A case of nicorandil-induced unilateral corneal ulceration

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Abstract

Nicorandil, a second-generation nitro derivative, has been reported to induce single or multiple ulcerations in many locations, including oral, anal, perianal, vulvovaginal, perivulval, penile, gastrointestinal, colic, peristomal and skin locations. Ocular locations are now highly suspected. Herein, we report the case of a 78-year-old woman who experienced corneal ulceration at second cataract surgery (right eye) while being treated with nicorandil for 3 years. Four years before, she had had an uneventful first cataract surgery (left eye). The ulcers healed within 6 weeks of simple withdrawal of nicorandil, an expected delay for this type of chemical ulcer. The substitution of nicorandil with classic nitric oxide donors has already been done without complication. Surgical intervention is unnecessary and inappropriate. Case reports of ocular side effects induced by nicorandil are rare and probably underestimated.

Introduction

Nicorandil (ADANCOR®; Merck Serono, Lyon, France, IKOREL®; Sanofi-Aventis France, Paris, France, etc.) is an original vasodilator used to control angina. This drug is the first and only association of nitrates and potassium channel activators (PCA), and it is considered a second-generation nitro derivative. The nicotinamide moiety that supports the PCA effect is also present in its metabolites. Initially marketed in Japan in 1984 by Chugai Co Ltd and later in European, Asian and Pacific countries, nicorandil was first found to be involved in the genesis of ulcers in 1997 (1). Since then, many cases of single or multiple nicorandil-induced ulcerations in oral, anal, perianal, vulvovaginal, perivulval, penile, gastrointestinal, colonic, peristomal and skin locations have been published (2). More recently, fistulae (3) and ocular locations (4) have been highly suspected. Surprisingly, neither PCA nor nitric oxide (NO) donors have been documented as inducing corneal ulcerations.

Case

A 78-year-old woman was admitted to our department in December 2011 after complaining of pain and photophobia of the right eye following cataract surgery performed 2 months earlier. Her medical history revealed an uneventful left eye cataract surgery 4 years earlier. She also had hypertension since 1984, hypothyroidism since 1985 and angina and venous thromboembolic disease with stent insertion in 2009.

On admission, her routine treatment was levothyroxin, celiprolol, felodipine and valsartan; warfarin and nicorandil were started in December 2009. Her ocular symptoms had begun 15 days after the surgery and she was immediately prescribed anti-herpes simplex virus medication (valacyclovir). When she presented, she had a persisting corneal ulceration (Figure 1). Valacyclovir was continued and local healing treatment (fluorometholone and sodium hyaluronate) was added. Ten days later, corneal ulceration had not improved;
a recent or maintained trauma, nicotinamide could increase the concentration of these two molecules in the whole body. In the case of nicotinamide, the endogenous pool of nicotinamide adenine dinucleotide phosphate (NAD/NADP), leading to abnormal distribution of the metabolites of nicorandil (20 mg/day) for 3 years before the second cataract surgery, which was complicated by corneal ulceration. In our case, the patient was not treated with nicorandil at first cataract surgery, which remained uneventful. However, she had been receiving nicorandil (20 mg/day) for 3 years before the second cataract surgery, which was complicated by corneal ulceration. In addition, the ulcers healed within 6 weeks of withdrawal of nicorandil, an expected delay for this type of chemical ulceration is based on the sequence of events, the exclusion of other pathologies and the spontaneous regression of the side effect when the drug was discontinued. Nicorandil ulcerations seem to occur at vulnerable sites, being peristomal after the Hartmann’s procedure, penile after circumcision and perianal after haemorrhoidectomy (5–7); they are also associated with implantation scarring after implanting a pace maker, diverticulosis, and so forth. In our case, the patient was not treated with nicorandil at first cataract surgery, which remained uneventful. However, she had been receiving nicorandil (20 mg/day) for 3 years before the second cataract surgery, which was complicated by corneal ulceration. In addition, the ulcers healed within 6 weeks of withdrawal of nicorandil, an expected delay for this type of chemical ulcer (15 days up to 4 months mainly depending on the location of the ulcer) (8). Case reports of ocular side effects induced by nicorandil are rare and probably underestimated (4).

The pathogenesis of nicorandil-induced ulcerations (direct toxicity of the drug, steal phenomenon, etc.) are not yet elucidated. A recent hypothesis suggested that, most frequently, in cases of prolonged high-dose treatment and/or after increased dosage, nicotinic acid and nicotinamide (two metabolites of nicorandil) may become unable to merge into the endogenous pool of nicotinamide adenine dinucleotide phosphate (NAD/NADP), leading to abnormal distribution of these two molecules in the whole body. In the case of a recent or maintained trauma, nicotinamide could increase blood flow at the edge of the raw area, inducing epithelial proliferation, while nicotinic acid may ulcerate this new epithelial tissue, ultimately flooding the whole scar (8).

Thus, this hypothesis of chemical ulceration is based on the effects of nicotinamide (PCA) coupled with the direct ulcerating effects of nicotinic acid, explained by an in vivo pKa of 4.9. The role of nicotinamide is strengthened by the fact that its vasodilating effects on blood tumour flow suggest that it may function as a radiosensitiser (9). Moreover, minoxidil, another PCA, acts directly on arterioles, dilating them without promoting oedema and leading to increased blood flow at the edge of the scar (10).

Discontinuation of nicorandil usually induces complete healing after a few weeks, mainly depending on the location of the ulcer. Surgical intervention is unnecessary and inappropriate, as it is ineffective and exacerbates morbidity (probably by digging the furrow for nicotinic acid). The replacement of nicorandil with a classic NO donor, under the aegis of a cardiologist, has already been done without complication.

This case confirms that nicorandil may induce ocular toxicity, which mostly occurs in the elderly and fragile population; a previously injured area, whether recent or maintained, symptomatic or not, is required for the genesis of nicorandil-induced ulcer and simply withdrawing nicorandil treatment results in complete healing.

Acknowledgements

None of the authors has conflict of interest to declare. No financial support was received for this article.

References