

Nicorandil associated anal ulcers: an estimate of incidence

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ABSTRACT

INTRODUCTION Nicorandil is a commonly prescribed antianginal medication that has been found to be associated with painful anal ulceration. The incidence of this complication is unknown. We have used the best data available to us to make an estimate of this figure in a health district with a remarkably stable population of approximately 200,000 people.

METHODS Using an electronic search of all letters generated from colorectal and gastroenterology clinics as well as endoscopy reports from January 2004 to November 2010, patients with anal ulceration who were taking nicorandil were identified. Other causes of ulceration were excluded by biopsy in the majority of cases. The central hospital and community pharmacy database was interrogated to estimate the number of patients who were prescribed nicorandil over a six-year period (2004–2010).

RESULTS A total of 30 patients (24 men, 6 women) with a median age of 79.5 years were identified who fulfilled the criteria of: taking nicorandil; having no other identified cause for anal ulceration; and achieving eventual healing after withdrawal of nicorandil. In the six-year period an estimated mean of 1,379 patients were prescribed nicorandil each year. The mean annual incidence of anal ulcers among nicorandil users is therefore calculated to be in the region of 0.37%.

CONCLUSIONS Anal ulceration appears to occur in approximately four in every thousand patients prescribed nicorandil each year. Prescribing physicians should explain the risk of this unpleasant complication to their patients.

KEYWORDS

Nicorandil – Adverse effects – Anal ulcer – Incidence – Epidemiology

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Nicorandil is a commonly prescribed antianginal medication and Watson *et al* first described its association with painful anal ulceration in 2002.¹ Since then, several other case series have confirmed this unusual complication of nicorandil.^{2,3} Nicorandil associated anal ulceration is usually diagnosed when other causes of anal ulceration have been excluded by biopsy.

The eventual disappearance of the anal ulcer almost always occurs on cessation of the medication, after a median period of 3–4 months,^{3,4} which also serves to confirm the diagnosis. The pain caused by the condition is often debilitating and failure to make the correct diagnosis has sometimes led to prolonged suffering, with an average duration of symptoms before correct diagnosis of two years.⁵ Patients have even been subjected to unnecessary treatments, including abdominoperineal resection, when the link between nicorandil and anal ulcer was not realised in time.² Anal ulcerations can occur with daily doses of nicorandil as low as 20mg and after a few weeks to several years of treatment.⁵

Anal ulceration is an uncommon complication of nicorandil and there are many aspects of the condition that are not understood, including its pathogenesis and incidence. We have therefore used the best data available to us to make

an estimate of the incidence of this condition in a health district with a remarkably stable population of approximately 200,000 people.⁶

Methods

Patients with nicorandil associated anal ulceration were identified by using an electronic search with the word ‘nicorandil’ of all letters generated from colorectal and gastroenterology clinics as well as endoscopy reports at Cumberland Infirmary from 1 January 2004 to 30 November 2010. These clinic letters and endoscopy reports were studied for demographic data including the patients’ age and sex, doses of nicorandil and the description of the nicorandil associated pathology. The electronic pathology reporting system was searched for histopathology reports of cases where other causes of anal ulceration were excluded by biopsy.

The central hospital and community pharmacy database (ePACT) was interrogated to estimate the number of nicorandil users in a six-year period from 2004 to 2010 in a catchment area corresponding closely to that of the district general hospital. From this database, the number of dispensed prescriptions for nicorandil was obtained for each month.

In order to calculate the relationship between the number of nicorandil prescriptions and the number of people taking this medication, a survey of 6 of the 29 general practices in the catchment area was conducted to ascertain the number of people taking a dose of 30mg of nicorandil, given these patients will have required administration of a combination of 20mg and 10mg tablets. The frequency of nicorandil prescription made to the patients in our catchment area was investigated by using the ePACT system during April to July 2011.

Results

A total of 30 patients (24 men, 6 women) with a median age of 79.5 years (range: 65–90 years) were identified who fulfilled the criteria of: taking nicorandil; having no other cause for anal ulceration identified; and achieving eventual healing with the withdrawal of nicorandil. Of these, 28 cases were seen in the colorectal department and the remainder in the gastroenterology department. The range of daily dose of nicorandil consumed by affected individuals varied from 20mg to 60mg.

Of the 30 patients, 17 had histological analysis to refute other causes of anal ulceration. The remainder were thought on macroscopic appearance to have nicorandil associated anal ulceration and underwent a period of observation off nicorandil to confirm healing of these ulcers. The ulcers occurred in all positions around the perimeter of the anus and the diameter of the ulcer varied from a pinhead size to 30mm.

In the 6-year period, a mean of 1,404 prescriptions of nicorandil were made every month. In the 6 general practices out of the 29 in our catchment area, 13% of the patients were prescribed 30mg doses, which would require separate prescriptions of a combination of 20mg and 10mg tablets.

Although the majority of the patients had nicorandil prescribed once a month, a minority were prescribed this for a different duration of time. We calculated over a 4-month period in selected general practices that 6,024 patients were prescribed nicorandil assuming that they required 60 tablets of either 10mg or 20mg per month as per the recommended prescribing practice in the *British National Formulary*.⁷ However, the number of prescribing episodes during the same period was 5,440, given that for example some patients were being prescribed nicorandil two months at a time. This means that there are $6,024 \div 5,440 = 1.11$ patients taking nicorandil per prescription event per month.

We can infer from the above information that a mean of $1,404 \times 1.11 \div 1.15 = 1,379$ patients were prescribed nicorandil each month. Moreover, these figures give an estimated incidence of anal ulceration of $(30^a \div 1,379^b) \div (71^c \div 12^d) \times 100 = 0.37\%$ among nicorandil users per annum. (Key: a = number of nicorandil anal ulcer cases; b = number of people prescribed nicorandil over the study period; c = number of months the study ran over; d = number of months in a year)

Our search of colorectal and gastroenterological reports and correspondence also brought to light cases of unexplained ulceration at other body sites in which nicorandil

might have been implicated. Eventual healing of ulcers occurred after cessation of nicorandil. The cases were of colonic ulceration ($n=7$), natal cleft ulceration ($n=2$), ileal ulceration ($n=2$), penile ulceration ($n=1$) and paraileostomy ulceration ($n=1$).

Discussion

Our study shows that anal ulceration occurs in approximately four in every thousand patients prescribed nicorandil each year. Most of the cases of nicorandil associated anal ulceration were referred to the colorectal surgical department, with a minority being seen by the gastroenterologists. Given the painful nature of this condition and its location at the anus, we are confident that our search strategy would have identified most if not all the cases presenting to medical practice in the catchment area of our district general hospital.

While previous case series and reports describe anal ulcerations occurring mostly in patients taking 30mg of nicorandil twice daily, doses as low as 20mg per day have been associated with anal ulceration,⁸ including two patients in our case series. The maximum duration of time reported from starting nicorandil to developing an anal ulcer is 66 months.⁹ As there is a wide range of dosage and duration of nicorandil therapy associated with anal ulceration, we have considered all nicorandil users to be at potential risk and included them all when calculating the incidence.

Cumbria has a relatively stable population compared with the rest of England and Wales.⁶ This minimises the potential bias caused by migration during a study period of six years.

The central and community pharmacy database logs all prescriptions dispensed in this geographical area. This number does not equate to the number of people taking the medication but we have been able to infer this by factoring in the periodicity of nicorandil prescription as well as the proportion of patients taking 30mg of nicorandil, which would require a combination of 10mg and 20mg tablets. We acknowledge that this is a potential source of error in our calculations but expect this to be minimal as the prescribing practices were not dissimilar between the general practices we interrogated.

It was not possible in this relatively small retrospective study to investigate for the presence of other factors that may influence the development of anal ulceration, such as age, co-morbidities and associated medications.

The identification of nicorandil associated ulcers in other anatomical locations in this study is in keeping with previous case reports.^{1,5,10} The fact that they are uncommon may delay prompt diagnosis.⁵ The appearance of unexplained non-healing ulceration in any anatomical site, even if it is not mucosal tissue, should prompt one to consider nicorandil as a potential cause.

Conclusions

To our knowledge there have been no other studies attempting a calculation of the incidence of nicorandil associated

anal ulceration. The risk of this unpleasant complication of nicorandil should be known by prescribing physicians as well as their patients. However, many patients often suffer for considerable periods of time before the complication is recognised,⁵ suggesting that some doctors may not be aware of this complication. Other aspects of this condition are as yet unknown, including its pathogenesis, as well as the other risk factors that may contribute to the development of anal ulceration in nicorandil users.

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References

1. Watson A, Al-Ozairi O, Fraser A *et al*. Nicorandil associated anal ulceration. *Lancet* 2002; **360**: 546–547.
2. Katory M, Davies B, Arasaradnam R *et al*. Nicorandil associated anal ulceration. *Colorectal Dis* 2004; **6**: 527.
3. Renwick AA, Chong DS, McMahon AJ. Chronic non-healing anal ulceration and nicorandil: further evidence of an emerging problem. *ANZ J Surg* 2004; **74**: 1,128–1,129.
4. Katory M, Davies, B, Kelty C *et al*. Nicorandil and idiopathic anal ulceration. *Dis Colon Rectum* 2005; **48**: 1,442–1,446.
5. Baker RP, Al-Kubati W, Atuf M, Phillips RK. Nicorandil-induced severe perianal ulceration. *Tech Coloproctol* 2007; **11**: 343–345.
6. Office for National Statistics. *Census 2001: Key Statistics for Health Areas in England and Wales*. London: TSO; 2003.
7. Joint Formulary Committee. *British National Formulary*. 62nd edn. London: BMJ Group and Pharmaceutical Press; 2011.
8. Watson A, Suttie S, Fraser A *et al*. Nicorandil associated anal ulceration. *Colorectal Dis* 2004; **6**: 330–331.
9. Cooke NS, Tolland JP, Dolan OM. Nicorandil-associated perianal ulceration: a case series of 10 patients. *Br J Dermatol* 2006; **154**: 199–200.
10. Kinney M, O'Rourke D, O'Kane H *et al*. Nicorandil induced penile ulceration. *Ulster Med J* 2010; **79**: 123–124.