Inflammation and Infection

Penile Ulceration Secondary to Nicorandil Use

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A B S T R A C T

Nicorandil is a medication used for treatment and prevention of angina pectoris. Its mode of action involves both arterial and venous vasodilation. Although there are numerous known side effects, one of the more unusual, adverse reactions is ulceration of the external genitalia. This case reports the finding of penile preputial ulceration secondary to the use of Nicorandil. The authors make some recommendations for management.

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Introduction

Nicorandil is an antianginal medication which is licensed for the prevention and long term treatment of angina. It works through two principle mechanisms of action. These are through ATP-sensitive potassium channels and nitrate-like channels. Activation of these receptors leads to peripheral venous dilation and to a lesser degree peripheral arterial vasodilatation. This in turn leads to reduced preload and strain on the heart. It is for this reason that Nicorandil is useful in the prevention of anginal symptoms. The IONA randomized trial in 2002 showed that Nicorandil therapy led to a significant reduction in major coronary events when compared to placebo.

Some of the principal side effects of Nicorandil therapy include dizziness, headache, cutaneous vasodilatation with flushing and tachycardia. In the latest edition of the BNF, rarely occurring side effects include intestinal, anal and skin ulceration.

Nicorandil has previously been linked with ulcers of the mouth, gastrointestinal tract, external genitalia, parastomal sites and other cutaneous sites. In this report we wish to identify a further case in which Nicorandil was the likely cause of penile ulceration.

Case report

A 78 year old man presented as an emergency with a defect in the dorsum of the prepuce through which the glans had herniated (Figs. 1 and 2). He had significant co-morbidity including symptomatic angina, type 2 diabetes mellitus, hypertension and renal failure. He was on more than 20 medications including Nicorandil. He was not on steroids and there was no history of trauma.

He related that he had been attending a dermatologist in recent weeks with an ulcer on the penile skin and had been advised to stop Nicorandil. Confused about his medication, he stopped the wrong tablet.

The glans was reduced, and to maintain the reduction, a urinary catheter was inserted (Fig. 3). The Nicorandil was stopped. The defect was much too large to expect primary wound healing and it was clear that circumcision would be required. It was necessary, however, to defer surgery until there was clear evidence of epithelial regrowth. To proceed earlier would certainly have resulted in wound failure and may have led to further necrosis of penile shaft skin.

First re-epithelialisation was observed at 4.5 weeks and circumcision was performed under local anesthesia at 8 weeks. The wound healed primarily and there were no complications.

Pathology of the specimen confirmed inflammatory/reactive changes in the vicinity of a healing ulcer. Nicorandil was permanently withdrawn and aside from other co-morbidities he remains well after two years.

Discussion

The first case to report an association between Nicorandil use and the development of ulcers on the penile skin was in 2007. Since then there have been some other reports of cases suggesting a link. Further to this there are a number of literature reports which have implicated Nicorandil in the development of ulcers elsewhere in the body, namely, along the GI tract, surgical wound sites, parastomal sites, and the vulval/vaginal area.

In the literature to date there are two suggested hypotheses for the pathogenesis of Nicorandil-induced penile ulceration. The first

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is that there may be a toxic effect of either the drug or one of its metabolites. The second, and more widely accepted, is known as the "vascular steal hypothesis." This hypothesis states that ulcers occur due to an alteration in the blood flow to the penis which, in turn, is supplied by an end artery. The need for an initial trauma to the skin (either surgically or otherwise) has also been suggested as an important factor in the development of Nicorandil-associated penile ulceration.

The differential diagnosis for penile ulcers, as in this case, includes a long list of infectious (e.g. syphilis), noninfectious (e.g. Crohn’s disease) and malignant causes. A biopsy of the lesion is extremely important early on to exclude malignancy.

This case, as well as previously described reports of Nicorandil-induced penile ulceration, suggest that the most effective treatment method is to withdraw the use of Nicorandil. In the cases discussed, this did lead to resolution of ulcers in weeks to months. In clinical practice this may not be practical due to the wide differential diagnosis list and the difficulty in recognition of Nicorandil as the cause. In previously reported cases where there was a delay in recognizing Nicorandil as the cause the attempted management has been surgical. The methods have been either surgical excision or circumcision however they only lead to increased morbidity for the patients concerned through wound breakdown or ulcer recurrence.

**Conclusion**

Ulceration at various sites is documented as a rare side effect of Nicorandil therapy. Whilst this has been more gastrointestinal and anal, there is also a clear association with penile ulceration as has been reported on a few occasions. The importance of a full history including medications list cannot be understated as in this case. Although malignancy and infection are a real possibility an open minded approach must be adopted when assessing these patients. Nicorandil use should be considered in the case of any nonhealing ulcer. Indeed, in some cases, the simple task of stopping the medication may obviate the need for the patient to undergo surgical intervention.

The authors would wish to recommend that for similar cases:

1. Nicorandil should be stopped and the patient’s physician informed.
2. The glans penis should be reduced and a catheter inserted to maintain reduction.
3. A period of observation may facilitate primary healing in some cases.
4. If circumcision be required it should be deferred until there is clear evidence re-epithelialisation.

Conflicts of interest
The authors have nothing to disclose.

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