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**ADVANCES IN THERAPEUTICS**

# NICORANDIL, GASTROINTESTINAL ADVERSE DRUG REACTIONS AND ULCERATIONS: A SYSTEMATIC REVIEW

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BACKGROUND

Nicorandil is a popular anti-anginal drug in Europe and Japan. Apart from common adverse drug reactions (ADR), its safety is satisfactory. Several reports have suggested a link with gastrointestinal ulceration and fistulas. The review aims to critically appraise, synthesize and present the available evidence of all known gastrointestinal ADR per anatomical location.

METHODS

The study complied with the PRISMA statement. Literature and pharmacovigilance databases were used to provide rate and/or calculate parameters (median age, median dose, history of symptoms, length of therapy, healing time after withdrawal of the drug). Differences in distribution of quantitative variables were analyzed via Mann-Whitney test. Correlation between quantitative variables was assessed with a Spearman's correlation coefficient. A p value $<0.05$ was significant.

RESULTS

Oral ulcerations occur in 0.19% of the subjects, anal ulcerations between 0.07–0.37%. Oral and distal GI involvements are the most common ADR (28-29% and 27-31% of all gastrointestinal ADR, respectively). The hepatobiliary system, the pancreatic and salivary glands are not affected by nicorandil exposure. The time to develop oral ulcerations is 74.0 weeks among people on <30mg/die versus only 7.55 weeks in individuals on higher

regimens (p=0.47). There is a significant correlation between dose and ulcer healing time (Spearman's 0.525, p<0.001).

CONCLUSIONS

Ulcerative disease is a very commonly reported GI-ADR. A delayed ulcerative tendency supports the hypothesis of an ulcerogenic metabolite. Nicorandil seems to act as necessary, but not always sufficient, cause of the ulcerations. Whether the action of the metabolites relies on a specific mechanism or a simple chemical ulceration still has to be established.

## BACKGROUND

Nicorandil was first used in 1984 in Japan for the management of angina and has been available in the UK since 1994. Despite not being FDA-approved, it is considered a safe and tolerable drug following observations from trials, everyday practice and prescription event monitoring studies. Withdrawals from study medication happened in 39.1% of participants (31.6% in the placebo group), in one of the largest trials ever conducted, the IONA[1,2]. It is also quite a popular choice. Prescription Cost Analysis (PCA) Data, containing information on the number of items and the net ingredient cost of all community prescriptions dispensed in England, shows average monthly expenses reaching 833,184 GBP between August 2013 and January 2014. Health Boards in Scotland have spent 2,863,347 GBP on nicorandil preparations in 2013. It is recommended as third-line medication for people on beta-blocker or calcium channel-blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated[3]. In 1997 the drug was called in question as cause of severe oral ulcers[4]: successively, a strong link between nicorandil and various lesions of the gastrointestinal tract was endorsed.

## PHARMACODYNAMICS

The use of nicorandil, (N-2-hydroxyethyl) nicotinamide nitrate, results in arterial and venous dilation due to a dual mechanism of action. It features a nicotinamide moiety responsible for the effect on $K^{+}_{ATP}$ channels coupled to nitric oxide (NO), with vasodilating properties[5-8].

Reduced sensitivity of the adenosine triphosphate ATP-dependent potassium channel to ATP augments the flow of potassium from the sarcolemmal potassium channel. This is followed by a hyperpolarization that closes voltage-dependent calcium channels in the cell membrane and increases calcium efflux through the sodium channel exchanger. Additionally, the NO stimulates the guanylate cyclase that increases cyclic guanosine monophosphate (cGMP) production and consequently decreases cytosolic-free calcium in vascular smooth muscle[9,10].

**PHARMACOKINETICS**

The usual dose is 10-20mg twice daily and up to 30mg twice daily may be used[11,12]. The drug is absorbed 30-45 minutes after ingestion with minimal first-pass metabolism in the liver and thus it features high bioavailability[13]. The bond to albumin and plasma protein is weak and most of the drug circulates unbound[13]. A steady state is achieved on the fourth day and repeated administrations cause accumulation of nicorandil and its metabolites (with little effect on the cardiovascular system)[14].

Maximum plasma concentrations are reached within 60 minutes of oral ingestion and are directly proportional to dosage[13]. Metabolism occurs by de-nitration of the molecule into the nicotinamide pathway. The two main biotransformations of nicorandil are de-nitration, leading to inactive N-(2-hydroxyethyl) nicotinamide, and reduction of the alkyl chain, leading to nicotinamide / nicotinic acid[15,16]. Further metabolism of these compounds is thought to produce non-toxic, water-soluble vitamin-B complex substances, incorporated into the endogenous NAD/NADP pool. Interestingly, parameters such as age, renal disease or interference with hepatic drug metabolising enzymes do not seem to

affect the pharmacokinetic parameters. In fact, when nicorandil is administered concomitantly with an inhibitor, (e.g. cimetidine) or an inducer (e.g. rifampicin) of hepatic microsomal oxidase, the pharmacokinetic profile of the former remains unchanged[14]. No evidence from the literature was found to support increased haematic concentrations of nicorandil after hepatic impairment or worsening side effects in patients with liver failure.

Following hepatic metabolism, the metabolites are mostly eliminated in the urine. The initial renal clearance has been estimated as 10mL/min, although there appears to be a second distribution phase, with low plasma levels after 8 hours, possibly caused by a slow release from the vascular tissues[14]. About 1% of the dose is excreted unchanged in urine and faecal excretion accounts for <2%.

The occurrence of gastrointestinal ADR in the form of ulcerative and fistulating disease, is underestimated[17-21] and the awareness of the problem is still suboptimal among physicians. No systematic review has ever been conducted, published or registered and such a study would assess the extent of the problem from a broader perspective.

## METHODS

The review focuses on gastrointestinal ADR documented in the human population in experimental and pragmatic settings, following oral and/or intravenous administration of nicorandil at any point since start of anti-anginal therapy. A direct comparison of GI-ADR attributed to other anti-anginal drugs is beyond the purpose of the review.

The primary outcome is to provide an incidence rate and summative information on the ulcerative and fistulating disease in patients on nicorandil, in the form of median age, median dose (mg), history of symptoms (median of weeks), time between start of therapy and onset of event (median of weeks) and healing time after withdrawal of drug (median of weeks). Distribution of values across different groups is assessed with a Mann-

Whitney U-test; correlation of quantitative data across groups is assessed with a Spearman's rho. A 5% significance is considered valid.

The secondary outcome is to provide a count and relative frequency of adverse drug reactions[22] in different gastrointestinal locations using reports from the WHO Adverse Drug Reaction Database and the Medicine & Health products Regulatory Agency (MHRA) Drug Analysis Print.

All studies documenting GI-ADR caused by the administration of nicorandil, in the form of experimental studies, cohort studies, case-control studies, case reports and critical studies are included. The study is conducted according to the PRISMA statement[23]. The search conducted between July and November 2013 was designed to access both published and unpublished materials with no fixed time span and comprised a search of Medline, CINAHL, EMBASE, Biomedical Reference Collection, Google Scholar and the Cochrane Library using the relevant keywords contained in the title, abstract and subject descriptors: *nicorandil, gastrointestinal, side-effect, adverse reaction, ulcer$, mucosa$, cutaneous, fistula$, hepatotoxicity, liver failure.* Works published in all languages have been considered.

Criteria for exclusion from the quantitative synthesis were limited to retracted literature and articles on nicorandil not featuring gastrointestinal ADR. Two independent reviewers critically appraised the literature using a standardised data extraction protocol (Fig 1).

## RESULTS

171 sources were included in the review and 92 used for the quantitative synthesis from an initial 2241 search results. 71 articles were included from other sources, such as the WHO-ADR and MHRA databases, the unpublished database of gastrointestinal ADR observed during the IONA trial and bibliographies of screened articles (Fig 2).

## GENERAL GASTROINTESTINAL SIDE-EFFECTS

The tolerability of nicorandil has been assessed numerous times in trials: Guermonprez et al. in 1993 conducted a randomised double-blind study with 123 patients to compare Nicorandil at 20mg twice daily to a regimen of diltiazem. The duration of the study was 3 months and no relevant ADR were noted apart from headache, dizziness, palpitation and asthenia as well as non-otherwise specified gastrointestinal disturbances[24]. Gastralgia and nausea only were reported by 10 patients (5.1%) during a one-year period of exposure to nicorandil[25]. In a multi-centre randomised parallel trial, where 57 participants were randomised to nicorandil, no gastrointestinal events were witnessed[26]; no significant reactions were noted in similar studies comparing nicorandil with other calcium channel blockers[27], isosorbide 5-mononitrate, isosorbide dinitrite[28-31] or β-blockers[32-36] or when nicorandil was added to a baseline therapy in settings of unstable angina[37] or acute myocardial infarction[38-43].

In one of the largest studies, the IONA, 194 adverse gastrointestinal events were documented in 163 participants of the nicorandil group (6.35%) vs 132 events among 110 placebo recipients (4.3%): the severity, the number of patients and statistical evaluation were not given in the original article[1,2]. When observed in detail however, the data provided by the authors[44] reveals that among those events, 5 cases of oral ulceration were found in the experimental and none in the control group; proctitis and rectal bleeding had been documented in 15 participants on the new anti-anginal but only 3 were reported in the control group, thus conferring a risk ratio (RR) of 5.0; also, 14 cases of diverticular disease and diverticulitis were flagged in the nicorandil group (only 3 episodes in the control group; RR 4.7).

Roland et al.[45] extracted data from the European clinical development programme for nicorandil, which included 1680 participants (healthy volunteers and

patients with angina pectoris). The total incidence of events reported among nicorandil recipients did not differ from those taking other anti-anginal drugs. The incidence of nausea and vomiting was estimated as 2.3%. The same author provides an estimated total incidence of general ADR from nicorandil exposure, extracting data from post-marketing surveillance covering 14,530 cases in Japan, and calculated it as 3.5%.

The first documented case of nicorandil-associated oral ulceration was published in France in 1997[4]. The link with ulceration, however, was not established unequivocally. A British prescription-event monitoring (PEM)[46] study in 1999 reiterated the safety of the drug within the gastrointestinal tract. Dyspeptic symptoms were the most commonly reported event and there were also a few cases of dysphagia. The study found a total of 55 patients with oral ulceration in a cohort of 13,620 patients (0.4%). Despite this being a significant number in comparison with other unspecified anti-anginal drugs (crude ratio 2.03, CI 1.48-2.74), a relation was not considered because of a lack of a dose-response effect[47]. Therefore the hypothesis endorsing a link between the drug and the oral ulcers was rejected. Successive reviews did not emphasize an ulcerative tendency of nicorandil[48-50].

The first report[4] preceded numerous others. It is now evident that the onset of ulceration involving the skin, mucosa or other tissues typically occurs following a period ranging from a few weeks to years. Reviews claim that ulcerations typically presents following higher doses of nicorandil (40–60mg/day) or following a dose increase; however, even lower regimens (10mg daily) have been reported to lead to the adverse reaction[51-53]. Charting data from all the literature, the median dose of nicorandil does not correlate with the onset time of the ulcers (Spearman's rho 0.164; $p=0.252$) but does correlate with healing time (Spearman's rho 0.525; $p=<0.001$) (Table 1).

According to the MHRA the total number of ADR following nicorandil exposure, since its introduction, is 2232. The number of gastrointestinal ADR is 797 (35.7% of the

total), of which 6 were deemed to be fatal. The WHO case-info report (with criteria restricted to suspected gastrointestinal reactions) contains 914 GI ADR from 12 different countries: 65 of those (7.1%) were defined as "serious". General gastrointestinal ADR are 21.7% and 28.9% in the MHRA and WHO databases, respectively. The anatomical distribution of ADR is presented below.

**ANATOMICAL DIVISION**

*Oral Cavity*: oral ulceration is the mostly commonly reported gastrointestinal side effect of nicorandil. With 5 participants over 2565 in the experimental group, the overall incidence of oral ulcers is estimated as 0.19%, using data from the IONA trial, which featured a mean follow-up of 1.6 years. In an observational study, a much higher proportion of oral ulcerations was seen (5% of patients[17]): In 3 cases, examination showed a pattern of chronic oral ulceration; in the other 2 cases there was a positive history for buccal ulcerations[17].

According to Cribier et al.[54], 3 out their 7 patients with oral ulcers already had a history of chronic aphthous ulcers: nonetheless, the ulcers that occurred while on nicorandil were unusually large and painful and did not show resolution after 3-4 days. A history of aphthous stomatitis could be a "cofactor"[17,55], as it was present in 23% of cases in one review of nicorandil-induced oral ulcerations[56]. Reichert et al.[4] was the first to describe mouth ulcers in 2 patients, mimicking a pattern of major recurrent aphthous stomatitis (MaRAS)[57]. Ulcers in MaRAS persist for up to 6 weeks and often heal with scarring. There is a tendency for the lesions to form heaped-up margins, which may lead to a suspicion of malignancy. MaRAS may produce lesions throughout the oral cavity, including the soft palate and tonsillar areas with possible extension to the oropharynx.

All of these features have been documented with nicorandil-related ulcerations: the overall median size of the oral ulcers[51,54,58-70] is 15mm (IQR 11.5 – 20.6). After this

review, consistent dissimilarity persists with regards to depth, size and base of the nicorandil-related oral ulcers. Deep, punched out appearances have been described[51] in addition to those of superficial extent only[58]. Irregular, linear, oval or round borders have been reported[51,54,59]. The base of the lesions is often described as yellow[59] or with a grey pseudomembrane[60]. On biopsy, most results showed non-specific ulceration[10,51,59,61,62,71]. A few reported an eosinophilic infiltrate[17,54,60,63] whilst one article described vasculitic features, possibly suggesting an element of hypersensitivity[72]. Dysphagia, weight loss and depression are common associations with nicorandil-induced recurrent aphthous stomatitis.

Withdrawal of nicorandil is a sufficient measure to allow oral ulcerations to heal, with a median time of 4.3 weeks (IQR 4.0 – 6.4). It has been suggested that the risk of oral ulceration increases significantly after reaching the threshold of 30mg/day[54,73]. Nevertheless, the odds of developing iatrogenic ulcers probably increase with cumulative exposure to nicorandil. Jang et al.[63] consented a patient for an oral provocation test: 5mg of nicorandil were administered to an individual who had previously developed deep ulcers on tongue and buccal regions whilst on 10mg of nicorandil (the medication had been suspended with resolution of the disturb). Two days after the test, he redeveloped small ulcers with greyish pseudomembranes, in the same areas.

124 patients with oral ulcers from the literature have been divided in two groups depending on their anti-anginal intake, whether <30mg/die (25 patients)[51-53,63-65,68,69,74-81] or ≥30mg/die (99 patient) [4,10,17,54,55,58-61,66,67,70-72,82-90]: the median time needed for the ulceration to develop was 74.0 weeks (IQR 19.4 – 197.7) in the first group, versus only 7.55 weeks (IQR 5.25–48.7) *(p=0.423,* Table 2*).*

Aphthous stomatitis, oral and gingival ulcerations and erosions are commonly reported events in the MHRA, constituting roughly 28% of the GI-ADRs; the proportion

is over 29% in the WHO database, excluding potentially significant events such as "glossitis" or "dysphagia".

*Salivary glands:* very rare reports of "dry mouth" have been made following exposure to nicorandil; neither the MHRA nor the WHO databases contain consistent data associating it with salivary gland pathology.

*Pharynx*: isolated involvement of the pharynx appears uncommon. It is highlighted 3 times (0.32%) in the WHO list, with all reports originating from the UK. Cupples et al.[71] reported one case of oral actinomycosis in a 73-year-old woman on nicorandil, who presented with chronic pharyngeal pain and featured an ulcerated, calcified lesion in the left tonsillar fossa, extending into the parapharyngeal space, as well as an ulceration involving the left buccal mucosa. While the former was found to show colonies of actinomyces, the histology of the buccal ulceration consisted of active, non-specific, chronic inflammation with a tendency of the inflammatory cell infiltrate to involve the striated muscle and vascular channels.

*Oesophagus:* there were no suspected ADR within the oesophagus in the literature. The MHRA however reports 6 (0.75%) cases of dysphagia and 5 oesophageal ulcers (0.63%), one oesophageal perforation (0.13%), 2 cases of gastro-oesophageal reflux (0.25%) and one case of oesophagitis (0.13%). The WHO presents 5 cases of oesophageal ulceration (0.55%), as well as 9 reports of gastro-oesophageal reflux (0.98%), one oesophageal haemorrhage and one perforation (0.11% each).

*Stomach and duodenum:* literature endorsing a strong link between nicorandil and gastric or duodenal side-effects was not found. The MHRA features 2 cases of gastric perforation (0.25% of GI ADRs), 1 of gastritis and 2 gastric ulcers, one of which caused haemorrhage. There is one reported case of maelena and one of haematemesis. There were 7 episodes of gastrointestinal bleeding (0.88%), not otherwise specified. Higher frequencies are listed in the WHO database: 8 cases (0.83%) of gastrointestinal bleeding,

in addition to 19 gastric ulcers (2.1%) and 3 (0.33%) gastric perforations. The causality assessment is challenging due to missing data, confounders and the fact that nicorandil has shown to be gastroprotective as a single dose in animal studies[91,92].

*Pancreas:* only one episode of pancreatitis has been described in the UK and appears on the MHRA and WHO reports. Overall, involvement of the pancreas does not appear to be a concern.

*Liver and biliary system:* excepting deranged liver function and jaundice in the pharmacovigilance databases, there is lack of information to sustain a relevant involvement of the hepatobiliary system following exposure to nicorandil. Isolated events of hepatic failure, hyperbilirubinaemia, jaundice and abnormal liver tests were noted and followed up in the PEM study but no further information about causality assessment was provided[46]. Hepatitis, jaundice, pruritus and cholestasis are reported as rare events in the British National Formulary[11].

*Jejunum:* isolated events affecting the jejunum have not been clearly documented, although pictures of widespread ulcerations involving the small and large bowels have been reported in the literature[62,93]. Broad terms such as "small intestinal ulcer" and "small intestinal perforation" are contained in the MHRA report, as well as "enterovesical fistula" and "enterocutaneous fistula", without further specification. These events, taken together, represent 1.1% of all MHRA reactions. A separate event is listed as "inflammatory bowel disease" without anatomical indication. The pharmacovigilance report of the WHO identifies 1 "small intestinal ulcer" (0.1%), 3 small intestinal perforations (0.3%) and 12 NOS "intestinal ulcerations" (1.3%).

*Ileum:* ulceration and perforation of the ileum during nicorandil therapy has been accurately described. King et al.[94] reported a 53-year-old woman with ischaemic heart and peripheral vascular disease, presenting with peritonitis. She also had a chronic leg ulcer of unknown aetiology, where the histology was uninformative. At laparotomy, she was

found to have a perforation and extensive ulcerations of the ileum, mandating a right hemicolectomy and ileal resection. The authors did not mention the dose, the length of the anti-anginal therapy nor whether nicorandil was withdrawn and what the final outcome was; it is however interesting to note that the patient suffered from a chronic cutaneous ulceration, diagnosed as pyoderma gangrenosum (as seen in other cases of nicorandil-induced skin ulceration)[95-99], treated with long-term steroids. Griffiths[93] replied to the article citing his experience with a 74-year-old woman, found to have isolated ulcers at the hepatic flexure and the distal small bowel. Swinscoe at al.[100] presented a case of ileal involvement, resulting in rectal bleeding. Remission was not obtained after withdrawal of aspirin and NSAIDs but was finally achieved when nicorandil was suspended. The histological features were consistent with ischaemia rather than inflammation.

The literature reports the involvement of the ileum in the context of surgical stomata as well[19,20,101,102]; apart from rare cases of cutaneous manifestation of Crohn's disease, peristomal ulcerations in clinical practice usually recognize a mechanical cause[103]. The drug is considered in fact the commonest cause of stoma ulceration in patients not affected by inflammatory bowel disease. The lesions, possibly triggered by trauma, regress following withdrawal of the medication. Nicorandil might also be the unexplored reason why a stoma had been fashioned in the first place[20].

*Caecum and ascending colon*: isolated involvement of the caecum by ulceration is recognized. Lee et al.[104] reported 2 individuals with caecal ulcerations in their series of 8 patients. The histology featured only inflammatory changes, without ischaemic features. A previous report[105] described similar lesions in the transverse and right colon of a 76-year-old lady. Histology was not suggestive of inflammatory bowel disease or mesenteric ischaemia. Ramos et al.[106] gave notice of a sigmoido-caecal fistula in a 76-year-old man on nicorandil, who suffered from a 6-month history of diarrhoea; again, no element was found to suggest a neoplastic or inflammatory origin. The WHO list features one case of

caecum perforation (0.1%), flagged in the UK and resulting in a life-threatening but not fatal event.

*Rest of Colon and Rectum:* nicorandil may be responsible for lesions varying from isolated colonic ulceration to severe widespread eroding patterns involving the whole colon. The clinical presentation in these cases features a history of diarrhoea, persistent lower abdominal pain and bleeding per rectum. In the IONA trial, proctitis, rectal disorders and bleeding affected 0.6% of participants[44]. The pharmacovigilance reports a relative frequency of colonic and rectal involvement of 6.8% (WHO) and 8.5% (MHRA).

Given the typical age of patients on nicorandil, the symptoms might be interpreted as exacerbations of diverticulitis: furthermore, it is likely that drug exposure during activation of diverticular disease does aggravate its severity. McDaid[107] conducted a case-control study among patients suffering from diverticular disease, to prove that nicorandil confers an increased risk of developing colonic fistulae: the odds ratio was 7.8 (CI 1.5–39.1; $p = 0.008$). Two important confounders, age and ischaemic heart disease, were found to be equally distributed between the two groups.

Smith and Lyon[20] supported this observation, after reviewing the records of 895 patients seen in the specialist clinic for stoma-related problems: 36 of them (4%) previously underwent surgery for diverticular disease; among the patients treated with nicorandil (12), there was increased incidence of enteric fistulae and bowel perforation (*two tailed Fisher's, $p<0.0001$*). All 12 individuals in the nicorandil group had stomal ulcers, compared to only 2 out of 24 in the non-exposed group. Despite this, the association between nicorandil and fistulating diverticular disease doesn't appear frequently reported in pharmacovigilance. Aggravation of diverticulitis, perforation and large bowel fistulae constitute 1.4% and 0.8% of GI events in the MHRA and WHO report: 0.5% of participants in the nicorandil group suffered from a significant exacerbation of diverticulitis (versus 0.1% in the control group) during the IONA[44].

*Anus*: involvement of the most caudal portion of the gastrointestinal tract is strongly associated with nicorandil, with the first report of perianal ulceration documented by Watson et al. in 2002[108]. Ulcerating lesions involving the perianal area represent 22.1% of the gastrointestinal adverse drug reactions reported to the WHO and 27.4% within the MHRA database. While no anal ulceration was formally mentioned in the IONA, it has been suggested that the overall incidence might be around 0.07%[18]. A higher rate was estimated by Colvin et al. (0.37%)[19] in their retrospective cohort study, where the number of exposed was calculated from prescriptions in general practices. The main features are gradual onset, pain, failure to heal and resolution on withdrawal of the drug.

In analogy with oral ulcerations, there is a tendency for the histology to be aspecific, with simple features of inflammation; a condition of vaginal leukoplakia with intra-epithelial neoplasia in the context of perianal, vaginal and perineal ulceration has been described[18], as well as elastophagocytosis with foreign body giant cells[109] and perianal actinomycosis[110]. Perianal fistulating disease whilst taking nicorandil appears more rare, constituting 1.9% and 1.2% of the MHRA and WHO gastrointestinal reaction reports, respectively. Data from the literature regarding 165 patients with ulcerations of the distal gastrointestinal tract[18-20,93,96,101,102,104-149] is presented in table 3.

## DISCUSSION

This review is the first that aims to provide a comprehensive view of the gastrointestinal involvement following exposure to nicorandil. It shows how different sites are involved with different frequencies.

Several hypotheses have been brought forward to explain the link between nicorandil and ulcers (Table 4). The vascular steal phenomenon has been cited as a possible explanation[108,146], however, animal studies demonstrate an anti-ulcer activity of nicorandil[91,92] and the presence of oral ulceration renders a hypothesis of ischemia in

the well-vascularized oral cavity doubtful[10]. A direct local toxic action induced by electrolyte disturbance has been considered, secondary to nicorandil's activity on ATP-sensitive potassium channels[150-152]; a hypersensitivity involving non-keratinizing squamous epithelium lining specific areas of the oral cavity and lower anal canal has been suggested[18]: this however would not explain the ulcerating and fistulating disease involving other segments of the gastrointestinal tract. Patel et al.[153] argued 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. Nicorandil has been shown to inhibit endothelial cell mitogenesis and proliferation in experimental settings[154,155] and in animal studies it has shown to hamper the inflammatory pathway, decreasing the production and release of tumor necrosis factor-alpha (TNF-α) and other mediators that pave the way for the healing process[156,157].

Trechot et al.[158-161] postulated an interaction between the metabolic pathways of the drug and the endogenous pool of nicotinamide adenine dinucleotide /phosphate (NAD/NADP). After saturation of the endogenous NAD/NADP pool, nicotinamide and nicotinic acid (pKa 4.9), accumulate and abnormally distribute in the tissues. The combination of vasodilation induced by the drug and chemical ulceration secondary to nicotinic acid would cause the ulceration. Hence, a fistulating disease would originate from an ulcerating lesion in a susceptible area (e.g. colonic diverticulosis). The same authors analysed an ulcerated skin biopsy from a patient exposed to nicorandil via mass spectrometry: they found high concentration of nicotinic acid (38μg/mg of dried skin biopsy) and nicotinamide (11μg/mg) in the cutaneous ulcer, as opposed to 21 and 4μg/mg of nicotinic acid and nicotinamide from a random non-ulcerated skin sample from the

same patient. Nicotinic acid and nicotinamide were estimated as <1μg/mg of dried skin biopsy in a control, not exposed to nicorandil (one of the authors)[21].

Nicotinic acid, or niacin, is a water-soluble B-complex vitamin that has been used to treat dyslipidaemia, as able to affect all lipid parameters[162]. In adipose tissue niacin inhibits the lipolysis of triglycerides by hormone-sensitive lipase. In previous systematic reviews, it has been associated with increased serum HDL-C[163] and reduction of cardiovascular events and stroke[164] but its routine use in prevention is controversial[165]. Its deficiency causes pellagra and its side effects are mainly represented by cutaneous flushing, dry skin, pruritus, skin rashes and achanthosis nigricans, as well as gout exacerbation and serious hepatotoxicity (high serum transaminases and hyperglicaemia[162]).

The hepatobiliary system does not appear to be commonly and significantly affected by nicorandil exposure. Although this is not in keeping with the hypothesis above[158-161], the accumulation of the allegedly ulcerogenic molecule would take place at the tissue level, likely without high serum concentrations observed in patients under niacin therapy.

There is a tendency to develop mucosal ulcerations earlier with higher dosages of nicorandil; anyhow, oral ulcerations have been reported with small doses and a concomitantly increased period of time for the onset. It also appears that the involvement of the colon and rectum take place in older, and possibly more frail, patients (Table 3). Topical and systemic steroids have been widely used to relieve symptoms from oral ulcers with little or no effect, as well as colchicine, antifungals, aciclovir or various antibiotics[4,10,51,54,58-61,63,67,68,79,87]; no healing has ever been observed, without a simultaneously enforced withdrawal or dose reduction of nicorandil. In anal ulcers, conservative measures (e.g. dressings, glyceryl trinitrate ointment or botulinum injection) without suspension of nicorandil are described to be not effective[113,130,145], let alone

a surgical intervention[119,126,130,133,147]. It is probable that pharmacogenetics are involved and some individuals preferentially metabolise the drug into more ulcerogenic daughter molecules.

Reports have emphasized how the drug can cause lesions elsewhere: non-gastrointestinal ulcerations occur in compromised, vulnerable regions, e.g. in the context of a large inguino-scrotal hernia[95], in an area undergoing intraoperative compression by a leg brace[97], in the perineal region following a fall onto the toilet[142], in the penile region following circumcision[99] or in a previously healing wound from a pacemaker insertion[166]. It is plausible that nicorandil might also delay healing, establishing a self-perpetuating inflammation; this might explain the existence of a secondary fistulating disease. The authors hope that these observations might increase physicians' understanding of the phenomenon and positively influence patient care.

## STRENGTHS, LIMITATIONS OF THE STUDY

The review provides a broad, comprehensive perspective of the knowledge available, as well as a retrospective, summative re-interpetation of data. The study suffers from literature heterogeneity and predominance of small studies, missing information, high amount of confounders and impossibility of causality assessment. To offer a broader and comprehensive picture, it is acknowledged that the study did not involve a formal weighing of sources of different quality.

## CONCLUSION

Nicorandil is an effective anti-anginal (as proven by a not infrequent decompensation of heart failure, when the medication is stopped) but the tendency of ulceration increases over time and with higher dosage. Oral ulcerations are seen in roughly

0.2% of patients, rectal involvement in up to 0.6%. Perianal ulcerations, according to observational studies only, occur in 0.07-0.37% of patients.

The hypothesis of the ulcerogenic metabolite appears to be the most convincing. Nicorandil seems to act as a necessary, but not always sufficient, cause at the origin of the ulcerations. It can be postulated that a triggering element should exist, whether that be a minor aphthosis, diverticulitis, ischaemic colitis, surgical or mechanical trauma, an anal abscess or even a simple pruritus ani; a bleeding diathesis exists for many patients on nicorandil, also on antiplatelet therapy. It still has to be clarified to what extent the action of nicorandil relies on a simple chemical ulceration, or whether it pivots on more complex interactions with the inflammatory pathway and immune system.

Last but not least, the establishment of a shared European ADR database could have raised the awareness of the association between nicorandil and ulcers more promptly. Thus, it would have provided better insight to physicians dealing with the ulcerative disease, increasing patient's safety and reducing morbidity and mortality.

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# Tables

| No. of patients | Median age | Median Daily Dose (mg) | History of symptoms (weeks) | Length of Nicorandil therapy (weeks) | Healing time (weeks) |
|---|---|---|---|---|---|
| 321 | 75 (IQR 72.0-79.5) | 40 (IQR 30-60) | 21.6 (IQR 10 – 60) | 100.8 (IQR 48.7 – 201.5) | 8.8 (IQR 4.3 – 15) |
| **Correlation with Median Dose (mg/die)** | | | | | |
| | | | | Spearman's rho | *p* |
| Median Age | | | | -0.106 | 0.40 |
| History of symptoms | | | | 0.298 | 0.148 |
| Length of Nicorandil therapy | | | | 0.164 | 0.252 |
| **Healing time** | | | | **0.525** | **<0.001** |

**Table 1.** Data synthesis from literature using 321 patients with gastrointestinal ulcers. A Spearman's correlation coefficient between median dose and individual quantitative variables was assessed. There is a significant correlation between the dose of nicorandil (mg/day) and the time needed for the ulcers to heal.

| No. of patients | Median age | Median Daily Dose (mg) | History of symptoms (weeks) | Length of Nicorandil therapy (weeks) | Healing time (weeks) | References |
|---|---|---|---|---|---|---|
| 124 | 75 (IQR 73.0-82.0) | 22.5 (IQR 15-40.0) | 13 (IQR 5.2 – 19.5) | 52 (IQR 8.6 – 104.0) | 4.3 (IQR 4.0 – 6.4) | [4,10,17,51-55,58-61,63-72,74-90] |
| **Group 1: Patients following a regimen <30mg/die** | | | | | | |
| 25 | 76 (IQR 73.25 – 83.75) | 15 (IQR 11.25 – 20.00) | 19.4 (IQR 6.2 – 52.5) | 74.0 (IQR 19.4 – 197.7) | 4.3 (IQR 3.5 – 6.8) | [51-53,63-65,68,69,74-80] |
| **Group 2: Patients following a regimen ≥30mg/die** | | | | | | |
| 99 | 74 (IQR 68.6 – 77.2) | 40 (IQR 31.25 –47.5) | 4.3 (IQR 9.0 – 17.3) | 7.5 (IQR 5.2 –48.7) | 4.3 (IQR 3.5 – 10.0) | [4,10,17,54,55,58-61,66,67,70-72,82-90] |
| **Difference in Distribution (Mann-Whitney U Test) between Group 1 and Group 2** | | | | | | ***p*** |
| Age | | | | | | 0.617 |
| History of symptoms | | | | | | 0.727 |
| Length of Therapy | | | | | | 0.423 |
| Healing Time | | | | | | 0.534 |

**Table 2.** Data synthesis from literature featuring oral ulcerations. Patients were additionally divided among those who were taking <30mg/day (group 1) and ≥30mg/day (group 2). A difference in the distribution of quantitative variables between the two groups was assessed.

| No. of patients | Median age | Median Daily Dose (mg) | History of symptoms | Length of Nicorandil therapy (weeks) | Healing time (weeks) | References |
|---|---|---|---|---|---|---|
| **Colonic and Anorectal Ulcerative and Fistulating Disease** | | | | | | |
| 165 | 75 (IQR 72 – 79.3) | 60 (IQR 40.0 – 60.0) | 26.0 (IQR 13.0 – 95.3) | 117 (IQR 61.8 – 188.5) | 13.0 (IQR 8.5.0 – 17.3) | [18-20,93,96,101,102,104-149] |
| Group 1: Colonic, Rectal and Parastomal Involvement | | | | | | |
| 42 | 78.5 (IQR 73.3 – 82.8) | 40 (IQR 40.0 – 57.5) | 19.5 (IQR 11.3 – 58.5) | 156 (IQR 52.0 – 208.0) | 13 (IQR 8.0 – 17.3) | [93,101,102,104-107,120,121,127,129,132,134-136,141,143,144,149] |
| **Group 2: Perianal ulceration and fistulation** | | | | | | |
| 123 | 74 (IQR 71.3 – 77.5) | 60 (IQR 40.0 – 60.0) | 47.6 (IQR 13.0 – 95.3) | 104 (IQR 67.2 – 169.0) | 12.0 (IQR 8.8 – 17.3) | [18,96,108-119,122-126,128,130,131,133,137-140,142,143,145-148] |
| **Difference in Distribution (Mann-Whitney U Test) between Group 1 and Group 2** | | | | | | ***p*** |
| **Age** | | | | | | **0.04** |
| History of symptoms | | | | | | 0.57 |
| Length of Therapy | | | | | | 0.88 |
| Healing Time | | | | | | 0.74 |

**Table 3.** Data synthesis from literature regarding colonic, rectal, stomal and anorectal ulcerations using 165 patients. Patients were additionally divided among those who suffered from colonic, stomal or rectal ulcers (group 1) and perianal involvement (group 2). A difference in the distribution of quantitative variables between groups was assessed.

| Hypothesis | Postulate | Counterargument |
|---|---|---|
| **Vascular Steal Phenomenon**[108,146] | Nicorandil-induced vasodilation would cause diminished blood supply in the affected regions | The most commonly involved regions are actually very well vascularised and they are not watershed areas. Nicorandil has shown to have anti-ulcer activity in animal studies. Only a few studies documented histological signs of ischaemia. |
| **Electrolyte Disturbance**[150-152,167] | Nicorandil's activity on ATP-sensitive potassium channels would determine a local toxic action with electrolyte disturbance. | The activity on ATP-sensitive potassium channels commences shortly after the drug absorption: differences in dosage and time of the onset of ulcerations are then difficult to explain. |
| **Hypersensitivity Hypothesis**[18] | Hypersensitivity towards the drug would manifest in non-keratinizing squamous epithelium lining areas of the oral cavity and lower anal canal. | The ulcerative tendency of nicorandil goes well beyond squamous epithelia of the oral cavity and anal canal; the lesions are frequently limited to a single well-defined area(s), despite a systemic exposure to the medication. |
| **Myosin Dephosphorilation**[153] | Nicorandil would dephosphorilate myosin filaments, thus hindering fibroblast's contractile capacity, thus wound healing. | Nicorandil would then have a limited role in the lesion aetiology and would only delay or hinder the healing process. In many cases, there is no clear history of triggering or promoting factor apart from nicorandil exposure. |
| **Toxic Metabolites**[21,158-160] | There would be a gradual accumulation of metabolites, i.e. nicotinamide and nicotinic acid, after saturation of the nicotinamide adenine dinucleotide/phosphate (NAD/NADP)pool. While the drug and some metabolites would still induce vasodilation, other derived molecules would have an ulcerogenic effect (i.e. nicotinic acid). | The enzymatic pathway involved in nicorandil metabolism has not been fully characterised and there is lack of data with regards to pharmacokinetic activity in hepatic impairment. Its allegedly ulcerogenic metabolite, nicotinic acid or niacin, does cause flushing and pruritus. Nevertheless, it is also associated with hepatotoxicity and this does not appear to be an accordingly frequent ADR. |
| **Modulation of inflammation and immune response**[156,157] | Experimental studies have shown that nicorandil inhibits oxidative stress-induced apoptosis in cardiac myocytes and decreases production and release of tumor necrosis factor- alpha (TNF-α) and other inflammatory mediators. Hence, it might hinder the inflammatory and immunological response that precedes the healing process. | This effect is plausible but its contribution to the onset of the ulcers is difficult to demonstrate, as it relies on local responses playing at tissue level. Besides, nicorandil patients have not been described to be otherwise immunocompromised and the ulcers are typically isolated lesions. |

**Table 4.** Summary of Aetiology Hypotheses