Eur J Clin Pharmacol (2013) 69:617–627
DOI 10.1007/s00228-012-1358-7

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Identification and weighting of the most critical "real-life" drug–drug interactions with acenocoumarol in a tertiary care hospital

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Received: 9 May 2012 / Accepted: 11 July 2012 / Published online: 19 August 2012

Abstract
Purpose The objective of this study was to identify the most clinically relevant drug–drug interactions (DDIs) at risk of affecting acenocoumarol safety in our tertiary care university hospital, a 2,000 bed institution.
Methods We identified DDIs occurring with acenocoumarol by combining two different sources of information: a 1-year retrospective analysis of acenocoumarol prescriptions and comedications from our Computerized Physician Order Entry (CPOE) system (n = 2,439 hospitalizations) and a retrospective study of clinical pharmacology consultations involving acenocoumarol over the past 14 years (1994–2007) (n = 407). We classified these DDIs using an original risk-analysis method. A criticality index was calculated for each associated drug by multiplying three scores based on mechanism of interaction, involvement in a supratherapeutic international normalized ratio (INR) (≥ 6) and involvement in a severe bleeding.
Results One hundred and twenty-six DDIs were identified and weighted. Twenty-eight drugs had a criticality index ≥ 20 and were therefore considered at high risk for interacting with acenocoumarol by increasing its effect: 75% of these drugs involved a pharmacokinetic mechanism and 14 % a pharmacodynamic mechanism. An unknown mechanism of interaction was involved in 11 % of drugs.
Conclusion Twenty-eight specific drugs were identified as being at high risk for interacting with acenocoumarol in our hospital using an original risk-analysis method. Most analyzed drugs interact with acenocoumarol via a pharmacokinetic mechanism. Actions such as the implementation of alerts in our CPOE system should be specifically developed for these drugs.

Keywords Acenocoumarol · Warfarin · Oral anticoagulant · Drug–drug interactions

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Introduction

Oral anticoagulants, especially vitamin K antagonists (VKAs; i.e. warfarin, phenprocoumone, acenocoumarol) are commonly prescribed and have proven to be highly effective in the prevention and treatment of thromboembolic diseases [1]. Warfarin is the most widely used oral anticoagulant worldwide, but this drug is not available in Switzerland where acenocoumarol and phenprocoumone are the two registered VKAs. Acenocoumarol is the VKA used in our institution.

Similar to other VKAs, acenocoumarol has a narrow therapeutic index. It is mainly metabolized by cytochrome P450 (CYP) 2C9 [2], but CYP1A2 and CYP2C19 also participate in the biotransformation of acenocoumarol [3]. *S*-acenocoumarol is metabolized completely by CYP2C9, whereas *R*-acenocoumarol is metabolized by CYP2C9 (50 %), CYP1A2 (30 %) and CYP2C19 (20 %). Unlike warfarin, acenocoumarol is not metabolized by CYP3A4 [3].

Because of these characteristics, there is a large inter- and intra-individual variation in dose response, and achieving a safe and effective anticoagulation is a complex task [4]. Doses of acenocoumarol are therefore determined based on the international normalized ratio (INR) response, with a value of 2.0–3.0 being the target in most indications [5]. Although major bleeding can occur at a therapeutic level, the risk of bleeding increases with increasing INR value [6]. Oral anticoagulants are frequently involved in adverse drug reactions (ADRs), especially haemorrhage, and are in the top ten drugs leading to hospital admissions due to ADRs [7–10].

Numerous environmental and genetic factors (e.g. tobacco, weight, sex, age and single nucleotide polymorphisms) influence the response to acenocoumarol treatment [5, 11]. Drug–drug interactions (DDIs) are an additional factor affecting the variability of anticoagulation and the occurrence of serious ADRs [4, 12–15]. These DDIs are well described in the literature, but their respective importance in clinical practice is difficult to determine, especially those involving acenocoumarol since most of the studies published to date have focused on warfarin. An additional limitation of the literature on this topic is that many reports are based on case studies, some of which are poorly documented [5].

According to several drug information compendia and electronic systems, more than 200 different compounds potentially interact with acenocoumarol [16–19]. Electronic databases can be used (such as Lexi-Interact® or Epocrates®) to identify DDIs, either stand-alone or integrated into a computerized physician order entry (CPOE) system. The problem of such systems is "alert fatigue", a phenomenon related to a high rate of irrelevant alerts leading physicians to override them [20–22]. Moreover, in most of these databases, warnings for acenocoumarol come from drug interactions with warfarin. This situation is not problematic for pharmacodynamic (PD) DDIs, but it can be problematic for pharmacokinetic (PK) DDIs because acenocoumarol is not metabolized by CYP3A4. Therefore, some DDIs alerts are not adapted to acenocoumarol.

Prospective risk analysis approaches are used in a number of high hazard industries and could be applied more systematically to health care [23, 24]. Among such methods, "failure modes, effects and criticality analysis" (FMECA) is a well-described tool that systematically assesses a given process. FMECA is recommended both by Veterans Affairs National Center for Patient Safety and the Institute for Healthcare Improvement [25], and it is now being used in health care to assess risk of failure and harm in processes as well as to prioritize the most relevant areas for process improvements [26–28]. FMECA has been used by hundreds of hospitals in a variety of Institute for Healthcare Improvement programs, including Idealized Design of Medication Systems (IDMS), Patient Safety Collaboratives and Patient Safety Summit. It identifies possible or likely errors ("failure modes") and measures what their effect may be even before they take place.

FMECA includes a quantitative evaluation of the criticality of each failure mode. The criticality indexes are calculated by multiplying three components: likelihood of occurrence, severity and detection on the basis of known or estimated data. Each failure mode is classified and the top critical events subsequently determined. This process is a very helpful tool to evaluate the acceptability of existing risks and to prioritize actions to improve the safety of the patient [23].

The aim of this study was to identify which DDIs likely to increase the effect of acenocoumarol could be implemented in the CPOE system of our hospital setting (a 2,000 bed university hospital). DDIs were also identified and then graded using a method inspired by FMECA in the aim to focus on the most clinically relevant DDIs.

Methods

Study population

Data were collected from adults treated with acenocoumarol for different indications in a tertiary care hospital.

Data extraction

Firstly, retrospective data on acenocoumarol prescriptions written between 1 May 2006 and 30 April 2007 were anonymously extracted from all medical services of our institution using the CPOE system (the services of surgery and psychiatry did not have computerized prescriptions at that time and were thus excluded). Information on doses,

treatment period, concomitant drugs and INR values was extracted for every acenocoumarol prescription. A systematic interaction analysis between acenocoumarol and concomitant drugs was performed for every case in which an INR of ≥6 was measured. This value was chosen to target interactions because an INR of ≥6.0 is associated with a significantly increased bleeding risk [29, 30]. All of the interacting drugs the patient received, if more than one, were regarded as being associated with the observed supratherapeutic INR. A systematic interaction analysis was also performed when blood products were administered during the acenocoumarol treatment because this treatment was considered to be a bleeding indicator.

Secondly, data extracted from the CPOE were supplemented by a retrospective analysis of consultations from the Division of Clinical Pharmacology and Toxicology (one of the six Swiss Regional Pharmacovigilance Centres). The aim of these consultations is to prevent or identify and evaluate reports of ADRs and therapeutic accidents. These consultations are electronically archived in an Access® application from which data were extracted from 1994 to the end of 2007. We analysed each consultation involving acenocoumarol which was requested from physicians working in our institution. From these data, we extracted co-medication (s) linked with a fluctuating INR, subtherapeutic INR and supratherapeutic INR and/or bleeding complications by patients treated with acenocoumarol.

Identification of clinically relevant DDIs

The potential of drugs to interact clinically with acenocoumarol in the University Hospitals of Geneva (HUG) was estimated by combining three different sources of information: the table of PK interactions developed by the Division of Clinical Pharmacology and Toxicology [31] and two online DDI detection systems: the online version of Lexi-Interact™ [17] and the online version of Theriaque®, a French database [32]. DDIs identified in our study were present in at least one of the three sources consulted.

All medications identified as having a potential to interact with acenocoumarol were classified by their mechanism of action as PK, PD or unknown.

Weighting of the clinically relevant DDIs

In order to focus on the most relevant DDIs liable to potentialize the effect of acenocoumarol and to add these as a warning in our CPOE, we weighted DDIs identified in the two retrospective studies using an original risk-analysis method based on the FMECA method. A criticality index was calculated for each associated drug by multiplying three scores.

The first score was based on the mechanism of the interaction and varyied from 1 to 10 depending on the exact mechanism involved (Table 1). Drugs that interact with acenocoumarol through a PK mechanism were classified as strong or weak inhibitors of CYP2C9, CYP2C19 and CYP1A2, based on the classification found in the table of PK interactions developed by the Division of Clinical Pharmacology and Toxicology [31]. The distinction between strong and weak inhibitor was defined based on the dissociation constant for inhibitor binding (K_I) of the drugs. These constants were determined through in vitro studies or from in vivo studies, when available. Because CYP2C9 is the major metabolic pathway of acenocoumarol, the highest rank of 10 was attributed to drugs known to strongly inhibit

Table 1 Weighting score according to the mechanism of the interaction, the frequency of involvement in a supratherapeutic INR and the frequency of involvement in a bleeding event

Weighting scores	Ranking
Mechanism of the interaction	
Pharmacokinetic	
Strong inhibitor of CYP2C9	10
Weak inhibitor of CYP2C9	8
Strong inhibitor of CYP2C19	5
Strong inhibitor of CYP1A2	5
Weak inhibitor of CYP2C19	3
Weak inhibitor of CYP1A2	3
Pharmacodynamic	
Strong pharmacodynamic interaction (antiaggregant effect)	10
Moderate pharmacodynamic interaction (SSRIs)	8
Unknown mechanism	1
Frequency of involvement in a supratherapeutic INR (INR ≥6)	
0	1
1–10	2
11–20	3
21–30	4
31–40	5
41–50	6
51–60	7
61–70	8
71–80	9
> 80	10
Frequency of involvement in a bleeding event	
0	1
1	4
2–3	6
4–5	8
6	10

INR, International normalized ratio; CYP, cytochrome P450; SSRIs, selective serotonin reuptake inhibitors

this cytochrome. A rank of 8 was attributed to weak inhibitors of CYP2C9. Given that CYP1A2 and CYP2C19 are minor metabolic pathways, the rank of 5 was assigned to strong inhibitors of these cytochromes and a rank of 3 to weak inhibitors. In terms of PD interactions, we gave the highest score of 10 to drugs used for their antiaggregant effect because there is a clear PD interaction between these drugs and VKAs [e.g. antiaggregant drugs and non-steroidal anti-inflammatory drugs (NSAIDs)] and a score of 8 to drugs interacting with VKAs through a PD mechanism but not as strongly documented as for antiaggregant drugs and NSAIDs. This latter category of drugs was essentially represented by selective serotonin reuptake inhibitors (SSRIs). When a drug interacted with acenocoumarol through both a PK and a PD mechanism, the highest rank was chosen. For example, the designated rank of clopidogrel is 8 based on its PK mechanism (weak CYP2C9 inhibitor) and 10 based on its PD mechanism (antiaggregant). The rank chosen for clopidogrel is therefore 10 (the highest rank of both). When a drug inhibited more than one CYP enzyme the highest ranking was also attributed. For example, fluconazole is a strong CYP2C9 and CYP2C19 inhibitor. The rank of this drug is therefore 10 due to its inhibitory effect on CYP2C9.

The second score depended on the frequency at which the drug was involved in a supratherapeutic INR (INR ≥6) and ranged from 1 to 10 (Table 1).

The third score depended on the frequency at which the drug was involved in a bleeding episode (Table 1). As proposed by the FMECA method, the criticality index was obtained by multiplying these three scores together. Based on these scores, we established a classification from the most to the less critical association.

Results

Identification of clinically relevant DDIs

Analysis of the data extracted from the CPOE system

There were a total of 61,814 hospitalizations during the study period, of which 2,439 (4 %) involved an acenocoumarol prescription, representing a total of 43,785 doses. The mean age of the study population was 74.2 years [95 % confidence interval (CI) 73.68–74.76], and 49 % of the patients were female.

A total of 957 different drugs were co-prescribed 214,131 times with acenocoumarol. Heparin and enoxaparin, the low-molecular-weight heparin of choice in our institution, were not taken into account because these drugs are prescribed in many indications in combination with VKA until the anticoagulant effect of the latter is reached (e.g. in case of deep vein thrombosis). Based on the three different sources for DDI detection described in the previous section, 154 of the 957 co-prescribed drugs were identified as having a potential interaction with acenocoumarol. These 154 drugs were prescribed 46,642 times with acenocoumarol, representing 22 % of all co-medications. The top ten drugs potentially interacting with acenocoumarol, were paracetamol (n=11,335), acetylsalicylic acid (ASA) (n=3,799), prednisone (n=3,382), tramadol (n=2,986), ceftriaxone (n=1,785), amlodipine (n=1,725), clopidogrel (n=1,549), pravastatin (n=1,099), ciprofloxacin (n=1,042) and amiodarone (n=963). Of the potential DDIs met with acenocoumarol, 22 % were PK interactions, 14 % were PD interactions, 9 % were associated with both mechanisms and 56 % of the remaining potential interactions had a mechanism of action not yet clearly understood.

In order to identify clinically significant DDIs with acenocoumarol more accurately, we analysed hospitalizations with INRs of ≥6, leading to the identification of 318 supratherapeutic INRs of which 89 % (n=283) of these cases had at least one potential DDI. Seventy-four different drugs were involved in these supratherapeutic INRs. For PK interactions, 29 different drugs interacted with acenocoumarol; in 97 % of the cases, drugs were represented by inhibitors of CYP2C9, CYP2C19 and/or CYP1A2. Amiodarone, valproate and azole antifungal drugs (econazole, fluconazole) represented the majority of these inhibitors. Eight different drugs had a PD mechanism of interaction with acenocoumarol, with ASA being the most predominant (78 %). Six drugs were classified has having both a PD and a PK mechanism of interaction, namely, SSRIs (49 %), clopidogrel (46 %) and ibuprofen (5 %). Thirty-one drugs (42 %) were classified has having an interaction with acenocoumarol that has not yet been clearly explained; this group was mainly represented by antibiotics (37 %), paracetamol (21 %), corticosteroids (13 %), statins (12 %) and levothyroxine (6 %).

Seven hospitalizations required the administration of blood products, such as fresh frozen plasma. Based on the fact that such products are administered in cases of major bleeding, drugs interacting with acenocoumarol at the time of bleeding were identified. A total of 17 different drugs were identified: ASA, amiodarone, bosentan, cefepim, ceftriaxone, ciprofloxacin, clarithromycin, clopidogrel, esomeprazole, fluvastatin, leflunomide, paracetamol, phenytoin, pravastatin, prednisone, the hydrochlorothiazide/irbesartan association and the imipenem/cilastatin association.

Clinical pharmacology consultations

Analysis of the clinical pharmacology consultations showed that acenocoumarol appeared in 407 consultations (3 %) among a total of 13,560 consultations and that for 225 (55 %) of these consultations the reason for the request was to determine if there was a DDI problem in the patient's

Table 2 Drugs interacting with acenocoumarol in clinical pharmacology consultations for difficulty in adjusting the INR

Supratherapeutic INR (n=91) (%)	Fluctuation of INR (n=21) (%)	Subtherapeutic INR (n=27) (%)
Amiodarone (11)	Fluconazole (14)	Carbamazepine (15)
Acetaminophen (7)	Amiodarone (10)	Phenytoin (7)
Acetylsalicylic acid (5)	Others (76)	Rifampicin (7)
Clopidogrel (5)		Others (71)
Esomeprazole (4)		
Simvastatin (4)		
Amoxicillin (3)		
Clavulanic acid (2)		
Ceftriaxione (2)		
Fluconazole (2)		
Voriconazole (2)		
Others (53)		

n, Number of observations

treatment either before or after the treating physician encountered difficulty in managing the INR. In 74 % of these 225 consultations (n=166), at least one clinically significant DDI was present, involving 114 different drugs. Three quarters of these drugs (n=82) shared the same metabolic pathway and interacted with acenocoumarol through a PK mechanism, with 60 % represented by substrates, inhibitors or inducers of CYP2C9, CYP2C19 or CYP1A2.

Drugs involved in PD interactions (n=32, 28 %) were essentially represented by antiplatelet drugs (e.g. ASA).

Of the 225 consultations requested, 52 % (n=117) concerned a difficulty in adjusting the INR, with 49 % relating to a supratherapeutic INR, 34 % to a subtherapeutic INR and 17 % to a fluctuating INR. At least one clinically relevant DDI with acenocoumarol was identified in 96 % of the consultations for a supratherapeutic INR, 55 % of the consultations for a subtherapeutic INR and 70 % of the consultations for a fluctuant INR. Drugs interacting most frequently with acenocoumarol in these three categories are reported in Table 2.

Physicians spontaneously reported 17 cases of bleeding associated with acenocoumarol to the pharmacovigilance centre. In 88 % of these reports, a clinically relevant DDI with acenocoumarol was observed, due most often to amiodarone, clopidogrel and ASA.

Weighting of clinically relevant DDIs

A total of 126 drugs were weighted, including the 74 drugs implicated in an INR of≥6 and the 114 drugs identified in the consultations of clinical pharmacology. Given that there were duplicates, the total number of drugs is 126 and not 188. Each drug identified was weighted and a criticality index was determined. The highest criticality index value was 640 and the lowest 1 (Table 3).

For example, the criticality index of amiodarone was 640 based on the multiplication of the three scores defined below:

Table 3 Drugs with a criticality index of ≥20

	INN (International Non-proprietary Name)	Criticality index
1	Amiodarone	640
2	Acetylsalicylic acid	600
3	Esomeprazole	400
4	Clopidogrel	240
5	Paracetamol	80
6	Fluvastatin	80
7	Celecoxib	80
8	Fluvoxamine	64
9	Leflunomide	64
10	Ciprofloxacin	60
11	Escitalopram	40
12	Diclofenac	40
13	Omeprazole	40
14	Metronidazole	30
15	Clarithromycin	24
16	Simvastatin	24
17	Econazole	24
18	Prednisone	20
19	Fluconazole	20
20	Valproic acid	20
21	Ibuprofen	20
22	Lysine acetylsalicylate	20
23	Imatinib	20
24	Miconazole	20
25	Pantoprazole	20
26	Voriconazole	20
27	Etodolac	20
28	Ketorolac	20

Table 4 Mechanism of interaction for the 28 drugs identified at highest risk to interact with acenocoumarol (Criticality index ≥ 20)

PK mechanism	PD mechanism	PK and PD mechanism	Unknown mechanism
Amiodarone	Etodolac	Celecoxib	Clarithromycin
Esomeprazole	Ketorolac	Fluvoxamine	Prednisone
Fluvastatin	Acetylsalicylic acid	Ibuprofen	Paracetamol
Ciprofloxacin	Lysine acetylsalicylate	Clopidogrel	
Omeprazole		Escitalopram	
Metronidazole		Diclofenac	
Simvastatin			
Econazole			
Fluconazole			
Valproate			
Imatinib			
Leflunomid			
Miconazole			
Pantoprazole			
Voriconazole			

PK, Pharmacokinetic; PD, pharmacodynamic

- Score for the mechanism of the interaction was 10, because amiodarone is a strong inhibitor of CYP2C9 (Table 1).
- Score for the association with a supratherapeutic INR was 8 (because amiodarone was involved more than 60 times in a supratherapeutic INR) (Table 1).
- Score for the association in a bleeding was 8 (because amiodarone was associated 4 times in a bleeding episode) (Table 1).

To target the most relevant DDIs and limit the number of alerts to implement in our CPOE, we considered drugs with a criticality index of ≥20, a number which we set arbitrarily, to be at the highest risk of interacting with acenocoumarol. Among the drugs tested, 28 had a criticality index of≥20 (Table 3). These drugs are essentially represented by five therapeutic classes: NSAIDs, proton pump inhibitors (PPIs), antibiotics, SSRIs and statins. When classified according to their mechanism of interaction, 75 % of the drugs had a PK mechanism of interaction with acenocoumarol (in some cases with an additional PD mechanism), 14 % a PD mechanism of interaction and 11 % had a mechanism of interaction that is not clearly explained (Table 4).

Discussion

Using specific data on the prescribing habits of the physicians in our institution, we were able to apply the original risk-analysis method described here to identify 28 frequently used drugs which had a very high risk to clinically interact with acenocoumarol; these fall into the group of the 200 drugs reported in the literature as potentially interacting with acenocoumarol. The results obtained are specific to acenocoumarol and are not derived from data collected with warfarin. These DDIs should be clearly identified in our CPOE system.

About two-thirds of these drugs were found to interact with acenocoumarol through a PK mechanism by inhibiting the CYPs responsible for acenocoumarol's biotransformation. Based on our weighting method, amiodarone, PPIs, statins, quinolones and azole antifungal drugs are involved in the highest proportion of these DDIs.

The drug at highest risk to clinically interact with acenocoumarol is amiodarone (criticality index = 640), a strong inhibitor of CYP2C9. This interaction has been identified years ago (first report 1988) and is well described in the literature (especially for warfarin) [19, 33, 34]. A close monitoring is recommended when this drug is administered with acenocoumarol, and given the long half-life of amiodarone, caution should also be taken several weeks after the treatment has been interrupted.

Esomeprazole also appears to have a high risk of interacting with acenocoumarol (criticality index=400). This isomer of omeprazole is the most prescribed PPI in our institution. PPIs are frequently associated with VKAs as a means to reduce the risk of gastro-intestinal bleeding. PPIs (esomeprazole, omeprazole, pantoprazole) are potent inhibitors of CYP2C19 and for this reason the prescribing of PPIs with a VKA is associated with a warning in most of the databases used to detect DDIs. For example, in the Lexicomp Online, the association of acenocoumarol and esomeprazole is summarized by the following information "*Esomeprazole may increase the serum concentration of Vitamin K Antagonists*", and it is recommended that the response to warfarin or acenocoumarol be monitored closely when used together with esomeprazole [35]. Our results are

similar with those published by Holbrook et al. [34] who classified omeprazole in the category of drugs with a level of causation of interaction "highly probable" in a review on warfarin and its drug interactions. However, the effect of PPIs on coumarin remains controversial. In a recent study, omeprazole significantly increased the area under curve (AUC) and half-life of *R*-warfarin in homozygous extensive metabolizers of CYP2C19 to levels comparable to those in poor metabolizers; however, no clinical consequence was observed [36]. To the best of our knowledge, no specific data on the interaction between PPIs and acenocoumarol are available. In a recent in vitro study, esomeprazole and omeprazole were considered as irreversible CYP2C19 inhibitors [37]. Moreover, in a crossover clinical study, a significant DDI was observed between high doses of omeprazole and clopidogrel in healthy subjects [38]. Considering the contribution of CYP2C19 in the metabolism of *R*-acenocoumarol (the isomer mainly responsible for the effect of acenocoumarol) and given the short half-life of PPIs (approximately 1 h) and controversial data, we consider that PPIs can be prescribed safely if the drug is not taken at the same time as acenocoumarol.

Two statins, simvastatin and fluvastatin, are in the category of clinically significant PK interactions. According to Holbrook et al., interaction between these two statins and warfarin can be considered to be clinically significant and the level of causation defined as "probable" [34]. The mechanism of interaction has not been established for all statins, but some statins clearly interact with VKAs by inhibiting CYP2C9 (e.g. fluvastatin). Simvastatin does not seem to have a major effect on CYP2C9, but an increased effect of warfarin or acenocoumarol in the presence of simvastatin has been observed in small retrospective studies and some case reports [39]. It was also observed that the average dose of warfarin in patients on simvastatin was reduced by 12 %. In the case of simvastatin, which binds to plasma proteins, a shift of plasma protein binding could explain the interaction [40].

Azole antifungal drugs appear also at high risk to clinically interact according to a PK mechanism with acenocoumarol. These DDIs are frequently reported and well described (inhibition of CYP2C9 and CYP2C19) [19, 34, 41].

Drugs which fell in the mixed PK and PD mechanisms category are the SSRIs (fluvoxamine, escitalopram), NSAIDs and clopidogrel. They are metabolized by or are inhibitors of CYPs involved in the acenocoumarol metabolism and also impact on the PD effects.

In the study of Holbrook et al. [34], the interaction between SSRIs (most particularly citalopram) and warfarin is classified as being clinically significant and the level of causation defined as "highly probable" [34]. Some SSRIs are metabolized by the same isoenzymes as oral anticoagulants. For example, fluvoxamine, an inhibitor of CYP1A2 and CYP2C9, appears to be the most likely SSRI to interact with warfarin [42, 43]. Pharmacodynamically, SSRIs could interact with acenocoumarol since the release of serotonin by platelets plays an important role in haemostasis [44, 45]. This mechanism has not been clearly explained, but recent epidemiological data have demonstrated that SSRIs could significantly increase the risk of gastro-intestinal bleeding [46, 47]. According to some studies, the use of SSRIs among the population treated with coumarins seems to place patients at an increased risk of bleeding [15, 48, 49]. A warning should be added to make the physician aware of this interaction.

DDIs between NSAIDs, including COX-2 inhibitors, and oral anticoagulants are clearly documented in the literature and are frequently highlighted in studies on interactions and oral anticoagulants [12, 41].

Our results suggest that the interaction between clopidogrel and acenocoumarol is important and can be considered as clinically significant through a PK and a PD mechanism. Clopidogrel inhibits CYP2C9 and has an antiaggregant effect. In the literature, data on this interaction are contradictory and limited. Clopidogrel is not mentioned in a literature review of interactions occurring with warfarin [34], but prescribing information provided by Swiss manufacturers clearly states that when prescribed with a VKA, clopidogrel may be associated with a significant increased risk of bleeding [50]. In addition, the association of clopidogrel, aspirin and warfarin significantly increase the risk of gastro-intestinal bleeding [51]. In a recent study, the risk of bleeding was significantly increased when clopidogrel was co-prescribed with warfarin [adjusted relative risk (AdjRR) 2.23, 95 % CI 1.48–3.36] in the elderly population [52].

In our study, three drugs, namely, paracetamol, prednisone and clarithromycin, represent most of the interactions that do not have a clearly explained mechanism.

Paracetamol is the analgesic of choice for patients using oral anticoagulants because this drug is justifiably considered to be safer than NSAIDs. Small prospective studies of various designs and case studies describe aberrant INR results in patients using paracetamol while concomitantly receiving warfarin. These INR elevations typically involved the ingestion of at least 2 g/day of paracetamol for several consecutive days [53]. In our study, paracetamol appears to be clinically interacting with acenocoumarol. This result can be explained by the fact that the association of these two drugs is characterized by a warning in the DDI databases consulted in our study. For example, Lexicomp Online contains the warning that patients taking paracetamol at higher doses and/or for longer duration may be at greater risk for experiencing a clinically significant interaction [54]. In our study, paracetamol was frequently associated with supratherapeutic INR. For this reason, this drug was identified as a potential clinical DDI when prescribed with acenocoumarol. Given that paracetamol is the analgesic of choice during VKA treatment and based on data reported in the literature data, this association should be represented by a warning only with paracetamol doses of >2 g/day.

Our results suggest that clarithromycin is a drug with a high risk of interacting with acenocoumarol in our institution. This drug has previously been reported as probably interacting with warfarin [34]. This interaction with warfarin is partially explained through a PK mechanism because clarithromycin is an inhibitor of CYP3A4 [55]. However, this is not the case with acenocoumarol because it is not metabolized by CYP3A4. Although the mechanism of this DDI is not well established, it is known that many antibiotics interact with VKAs [56].

The interaction of prednisone with VKAs is reported in the Lexicomp Online, and the severity of this DDI is classified as major. The mechanism by which corticosteroid use is associated with an increase in INR and decrease in warfarin dose requirements is not clear [57]. The prescribing information provided by Swiss manufacturers states that prednisone may decrease or increase the anticoagulant effect of the oral anticoagulant [50].

Interactions with an oral anticoagulant, especially with warfarin, are well described in the literature, but "real-life" data on the actual occurrence of such interactions are scarce. CPOE systems are valuable databases that can be used to study "real-life" conditions. Few studies have analysed the frequency and type of potential drug interactions during anticoagulant therapy with VKAs using CPOE systems. Moreover, the majority of these studies have analysed DDIs with warfarin because this drug is the VKA of choice in many countries [41]. Although PD interactions are identical for warfarin and acenocoumarol, this is not the case for all PK interactions as acenocoumarol, unlike warfarin, is not metabolized by CYP3A4 [3].

A retrospective cohort study (1991–2003) that included phenprocoumone and acenocoumarol users in the Netherlands (n=76,455) demonstrated that potential DDIs occur frequently in daily practice, with two-thirds of patients being confronted with an increased risk of bleeding. NSAIDs and antibacterial drugs were the most frequently interacting drugs. In this study, 24 individual drugs and 11 drug groups interacting with VKAs according to the central database used in Dutch pharmacies were taken into account [12]. The same authors, using the same methodology, but including new users of phenprocoumone or acenocoumarol, subsequently identified the main comedications associated with major bleeding episodes during anticoagulant therapy as antibacterial drugs, NSAIDs, antithrombotic drugs and tramadol [58]. In a study based on the Norwegian spontaneous reporting system, data on warfarin-associated bleeding events (n=289) as a consequence of drug interaction were detected in more than 50 % of the cases involving antibacterials, NSAIDs/COX-2 inhibitors and heparins [59]. These results are also in accordance with our study.

Snaith et al. used the computerized prescribing data retriever from primary care practices in Scotland to investigate the prevalence of prescriptions that might rise the risk of clinically relevant DDIs in a warfarinized population (n=17,861) [41]. NSAIDs, antibacterials and antithrombotics were the most frequently prescribed drug groups with a potential for DDIs. Another study investigated the frequency and clinical consequences of warfarin drug interactions using medical records of 6,772 warfarin-treated patients hospitalized in Finland (1996–2004). In this study, 48 % of patients were exposed to interacting co-medications. The adjusted odds ratio (OR) for bleeding was highest for CYP2C9 inhibitors (OR 3.6, 95 % CI 2.4–5.6), while NSAIDs, coxibs and SSRIs were also associated with a significant bleeding risk (OR 2.6, 95 % CI 1.6–4.2; OR 3.1, 95 % CI 1.4–6.7; OR 2.6, 95 % CI 1.5–4.3, respectively). The OR for the platelet aggregation inhibitor group was 1.6 (95 % CI 0.8–3.1) [15].

A recent cohort study using a health insurance claims database showed that 80 % of atrial fibrillation patients were receiving at least one warfarin-potentiating medication while taking warfarin. Patients who used these medications had a 26 % higher risk of haemorrhage than those who did not use these drugs. The likelihood of haemorrhagic events was significantly increased with the use of potentiating drugs from the following therapeutic classes: anticoagulants (OR 1.91), anti-infectives (OR 1.76), antiplatelets (OR 1.56) and analgesics (OR 1.33) [60]. In another recent retrospective study in an elderly population (n=17,600) who used warfarin, bleeding-related hospitalization rates were significantly increased when warfarin was co-prescribed with aspirin (AdjRR 1.44, 95 % CI 1.00–2.07), clopidogrel (AdjRR 2.23, 95 % CI 1.48–3.36), clopidogrel with aspirin (AdjRR 3.44, 95 % CI 1.28–9.23), amiodarone (AdjRR 3.33, 95 % CI 1.38–8.00) and antibiotics (AdjRR 2.34, 95 % CI 1.55–3.54) [52]. The majority of the drugs identified through these studies are identical to those identified in our study.

Various studies recommend reducing alert fatigue by lowering the number of alerts being sent to the clinician and by increasing alert specificity [61, 62], but the identification of high-priority DDIs for use in electronic health records is still the subject of ongoing debate and can differ from one institution to another [63]. The major advantage of our method, which is adapted from the FMECA, lies in its simplicity and the quantitative evaluation it allows by combining three complementary factors based on pharmacological characteristics and clinical effects of drugs. This method helped us to identify the most critical DDIs with acenocoumarol in order to specifically develop computerized clinical decision support for these high-risk associations. This method could be applied in other institutions equipped with a CPOE in order to customize and focus on "high risk" DDI alerts. Most of the DDIs identified were due to a PK mechanism. We are of the opinion that it is important to add these DDIs as a warning in our CPOE because it is difficult to memorize which cytochrome is responsible for the metabolism of a specific drug. A warning for

the need for close monitoring through more frequent INR controls should be advised when such a drug is introduced or stopped by a patient treated by acenocoumarol. The results of our study also indicated that for the PD interactions identified in our study, a warning should be added. This kind of DDIs is difficult to manage because the risk of bleeding is continuous over time and can not be determined through the INR value. These drugs should be avoided in combination with acenocoumarol unless proven to provide benefit that outweighs the risk of bleeding.

There are some limitations to our study that should be considered. First, it is a retrospective study, and some data were not available, such as patient characteristics, comorbidities, length of therapy. Similar to DDIs, these data may be involved in the risk of overanticoagulation. As patients may receive different potentially interacting drugs, the association is not always clear, and more detailed data on each patient would have allowed us to clarify some of the drug associations, such as those for the prescription of esomeprazole and paracetamol. Secondly, despite the fact that pharmacological and clinical parameters (INR elevation and bleeding events) were considered to be the mechanism of the interaction, the final score of 20 for the criticality index was chosen arbitrarily. The method we adopted did not allow us to determine the criticality index for drugs at risk to decrease the effect of acenocoumarol because the score was focused on supratherapeutic INRs and bleeding episodes.

Conclusion

In this study, we targeted drugs at high risk to interact clinically with acenocoumarol based on our analysis of the prescribing data from the computerized physician order entry system of our institution. The drugs interacting phamacokinetically with acenocoumarol represent the major part of the DDIs identified. To improve the safety of acenocoumarol prescription in our institution, actions such as implemented alerts for these drugs in our computerized physician order entry system should be prioritized. This method can be applied to other drugs known to be subject to many drug interactions.

Conflict of interest None.

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