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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Concurrent use of tramadol and oral vitamin K antagonists and the risk of excessive anticoagulation: a register-based nested case–control study

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Abstract
Objectives The objective was to assess whether the concurrent use of tramadol and vitamin K antagonists (VKAs) leads to an increased risk of excessive anticoagulation.
Design The study was designed as a case–control study, nested within users of VKA and with tramadol use as our main exposure. We used conditional logistic regression to control for potential confounders.
Setting Prescription data from primary care were obtained from Odense Pharmacoepidemiological Database (OPED). Information about hospital admissions was obtained from the patient administrative system of Funen County (FPAS).
Subjects Both cases and controls were selected from users of VKA. Cases were defined by being hospitalised with a main diagnosis indicating excessive anticoagulation. For each case, we selected 15 controls among VKA users, matched by age and sex.
Main outcome measure Odds ratio for experiencing excessive anticoagulation attributable to the use of tramadol.
Results A total of 178 patients were included, 30 of which were exposed to tramadol, along with 2643 controls, 114 of which were exposed to tramadol. The adjusted odds-ratio for experiencing excessive anticoagulation during use of tramadol was 3.1 (1.9–5.2). This corresponds to, on average, one excess case per 250 treatment years (CI 125–584). The result is potentially confounded by concomitant paracetamol use and the presence of acute illness.
Conclusion Caution is advised when using tramadol in patients using VKA, and if possible, an alternative pain-medication should be used.

Keywords Warfarin · Adverse drug-reactions · Epidemiology

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Introduction

Vitamin K antagonists (VKAs) are currently still the drugs of choice for the prevention of thromboembolism in patients with atrial fibrillation/flutter or venous thrombotic disease. Each patient requires an individual dose of VKA, as guided by the measurement of the international normalized ratio (INR) [1, 2]. Reaching the desired INR target is essential to patient safety, as below-target INR is associated with thromboembolic events, while above-target INR (excessive anticoagulation, EA) leads to haemorrhagic complications [2–5].

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In this matter, drug-drug interactions play a significant role, as many drugs either increase the effect of VKA directly (pharmacodynamic interactions) or change the absorption or elimination of VKA (pharmacokinetic interactions) [6, 7]. A suspected interaction exists between VKA and the weak opioid tramadol, which potentially should increase the effect of VKA, leading to EA. This potential interaction is, however, founded solely on a few case reports [8–11]. To our knowledge only a single controlled study has looked into this interaction, a small randomized controlled trial on 19 patients, showing no significant interaction between tramadol and phenprocoumon [12].

To further investigate the interaction potential of VKAs and tramadol, we performed a case–control study nested within users of VKA to assess whether use of tramadol increases the risk of EA.

Methods

The main exposure in our study was tramadol and the outcome was status as case, i.e. experiencing EA and having an admission caused by elevated INR-levels. Since all cases and controls were selected among ongoing users of VKA, an association between tramadol use and EA would indicate the presence of an interaction, whereby concurrent use of tramadol and VKA would increase the risk of EA.

Setting and material

Data was extracted from two data sources, the patient administrative system of Funen County (FPAS) and the Odense University Pharmacoepidemiological Database (OPED). In brief, FPAS holds data on all secondary care contacts, i.e. all hospital admissions and ambulatory contacts, for the population of Funen County (population 480,000) since 1977. The diagnoses were encoded according to ICD8 until 1994 and ICD10 thereafter. ICD9 was never used in Denmark. OPED is a research prescription database that contains information on redeemed, reimbursed prescriptions for the citizens of Funen County since 1990 [13]. Drugs that are not qualified for reimbursement (e.g. oral contraceptives, hypnotics, sedatives, dieting products, certain antibiotics and OTC drugs) are not recorded. Among the data included are identifiers of the patient, the pharmacy and the prescriber, a full account of the dispensed product and the date of dispensing. The indication and the dose instruction are not recorded. The product is, among other things, described in terms of the defined daily dose (DDD) and the hierarchical anatomical-therapeutic-chemical (ATC) code developed by the WHO for drug utilization studies [14]. OPED also contains a demographic module with information on residency, migration, births and deaths, which allowed us to account for censoring.

Data sources were linked by use of the Personal Identification Number, a unique identifier assigned to all Danish citizens since 1968 that encodes gender and date of birth [15].

For the purpose of this study, we extracted all prescriptions redeemed by VKA-users in the Funen area during the period July 1999 through March 2011. VKA-users were defined as having redeemed at least one prescription for one of the two VKA available on the Danish market, warfarin and phenprocoumon, within the same period.

Cases

Cases were defined by being at least 16 years old and having a hospital admission caused by elevated INR-levels (with or without bleeding). These admissions were taken as all admissions with the Danish ICD10 discharge code [16] (a slightly modified version of the original ICD10 classification [17]) of either DT88.8 K (dysregulated VKA-treatment) DT45.0 (Poisoning with drug with known systemic haematological effect) or DT45.9 (Poisoning with drug with effect on coagulation) as the main diagnosis within Funen County during the period from January 1, 2000 through March 2011. We extracted all such cases from the FPAS. We have previously validated a subset of 107 admissions, finding an average INR of 9.2 with 22 % having a verified bleeding episode [18].

Controls

Controls were sampled from the cohort of all VKA users as defined by the exposure criteria below. We used a risk-set sampling strategy where controls were sampled in a 15:1 ratio among all persons who were current VKA users on the index date of a case and matched to the case with respect to gender and exact birth year. The controls were then assigned an index date identical to the corresponding case. We allowed that subjects could be elected as controls before they became cases and that subjects could be elected as controls more than once. Therefore, the generated odds ratio (OR) is an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study based on the same source population [19]. As not all cases had 15 eligible controls, the final control:case ratio deviates slightly from 15:1.

Exposure definition

The main problem with analyzing analgesic and VKA use is that treatment can be either episodic or continuous and that

it may be difficult to determine which prescriptions belong to the same episode. Also, it is difficult to determine the average or individual doses. We used data from the mid-period year, 2005, and performed some exploratory analyses to define the time windows that should be assigned to each prescription. An analysis of waiting time distributions using weekly intervals showed that two consecutive warfarin prescriptions that were more than 12 weeks apart were unlikely to belong to the same episode [20]. Corresponding intervals for phenprocoumon and tramadol were 26 and 8 weeks. The exposure periods assigned to a prescription on warfarin, phenprocoumon and tramadol were thus 84, 182, 56 days, always starting on the day of redeeming the prescription. If the next prescription on the specific drug occurred within the assigned exposure period, we assumed that the treatment had continued. If it occurred later, we assumed that treatment had been paused. No allowance was made for overlap between periods assigned to prescriptions within the same episode, i.e. the period assigned to each prescription was not expanded if multiple prescriptions were redeemed within a short interval. The same exposure period was also assigned to single prescriptions or the last prescription in a treatment episode, unless follow-up was terminated for one of the reasons below.

We followed all subjects from the first VKA prescription within the study period until the earliest of the following: admission with a case-defining event, death, emigration or end of study. Only periods of VKA use were included in follow-up.

For other drugs included in the analyses as potential confounders, we defined current use simply by the occurrence of a prescription within a 90-days time window before the index date.

Analysis

The analysis conformed to a conventional matched case–control study, nested within the cohort of current VKA users. Our main outcome was the odds ratio (OR) of experiencing EA attributable to the use of tramadol as estimated using conditional logistic regression, while controlling for potential confounders. The variables included as potential confounders were VKA treatment started less than 91 days before index date and the following drugs that are known or suspected to interact with VKA: paracetamol, high- or low-dose acetylsalicylic acid, SSRIs, amiodaron and NSAID. The following potential confounders have not been included, as they are too rare or to weakly associated with increased INR to be able to introduce any significant confounding: esomeprazole, omeprazole, azathioprine, azithromycin, fluconazole, ciprofloxacin, sulfamethizol and amoxicillin. Age and gender were handled by the matching procedure. Results are presented with 95 % confidence intervals whenever warranted.

Cases that for some reason did not fulfill our definition for current use of use of VKA on their index dates, e.g. by having unusually long intervals between redeeming VKA prescriptions, were excluded along with their matched controls (n=47). To account for the selection of the same individual as control on more than one occasion, we used the robust estimator technique to widen the confidence intervals for ORs [21].

We performed several sub-group analyses limited to certain sub-sets of users specified by sex, age, newly initiated VKA-treatment, users of either warfarin and phenprocoumon and with or without concurrent use of paracetamol. Furthermore, we varied the exposure looking at different amounts of cumulative exposure of tramadol. As chronic users of tramadol might have had their VKA dosage adjusted to account for an influence from tramadol, we finally analysed for newly introduced tramadol treatment, i.e. the first ever tramadol prescription occurring less than 30 days prior to index date.

We used the "number needed to treat for one additional patient to be harmed" (NNTH) principle to calculate the risk of EA in absolute terms [22]. It was slightly modified to estimate the required person-time of exposure rather than the count of exposed subjects [23]. If ER_{unexp} denotes the event rate among unexposed subjects in the source population, the NNTH can be calculated simply as [22, 23]

$$\mathrm{NNTH} = \frac{1}{\mathrm{ER}_{\mathrm{unexp}} \cdot (\mathrm{OR} - 1)} \quad (1)$$

Results

We identified 178 first-time admissions with EA within the study period. There were 83 men and 95 women (47 and 53 %) and their median age was 76 (IQR 65–83). Their demographic characteristics and other details are listed in Table 1.

Among the cases and controls, 30 (17 %) and 114 (4 %) were exposed to tramadol. The crude and adjusted ORs association between tramadol and EA were 4.6 (CI 2.9–7.1) and 3.1 (CI 1.9–5.2). The ORs calculated for various subgroups defined by age, gender and choice of VKA are shown in Table 2. Due to low power, these analysis did not allow a clear evaluation of the effect in the different subgroups. However, the finding is seemingly consistent across most subgroups, such as gender (OR, 2.6 vs. 4.0) and type of VKA (OR, 3.1 vs. 3.9), although with a somewhat higher OR in those <60 years (OR, 9.5) compared to those ≥60 years (OR, 2.7). Table 2 also shows the tramadol—EA association if we define tramadol exposure by different cumulative quantities redeemed within the past 3 months.

Table 1 Characteristics of cases of excessive anticoagulation and their matched controls

	Cases (n=178)	Controls (n=2,643)
Men	83 (47 %)	1,242 (47 %)
Women	95 (53 %)	1,401 (53 %)
Age in years, median (IQR)	76 (65–83)	76 (65–83)
Warfarin	159 (89 %)	2,380 (90 %)
Phenprocoumon	19 (11 %)	263 (10 %)
Recent start of VKA	92 (52 %)	333 (13 %)
Concurrent use of:		
Tramadol	30 (17 %)	114 (4 %)
Paracetamol	55 (31 %)	334 (13 %)
NSAIDs	22 (12 %)	151 (6 %)
High- or low-dose aspirin	34 (19 %)	452 (17 %)
SSRI	18 (10 %)	152 (6 %)
Amiodaron	3 (2 %)	31 (1 %)

IQR InterQuartile Range

There was a cumulative exposure of 82,317 person years for VKA use in our source population during the study period, giving rise to 178 cases. Among these cases, 30 were exposed to tramadol (in 4,506 person years). The incidence rate of EA is thus (178–30)/(82,317y–4,506y)= 1.9 (1000 years)$^{-1}$ among VKA users unexposed to tramadol and 30/4,506y=6.7 (1000 years)$^{-1}$ among VKA users exposed to tramadol. The corresponding NNTH for the use of tramadol among VKA users is 250 year^{-1} (CI, 125–584).

Discussion

We have found a strong and statistically significant correlation between the use of tramadol and the risk of EA among VKA-users. To our knowledge this is the first study to show such an association.

The main strength of our study lies in the use of a true population based approach, using a large data material with good quality prescription data and a reliable diagnosis code of EA [18, 24].

The primary weakness of our study is lacking information concerning certain risk factors for EA: use of paracetamol or other analgesics bought over-the-counter or concurrent use of certain antibiotics (neither of which is covered by our database) or a history of alcohol-abuse.

The narrow case-definition, only including seriously dysregulated VKA-patients, should provide a high specificity but may lack in sensitivity since most cases of EA may never be admitted. This should be of small importance for the relative effect, but may result in under-estimation of the absolute risk and NNTH. While we do not expect significant

Table 2 The odds ratios associating tramadol use with excessive anticoagulation among users of vitamin K antagonists by subgroup and by pattern of use

Subgroup	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR	Adjusted OR [a]
All cases	30/148	114/2,529	4.6 (2.9–7.1)	3.1 (1.9–5.2)
Men	15/68	44/1,198	6.0 (3.2–11.4)	4.0 (1.9–8.3)
Women	15/80	70/1,331	3.6 (2.0–6.7)	2.6 (1.2–5.3)
Age <60 years	5/28	8/468	10.7 (3.2–35.6)	9.5 (2.6–35.2)
Age ≥60 years	25/120	106/2,061	4.1 (2.5–6.5)	2.7 (1.5–4.8)
Choice of VKA				
Warfarin	26/133	98/2,282	4.6 (2.9–7.3)	3.1 (1.7–5.4)
Phenprocoumon	4/15	16/247	4.6 (1.3–15.6)	3.9 (1.0–15.5)
Without concurrent use of paracetamol	15/108	57/2,252	6.0 (3.2–11.3)	6.7 (3.3–13.7)
With concurrent use of paracetamol	15/40	57/277	1.7 (0.8–3.9)	1.7 (0.6–4.9)
Exposure pattern				
VKA started less than 3 months ago	15/77	21/312	2.7 (1.0–7.2)	2.3 (0.8–6.9)
First ever tramadol prescription <1 month ago	6/148	14/2,529	6.7 (2.5–17.5)	4.5 (1.4–14.4)
Amount of tramadol dispensed last 90 days				
0–10 DDD	11/148	33/2,529	5.1 (2.6–10.3)	3.6 (1.6–8.1)
11–30 DDD	10/148	34/2,529	5.4 (2.6–11.5)	5.0 (2.0–12.1)
>30 DDD	9/148	47/2,529	3.6 (1.7–7.7)	1.9 (0.8–4.5)

[a] Potential confounders were controlled by conditional logistic regression. The variables included as potential confounders were VKA treatment started less than 91 days before index date and the following drugs that are known or suspected to interact with VKA: paracetamol, high- or low-dose acetylsalicylic acid, SSRIs, amiodaron and NSAID. Age and gender were handled by the matching procedure

misclassification of exposure, any misclassification will be non-differential and thus have a conservative impact on the obtained risk estimates.

Our findings may potentially be confounded. As people using tramadol also might use paracetamol, a potential confounder is newly initiated use of paracetamol as this is known to be a risk factor for experiencing EA [25]. Although paracetamol is available over the counter, some is sold on prescription and reimbursed and therefore covered by our database. The data coverage of paracetamol is roughly 37–45 % [26]. The stratified analysis with and without known concurrent use of paracetamol presented in Table 2 does suggest some effect-modification, but no confounding as the average of the two estimates equals our main finding. However, taking into account the low data coverage, we cannot rule out residual confounding. NSAID use might also be a confounder. NSAIDs do not affect INR but may increase the risk of bleeding by other mechanisms [27], thereby lowering the threshold for becoming a case. We were able to include most of the NSAID use in our multivariable model. For the NSAIDs, the data coverage is virtually complete, except for ibuprofen (ATC, M01AE01) which is 67–69 % [26].

Another potential confounder is acute illness, including fever and diarrhea which are known risk factors for experiencing EA [28, 29], and might be correlated to the indication for use of tramadol. To explore this suspicion, we performed a crude re-analysis of our data looking at codeine-exposure instead of tramadol-exposure, and finding an OR of 1.4 (CI, 0.4–4.7). The indication for codeine is largely similar to tramadol. The low OR for codeine suggests that residual confounding by acute illness is of minor importance.

Our results are in apparent contradiction to those of Boeijinga et al. [12], who did not find an interaction between tramadol and phenprocoumon in a randomized cross-over trial, where administration of three daily doses of 50 mg tramadol resulted in no apparent changes in average INR. One possible explanation is that they did not consider the CYP-genotype status of their test-subjects. Although the average INR of their 19 test-subjects did not differ significantly between tramadol and placebo-treatment, it is apparent from their data that three subjects clearly showed an increase in INR during tramadol treatment. A Swedish study, by Hedenmalm et al. [30], suggests that the interaction might be potentiated in patients with decreased CYP2D6-activity. In these patients, tramadol metabolism could be shunted from CYP2D6 to CYP3A4 and thus influence the metabolism of warfarin via competitive inhibition of CYP3A4 [30]. A possible unifying hypothesis of these observations, including our study, is that the interaction might only be relevant for a subset of patients, with CYP2D6 mutations, and not for anyone else. The prevalence of poor metabolizers is approximately 10 % in the Danish population [31]. Unfortunately we do not have data on the CYP status for the subjects included in our study. Compared to warfarin, phenprocoumon metabolism is less dependent on the polymorphic CYP2C9 enzyme, while it may be more prone to CYP3A4-mediated drug interactions [32]. However, the ORs found for phenprocoumon and warfarin were quite similar which suggests that other mechanisms might also play a role.

We have not found other proposed mechanisms for the potential pharmacokinetic interaction in the literature than the above. To our knowledge, tramadol does not have anti-haemostatic properties of its own. A pharmacodynamically based interaction is thus unlikely.

While our main analysis includes all tramadol exposures, it is apparent from Table 2 that newly initiated use of tramadol shows a much stronger association with EA. This observation is compatible with a genuine interaction. If tramadol is introduced while the patient already takes VKA it will decrease the VKA clearance and induce EA. If the tramadol treatment continues, a new steady-state will emerge with lower VKA dose requirements. If the VKA dose is adjusted to the new, lower dose requirements, there would be a low risk of EA again.

The finding that half of our exposed cases have recently initiated VKA treatment is not surprising as recently initiated VKA treatment is a potent risk factor for EA [33, 34].

While the interaction is statistically significant it is important to bear in mind the estimated NNTH of 250 person years. One could therefore very well argue that in situations where other pain medications are not usable, tramadol might still be considered a valid treatment option, at least if carefully monitored with INR measurements.

In conclusion, caution is advised when using tramadol in patients using VKA, and if possible, alternative pain-medication should be used.

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