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ORIGINAL REPORT

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.
Conclusions The approach successfully identified an interaction between tramadol and VKA. However, associations observed for other drugs with no known VKA interaction suggest that the current approach may have too low specificity to be useful as a screening tool, at least for drugs for which time-varying confounding may be present. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—self-controlled case series; warfarin; vitamin K antagonists; drug–drug interactions; Denmark; pharmacoepidemiology

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INTRODUCTION

When treating patients with vitamin K antagonists (VKAs), maintaining tight international normalized ratio (INR) control balances the benefits and risks of anticoagulation (AC). Below-target INR is associated with risk of thromboembolism, whereas above-target INRs increase bleeding risk.[1–4] Drug–drug interactions are a significant consideration in AC management, as many drugs either increase the effect of VKAs directly (pharmacodynamic interactions) or change the metabolism of VKAs (pharmacokinetic interactions).[5,6] However, evidence of clinical outcomes associated with putative interactions is often sparse and limited to case reports. This evidence gap limits our understanding of which potential interactions are clinically significant. A comparison of four major sources of drug–drug interaction information reported that up to 72% of interactions marked at the highest level of significance in one source were not even mentioned in the other three sources.[7]

To be able to provide clinical evidence of drug–drug interactions with VKAs, we constructed a database of Danish VKA-treated patients that includes drug utilization data and INR test results. We present the database and proposed methodology for assessing associations between the use of concomitant drugs

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and out-of-range INR measurements. We demonstrate the approach using the example of the possible interaction between VKAs and tramadol, as use of tramadol has previously been associated with increased INR among VKA users.[8–11]

SETTING

We linked drug data from the Odense University Pharmacoepidemiological Database (OPED) to INR data from the anticoagulant management database Thrombobase.

The Odense University Pharmacoepidemiological Database is a research prescription database that contains information on redeemed, reimbursed prescriptions for the citizens of Funen County since 1989.[12] Drugs that are not qualified for reimbursement (e.g., oral contraceptives, hypnotics, sedatives, dieting products, certain antibiotics, and over-the-counter (OTC) drugs) are not recorded. Data elements include patient identifiers, the pharmacy and the prescriber details, an account of the dispensed product, and the date of dispensing. The indication and the dosing instructions are not recorded. Drug products are characterized in terms of the defined daily dose and the hierarchical anatomical-therapeutic-chemical (ATC) code developed by the WHO for drug utilization studies.[13] OPED also contains a demographic file with information on residency, migration, births, and deaths.

Thrombobase is a clinical database receiving data from patients receiving VKA treatment. Data processing is based on the ACURE® AC software (IBM, Denmark), used at three outpatient clinics at Odense University Hospital and by 50 general practitioners. The AC software is used for follow-up and dosage control of VKAs. For each treatment episode, the indication for treatment, choice of VKAs (warfarin or phenprocoumon), dose, and target INR are recorded. For each INR measurement, the INR value, date, revised dose of VKAs, temporary suspensions, and interval between INR measurements are recorded. Data on INR measurements are transferred electronically from the laboratory to the AC software and Thrombobase, thus eliminating errors caused by transfer of information from one system to another. In the period of 1998 to 2012, Thrombobase covered approximately 7400 unique patients.

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.[14]

METHODS

We used a self-controlled case-series (SCCS) approach as described by Farrington.[15] In brief, this involves following each VKA user over time and comparing the rate of out-of-range INR measurements between follow-up classified as exposed (in this case, to concomitant tramadol and VKA use) and unexposed (i.e., VKA-only-exposed) for each patient.

Self-controlled case series

The SCCS is an epidemiological design that is "self-controlled," that is, widely robust toward confounders that are stable over time. The SCCS is essentially a cohort design but differs from the conventional cohort study in three key aspects. First, it is a case-only design in which only subjects who experience the outcome of interest are included in the analysis. Second, follow-up after the outcome is included, thereby allowing for more than one occurrence of the outcome per subject. Third, all comparisons are performed within the same individual, as opposed to between individuals, such that the calculations are conditioned on the individual. Each individual's person-time is categorized by exposure (as well as potential confounders), and the incidence rate ratio (IRR) describing the association between the exposure and the outcome can be estimated using a conditional Poisson regression model.[16] By conditioning on the individual, only those with variation in exposure—that is, with both concomitant tramadol and VKA-exposed time and VKA-only-exposed time—contribute to the main estimate.

The within-person comparison ensures that confounders—both measured and unmeasured—that are stable over the observation period do not affect the estimate. Furthermore, all individual effects cancel out, and the age-dependent baseline incidence is handled implicitly in the underlying multinomial Poisson model.[17] For this study, the SCCS was preferred over other self-controlled designs, such as the case-crossover design,[18] because of its ability to handle multiple outcomes, thereby preserving statistical efficiency, and because of its ability to handle chronic exposure.[16]

Cohort and outcome definition

After linking the OPED and Thrombobase databases, we identified individuals who in the period of 1998 to 2012 met the following criteria: (i) residency in Funen, thereby being covered by the prescription database OPED; (ii) ≥18 years old; and (iii) at least 90 days of continuous VKA treatment (as early treatment is associated with an increased risk of off-target INR measurements[19,20]) with a target INR range of 2.0 to 3.0 for that episode. We defined the cohort entry date as the first date on which all criteria were met. We truncated the VKA treatment episode if >120 days

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passed without an INR measurement. Subsequent treatment episodes were eligible for inclusion after a new 90-day stabilization period. We also required a new 90-day stabilization period following VKA switching (e.g., from phenprocoumon to warfarin).

We included individuals that had at least one outcome during an eligible VKA treatment episode, as those without an event do not contribute to the SCCS analysis. We defined the primary outcome as having a high INR value, defined by an INR measurement ≥4.0.

We also excluded individuals with no exposure to tramadol during an eligible VKA treatment episode because subjects with no exposure variation do not contribute to the main estimate.

Individuals were eligible to contribute follow-up until they discontinued VKA treatment, initiated home INR monitoring, migrated, died, or until the end of the study period (17 November 2012).

It is likely that individuals with high INR values are monitored more closely over the short term, during which they are likely to have another high INR value measured, which should not be considered a new outcome in itself. Conversely, users with INR measurements <2.0 are unlikely to have a high INR value at their next measurement. Therefore, when individuals had an outcome or had an INR value <2.0, we censored follow-up until the individual had a new INR measurement within the target range of 2.0–3.0, at which time we resumed follow-up.

Exposure

Our main exposure of interest was concomitant tramadol (ATC N02AX02) and VKA use. An individual was considered exposed from the day of redeeming a prescription for tramadol and until 30 days after the estimated duration of the prescription had been exceeded. The 30-day grace period was used to allow for some nonadherence. As the expected duration of each prescription is not recorded in OPED, we assumed a standard daily consumption of two tablets for immediate release formulations, one tablet for controlled release formulations, and 1 ml (100 mg) for oral drops. We made no corrections for overlap between prescriptions (i.e., stockpiling). We varied these assumptions in sensitivity analyses described in the succeeding texts.

Analysis

Our parameter of interest was the IRR comparing the rate of an INR ≥ 4.0 during concomitant tramadol and VKA-exposed time to that during VKA-only-exposed time. We used conditional Poisson regression to perform the within-person analysis.[17,21]

We also estimated a measure of the absolute increase in risk, the naturalistic "exposure needed for one additional patient to be harmed" (ENH) as proposed Hallas *et al.*[22]:

$$(1)\ ENH = \frac{PT_{\exp}}{\left(\frac{IRR-1}{IRR}\right) n_{\exp}}$$

$PT_{\exp}$ denotes the cumulative amount of exposed person-time among those eligible to enter analysis (i.e., not restricted to those experiencing an outcome), and $n_{\exp}$ denotes the total number of exposed outcomes.

All analyses were performed using STATA Release 13.0 (StataCorp, College Station, TX, USA).

Supplementary and sensitivity analyses

We conducted a number of supplementary analyses. First, we performed age-specific, sex-specific, and drug-specific (i.e., warfarin or phenprocoumon) subgroup analyses. Secondly, we examined three alternative outcome definitions: (i) INR measurements of INR ≥ 5.0; (ii) INR measurements that led to a reduction in VKA dose; and (iii) INR measurements that led to temporary suspension of VKA treatment. To assess potential surveillance bias as a result of more frequent INR monitoring following initiation of concomitant tramadol, we also examined two low-INR outcomes, defined as an INR < 1.8 and INR < 1.5.

We also repeated our main analysis with codeine (ATC R05DA04). Codeine is a drug used mainly for the same indication as tramadol (weak to moderate pain) and, to our knowledge, has not been suspected to interact with VKA treatment. We also changed the exposure to concomitant use of other drug classes not known or suspected to interact with VKA treatment: beta-blockers (ATC C07A), penicillin (J01C), drugs used locally in either eyes or ears (S), angiotensin-converting-enzyme (ACE) inhibitors (C09A and C09B), calcium channel blockers (C08CA), thiazides (C03AA, C03AB, C09BA, and C9DA), morphine (N02AA01), oxycodone (N02AA05), furosemide (C03CA01), low-dose aspirin (B01AC06 and N02BA01), inhaled steroids (R03BA), and inhaled beta-agonist (R03AC). We assumed a 90-day treatment duration for each prescription, except for eye and ear drugs (30 days) and penicillin (10 days), while adding in a 30-day grace period as in the main analysis.

In sensitivity analyses, we varied the exposure definition by changing the 30-day grace period for the duration of each tramadol prescription to 0 and 60 days. We also restricted the concomitant tramadol and VKA-exposed person-time to 90 days after the first-ever tramadol prescription. Finally, we included

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time since last INR measurement (categorized as 1–8, 9–15, 16–22, 23–29, 30–43, or ≥44 days) as a time-varying variable in the Poisson regression.

Data protection and ethics

The study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for registry-based studies.[23]

RESULTS

We identified 7162 VKA users in Thrombobase. Following exclusions and restriction to those both experiencing the outcome of interest and exposed to tramadol, the final cohort consisted of 513 individuals who were followed for a total of 2395 person-years and had 31 873 INR measurements (Table 1). At cohort entry, the median age was 68 years, and the majority used warfarin (73.5%) instead of phenprocoumon (26.5%; Table 2).

The 513 eligible individuals had 1582 INR measurements ≥4.0: 359 were during the 340 person-years of follow-up exposed to tramadol, while 1223 were during the 2055 person-years of follow-up exposed to VKAs alone. The SCCS analysis yielded an IRR of 1.80 (95% confidence interval [CI], 1.53–2.10; Table 3). Subgroup analyses of age and gender yielded materially similar results as the main analysis. We observed a higher IRR among individuals using phenprocoumon compared with warfarin (3.37 [95%CI, 2.50–4.53] vs 1.46 [95% CI, 1.20–1.76]; Table 3).

The ENH in the main analysis was 3.0, corresponding to one excess outcome (INR measurement ≥4.0) for each 3.0 years of concomitant tramadol and VKA exposure.

Our supplementary analyses resulted in larger relative associations when using stricter outcome definitions. The IRR for an INR measurement ≥5.0 was 2.30 (95%CI, 1.74–3.05; Table 4). The corresponding IRRs were 5.70 (95%CI, 3.47–9.38) and 1.62 (95%CI, 1.15–2.29) for phenprocoumon and warfarin, respectively. Because rates of the stricter outcome were lower than that of the main outcome measure, ENHs were larger in these analyses. With an outcome defined as INR < 1.5, we found associations similar in strength to those of the main analysis (Table 4).

Table 2. Baseline characteristics of analysis-eligible individuals

	All subjects ($n = 513$)
Age, median (IQR)	68 (60–75)
Male	283 (55.2%)
Female	230 (44.8%)
Type of VKAs	
Warfarin	377 (73.5%)
Phenprocoumon	136 (26.5%)
Indication for VKA use	
Atrial fibrillation	245 (47.8%)
Heart valve replacement	162 (31.6%)
Deep vein thrombosis	30 (5.8%)
Pulmonary embolism	28 (5.5%)
Other	48 (9.4%)

IQR, interquartile range; VKA, vitamin K antagonist

The analysis of codeine resulted in an overall IRR of 1.16 (95%CI, 0.87–1.54); IRRs were 1.77 (95%CI, 1.01–3.11) and 1.04 (95%CI, 0.75–1.45) for phenprocoumon and warfarin, respectively (Table 5). Among the other drugs, the largest IRR was seen for morphine (IRR, 2.45; 95%CI, 1.75–3.45), 5.08 (95%CI, 2.63–9.79) for phenprocoumon and 1.89 (95%CI, 1.27–2.81) for warfarin. Other drugs, including oxycodone, penicillin, beta-blockers, furosemide, and inhaled beta-agonists, also resulted in elevated IRRs.

Varying the grace period had little effect on the results (data not shown). When only considering the first 90 days after the first tramadol prescription as exposed time, the overall IRR increased to 2.30 (95%CI, 1.79–2.95), 1.86 (95%CI, 1.36–2.55) for warfarin, and 3.95 (95%CI, 2.61–5.98) for phenprocoumon. Adjustment for time since last INR measurement slightly increased the overall IRR to 1.88 (95%CI, 1.60–2.20).

DISCUSSION

We developed a linked database of prescription drug data and INR test results for VKA-treated patients

Table 1. Patient selection into the self-controlled case-series analysis

Step	Unique individuals	Person-years	INR measurements	INR measurements ≥4.0
All	7162	16 162	241 808	10 601
Limited to those living in Funen	6131	14 046	210 438	9321
Excluding those <18 years of age	6127	14 044	210 374	9319
Excluding the first 90 days in each episode	4342	11 218	163 438	7068
Excluding 90 days following drug changes	4340	11 181	162 373	6992
Excluding target INR outside 2–3	4208	9992	143 303	5466
Excluding those who measure INR at home	4132	9792	141 514	5396
Excluding time after out-of-range INR	4054	8674	111 181	3616
Only including those experiencing an outcome	1560	5596	74 200	3616
Only including those using tramadol during follow-up	513	2395	31 873	1582

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Table 3. Association between concomitant tramadol and vitamin-K antagonist exposure and having an INR ≥ 4.0

		Exposed		Unexposed			ENH (PY^{-1})
Subgroup	Individuals*	PY	Events	PY	Events	IRR	
All	513	340	359	2055	1223	1.80 (1.53–2.10)	3.0
Male	283	164	159	1214	688	1.74 (1.40–2.16)	3.4
Female	230	176	200	841	535	1.86 (1.48–2.34)	2.6
Age <60 years	116	55	73	334	215	1.92 (1.25–2.93)	2.3
Age 60–79 years	388	216	204	1348	764	1.72 (1.41–2.10)	3.3
Age 80+ years	163	70	82	373	244	1.79 (1.26–2.53)	2.9
Users of warfarin	412	233	255	1341	896	1.46 (1.20–1.76)	4.3
Users of phenprocoumon	138	107	104	710	327	3.37 (2.50–4.53)	1.7

Note: PY, person-years; ENH, "exposure needed for one additional patient to be harmed".
*As individuals might contribute to more than one age category or use more than one drug, the numbers may not add up to 513.

Table 4. Supplementary analyses of the tramadol–vitamin K antagonist interaction, using alternative outcome definitions

		Exposed		Unexposed			ENH
Analysis	Individuals	PY	Events	PY	Events	IRR	(PY^{-1})
Outcome: INR ≥ 5.0							
All	260	179	114	1126	316	2.30 (1.74–3.05)	7.5
Users of warfarin	207	125	76	695	237	1.62 (1.15–2.29)	12.0
Users of phenprocoumon	81	54	38	429	79	5.70 (3.47–9.38)	4.2
Outcome: reduced dosage							
All	752	402	1140	2382	4832	1.37 (1.25–1.49)	1.4
Users of warfarin	615	289	851	1584	3484	1.29 (1.17–1.43)	1.6
Users of phenprocoumon	187	112	289	793	1348	1.56 (1.31–1.86)	1.1
Outcome: paused treatment							
All	146	110	61	545	151	2.15 (1.45–3.20)	14.8
Users of warfarin	99	64	34	288	95	1.61 (0.94–2.76)	27.2
Users of phenprocoumon	57	45	27	257	56	3.31 (1.79–6.13)	7.0
Outcome: INR < 1.8							
All	734	414	645	2384	2647	1.25 (1.11–1.41)	3.4
Users of warfarin	608	299	506	1617	2109	1.12 (0.98–1.29)	5.6
Users of phenprocoumon	176	114	139	761	538	1.85 (1.44–2.38)	1.8
Outcome: INR < 1.5							
All	389	250	178	1321	569	1.70 (1.37–2.13)	6.2
Users of warfarin	329	181	134	920	491	1.41 (1.10–1.82)	8.6
Users of phenprocoumon	92	68	44	398	78	3.81 (2.29–6.35)	3.8

Note: PY, person-years; ENH, "exposure needed for one additional patient to be harmed".

and demonstrated the use of SCCS analysis to assess associations between use of drugs and off-target INR values. While the analysis showed an expected association for concomitant use of tramadol and VKAs, some other drugs with no expected interaction also produced associations of similar strength. We also observed an association between tramadol and VKA exposure and low INR values.

The main strength of the database is the availability of high-quality prescription data[12] linked to detailed data on INR measurements. The use of the SCCS approach inherently controls for time-invariant unmeasured confounding. The most important limitation of the approach is that the database does not contain data on underlying conditions (e.g., infections, minor trauma, etc.) that might influence INR control and therefore act as time-varying confounders. Also, hospitalizations as result of major bleeding events cannot be identified in the database. However, we suspect that such major bleeding events would be rare relative to the outcome of an INR value ≥4.0. Further, we have previously shown that the majority of patients using VKAs who are admitted to the hospital with "excessive AC" or "bleeding" are not actively bleeding but are admitted on the basis of an elevated INR measure[10], which would be captured in our database and included in our study. In relation to the choice of study design, the SCCS design can result in biased effect estimates if the outcome, that is, having an elevated INR value, affects the likelihood of future exposure[16], that is, use of tramadol. If physicians discontinue use of tramadol in patients presenting with an

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Table 5. Supplementary analyses using other drugs concomitantly with vitamin K antagonists as the exposure

		Exposed		Unexposed			
Analysis	Individuals	PY	Events	PY	Events	IRR	ENH (PY^{-1})
Codeine							
All	165	130	121	628	397	1.16 (0.87–1.54)	10.2
Users of warfarin	133	89	87	432	296	1.04 (0.75–1.45)	36.4
Users of phenprocoumon	42	41	34	195	101	1.77 (1.01–3.11)	3.4
Beta-blockers							
All	939	2197	1567	1247	643	1.47 (1.29–1.69)	6.8
Users of warfarin	838	1778	1333	825	489	1.37 (1.17–1.60)	8.0
Users of phenprocoumon	151	417	234	420	154	1.69 (1.27–2.26)	6.0
Penicillin							
All	1055	453	470	4250	2337	1.68 (1.51–1.87)	3.3
Users of warfarin	841	311	341	2824	1709	1.56 (1.38–1.77)	3.7
Users of phenprocoumon	283	141	129	1419	628	2.08 (1.70–2.55)	2.7
Eye and ear drugs							
All	534	409	240	2241	1196	0.89 (0.74–1.06)	—
Users of warfarin	423	268	178	1444	850	0.91 (0.74–1.12)	—
Users of phenprocoumon	156	140	62	794	346	0.82 (0.58–1.17)	—
ACE inhibitors							
All	745	1901	1265	1111	605	1.28 (1.10–1.48)	10.5
Users of warfarin	627	1421	1033	737	440	1.28 (1.08–1.52)	9.7
Users of phenprocoumon	161	479	232	372	165	1.12 (0.81–1.54)	26.7
Calcium channel blockers							
All	331	687	393	768	449	0.95 (0.79–1.15)	—
Users of warfarin	295	547	331	562	351	0.87 (0.70–1.08)	—
Users of phenprocoumon	58	139	62	205	98	1.18 (0.74–1.89)	24.2
Thiazides							
All	540	947	621	1398	793	0.97 (0.84–1.12)	—
Users of warfarin	450	729	501	904	565	0.99 (0.83–1.17)	—
Users of phenprocoumon	122	216	120	493	228	0.98 (0.74–1.31)	—
Morphine							
All	113	79	104	396	216	2.45 (1.75–3.45)	1.7
Users of warfarin	91	62	79	278	165	1.89 (1.27–2.81)	2.2
Users of phenprocoumon	27	17	25	118	51	5.08 (2.63–9.79)	1.1
Oxycodone							
All	110	73	86	422	259	1.85 (1.32–2.59)	2.3
Users of warfarin	99	58	71	292	181	1.83 (1.23–2.72)	2.3
Users of phenprocoumon	25	14	15	130	78	2.29 (1.01–5.18)	1.8
Furosemide							
All	892	1945	1443	1428	767	1.42 (1.25–1.62)	6.4
Users of warfarin	731	1389	1100	936	569	1.33 (1.15–1.55)	7.4
Users of phenprocoumon	217	553	343	488	198	1.49 (1.16–1.92)	6.2
Low-dose aspirin							
All	616	1336	859	980	602	1.12 (0.97–1.30)	21.4
Users of warfarin	560	1142	751	643	461	0.98 (0.83–1.16)	—
Users of phenprocoumon	90	192	108	336	141	2.18 (1.51–3.13)	4.3
Inhaled steroid							
All	142	198	160	386	240	1.26 (0.96–1.65)	9.2
Users of warfarin	109	128	117	231	172	1.29 (0.94–1.78)	8.1
Users of phenprocoumon	45	69	43	154	68	1.19 (0.71–1.99)	12.9
Inhaled beta-agonist							
All	288	327	283	950	505	1.57 (1.28–1.93)	4.5
Users of warfarin	220	212	218	555	328	1.65 (1.29–2.10)	3.7
Users of phenprocoumon	94	114	65	394	177	1.37 (0.92–2.05)	8.0

Note: PY, person-years; ENH, "exposure needed for one additional patient to be harmed".

elevated INR value, this would lead to upward bias. Lastly, the SCCS, as other self-controlled designs, is more sensitive to exposure misclassification than conventional cohort studies[16].

The potential interaction between tramadol and VKAs was first described in a few case reports.[8,24–26] In a previous case-control study among VKA users of the association between use of tramadol and being admitted to the hospital as a result of either bleeding or elevated INR levels, we found an overall OR of 3.1 (95%CI, 1.9–5.2), with similar ORs for warfarin and phenprocoumon (3.1 [95%CI, 1.7–5.4] and 3.9 [95%CI, 1.0–15.5], respectively).[11] While a small crossover trial failed to show any interaction with phenprocoumon,[9] three

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of the 19 participants did show a marked increase in INR during tramadol treatment.[9] One possibility is that this is explained by genetic susceptibility related to the metabolism of VKAs among a subgroup of patients. If metabolic pathways are implicated, the interaction potential would probably differ between phenprocoumon and warfarin because their metabolic pathways are largely dissimilar.[27] Further studies are required to determine whether metabolic pathways are involved.

We estimated the ENH for all interactions. Generally, unusually small values were observed compared with other scenarios[22,28], suggesting a high incidence rate of the outcome for the subjects affected by the interactions. The strengths of associations were mostly moderate. This apparent contradiction is explained by the fact that the incidence rates of the outcomes are very high. Even small increases in relative risk translate into a substantial attributable risk.

Our observed associations for drugs for which no interactions were expected warrant further discussion. We consider three possible explanations: (i) surveillance bias; (ii) bias as a result of time-varying confounding; and (iii) that the results might represent true but unrecognized drug–drug interactions.

Surveillance bias could affect our results if individuals had more frequent INR measurements during exposed versus unexposed follow-up time, as more frequent INR measurement increases the cumulative probability of identifying at least one out-of-target INR value. The suspicion that tramadol interacts with VKAs could prompt the treating physician to measure INR more frequently after the patient has started tramadol. The finding that tramadol is associated with both high and low INR values (Table 4) indicates that such a bias may be present. Another explanation for this finding could be that the use of tramadol, which is often used on an "as needed" basis, destabilizes the VKA treatment, as the dose of VKAs is continuously adjusted to alternating periods of use or nonuse of tramadol.

With respect to time-varying confounding, conditions such as acute illness, fever, diarrhea, and eating less, in general, have been identified as risk factors for out-of-target INR values.[20,29,30] If drugs such as opioids or antibiotics are prescribed more often when a patient is experiencing such conditions, as compared with other times, confounding will result. Such confounding by indication could also affect other study designs and could therefore also explain the finding of our previous case-control study of the interaction between tramadol and VKAs.[11] Alternatively, other drugs prescribed at the same time as the drug of interest, including OTC drugs not covered by our database, could also induce confounding if these other drugs affect INR.

Lastly, the finding of associations between high INR values and concomitant VKA use with morphine, oxycodone, penicillin, beta-blockers, and inhaled beta-agonists might represent true drug–drug interactions. To our knowledge, no previous controlled studies have documented any such interactions for any of the drug classes, except perhaps for the penicillins.[5,6] Substantial evidence indicates that beta-blockers, ACE inhibitors, and the calcium channel blockers do not interact with VKAs.[31] The large association for concomitant morphine and phenprocoumon use warrants further investigation, although it is likely that this finding is, at least partially, because of time-varying confounding.

In order to use the database for screening purposes, further methodological work is needed. One possible improvement could be inclusion of data on time-variant confounders such as infections or trauma or proxies hereof such as prescriptions for antibiotics or contacts to the patients' physician or emergency ward. Further, surveillance bias might be partly remedied if the model accounted for changes in the frequency of INR measurements over time for the single individual.

In conclusion, we have presented a linked drug and INR database and proposed the use of SCCS analysis as a screening tool to detect drug interactions with VKAs. While the analysis identified the anticipated interaction between tramadol and VKAs, the associations observed for a range of drugs not known to interact with VKAs suggest that the specificity of the current approach may be low. Time-varying confounding, as a result of factors such as infections or other acute illnesses, and surveillance bias likely play a role in the low specificity. Strategies to address these sources of bias should be investigated to determine whether specificity of the approach can be improved. In addition, a more comprehensive evaluation involving additional known VKA interactions will elucidate the sensitivity of the approach.

CONFLICT OF INTEREST

Mr. Pottegård and Mr. Christensen declare no conflicts of interest.

Dr. Wang is a paid consultant to Aetion, Inc., which provides software for evaluating drug safety and effectiveness. Dr. Gagne is Principal Investigator on an unrelated investigator-initiated unrestricted research grant from Novartis Pharmaceuticals Corporation to the Brigham and Women's Hospital. Dr. Larsen has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim and has been on the speaker bureaus for Bayer, Bristol-Myers Squibb/Pfizer, Roche Diagnostics, Boehringer Ingelheim and Takeda Pharma.

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KEY POINTS

- We present a database of prescription drugs and INR data that, using a self-controlled case-series design, can be used to assess drug–drug interactions with vitamin K antagonists.
- The approach identified the putative interaction with tramadol. However, other drugs with no known or suspected interaction also gave rise to significant results.
- Further methodological work is needed to increase the specificity of our approach.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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