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1 **Voriconazole topical cream formulation: evidence for stability and antifungal activity**

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16

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*

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27

28 **1. Introduction**

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

43 **2. Materials and methods**

44 **2.1. Preparation of voriconazole cream**

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

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

60 **2.2 Sample analysis**

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

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

79 Forced degradation studies were performed to demonstrate the stability-indicating capability of
80 the HPLC method in cream. To generate photodegradation products, samples were exposed to
81 artificial weathering light, using a xenon test chamber Q-SUN Xe-1 operating in window mode
82 (Q-Lab Corporation, Saarbrücken, Germany). The light beam, presenting a characteristic
83 spectrum ranging from 300 to 800 nm, was delivered at an intensity of 1.50 W/m² at 420 nm
84 (UV irradiance from 300 to 400 nm: 66.5 W/m²; illuminance: 119.6 klx). Samples were
85 monitored for pH by using a SevenEasy S20 pH meter (Mettler-Toledo, Viroflay, France) with
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
90 ($y=0.3928\pm 0.0025x - 2.0434\pm 0.5294$, $r^2 = 0.9995$). The intraday (n = 5) and interday (n = 3)
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,
93 respectively. Slight degradation of VCZ was observed upon exposure to acidic conditions
94 without the appearance of degradation products. With photolytic stress condition, the
95 degradation of VCZ was less than 10% with the appearance of degradation peaks. VCZ was
96 more decomposed in alkaline, oxidative, and thermal stress conditions. The peaks of
97 degradation products were well separated from the intact drug, with VCZ concentrations
98 reduced by 3.7 to 36.4% compared to the initial concentration, indicating the suitability of the
99 assay to determine the stability of VCZ. Typical HPLC chromatograms of the standard VCZ
100 and VCZ extracted from cream are represented in Fig. 1. HPLC chromatograms of degraded
101 voriconazole are shown in Fig. 2.

102 **3.2. Physical Stability of voriconazole**

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

111 **3.3. Case report**

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

127 **4. Discussion and Conclusions**

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

135

136 **Declarations**

137 **Funding:** No funding

138 **Competing Interests:** None

139 **Ethical Approval:** Written informed consent was obtained from the patient for publication of
140 this case report.

141

142 **References**

- 143 1. Scott LJ, Simpson D. Voriconazole: a review of its use in the management of invasive fungal
144 infections. *Drugs* 2007;67:269-298. <https://doi.org/10.2165/00003495-200767020-00009>.
- 145 2. Elewa H, El-Mekaty E, El-Bardissy A, Ensom MH, Wilby KJ. Therapeutic Drug Monitoring
146 of Voriconazole in the Management of Invasive Fungal Infections: A Critical Review. *Clin*
147 *Pharmacokinet* 2015;54:1223-1235. <https://doi.org/10.1007/s40262-015-0297-8>.
- 148 3. Kofla G, Ruhnke M. Voriconazole: review of a broad spectrum triazole antifungal agent.
149 *Expert Opin Pharmacother* 2005;6:1215-1229. <https://doi.org/10.1517/14656566.6.7.1215>.
- 150 4. Jeu L, Piacenti FJ, Lyakhovetskiy AG, Fung HB. Voriconazole. *Clin Ther* 2003;25:1321-
151 1381. [https://doi.org/10.1016/s0149-2918\(03\)80126-1](https://doi.org/10.1016/s0149-2918(03)80126-1).

- 152 5. Xing Y, Chen L, Feng Y, Zhou Y, Zhai Y, Lu J. Meta-analysis of the safety of voriconazole
153 in definitive, empirical, and prophylactic therapies for invasive fungal infections. *BMC Infect*
154 *Dis* 2017;17:798. <https://doi.org/10.1186/s12879-017-2913-8>.
- 155 6. Chappe M, Vrignaud S, de Gentile L, Legrand G, Lagarce F, Le Govic Y. 2018. Successful
156 treatment of a recurrent *Aspergillus niger* otomycosis with local application of voriconazole. *J*
157 *Mycol Med* 2018;28:396-398. <https://doi.org/10.1016/j.mycmed.2018.03.009>.
- 158 7. Ashara KC, Paun JS, Soniwala MM, Chavda JR. Microemulgel of Voriconazole: an
159 Unfathomable Protection to Counter Fungal Contagiousness. *Folia Med (Plovdiv)*
160 2017;59:461-471. <https://doi.org/10.1515/folmed-2017-0051>.
- 161 8. Gu P, Li Y. Development and validation of a stability-indicating HPLC method for
162 determination of voriconazole and its related substances. *J Chromatogr Sci* 2009;47:594-598.
163 <https://doi.org/10.1093/chromsci/47.7.594>.
- 164 9. Weiss J, Ten Hoevel MM, Burhenne J, Walter-Sack I, Hoffmann MM, Rengelshausen J,
165 Haefeli WE, Mikus G. CYP2C19 genotype is a major factor contributing to the highly variable
166 pharmacokinetics of voriconazole. *J Clin Pharmacol* 2009;49:196–204.
167 <https://doi.org/10.1177/0091270008327537>.
- 168 10. Lortholary O, Obenga G, Biswas P, Caillot D, Chachaty E, Bienvenu AL, Cornet M, Greene
169 J, Herbrecht R, Lacroix C, Grenouillet F, Raad I, Sitbon K, Troke P; French Mycoses Study
170 Group. International retrospective analysis of 73 cases of invasive fusariosis treated with
171 voriconazole. *Antimicrob Agents Chemother* 2010;54(10):4446-4450.
172 <https://doi.org/10.1128/AAC.00286-10>.
- 173 11. Nucci M, Marr KA, Vehreschild MJ, de Souza CA, Velasco E, Cappellano P, Carlesse F,
174 Queiroz-Telles F, Sheppard DC, Kindo A, Cesaro S, Hamerschlak N, Solza C, Heinz WJ,
175 Schaller M, Atalla A, Arikian-Akdagli S, Bertz H, Galvão Castro C Jr, Herbrecht R, Hoenigl M,
176 Härter G, Hermansen NE, Josting A, Pagano L, Salles MJ, Mossad SB, Ogunc D, Pasqualotto

177 AC, Araujo V, Troke PF, Lortholary O, Cornely OA, Anaissie E. 2014. Improvement in the
178 outcome of invasive fusariosis in the last decade. *Clin Microbiol Infect* 20(6):580-585.
179 <https://doi.org/10.1111/1469-0691.12409>.

180 12. Cornely OA, Cuenca-Estrella M, Meis JF, Ullmann AJ. 2014. European Society of
181 Clinical Microbiology and Infectious Diseases (ESCMID) Fungal Infection Study Group
182 (EFISG) and European Confederation of Medical Mycology (ECMM) 2013 joint guidelines on
183 diagnosis and management of rare and emerging fungal diseases. *Clin Microbiol Infect* 2014;20
184 Suppl 3:1-4. <https://doi.org/10.1111/1469-0691.12569>.

185 13. Al-Hatmi AMS, Bonifaz A, Ranque S, Sybren de Hoog G, Verweij PE, Meis JF. Current
186 Antifungal Treatment of Fusariosis. *Int J Antimicrob Agents* 2018;51(3):326-332.
187 <https://doi.org/10.1016/j.ijantimicag.2017.06.017>.

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





