Therapie (2018) xxx, xxx—xxx

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PHARMACOVIGILANCE

Nicorandil and cutaneous ulcerations, their misdiagnosis and consequences: Illustration by five cases reports and a review of the French pharmacovigilance database

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Received 5 December 2017; accepted 16 January 2018

KEYWORDS
Nicorandil;
Cutaneous ulcerations;
Adverse drug reaction

Summary While physicians increasingly recognize nicorandil-related mucocutaneous ulcerations, there are still misdiagnoses, particularly in the case of unusual location and late onset ulceration after nicorandil introduction. The goal of our study was to remind clinicians about the link between nicorandil use and the development of cutaneous ulcerations and to highlight the risk of misdiagnosis. We describe five reports diagnosed by the same dermatologist, complemented by an analysis of the French pharmacovigilance database (FPVD) from 1 January 1994 to 5 January 2017. During this period, 28 reports of strict cutaneous ulcerations due to nicorandil, in addition to our five reports, were registered in the FPVD. For those 28 reports, the time to onset between nicorandil introduction and cutaneous ulcerations was quite long and exceeded one year in 16 reports (information specified in 25 reports). The delay between

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https://doi.org/10.1016/j.therap.2018.01.004

Please cite this article in press as: Béné J, et al. Nicorandil and cutaneous ulcerations, their misdiagnosis and consequences: Illustration by five cases reports and a review of the French pharmacovigilance database. Therapie (2018), https://doi.org/10.1016/j.therap.2018.01.004

ulcerations observation and nicorandil discontinuation was variable, with immediate diagnosis in seven reports, but ranged from fifteen days to twelve years in 21 reports. The main locations were lower limbs, thorax and face. Ulcerations could be localized on surgery or trauma scars. Regression after nicorandil discontinuation was observed in all but two reports and ranged from three days to three months. Characteristics were comparable in our five patient's series. All patients exposed to nicorandil and healthcare practitioners prescribing nicorandil should be aware of the risk of cutaneous ulcerations to enable early diagnosis and drug withdrawal. The risk of misdiagnosis of this serious adverse drug reaction, along with the risk of sequelae, the costs of unnecessary additional investigations and the recent update on nicorandil as second-line treatment for stable angina, with existing alternative drugs, question about the benefit/risk balance of nicorandil.

Abbreviations

CIOMS	Council for international organizations of medical sciences
FPVD	French pharmacovigilance database
IQR	interquartile range
MedDRA	medical dictionary for regulatory activities
WHO	World health organization

Introduction

Poor ulceration healing affects many people each year and is generally linked to an underlying clinical condition, such as trauma, surgery, vascular disease, diabetes or aging. In addition, some drugs may be involved in ulceration development and need to be recognized as a possible aetiology to limit diagnosis wandering. Indeed, an increasing number of skin reactions, including ulceration, have been described as drug-induced. Notable examples include hydroxyurea and vitaminute K antagonist exposure [1,2].

Nicorandil, a potassium-channel activator used since 1994 in the treatment of angina symptoms, is also widely reported to be involved in mucocutaneous ulcerations, mainly occurring in the mouth and the perianal region [3–5]. This risk was communicated to healthcare professionals in 2012 and 2015 in France [6,7]. While physicians increasingly recognize nicorandil-related mucocutaneous ulcerations there are still misdiagnoses, particularly in the case of unusual locations and late onset ulceration after nicorandil introduction.

The goal of our study was to remind clinicians about the link between nicorandil use and cutaneous ulcerations development and to highlight the risk of misdiagnosis. We describe five reports diagnosed by the same dermatologist, complemented by a descriptive analysis of the French pharmacovigilance database (FPVD).

Materials and methods

We firstly described a cluster of cutaneous ulcerations after nicorandil exposure in five patients observed by the same dermatologist (OC). Then, we selected and analysed all reports of cutaneous ulcerations involving nicorandil exposure recorded in the FPVD between 1st January 1994 and 5th January 2017. Reports were selected using the medical dictionary for regulatory activities (MedDRA) preferred-term ''skin ulcer'' crossed with ''nicorandil'' exposure (only reports where nicorandil was ''suspected'' were selected) [8]. The database was queried on 5th January 2017. We then excluded all reports of mucocutaneous ulcerations to strictly limit the study to cutaneous lesions.

We recorded patients' general characteristics (age, gender), data on ulcerations [location, time to onset, risk factors and seriousness (the seriousness was categorized using the criteria formulated by Council for international organizations of medical sciences [CIOMS], namely death, life-threatening factors, hospitalization or prolongation of hospitalization, disability/incapacity, congenital anomaly/birth defect and other adverse drug reactions [ADRs] considered serious by the reporter [9]), data on drug exposure (nicorandil and any other drug suspected) and ulcerations history (occurrence, medical care, delay to diagnosis of drug induced ulceration, evolution).

The FPVD records all spontaneous reports of adverse drug reactions (ADRs) collected by the 31 French regional pharmacovigilance centres since 1985 [10,11]. According to World health organization's (WHO) definition, ADR is ''a response to a drug that is noxious and unintended and occurs at doses normally used in man'' [12]. Healthcare professionals have a legal requirement to report all ADRs to their regional pharmacovigilance centre. Every ADR report is analysed by a college of pharmacologists and physicians in the regional pharmacovigilance centre. Causality is assessed for every suspected drug according to the French imputability method [13]. ADRs are then registered in the FPVD and encoded according to the MedDRA classification.

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