

Voriconazole topical cream formulation: evidence for stability and antifungal activity

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▶ To cite this version:

Camille Bouchand, David Nguyen, Philippe-Henri Secretan, Fabrice Vidal, Romain Guery, et al.. Voriconazole topical cream formulation: evidence for stability and antifungal activity. International Journal of Antimicrobial Agents, 2020, 56 (3), pp.106083. 10.1016/j.ijantimicag.2020.106083 . hal-03492491

HAL Id: hal-03492491 https://hal.science/hal-03492491

Submitted on 30 Aug 2022

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17 Abstract

18	Voriconazole systemic use might be restricted by adverse events such as hepatotoxicity and
19	neurotoxicity or drug-drug interactions. Topical application on skin could help to better treat
20	local infection and limit unwanted whole-body exposure. Topical cream voriconazole was
21	stable for 90 days under refrigerated condition. After oral voriconazole treatment failure, the
22	patient was successfully treated with the topical 1% voriconazole cream.
23	
24	Keywords
25	voriconazole; stability; topical; skin infection; fungi; Fusarium solani
26	

28 **1. Introduction**

29 Voriconazole (VCZ) is a broad-spectrum triazole antifungal agent which is widely used in the treatment of invasive fungal infections.¹⁻⁴ Its potential serious adverse effects could limit its 30 use.⁵ In case of intolerance to systemic administration (oral or parenteral), serious adverse 31 events or contraindications, topical skin VCZ treatment could be proposed to patients with 32 fungal skin infections.^{6,7} In this study, we investigated the stability of 1% VCZ cream and its 33 activity in a 30-year old patient with skin fusariosis, with a background of Hyper-IgE syndrome 34 (HIES) due to STAT3 deficiency (i.e., a rare autosomal dominant primary immunodeficiency). 35 The patient was admitted to our hospital for pretibial skin lesions with crusted areas. He had a 36 history of eczematous dermatitis, lymphoma, recurrent respiratory tract infections, and 37 onychomycosis. Skin biopsies were positive to Fusarium sp, and an MRI of the leg showed 38 cutaneous and subcutaneous involvement of the anterolateral proximal part of the left leg. The 39 40 patient was treated with oral VCZ, but during follow-up, the skin fusariosis worsened. Topical treatment with VCZ 1% was started as an adjunct to oral VCZ, and after four months of this 41 42 treatment, the patient was considered cured.

43 **2. Materials and methods**

44 2.1. Preparation of voriconazole cream

VCZ cream was prepared by mixing 1 g of VCZ for injection containing 45 hydroxypropylbetacyclodextrin and lactose (Accord Healthcare, France) into 100 g of a topical 46 vehicle (Excipial Hydrocrème, Galderna, La Defense, France), and transferred in empty 47 ointment tube (COOPER, Melun, France). The topical vehicle contains aqua, paraffin oil, 48 isopropyl myristate, cetearyl alcohol, glyceryl stearate, pentylene glycol, and polysorbate 20. 49 The tubes were kept sealed until the day of analysis, stored either under refrigeration (at 4-8°C; 50 51 n = 27) or at room temperature (22-25°C; n = 27). To minimize the risk of microbial contamination, the 1% VCZ topical cream was prepared under a laminar flow. Moreover, the 52

topical base used in the study was microbiologically controlled according to the European Standard ISO 17516:2014 (https://www.iso.org/obp/ui/#iso:std:iso:17516:ed-1:v1:en) which specified absence in 1 g of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and total coliforms and fecal coliforms. The Excipial certificate of compliance gave some specifications such as pH around 5.4, total aerobic microbial count <100 cfu/g, total combined yeast count <10 cfu/g, absence of *P. aeruginosa and S. aureus*. The shelf life of the vehicle was 36 months.

60 **2.2 Sample analysis**

On days 0, 3, 7, 14, 21, 30, 45, 60 and 90, one gram of cream of each tube was diluted with 61 water to obtain a theoretical final concentration of 200 µg/mL. The contents of the volumetric 62 flask were mixed for 30 min to enable complete dissolution of VCZ. The mixture was 63 centrifuged at 15,000 rpm and 20 µL of the supernatant were injected into a high-performance 64 65 liquid chromatograph (HPLC). Three tubes were analyzed in triplicate for each condition at the designed time points. The HPLC method of Gu et *al*. was adapted.⁸ A liquid chromatography 66 (LC) system (Dionex Ultimate 3000, ThermoScientific, Villebon-sur-Yvette, France) 67 comprised a RS-3000 degasser, a HPG-3000 pump, a WPS-3000 autosampler, a column oven, 68 and a RS-3000 diode array detector. Data acquisition (e.g. peak time, area) was carried out 69 using in line Chromeleon® software (Thermo Scientific, V6.80 SR15b build 4981). A 70 Lichrospher 100 C₈ column (dimensions, 250 by 4.0 mm; and particle size, 5 µm; Merck, 71 Fontenay-sous-Bois, France) was used. The column temperature was 25°C, and the flow rate 72 was 1.0 mL/min. Isocratic elution was performed using purified water and acetonitrile (50:50, 73 v/v) as the mobile phase. The UV absorbance detector wavelength was set at 254 nm. 74 Calibration standard and quality control (QC) stock solutions of VCZ (1 mg/ml) were prepared 75 in water independently. Working solutions of VCZ were prepared daily by serial dilution of 76

stock solutions with mobile phase to prepare calibration standards (0.05, 0.1, 0.15, 0.2, 0.25,
and 0.3 mg/mL) and QC samples (0.05 and 0.3 mg/mL).

Forced degradation studies were performed to demonstrate the stability-indicating capability of 79 the HPLC method in cream. To generate photodegradation products, samples were exposed to 80 artificial weathering light, using a xenon test chamber Q-SUN Xe-1 operating in window mode 81 (Q-Lab Corporation, Saarbrücken, Germany). The light beam, presenting a characteristic 82 spectrum ranging from 300 to 800 nm, was delivered at an intensity of 1.50 W/m2 at 420 nm 83 (UV irradiance from 300 to 400 nm: 66.5 W/m2; illuminance: 119.6 klx). Samples were 84 monitored for pH by using a SevenEasy S20 pH meter (Mettler-Toledo, Viroflay, France) with 85 86 a calibrated InLab® Expert Pro-ISM pH sensor (Mettler-Toledo, France).

87 **3. Results**

88 **3.1.** Analysis

89 Good linearity over range of concentrations from 0.05 to 0.3 mg/mL was observed $(y=0.3928\pm0.0025x - 2.0434\pm0.5294, r^2 = 0.9995)$. The intraday (n = 5) and interday (n = 3)90 91 accuracies (percent bias) were within $\pm 1.1\%$, and precisions (coefficients of variation) were 92 within 3%. The lower limits of detection and quantification were 0.001 and 0.004 mg/mL, respectively. Slight degradation of VCZ was observed upon exposure to acidic conditions 93 without the appearance of degradation products. With photolytic stress condition, the 94 degradation of VCZ was less than 10% with the appearance of degradation peaks. VCZ was 95 more decomposed in alkaline, oxidative, and thermal stress conditions. The peaks of 96 degradation products were well separated from the intact drug, with VCZ concentrations 97 98 reduced by 3.7 to 36.4% compared to the initial concentration, indicating the suitability of the assay to determine the stability of VCZ. Typical HPLC chromatograms of the standard VCZ 99 100 and VCZ extracted from cream are represented in Fig. 1. HPLC chromatograms of degraded voriconazole are shown in Fig. 2. 101

102 **3.2.** Physical Stability of voriconazole

Under refrigerated conditions (4-8°C), 1% VCZ cream was stable for 90 days, with a dosage of 103 $0.97 \pm 0.02\%$ on day 90 (Fig. 3); the minimum requirement of the Food and Drug 104 105 Administration (https://www.fda.gov/media/69957/download) is ≥90% of initial dosage. The cream under refrigerated condition was smooth, thick, and odorless throughout the study period. 106 107 Instead, at room temperature (22-25°C), the cream dissociated into two phases at day 21 to turn liquid. Negligible changes in pH were observed for refrigerated condition (mean \pm SD, 5.19 \pm 108 109 0.08) and room temperature (mean \pm SD, 5.20 \pm 0.07). The stability of individual excipients used in formulation was not performed. 110

111 **3.3.** Case report

The clinical activity of topical VCZ was preliminarily investigated in a 30-year-old man with a 112 cutaneous F. solani infection on his right forearm. The fungal infection was focused on 113 114 histological examination with periodic acid Schiff and Grocott's stains, and was confirmed by polymerase chain reaction (PCR) assay. For which, he received oral VCZ treatment at 200 mg 115 twice daily. The plasma sample analysis of the drug revealed plasma VCZ concentrations 116 117 fluctuating and often below 1 mg/L, despite the increase in doses. One hypothesis to explain the treatment failure was the variability of systemic VCZ exposures based on genetic 118 polymorphisms in CYP2C19. The CYP2C19 poor metabolizers have demonstrated higher VCZ 119 systemic levels.⁹ The genetic polymorphism in the CYP2C19 gene of the patient was normal. 120 Thus, the other hypothesis was the poor compliance to therapy. The unsuccessful oral treatment 121 of VCZ resulted in the introduction of an additional topical application with the 1% VCZ cream 122 once daily with an occlusive patch. Within three months of local application and the 123 discontinuation of oral treatment, the healing of the Fusarium skin lesion was complete. Related 124 to the skin infection, the patient revealed a pulmonary infection to *Pseudomonas aeruginosa* 125 treated with ceftazidime and ciprofloxacin. 126

127 **4. Discussion and Conclusions**

The most effective drugs against *Fusarium* are considered to be amphotericin B and VCZ.¹⁰⁻¹² The MIC ranges of VCZ for the clinical *Fusarium* strains were 1 to 16 μ g/mL.¹³ Thus, the 1% VCZ cream was justified for skin infections caused by *Fusarium* species. To our knowledge, this is the first report showing the stability of VCZ cream and its clinical efficacy in a patient with *F. solani* skin infection. Our preliminary results support the need for a pilot study to further investigate the efficacy and safety of VCZ cream for the management of cutaneous and subcutaneous fungal infections due to susceptible pathogens.

135

136 **Declarations**

137 **Funding**: No funding

138 Competing Interests: None

Ethical Approval: Written informed consent was obtained from the patient for publication ofthis case report.

141

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188

189 **Figure captions**

- 190 Figure 1. Typical HPLC chromatograms of the standard voriconazole (A) and voriconazole
- 191 extracted from cream (B)
- 192 Figure 2. HPLC chromatograms degraded voriconazole
- 193 Figure 3. Stability of 1% voriconazole at refrigerated and room temperatures









