

# Nicorandil and prepuce ulcers

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**The authors provide an illustrated account of three elderly patients on long-term high-dosage nicorandil therapy who presented with eroding foreskin ulcers.**

Eroding ulcerations of the prepuce from prolonged nicorandil usage have been reported infrequently.<sup>1,2</sup> These ulcers are usually non-purulent with a punched-out appearance and overhanging edges, eroding into deeper tissues. Healthcare practitioners, particularly those in genitourinary medicine, geriatric medicine, general practice and general surgery, should be aware of this association to avoid delay in management. Early identification of the causative factor prevents progressive erosion, which may result in a large defect in the foreskin appearing as autocircumcision.

## NICORANDIL

Nicorandil (2-[(pyridine-3-carbonyl)amino]ethyl nitrate) is a potassium-channel activator with a nitrate component. It has been in use as a vasodilator for more than 20 years and has been commonly prescribed for prophylaxis and treatment of stable angina. Nicorandil has a dual action, beneficial in the treatment of angina and ischaemic heart disease by way of reducing pre- and afterload and increasing the coronary artery blood flow.

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## PATIENT A

An 84-year-old man from a nursing home was found to have a painful, punched-out ulcer on the dorsal prepuce, which had been slowly increasing in size for nearly 2 years. He had been taking nicorandil 20mg once daily for 9 years (Figure 1).



**Figure 1. Punched-out foreskin ulcer in patient A**

Nicorandil activates soluble guanylate cyclase by binding the haem moiety and increasing intracellular cGMP levels. This causes dephosphorylation of the myosin light chain, leading to smooth muscle relaxation and resultant vasodilatation. Membrane-bound ATP-dependent potassium channels are also opened by nicorandil, leading to further vasodilatation. Nicorandil-mediated mitochondrial potassium-channel opening also appears to provide cardioprotection against ischaemia.<sup>3</sup>

Even though the association of chronic mucosal ulceration and prolonged usage of nicorandil has been known for some time,<sup>1,3-5</sup> foreskin ulceration associated with use of nicorandil has been identified only relatively recently, with few reports in the literature so far.<sup>1,2</sup>

## DISCUSSION

Nicorandil has been known as a causative factor of many aphthous ulcers<sup>3-6</sup> and painful perianal,<sup>7</sup> vulval<sup>8</sup> and peristomal<sup>9</sup> ulceration. The exact mechanism for ulcer development remains unclear. Putative causative factors include toxic metabolites of nicorandil and the vascular steal phenomenon.<sup>3</sup>

Patel and Harding<sup>3</sup> argued against the toxic metabolite hypothesis to substantiate ulcer occurrence in gastrointestinal and mucocutaneous areas, as nicorandil metabolites are excreted through the kidneys. The vascular steal phenomenon was also thought unlikely, as the ulcer sites are well vascularised, the surrounding skin appearing healthy with no histological evidence of ischaemia. They suggest nicorandil, in a dose-dependent manner, dephosphorylates myosin, which hinders the actin filament contraction necessary for cell migration, which is needed for repair of mucosal microtrauma and healing of surgical wounds.

Furthermore, there have been reports that nicorandil prevents neutrophil rolling, migration and activation, which may hinder the early inflammatory phase of wound healing.<sup>10</sup> Yasu *et al.* found that nicorandil suppresses activation of polymorphonuclear leukocytes (PMNLs), resulting in reduction of PMNL migration into tissue upon ischaemia/reperfusion. They also found that nicorandil, along with the mitochondrial KATP channel opener diazoxide and the nitric oxide donors nitroglycerin and isosorbide

### PATIENT B

An 87-year-old man was referred to urology in view of a progressive ulcer on the foreskin exposing the glans. He had been on nicorandil 20mg twice daily for 15 years. Biopsy of the ulcer edge ruled out malignancy (Figure 2).



Figure 2. Eroding ulcer exposing the glans in patient B

### PATIENT C

A 72-year-old man presented to urology with a painful small ulcer on the foreskin 12 months after commencing nicorandil 20mg twice daily. The ulcer healed completely within 4 weeks of stopping the medication (Figure 3).



Figure 3. Early painful ulcer on the foreskin in patient C

### CONCLUSION

Accurate diagnosis is required for successful wound-care management. It is also important to identify the causative factor for prevention of ulcer formation. Stopping nicorandil is required for ulcer healing and circumcision may be necessary when there are large defects in the foreskin. Healthcare practitioners, particularly those in genitourinary medicine, geriatric medicine, general practice and general surgery, should be aware of the association between nicorandil and genital ulceration to avoid delay in diagnosis and halt ulcer progression by either dose reduction or discontinuation.

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dinitrate, suppressed pseudopod projection in human PMNLs treated with 10(-9)-formyl-methionyl-leucyl-phenylalanine and subjected to shear stress (5 dyn/cm<sup>2</sup>) with a cone-and-plate shear device.<sup>10</sup>

Clinically these ulcers are typically localised, non-purulent and painful. The base of the ulcer may have scant evidence of granulation tissue and the ulcer may penetrate into the deeper tissue. Perianal ulcers can sometimes extend to the sphincter area. In the foreskin, the ulcer may progress, causing large defects in the foreskin, exposing the glans.

Histological examination of the ulcer usually reveals diffuse elastophagocytosis, myxoid granulation tissue, with fibrin deposition and mixed inflammatory cell

infiltrate; although vasculitis and granuloma formation may be absent.<sup>3</sup> The association of mucosal ulcers has been observed to be more common among patients who are on higher doses at or above 20mg twice daily. In some cases the ulceration develops after a dosage increase. There has been no difference in the incidence between males and females who develop such lesions.

The ulcers develop within a few weeks or after many months of initiating nicorandil therapy.<sup>3</sup> Once the medication is discontinued, the associated pain usually disappears within weeks and complete healing occurs thereafter. If the size of the prepuce defect is large, complete healing may take 2–6 months. Large foreskin defects may require formal circumcision.