Change in International Normalized Ratio among patients treated with dicloxacillin and vitamin K antagonists

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Change in International Normalized Ratio Among Patients Treated With Dicloxacillin and Vitamin K Antagonists

A challenge in the use of vitamin K antagonists (VKAs) is the potential for drug-drug interactions, resulting in insufficient or excessive anticoagulation. Solid data are lacking for most alleged interactions. In case reports, the commonly used antibiotic dicloxacillin has been reported to lower the anticoagulant effect of warfarin, the most used VKA.

Methods | Patients currently taking warfarin were identified via the anticoagulant database Thrombobase, a clinical database of all VKA-treated patients (N=7400) followed up by 3 outpatient clinics and 50 general practitioners in Funen, Denmark. All international normalized ratios (INRs) are recorded.

We included all patients who filled a prescription for dicloxacillin while receiving warfarin therapy between March 1998 and November 2012 (as ascertained via the population-based prescription register Odense Pharmacoepidemiological Database). Registry-based studies are exempt from ethical review in Denmark.

Measures of INR were grouped by the week relative to dicloxacillin exposure. For individuals with multiple measurements in rapid succession (≤5 days between measurements), only the first measurement was included.

We compared the last INR measurement before dicloxacillin exposure with the first measurement within weeks 2 to 4 after exposure and compared those with INR measurement within weeks 2 to 4 before exposure.
FEST

FarmakoEpidemiologisk Studie i Tvillinger
Pharmacoepidemiological assessment of drug interactions with vitamin K antagonists

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ABSTRACT

Purpose  We present a database of prescription drugs and international normalized ratio (INR) data and the applied methodology for its use to assess drug–drug interactions with vitamin K antagonists (VKAs). We use the putative interaction between VKAs and tramadol as a case study.

Methods  We used a self-controlled case series to estimate the incidence rate ratio (IRR) comparing the rate of INR measurements of ≥4.0 in concomitant tramadol and VKA-exposed periods to VKA-only-exposed periods. Secondary analyses considered specific subgroups, alternative exposure criteria, alternative outcome definitions, and other drugs.

Results  We identified 513 VKA users with at least 1 INR measurement ≥4.0 and concomitant tramadol and VKA exposure during the observation period. The overall IRR was 1.80 (95% confidence interval [CI], 1.53–2.10), with a stronger association among users of phenprocoumon compared to warfarin (IRR, 3.37; 95%CI, 2.50–4.53 and IRR, 1.46; 95%CI, 1.20–1.76, respectively). We observed larger IRRs with stricter outcome definitions. Concomitant tramadol and VKA exposure was also associated with an increased rate of low INR measurements (i.e., <1.5; IRR, 1.70; 95%CI, 1.37–2.13). Morphine and, to some extent, oxycodone, penicillin, beta-blockers, and inhaled beta-agonists were associated with high INR.
<table>
<thead>
<tr>
<th>Analysis</th>
<th>Individuals</th>
<th>IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: INR ≥ 5.0</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>260</td>
<td>2.30 (1.74–3.05)</td>
</tr>
<tr>
<td>Users of warfarin</td>
<td>207</td>
<td>1.62 (1.15–2.29)</td>
</tr>
<tr>
<td>Users of phenprocoumon</td>
<td>81</td>
<td>5.70 (3.47–9.38)</td>
</tr>
<tr>
<td><strong>Outcome: INR &lt; 1.5</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>389</td>
<td>1.70 (1.37–2.13)</td>
</tr>
<tr>
<td>Users of warfarin</td>
<td>329</td>
<td>1.41 (1.10–1.82)</td>
</tr>
<tr>
<td>Users of phenprocoumon</td>
<td>92</td>
<td>3.81 (2.29–6.35)</td>
</tr>
</tbody>
</table>
FAILURE = PRE-SUCCES
Interaktionsoplysninger for **dicloxacillin og warfarin**

**Kombinationen kan anvendes under visse forholdsregler.**

**Rekommandation**

INR bør monitoreres ved samtidig behandling.

**Interaktioner**

Warfarin har et smalt terapeutisk indeks, og en lang række lægemidler, naturlægemidler, kosttilskud og vitaminer interagerer med warfarin.


**Lægemidler, der nedsætter effekten af warfarin (nedsætter INR):**

Aprepitant, azathioprin, bosentan, carbamazepin, chlordiazepoxid, ciclosporin, colestyramin, **dicloxacillin**, influenza vaccine, mesalazin, phenobarbital, perikon, raloxifen, ribavirin, rifampicin, ritonavir, sucralfat, sulfasalazin, telmisartan og vitamin C i store dooser.
Interaktionsoplysninger for **dicloxacillin og warfarin**

Kombinationen kan anvendes under visse forholdsregler.

**Rekommandation**

INR bør monitoreres ved samtidig behandling

**Konklusion**

I et prospektivt studie observeres et beskedent fald i patienternes PT på 9,1 % (svarende til 1,9 sekunder) mellem warfarin og dicloxacillin. To kasuistikker viser fald i INR ved kombinationsbehandlingen.

**Klinisk betydning**

mulig

**Dokumentationsgrad**

ringe dokumenteret
The potential drug–drug interaction between proton pump inhibitors and warfarin

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ABSTRACT

Background Proton pump inhibitors (PPIs) have been suggested to increase the effect of warfarin, and clinical guidelines recommend careful monitoring of international normalized ratio (INR) when initiating PPI among warfarin users. However, this drug–drug interaction is sparsely investigated in a clinical setting. The aim was to assess whether initiation of PPI treatment among users of warfarin leads to increased INR values.

Methods The study was an observational self-controlled study from 1998 to 2012 leveraging data on INR measurements on patients treated with warfarin from primary care and outpatient clinics and their use of prescription drugs. Data were analyzed in 2015. We assessed INR, warfarin dose, and dose/INR ratio before and after initiating PPI treatment using the paired student’s t-test.

Results We identified 305 warfarin users initiating treatment with PPIs. The median age was 71 years (interquartile range 63–78 years), and 64% were men. The mean INR in the 70 days prior to PPI initiation was 2.6 (95%CI 2.5–2.8) and 2.6 (95%CI 2.5–2.7) in the period 1–3 weeks after PPI initiation (p = 0.67). Further, neither mean warfarin dose nor the dose/INR ratios were significantly different before and after PPI initiation. Sensitivity analyses revealed no differences among individual PPIs.

Conclusions We found no evidence of a clinically meaningful drug–drug interaction between PPIs and warfarin in a Northern European patient population of unselected patients from an everyday outpatient and primary care clinical setting. Thus, we do not support the recommendation to “cautiously monitor” users of warfarin initiating PPI treatment. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—proton pump inhibitors; vitamin K antagonists; drug interactions; adverse drug reactions; pharmacoepidemiology

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Comparison of the Five Danish Regions Regarding Demographic Characteristics, Healthcare Utilization, and Medication Use—A Descriptive Cross-Sectional Study

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