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Antimycotic treatment of oral candidiasis in warfarin users

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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.

Clinical significance

- Miconazole oral gel and systemic fluconazole are associated with marked increases in international normalized ratio (INR) during warfarin use.
- Nystatin oral solution does not appear to interact with warfarin treatment.

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.

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Ditte B. Iversen, Maja Hellfritzsch and Anton Pottegård are responsible for conceptualization.

Anton Pottegård is also responsible for methodology, resources, formal analysis, data curation and supervision.

Ditte B. Iversen and Maja Hellfritzsch are responsible for writing the original draft.

All authors have participated in reviewing and editing the manuscript.

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Figure 1. Changes in mean INR before and after initiation of miconazole oral gel (blue/dotted), systemic fluconazole (red/solid) and nystatin oral solution (green/dashed).

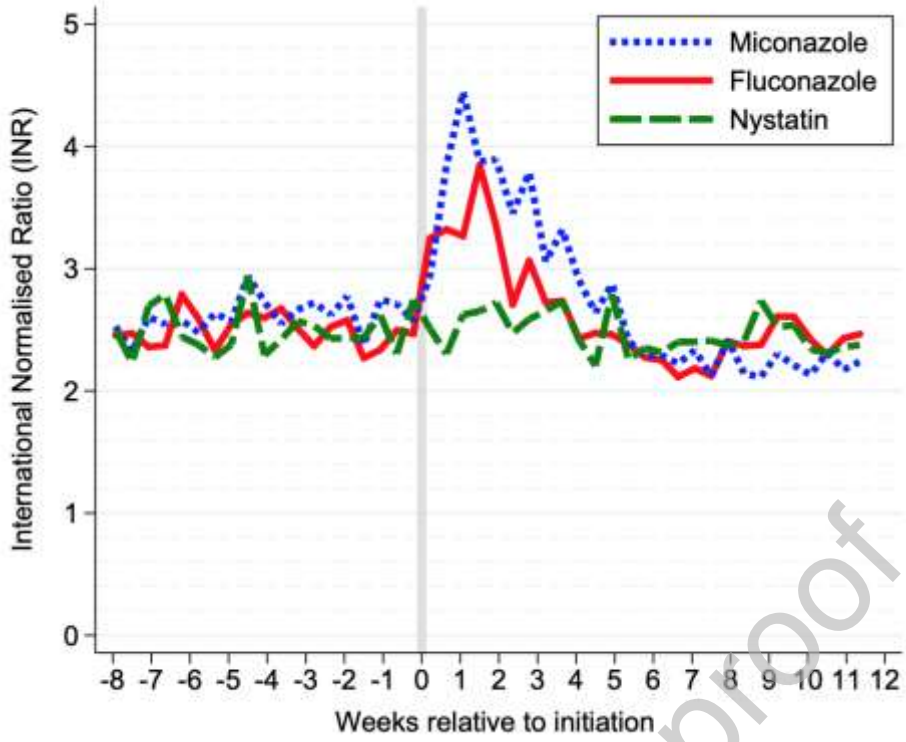

Table 1. Characteristics of study population.

	Miconazole (n=330)	**Nystatin (n=399)**	**Fluconazole (n=413)**
Age, median (IQR)	76 (70-83)	78 (70-84)	76 (67-83)
Female sex %	56%	58%	59%
Charlson comorbidity index			
Median (IQR years)	1 (0-3)	2 (0-3)	2 (0-3)
0	125 (38%)	130 (33%)	158 (38%)
1-2	114 (35%)	150 (38%)	145 (35%)
≥3	91 (28%)	119 (30%)	110 (27%)
CHA2DS2-VASc			
Median (IQR)	4 (3-5)	4 (3-5)	4 (2-5)
0-1	16 (4.8%)	28 (7.0%)	66 (16%)
2-3	119 (36%)	130 (33%)	123 (30%)
4-5	149 (45%)	175 (44%)	154 (37%)
≥6	46 (14%)	66 (17%)	70 (17%)
HASBLED			
Median (IQR)	3 (2-3)	3 (2-3)	3 (2-3)
0-1	31 (9.4%)	46 (12%)	76 (18%)
2	107 (32%)	115 (29%)	128 (31%)
3	124 (38%)	150 (38%)	131 (32%)
≥4	68 (21%)	88 (22%)	78 (19%)

Number of concomitant drugs used			
Median (IQR)	10 (7-13)	11 (7-14)	10 (7-13)
0-4	24 (7.3)	29 (7.3%)	44 (11%)
5-8	81 (25%)	97 (24%)	120 (29%)
9-12	128 (39%)	119 (30%)	128 (31%)
13-16	53 (16%)	89 (22%)	74 (18%)
≥17	44 (13%)	65 (16%)	47 (11%)
Number of hospitalizations in the last year			
0	133 (40%)	119 (30%)	163 (39%)
1	58 (18%)	89 (22%)	79 (19%)
2	53 (16%)	53 (13%)	59 (14%)
≥3	86 (26%)	138 (35%)	112 (27%)

Abbreviations: IQR, interquartile range.

Table 2. Mean INR as well as the proportion with an INR >5 before and after antimycotic initiation in warfarin users.

		Mean INR values				**INR > 5**	
Exposure	**Number exposed**[1]	**Mean INR Before/after**	**Mean difference with CI**	***P*-value for mean difference in INR**[2]	**Median change in INR with CI**	**Proportion with INR >5 Before/after (%)**	**P-value for difference in proportion with INR >5**[3]
Miconazole oral gel	206	2.57/ 3.84	1.27 (0.94-1.59)	<0.001	0.80 (-0.40-2.70)	5.5 / 30.1	<0.01
Nystatin oral	253	2.53/ 2.61	0.08 (-0.10-	0.383	0.00 (-0.50-	3.1/ 7.5	=0.05

solution			0.25)		0.80)		
Fluconazole, systemic	263	2.46/ 3.29	0.83 (0.61-1.04)	<0.001	0.60 (-0.20-1.70)	4.3/ 15.3	<0.01

Abbreviations: INR, International normalized ratio; CI, Confidence interval

[1] All warfarin users with a relevant INR measurement before and after initiation of antimycotic treatment.

[2] INR measurement within 8 weeks prior to treatment compared to INR measurement 7-20 days after antimycotic initiation using a paired *t* test.

[3] Proportion with an INR >5 before antimycotic initiation (day -21 to -8) compared to the proportion with and INR >5 after antimycotic initiation (7 to 20 days) using a Fisher's exact test.