Antimycotic Treatment of Oral Candidiasis in Warfarin Users

Iversen, Ditte B.; Hellfritzsch, Maja; Stage, Tore B.; Aabenhus, Rune M.; Lind, Bent S.; Pottegård, Anton

Published in:
American Journal of Medicine

DOI:
10.1016/j.amjmed.2020.10.018

Publication date:
2021

Document version:
Accepted manuscript

Antimycotic treatment of oral candidiasis in warfarin users

Ditte B. Iversen, MSc Pharm[a,b]
Maja Hellfritzsch, MD, PhD[a,c]
Tore B. Stage, MSc Pharm, PhD[a]
Rune M. Aabenhus, MD, PhD[d]
Bent S. Lind, MD, DMSc[e,f]
Anton Pottegård, MSc Pharm, PhD[a]

a) Clinical Pharmacology and Pharmacy, Department of Public health, University of Southern Denmark, Odense
b) Hospital Pharmacy Funen, Odense University Hospital, Odense C, Denmark
c) Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark
d) Department of Public Health, Section of general practice, University of Copenhagen, Denmark
e) Department of Clinical Biochemistry, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
f) Copenhagen Primary Care Laboratory (CopLab) Database, Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Denmark

Funding sources: No specific funding was obtained for this study.

Conflict of interest: None

Verification from all authors: All authors had access to the data and a role in writing the manuscript.

Article type: Brief observation

Key words: Antimycotics, warfarin, drug interactions

Running head: Drug-drug interactions between antimycotics and warfarin

Correspondence
Ditte B. Iversen
Clinical Pharmacology and Pharmacy, Department of Public health
University of Southern Denmark, Odense
J.B. Winsløws Vej 19, 2
5000 Odense C, Denmark
E-mail: dbiversen@health.sdu.dk
Phone: 0045 248599

Abstract

Purpose

Azole antimycotics and nystatin oral solution are used to treat oral candidiasis. Azoles inhibit cytochrome (CYP) P450-dependent metabolism of warfarin, which could increase the anticoagulant effect of warfarin. Nystatin is not expected to interfere with warfarin metabolism, but current data are conflicting. With this study, we aimed to explore the potential drug-drug interactions between warfarin and azole antimycotics used in the treatment of oral candidiasis, that is, systemic fluconazole, miconazole oral gel, and nystatin oral solution.

Methods

By linking clinical data on international normalized ratio (INR) measurements with administrative data on filled prescriptions of warfarin and antimycotics during 2000-2015, we explored INR changes in warfarin users relative to initiation of systemic fluconazole (n=413), miconazole oral gel (n=330), and nystatin oral solution (n=399).

Results

We found a significant increase in mean INR of 0.83 (95% confidence interval (CI) 0.61 – 1.04) and 1.27 (95% CI 0.94 – 1.59) following initiation of systemic fluconazole and miconazole oral gel, respectively. Also, the proportion of patients experiencing an INR-value above 5 was increased after initiation of fluconazole (from 4.3% to 15.3%) and miconazole (from 5.5% to 30.1%). INR was unaffected by initiation of nystatin oral solution (mean change 0.08; 95% CI -0.10 – 0.25).

Conclusion

Initiation of systemic fluconazole and miconazole oral gel was associated with increased INR in warfarin users. A similar association was not found for nystatin oral solution, which thus appears to be the safest alternative when treating oral candidiasis in warfarin users.

Introduction

The oral anticoagulant warfarin is highly susceptible to drug-drug interactions due to its narrow therapeutic interval and extensive hepatic metabolism (1). Concomitant treatment with azole antimycotics, known inhibitors of warfarin metabolism through cytochrome (CYP) P450 enzymes, have been associated with marked increases in the anticoagulant effect of warfarin, as measured by the international normalised ratio (INR) (2, 3). Systemic fluconazole and miconazole oral gel, are both used in treatment of oral candidiasis (4).

An alternative to the azoles, nystatin oral solution, has been investigated in previous studies, resulting in conflicting data regarding nystatin's potential to affect INR (3, 5).

To inform the choice of antimycotic drug therapy for oral candidiasis in warfarin users, we investigated these potential drug-drug interactions by linking exposure to antimycotic therapy to changes in INR-values.

Methods

Within a cohort of warfarin users, we identified patients filling an antimycotic prescription, and compared INR values before and after antimycotic initiation.

Study population

We identified a cohort of adult (≥18 years) warfarin users from Denmark from 2000-2015. Patients with ≥2 INR measurements recorded in the Copenhagen Primary Care Laboratory (CopLab) database were included as previously described (6). Within this cohort, we obtained data from the Danish National Prescription Registry (7) on incident outpatient prescription fills on the antimycotics used in oral candidiasis in Denmark, that is systemic fluconazole (ATC-code

J02AC01), miconazole oral gel (A01AB09) and nystatin oral solution (A07AA02). Of note, the treatment indication is not available in the prescription registry. Warfarin users were included filling their first antimycotic prescription during warfarin treatment. To ensure the possibility of intraindividual comparison, ≥1 INR measurement recorded before and after inclusion (within 8 weeks) was required.

We described the study population for each study drug according to age, sex, Charlson comorbidity score, CHA2Ds2-VASc, HASBLED, number of concomitant drugs used, and number of hospitalizations in the last year.

Main analysis

We performed several analyses to explore INR changes relative to initiation of antimycotic therapy, serving as a proxy for drug-drug interaction between warfarin and antimycotics. First, changes in mean INR values were described graphically in relation to antimycotic initiation. Second, for patients with an INR-measurement within 1-3 weeks (7-20 days) after antimycotic initiation, INR values were compared to the pre-treatment INR (within 8 weeks prior to treatment) using a paired *t* test. Third, the proportion of patients experiencing at least one INR measurement >5 during the same period following antimycotic initiation was compared to the proportion during a similar 2-week window before antimycotic initiation (day -21 to -8) using Fisher's exact test. INR above 5 was set as a cut-off because it is associated with increased risk of bleeding (8).

Sensitivity analyses

In sensitivity analyses, patients with a registration of mechanical heart valves in the Danish National Patient Registry and INR measurements labelled as potentially imprecise were excluded.

Furthermore, we performed a sensitivity analysis excluding warfarin users exposed to other drugs that might interfere with warfarin and INR during the observation window (2).

Results

The characteristics of the cohort is presented in **Table 1**. Mean INR before and after initiation of systemic fluconazole, miconazole oral gel and nystatin oral solution is described in **Figure 1**. In patients initiating fluconazole and miconazole, we observed statistically significant increases in mean INR of 0.83 (95% confidence interval (CI) 0.61 – 1.04) and 1.27 (95% CI 0.94 – 1.59), respectively (**Table 2**). Similarly, a marked increase was observed in the proportion of patients with an INR >5 following initiation of systemic fluconazole (from 4.3% to 15.3%, $p<0.01$) and miconazole oral gel (from 5.5% to 30.1%, $p<0.01$). Maximum INR increase was observed 2 weeks after initiation of fluconazole and 1.5 week after initiation of miconazole. Normalisation of INR was observed 4 and 5 weeks after initiation of fluconazole and miconazole, respectively (**Figure 1**). Initiation of nystatin oral solution was not associated with a change in mean INR (**Table 2**, **Figure 1**). However, the proportion of patients with an INR >5 also increased among nystatin initiators from 3.1% before to 7.5% after initiation ($p=0.05$).

The two sensitivity analyses yielded results similar to the main analysis (data not shown).

Discussion

We found a strong association between initiation of systemic fluconazole and miconazole oral gel and increased INR values in warfarin users. Nystatin oral solution was not associated with relevant changes in INR.

The primary strength of this study is the large number of available, consecutive INR measurements from a real-world clinical setting (6). The principal limitation of the study is the lack of clinical outcome data. It is unclear whether the observed transient INR increase infers a clinically relevant risk of bleeding. However, prior studies have demonstrated a clinically significant increased bleeding risk when INR rise above 4.5 (8). Moreover, we do not have the exact date of treatment initiation (only date of prescription fill) and no data on early treatment discontinuation of antimycotic therapy or warfarin dose adjustments. Both sources of misclassification may have biased our results towards a less significant impact of antimycotics on the anticoagulant effect of warfarin. Finally, lack of indication for antimycotic prescribing is a limitation. However, it is reasonable to assume that the effect of antimycotics on INR levels is independent of the indication. Thus, we find it acceptable to extrapolate these data to guide healthcare professionals in the treatment of oral candidiasis.

The increase in INR in use of miconazole oral gel and systemic fluconazole is in line with the known interaction potential of fluconazole and miconazole. Both are potent inhibitors of CYP2C9 (9), which catalyses the metabolism of warfarin, leading to increased anticoagulation as reflected by higher INR-values (9). Miconazole is a stronger inhibitor of CYP2C9 compared to fluconazole (9) which may explain the stronger apparent effect of miconazole on warfarin metabolism as reflected by the higher INR increase. Clinicians should therefore, be aware of drug-drug interactions between both systemic fluconazole and miconazole oral gel and warfarin and monitor and adjust treatment accordingly.

A previous case-series in eight patients indicated that nystatin oral solution increased INR-values among warfarin patients (5). In contrast, a self-controlled study found no INR-changes relative to nystatin initiation (3). Also, the negligible gastrointestinal absorption of nystatin and no known interference with CYP enzymes do not support the likelihood of a drug-drug interaction with

warfarin (10). Accordingly, we did not observe any change in mean INR following nystatin initiation. However, we observed a small absolute increase in the proportion of patients with an INR >5 before and after initiation of nystatin oral solution. While this might be a chance finding, alternative explanations include a drug-drug interaction mediated through unknown pathways as well as confounding by indication. Regarding the latter, oral candidiasis may in itself lead to slight INR-increases, as has been shown for other infections (11). If so, the estimates for INR changes following initiation of miconazole and fluconazole may overestimate the effect of the potential drug-drug interaction with warfarin in itself.

In conclusion, treatment with systemic fluconazole and miconazole oral gel was associated with clinically relevant increases in INR-values in warfarin users. Limited or no INR-changes was observed for users of nystatin oral solution, which may, thus, be the safest antimycotic alternative when treating oral candidiasis in warfarin users.

Acknowledgments

Martin Thomsen Ernst (University of Southern Denmark) is acknowledged for help with data management.

References

1. Johnson JA. Warfarin pharmacogenetics: a rising tide for its clinical value. Circulation. 2012;125(16):1964-6.

2. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005;165(10):1095-106.

3. Hellfritzsch M, Pottegard A, Pedersen AJ, Burghle A, Mouaanaki F, Hallas J, et al. Topical Antimycotics for Oral Candidiasis in Warfarin Users. Basic Clin Pharmacol Toxicol. 2017;120(4):368-72.

4. Garcia-Cuesta C, Sarrion-Pérez MG, Bagán JV. Current treatment of oral candidiasis: A literature review. J Clin Exp Dent. 2014;6(5):e576-82.

5. Kovac M, Mitic G, Kovac Z. Miconazole and nystatin used as topical antifungal drugs interact equally strongly with warfarin. J Clin Pharm Ther. 2012;37(1):45-8.

6. Engell AE, Svendsen ALO, Lind BS, Andersen CL, Andersen JS, Willadsen TG, et al. Drug-drug interaction between warfarin and statins: A Danish cohort study. Br J Clin Pharmacol. 2020.

7. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2017;46(3):798-f.

8. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet. 1996;348(9025):423-8.

9. Niwa T, Shiraga T, Takagi A. Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 activities in human liver microsomes. Biol Pharm Bull. 2005;28(9):1805-8.

10. Schafer-Korting M, Blechschmidt J, Korting HC. Clinical use of oral nystatin in the prevention of systemic candidosis in patients at particular risk. Mycoses. 1996;39(9-10):329-39.

11. Hellfritzsch M, Lund LC, Ennis Z, Stage T, Damkier P, Bliddal M, et al. Ischemic Stroke and Systemic Embolism in Warfarin Users With Atrial Fibrillation or Heart Valve Replacement Exposed to Dicloxacillin or Flucloxacillin. Clin Pharmacol Ther. 2020;107(3):607-16.