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BACKGROUND AND IMPORTANCE

Candida glabrata (*C. glabrata*) is the second leading cause of vulvovaginal candidiasis (8% of cases). [1-5]

Recommendations to treat azole resistance (AR) *C. glabrata* vulvovaginal candidiasis (VVC) are intravaginal boric acid capsules (1st line), intravaginal nystatin suppositories (2nd line) and, as 3rd line, flucytosine cream (17 % or 15,5%) or amphotericin B cream. [1-4]

Vaginal flucytosine and amphotericin are not commercially available, so an extemporaneous formulation has to be developed.

AIM AND OBJECTIVES

To compound flucytosine 15,5% intravaginal gel and to evaluate the effectiveness and safety in a AR *C. glabrata* VVC patient.

MATERIALS AND METHODS

Literature review to investigate the above-mentioned compounding magistral formulations described.

Effectiveness and safety was assessed by clinical monitoring, analytical monitoring and patient interview.

RESULTS

A 47-years-old woman with recurrent VVC since March 2020 was treated with oral fluconazole, oral lactobacillus/lingonberry and multiple intravaginal drugs (clotrimazole, nifurantel, nystatin, benzydamine, estriol + lactobacillus and boric acid). In March 2022, a positive culture for *C. glabrata* strain was isolated, exhibiting antifungal sensitivity only to caspofungin, flucytosine and micafungin.

Four flucytosine formulations for vaginal application were identified in literature. [5-8] We compounded flucytosine 15,5% gel by reducing fourteen 500 mg flucytosine tablets to a fine powder in a mortar. The powder was then moistened with 5mL of glycerin to form a smooth paste, which was then added to 40gr of a lubricating vaginal gel base. Shelf-life of was given for 14 days, stored at room temperature. Vaginal applicators were used to apply the gel intravaginally at bed time for 19 days.

Flucytosine 15,5% intravaginal gel

Flucytosine tablets 500mg [Ancotil®]	7 gr
Glycerin 85%	5 mL
Lubricating vaginal gel base [K-Y Gel®]	40 gr

Reduce flucytosine tablets to a fine powder. Levigate with glycerin to form a smooth paste, then add to lubricating vaginal gel base.

Aply 5gr intravaginal, at bed time. Use gloves.

Shelf-life: 14 days at room temperature

RESULTS

March 2020 - March 2022

Multiple systemic and topic treatments

Recurrent vulvovaginal itching, burning and discharge

C. glabrata only sensitive to caspofungin, flucytosine and micafungin

(March 2022)

April 2022

• Flucytosine gel – 5gr intravaginal, at bed time (19 days)

• Active pharmacovigilance a (D4, D11, D19) - none ADRs

May 2022 - August 2022

• Negative vaginal culture at weeks 2,4,6.

• Normal hemogram, blood count, renal and hepatic function

• Asymptomatic



Three active pharmacovigilance interviews were carried out to verify tolerability and side effects. The patient reported only vaginal discharge, no pain, pruritus or rash.

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Active pharmacovigilance program

Drug: Flucytosine 15,5% intravaginal gel
Batch : _____ Expiration date: _____
Date ___/___/___ Pharmacist _____

Patient identification

Gender (M/F) _____ Ethnicity _____ Age _____
Process number _____
Group of risk
 Child Elderly Pregnant breast-feeding Co-morbidities
 Liver or kidney failure Other _____
Concomitant therapy: _____

ADR FREQUENCY (SPC)	ADVERSE REACTION	YES/NO
VERY COMMON		
COMMON		
UNCOMMON	Itching, rash, urticaria	
SEVERE		
RARE		
UNEXPECTED	Systemic effects such as abdominal pain, diarrhea, vomiting, myelosuppression, increased bilirubin levels, increased ALT, AST, jaundice	

Adverse Reaction Classification

Mild Moderate Severe Unexpected

Analytical evaluation (blood count, renal and hepatic function) was performed, without revealing any change. Vaginal culture was negative at week 2, 4 and 6 after treatment. Patient remained asymptomatic until the last evaluation in August 2022.

CONCLUSION AND RELEVANCE

The flucytosine 15,5% intravaginal gel formulation fulfilled an unmet need, enabling the effective resolution of AR *C. glabrata* VVC.

The active monitoring of its use allowed us to collect real context data on safety, verifying the absence of adverse effects and good tolerance.

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