers[5] or even carcinoma.

CASE REPORTS

Case 1

An 85-year-old Caucasian female was referred by her general medical practitioner with recurrent oral ulceration. She had been referred two years previously, but the ulcers had healed on presentation. She had a history of large painful oral ulcers typically lasting three months before healing. She had a medical history of angina, hypothyroidism and cancer of the stomach. Daily medications included Nicorandil 20md BD, GTN spray and thyroxine. Examination revealed a large ulcer left-hand side dorsum of tongue approximately 1 × 4 cm with what appeared to be a fibrinous yellow base and furred surface in the midline of the dorsum of the tongue. There was no associated cervical lymphadenopathy and the rest of the oral mucosa appeared healthy (Fig. 1).

Case 2

A 64-year-old Caucasian male referred for an urgent appointment with regard to a suspicious oral ulcer. An ulcer had been present on the tongue for one month. He had a medical history of ischemic heart disease and pulmonary embolus. He had been taking Nicorandil 10 mg BD for the previous nine months. On examination there was an ulcer on the right lateral border of the tongue approximately 1 cm diameter and on the soft palate. The lesion was biopsied to exclude sinister pathology. The histology showed fibroepithelial hyperplasia (Fig. 2).

Case 3

An 82-year-old Caucasian female referred from ENT with painful oral ulceration. The lesion had been treated with topical corticosteroids which offered no relief. She had a medical history of ischemic heart disease, angina and rheumatoid arthritis. She had

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Refereed Paper
Received 13.09.04; Accepted 15.11.04
doi: 10.1038/sj.bdj.4812350

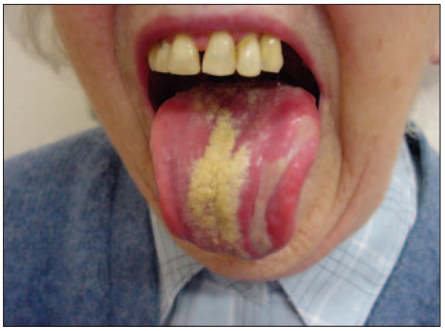

Fig. 1 Large ulcer on dorsum of tongue

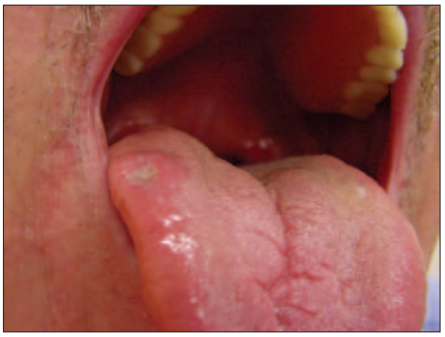

Fig. 2 Ulcer with histology showing fibroepithelial hyperplasia

been taking Nicorandil 30md BD since 2000. Intra-oral examination revealed extensive ulceration in the lingual sulcus, anterior labial sulcus and right lateral border of the tongue. Correspondence with her cardiologist resulted in her stopping the Nicorandil and complete resolution of the oral ulceration without scarring within four weeks (Fig. 3).

Case 4

A 76-year-old Caucasian female was referred by her general dental practitioner. She had a persistent ulcer in her left cheek for the previous six months and other recurrent ulcers elsewhere in her mouth. These ulcers had caused her a great deal of distress and resulted in weight loss. She had a medical history of ischemic heart disease for which she had been treated with coronary artery stents and Nicorandil 20 mg BD. On examination there was a large ulcer present on her left buccal mucosa. Biopsy of the lesion showed histopathology of traumatic eosinophilic ulceration.

Case 5

An 83-year-old Caucasian female was referred by her general dental practitioner for persistent oral ulceration. She presented with a six month history of an ulcer in her lower labial sulcus. She had a medical history of hypertension and angina and was being treated with Nicorandil 10 mg BD. She had started her Nicorandil six months previously. Correspondence with her cardiologist resulted in her stopping the Nicorandil and complete resolution of the oral ulceration without scarring within four weeks (Fig. 4).

Case 6

A 64-year-old Indian female referred by her general dental practitioner for assessment of a suspicious looking oral ulcer. She had a medical history of type 1 diabetes mellitus and ischemic heart disease for which she had been prescribed Nicorandil 20 mg TDS. Examination revealed no extra-oral abnormalities or cervical lymphadenopathy. Intra-orally there was an ulcer present on the left lateral border of the tongue. This was 1 cm diameter with no induration. Initially this was treated with topical corticosteroids, to no effect. An incisional biopsy showed histopathology of traumatic eosinophilic ulceration and a further sample sent for immuno-fluorescence came back with a negative result.

Case 7

A 76-year-old Caucasian female was referred by her general dental practitioner for investigation of a large ulcer present for some nine weeks. This ulcer had been unsuccessfully treated with topical corticosteroids. The patient reported the ulcer being very painful. She had a medical history of type 2 diabetes mellitus and ischemic heart disease. She was taking Nicorandil 30 mg BD and had been for the last six months. On examination there was an ulcer on the left hand side dorsum of tongue approximately 1 × 1.5 cm. The ulcer was non-indurated with a yellow slough at the base. Her cardiologist was consulted and her Nicorandil stopped. This caused the ulcer to slowly reduce in size and heal after four weeks (Fig. 5).

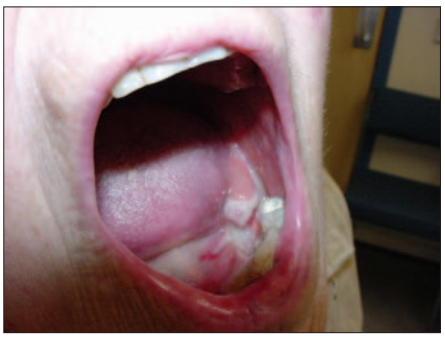

Fig. 3 Ulceration in lingual sulcus

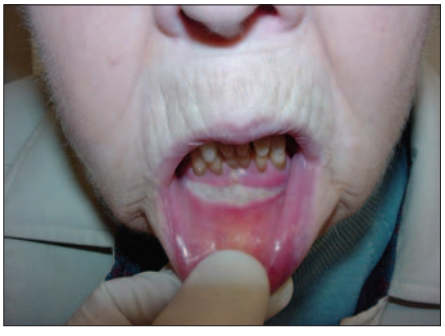

Fig. 4 Lower labial sulcus ulcer

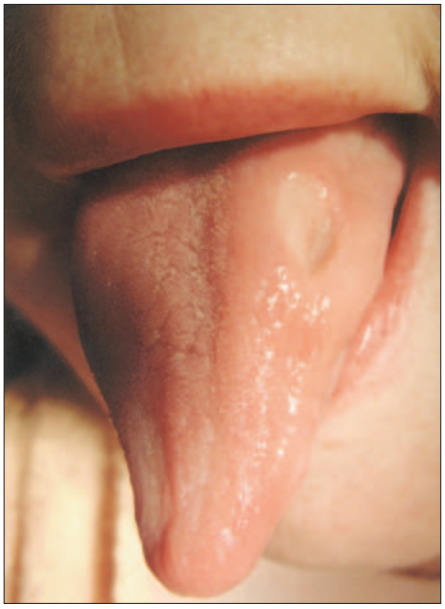

Fig. 5 Ulcer starting to heal at four weeks

DISCUSSION

The cases we have described here share many of the same characteristics as those previously reported. This case series highlights that despite a growing amount of evidence linking Nicorandil to oral ulceration, many general dental and medical practitioners are still unaware of the association and continue to refer to a specialist for diagnosis. However it is important to reinforce that long standing, non-healing oral ulceration requires investigation.

There has been suggestion that there is a minimal dose required to induce oral ulceration[4] or that there may be a dose dependent mechanism in place since in some reported cases the ulceration is induced after there is an increase in the Nicorandil dose.[6] In the patients reported here the ulceration occurs across a range of doses from 20–60 mg per day; other reports have shown oral ulceration from 10–80 mg (across the recommended dose range).[9] This would indicate that for an individual there may be a threshold dose required before oral ulcers are induced but this dose may alter between individuals. For some the threshold dose required to induce ulceration may be below the minimum therapeutic dose.

Other studies suggest that a previous history of aphthous ulceration may predispose a person to the development of Nicorandil induced ulcers, yet there are plenty of cases of Nicorandil induced ulceration occurring in patients without a history of

aphthous ulceration.[3–7] None of our patients complained of ulcers prior to presentation with their Nicorandil induced oral ulceration.

In other studies ulceration has started at varying times after initiation of Nicorandil, from four weeks[5] to 36 months.[6] The ulcers themselves are reported in the literature to be of similar appearance in similar sites to our patients'; that is, having a non specific appearance occurring most frequently on the tongue but also on the fauces, buccal mucosa, gingival mucosa, labial mucosa and hard palate. They may be several centimetres in size and tend to have a consistent appearance from patient to patient. The appearance of these ulcers is similar to that of major aphthous ulceration.

Further investigation of these lesions is usually non-contributory to a diagnosis although may be required if sinister pathology is suspected. Biopsies of Nicorandil induced ulceration are frequently non-specific be that by lesional biopsy or immunoflorescence.[5,6] One case series from the literature reports that laboratory tests such as white cell count, haemoglobin and platelet counts, erythrocyte sedimentation rates and renal and liver functions proved to be normal.[6]

Treatment of these ulcers is best achieved by stopping the Nicorandil,[8] which must be done in consultation with the patient's cardiologist or general practitioner. Complete healing occurs in all of the case reports where the Nicorandil was stopped, with no mention of relapse. After withdrawal of Nicorandil the pain rapidly decreased and the lesions healed rapidly with a 1[6]–5 week time span.[4] In our patients the ulcers healed without scarring but other studies have suggested that these ulcers may heal leaving a visible scar.[3]

Treatment of these ulcers has also been described using thalidomide or colchicine, which cased the ulcers to heal but then immediate relapse once the medication was stopped.[6] Systemic steroids and colchicine failed to prevent new lesions appearing in another study.[2] Topical steroids have not been able to induce ulcer healing[7] but systemic steroids have improved pain for one patient.[2] These findings are consistent with our series and the only successful treatment was found to be withdrawal of the Nicorandil.

The precise mechanism of Nicorandil causing the ulceration is unknown. One case report did suggest that metabolites of Nicorandil could concentrate in the saliva, especially in elderly patients,[7] however there is no other evidence to support this.

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