

Topical Antimycotics for Oral Candidiasis in Warfarin Users

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Abstract: Treatment for oral candidiasis in warfarin users may be complicated by drug–drug interactions (DDIs) between warfarin and topically applied antimycotics. However, current knowledge of these putative DDIs is merely based on case series. We therefore performed a cohort cross-over study with the objective to evaluate the potential DDIs between warfarin and miconazole oral gel or nystatin oral solution. The cohort consisted of individuals using warfarin in the period of 1998–2012 ($n \approx 7400$). We collected data on cohort members' measurements of the international normalized ratio (INR) from a clinical database, and obtained information on their use of topically applied miconazole and nystatin from a regional prescription register. Potential DDIs were assessed by comparing INR values before and after initiation of an antimycotic drug. Among 17 warfarin users exposed to miconazole oral gel, the mean INR increased from 2.5 (95% CI: 2.1–2.8) to 3.8 (95% CI: 2.8–4.8) after exposure, corresponding to a mean INR increase of 1.4 (95% CI: 0.3–2.4). Among 30 warfarin users exposed to nystatin oral solution, the mean INR was 2.7 (95% CI: 2.3–3.1) before and 2.5 (95% CI: 2.2–2.9) after exposure. In conclusion, we found evidence supporting a clinically relevant drug–drug interaction between warfarin and miconazole oral gel. In contrast, we did not find any indication of an interaction between warfarin and nystatin oral solution. Nystatin rather than miconazole should be preferred when treating warfarin users for oral candidiasis.

Warfarin is widely used in the prophylaxis and treatment of thrombosis [1,2]. As warfarin is metabolized by the cytochrome P450 system (CYP), especially CYP2C9 [3], warfarin users are susceptible to drug–drug interactions (DDIs). Warfarin has a narrow therapeutic index, and even minor DDIs may therefore have serious consequences [4].

Many warfarin users are elderly persons with a high frequency of comorbid conditions and concomitant medications [5] who are at increased risk of developing local fungal infections, primarily oral candidiasis [6]. Due to disadvantages of systemic antimycotic therapy (e.g. greater potential for DDIs and development of treatment-resistant fungal strains), topically applied clotrimazole, miconazole or nystatin is generally recommended internationally as the first-line choice of treatment for oral candidiasis [6]. In Denmark, only miconazole and nystatin are marketed for this indication. The effectiveness of nystatin and miconazole against oral candida infections is considered comparable [7]. The potential for the development of treatment resistance is considered lower for nystatin compared to treatment with azoles, including miconazole [8].

Miconazole is a strong inhibitor of CYP2C9 [9]. Gastrointestinal absorption of miconazole occurs to some extent when administered as an oral gel [10]. Increased values of international normalized ratio (INR) and bleedings after concomitant treatment with warfarin have been described in case reports [11,12] and in a small case series of six patients [13]. On the

other hand, gastrointestinal absorption of nystatin is negligible when taken as an oral solution [14]. Furthermore, nystatin does not inhibit the CYP450 system [15], and DDIs involving nystatin have not been conclusively confirmed. Despite this lack of biological plausibility for DDIs, a recent case series reported substantially increased INR values and bleedings in patients using warfarin and nystatin concomitantly, leading to speculations on the safety of nystatin in this setting [16].

To provide clinicians with support for decision-making, we studied the significance of putative DDIs between warfarin and miconazole oral gel or nystatin oral solution by conducting a self-controlled study assessing INR changes in warfarin users exposed to these antimycotics.

Materials and Methods

In a cohort of persons using warfarin in the period from 1998 to 2012, we identified individuals filling a prescription for either miconazole oral gel or nystatin oral solution and compared INR values before and after exposure using a paired *t*-test.

Data sources. Thrombobase [17] is a clinical database gathering information on vitamin K antagonist (VKA)-treated patients in Funen County, Denmark. The database includes information on type of VKA, indication, dose, and all measured INR values for all VKA-treated patients from 50 general practitioners as well as three outpatient clinics at Odense University Hospital. During the study period, around 7400 patients were included in the database. Thrombobase has previously been used successfully to assess specific DDIs involving warfarin [18–20].

Odense Pharmacoepidemiological Database (OPED) is a regional prescription register holding data on all filled prescriptions of

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reimbursable drugs in the Region of Southern Denmark (including Funen County) [21].

We linked data from the two registers through a personal identifier (the 'CPR number') unique to each Danish citizen [22], which is registered upon every contact with the Danish healthcare system (e.g. when filling a prescription).

Study population. The study was designed as a cohort cross-over study. We identified a cohort of warfarin users with corresponding INR measurements in Thrombobase. Persons were included in the study population upon the first filling of an antimycotic prescription (index date), and observed 10 weeks before and 4 weeks after the index date (observation period) with respect to INR measurements. Information on dispensed prescriptions for miconazole oral gel (ATC code A01AB09) and nystatin oral solution (ATC code A07AA02) among cohort members was retrieved from OPED.

To ensure inclusion of warfarin users who could be expected to have otherwise stable INR values and valid INR measurements, we applied the following exclusion criteria: (i) initiation of warfarin <3 months before index date, (ii) filling of a prescription for another study drug (miconazole oral gel or nystatin oral solution) or for a systemic antimycotic drug during the observation period, (iii) self-monitored warfarin therapy, (iv) target INR outside the normal 2.0–3.0 range and (v) age <18 years at inclusion.

If a patient had two or more treatment episodes meeting the eligibility criteria, only the first such episode was included in the analysis.

Analysis. We considered changes in INR associated with exposure to antimycotic drugs as a proxy for DDIs. We did this by comparing the last INR value before index date with the first INR value measured

within 4–28 days after index date for each individual patient, reporting *t*-test-based 95% confidence intervals (95% CI) for before–after comparisons of means. To ensure the paired nature of the data, patients had to have both a 'before' and an 'after' INR measurement to be included in the analysis. In a sensitivity analysis, we excluded patients with warfarin dosing adjustments within the 70-day period prior to the index date (index date included).

All analyses were performed using STATA Release 14.1 (Stata-Corp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency. In Denmark, purely register-based studies do not require ethical approval.

Results

Miconazole oral gel was initiated in 53 warfarin users registered in the database. Lack of INR values either before or after exposure led to exclusion of 26 of these patients, and another 10 patients fulfilled one or more additional exclusion criteria (fig. 1). Thus, 17 patients contributed to the analysis. Clinical characteristics of the included sample are presented in table 1. The mean INR before and after miconazole initiation was 2.5 (95% CI: 2.1–2.8) and 3.8 (95% CI: 2.8–4.8), respectively, corresponding to a mean increase in INR of 1.4 (95% CI: 0.3–2.4). Of the 17 patients included in the analysis, 11 patients (65%) experienced an increase in INR after exposure to miconazole (fig. 2A). The sensitivity analysis of patients without recent warfarin dose adjustment (*n* = 6) yielded similar, but less precise results. In this group, mean INR before and after miconazole initiation was 2.6

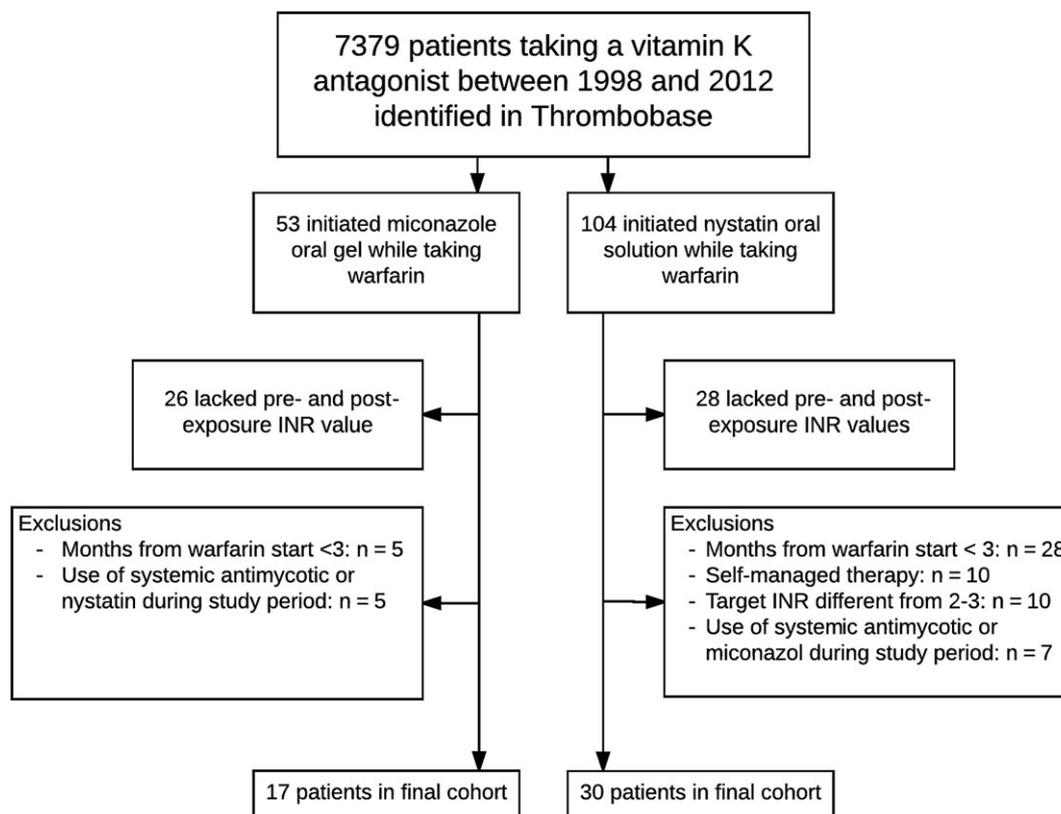


Fig. 1. Flow chart of the study population. Identification of stable warfarin users exposed to a potential drug–drug interaction. INR, international normalized ratio.

Table 1.

Baseline characteristics. Warfarin users filling a prescription of a topical antimycotic drug during the study period.

	Miconazole (n = 17) n (%)	Nystatin (n = 30) n (%)
Male sex	8 (47)	16 (53)
Age, median (IQR, years)	67 (61–77)	73 (66–79)
Indication for warfarin treatment		
Atrial fibrillation	6 (35)	16 (53)
Mechanical heart valves	5 (29)	8 (27)
Venous thromboembolism	1 (6)	3 (10)
Other	5 (29)	3 (10)

IQR, interquartile range.

(95% CI: 2.1–3.1) and 4.0 (95% CI: 1.4–6.6), respectively, resulting in a mean INR increase of 1.4 (95% CI: –1.2 to 3.9).

Of the 104 patients initiating nystatin oral suspension while taking warfarin, 30 fulfilled the inclusion criteria (fig. 1). Clinical characteristics were similar among nystatin and miconazole users (table 1). The mean INR before and after filling a prescription for nystatin was 2.7 (95% CI: 2.3–3.1) and 2.5 (95% CI: 2.2–2.9), respectively, corresponding to a mean decrease in INR of –0.2 (95% CI: –0.4 to 0.7) (fig. 2B).

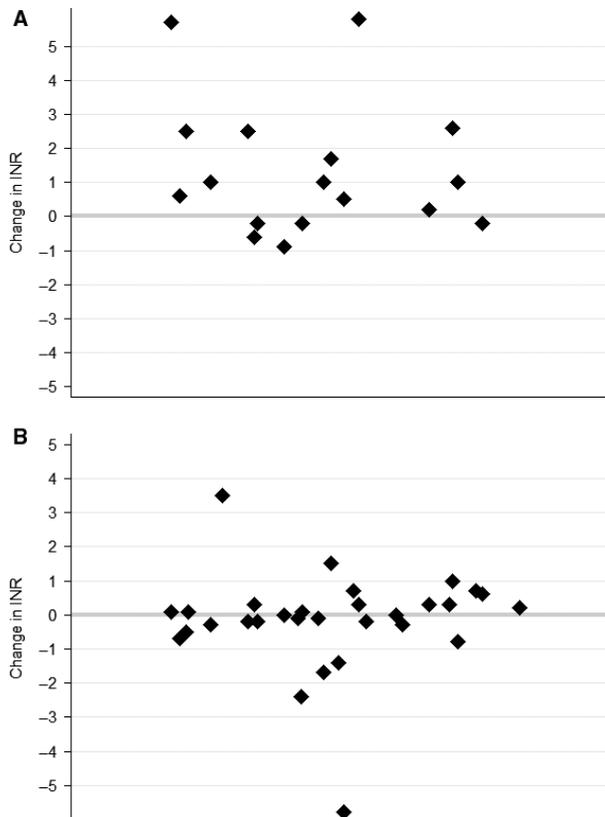


Fig. 2. Changes in the level of international normalized ratio (INR) for the individual warfarin user exposed to an antimycotic drug. (A) INR changes after exposure to miconazole oral gel. (B) INR changes after exposure to nystatin oral solution.

As a *post hoc* sensitivity analysis, we restricted the post-exposure period from 28 to 21 days. This yielded results similar to those of the main analysis (data not shown).

Discussion

This study is the first to provide controlled clinical evidence concerning potential DDIs between warfarin and topically applied antimycotics used in the treatment for oral candidiasis. INR values increased during treatment with miconazole oral gel, while they remained unchanged during treatment with nystatin oral solution.

Our findings of increased INR values in warfarin users after co-prescription of miconazole oral gel are in line with multiple case reports [12], a recent case series [13] and pharmacokinetic data [23]. Overall, current evidence thus supports the presence of a clinically relevant DDI between warfarin and topical miconazole [12].

To our knowledge, only one previous study has examined the potential DDI between warfarin and nystatin [16]. In a retrospective case series, INR was reported to increase from a mean of 2.5 (range 2.0–3.5) to 10.6 (range 4.5–19.3) in eight warfarin users after initiation of topical nystatin treatment. Bleeding complications were reported among four of these patients. However, the data collection is insufficiently described, and the authors did not provide any potential mechanism to support the reported effect of nystatin on warfarin's anticoagulant activity [16]. Overall, their findings are unlikely to reflect a representative sampling of the clinical population at risk, and contrast with the findings of the present study as well as a recent literature review and analysis of UK adverse drug reaction surveillance reports finding no evidence of a DDI between nystatin and warfarin [12].

The observed difference between the two drugs with regard to interaction potential with warfarin is most likely explained by different interference with the CYP450 system. Whereas miconazole is known to inhibit CYP2C9 [9], no examples of interactions between nystatin and the CYP450 system have been described. The observations in the present study are therefore unlikely to be related to differences in bioavailability related to the different drug formulations (i.e. oral gel and oral solution).

Bleedings, and especially intracranial haemorrhage, are feared complications of warfarin therapy. The risk of bleeding increases with increasing INR [4]. As an example, Hylek *et al.* [24] reported that an increase in INR from 2.5 to 4.0, that is an increase similar to the one observed after miconazole exposure in the present study, corresponds to an increase in the incidence rate of intracranial haemorrhage from 0.5/100 person years to 2.7/100 person years. Of note, data on relevant clinical outcomes such as bleeding were not available in the present study.

The main strength of our study pertains to our relatively large study sample, representing unselected warfarin users from everyday clinical settings, and the use of data obtained from routine care independently of exposure or outcome status. Furthermore, inherent in this self-controlled design is

control for all potential factors (confounders) that can be assumed stable during the observation period, such as patient age and chronic comorbidity [25]. The study is also prone to some limitations. We employed rather strict exclusion criteria to reduce interference from other factors potentially causing INR changes. Furthermore, we only included individuals with an INR measurement before as well as after exposure in the analysis. These requirements led to exclusion of a substantial proportion of the exposed individuals, which may impact the generalizability of our results. Also, if the physician is aware of a potential drug–drug interaction, he or she might implement more intensive monitoring of the patient and mitigate the effect of the interaction by dose adjustments. However, the effect of such awareness would likely be largest for miconazole, resulting in an attenuation of the observed associations, which therefore strengthens the confidence in our findings. As topical clotrimazole is not used for buccal infections in Denmark, we were unable to investigate a potential interaction between warfarin and this antifungal agent. Of note, there are no reports suggesting the existence of such a DDI [15], which is further supported by the fact that clotrimazole is poorly absorbed when applied topically and does not interact with CYP2C9 [9]. Finally, it may also be considered whether the indication for oral antimycotics could have an influence on INR values, for example mediated by low food intake in patients with oral candidiasis. However, the fact that we do not find signs of interaction with both drugs contradicts this possibility.

In conclusion, our study provides evidence substantiating the existence of a clinically relevant DDI between miconazole and warfarin. In contrast, we did not find any indication of an interaction between warfarin and nystatin oral solution. In patients receiving warfarin, nystatin oral solution would thus appear to be the safest drug of choice for oral candidiasis, while miconazole should be avoided or used with caution in this setting.

Disclosure

A.J.T. Pedersen, A. Burghle, F. Mouaanaki and P. Damkier declare no conflicts of interest. M. Hellfritzsich has received speaker honorarium from Bristol-Myers Squibb. E.L. Grove has received speaker honoraria from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer and has previously participated in advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim and Bristol-Myers Squibb. A. Pottegård and J. Hallas have participated in projects funded by Boehringer Ingelheim, with funds paid to the institution where they were employed.

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