Excessive anticoagulation with warfarin or phenprocoumon may have multiple causes

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ABSTRACT

INTRODUCTION: Excessive anticoagulation with vitamin K antagonists is a serious condition with a substantial risk of an adverse outcome. We thus found it of interest to review a large case series to characterize the underlying causes of excessive anticoagulation.

MATERIAL AND METHODS: Patients were identified both retrospectively and prospectively. The inclusion criteria were an international normalized ratio (INR) > 6.5 *or* INR > 3.5 and significant bleeding. Patient charts were reviewed for a predefined set of possible causes: Drug-drug interactions, alcohol abuse, disease, start-up or recent change in dosage and dosage errors.

RESULTS: In 86 of 107 admissions one or more causal event were identified. The two most common causes of excessive anticoagulation were disease and drug-drug interactions. The two most common drug-drug interactions were with paracetamol and tramadol. In 44 admissions, a single cause was identified; in 42, two or more causes were identified.

CONCLUSION: Although it is difficult to identify single initiatives that may reduce the number of admissions due to excessive anticoagulation, interesting areas include a stronger focus on frequent INR control during the various states of disease and heightened attention to drug-drug interactions.

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Vitamin K antagonists (VKAs) are the drugs of choice for the prevention of thromboembolism in patients with atrial fibrillation/flutter or venous thrombotic disease. In Denmark, the only available VKAs are warfarin and phenprocoumon [1], while other countries also use acencoumarol and dicoumarol. The use of VKA is rising rapidly in Denmark, which saw a five-fold increase from 1997 to 2010 (from 2.9 m defined daily doses (DDD) to 15.6 m DDD).

Reaching the international normalized ratio (INR) target is essential to patient safety. Below-target INR is associated with thromboembolic events, whereas above-target INR leads to haemorrhagic complications. In Norway, up to 50% of all side effect reports are related to anti-thrombotic treatment [2] and warfarin is the single drug causing most fatal adverse events [3]. It is estimated that 40% of these adverse events were preventable [4]. In Denmark, warfarin is one of the two drugs most commonly involved in reported adverse events [5]. We thus found it of interest to review a large case series of life-threatening incidents of excessive anticoagulation during VKA treatment and to characterise the underlying causes of excessive anticoagulation.

MATERIAL AND METHODS

The study was conducted at Emergency Ward at Odense University Hospital, Odense, Denmark. The ward daily receives approx. 25 internal medicine patients in the fields of pulmonary, infectious, rheumatological, gastroenterological, endocrinological and geriatric medicine. Warfarin and phenprocoumon are the only VKAs available in Denmark, with warfarin being used more (15.6 m DDD/year) than phenprocoumon (0.8 m DDD/year).

Patients were identified both retrospectively and prospectively. The inclusion criteria were INR > 6.5 or INR > 3.5 and significant bleeding. Patients were included into the study more than once if presenting with several distinct bleeding episodes. Retrospective patients were found using the database "Fyns Amts Patient-administrative System". We retrieved all patients admitted with any of the Danish International Classification of Diseases 10 (ICD-10) diagnosis codes T45.0A, T45.9 or T88.8K, between 11 December 2008 and 4 February 2011. The 100 most recent admissions meeting the inclusion criteria were selected.

Drug-drug-interactions are a frequent cause of excessive anticoagulation during treatment with vitamin K antagonists.

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Prospective patients were identified in the period from 12 February 2011 to 21 March 2011.

Patient charts were reviewed for all included patients, and all possible causes of an elevated INR or increased bleeding were recorded in a pre-defined form. For prospective patients, any missing information was, when possible, retrieved through patient interviews. As we found that no additional information was collected through the interviews, we pooled the prospective and retrospective patients for the subsequent analysis.

Current medication was identified via the patient chart. If information from the primary care physician or nursing home was given in the patient chart, this was used. When such information was not available, the medication prescribed by the admitting physician was used. The medication was compared to any previous admissions with a view to registering any changes.

All medications were recorded and the presence and significance of drug-drug interactions were determined using the criteria described below. The criteria applied for the remaining included cases of excessive anticoagulation are also listed below.

The study was approved by the Danish Data Protection Agency. Patients gave informed consent prior to interviews.

Possible causes of excessive anticoagulation

We included the following possible causes of excessive anticoagulation: drug-drug interactions, alcohol abuse, disease, start-up or recent dose adjustment and dosage errors.

Drug-drug interactions

A large number of drugs may potentially interact with VKA. Interactions are commonly categorized as pharmacokinetic, which affect absorption, distribution, metabolism or excretion of VKA, and pharmacodynamic, which alter the risk of bleeding without affecting the pharmacokinetic parameters. Unfortunately, authoritative sources often disagree on whether a potential interaction is clinically relevant or not [6].

The following criteria were used to decide whether a given drug interacted with VKA treatment.

A given drug was marked as interacting if one of the following criteria were met:

- The drug was marked as having a significant interaction at Interaktionsdatabasen.dk, the most comprehensive Danish drug-drug interaction database.
- The drug was marked as interacting at micromedex.dk and either Holbrook et al [7] (warfarin) or Jobski et al [8] (phenprocoumon).
- Where Micromedex.dk referred to studies more recent than Holbook et al, Micromedex.dk was accepted as the only source.

The following rules were used to decide if a given interaction was significant to excessive anticoagulation:

- Pharmacokinetic interactions were included as significant in the following cases:
  a. Drugs increasing the effects of VKAs that were newly prescribed or increased in strength.
  b. Drugs decreasing the effects of VKAs that were discontinued or reduced in strength.
  c. Drugs either reducing or increasing the effects of VKAs to be administered “as needed”.
- Pharmacodynamic interactions were included as significant if the patient experienced a bleeding episode.
- Levothyroxin was *only* classified as significant if thyroid treatment had recently been initiated.

Alcohol abuse

Chronic alcohol abuse has been shown to be associated with an increase in warfarin metabolism; thus, a change from chronic alcoholism to abstinence increases the risk of an elevated INR [9]. There is disagreement as to whether an acute increase in alcohol consumption or

TABLE 1

Baseline characteristics of included patients.

Basic description	
Median age (IQR), years	76 (68-85)
Males, n (%)	56 (52.3)
Average INR	9.2
Patients with verified bleeding, n (%)	23 (21.5)
Median number of drugs (IQR)	7 (5-9)
Warfarin patients, n (%)	100 (93.5)
Average dose (range), mg/week	30,58 (8.75-61.25)
Phenprocoumon patients, n (%)	7 (6.5)
Average dose (range), mg/week	13.3 (5.25-21)
Indicating disease,[a] n (%)	
Atrial fibrillation	77 (72.0)
Lung embolus	14 (13.1)
Deep vein thrombosis	14 (13.1)
Mechanical aortic valve or artificial heart valve	10 (9.3)
Other	4 (3.7)
Dosing scheme,[b] n (%)	
Fixed	28 (26.2)
Alternating	33 (30.8)
Unknown	46 (43.0)

INR = international normalized ratio; IQR = interquartile range.
a) The sum of diseases is greater than 107 since one patient can have more than one indicating disease.
b) Fixed refers to patients taking the same dose every day. Alternating refers to patients using different doses depending on e.g. weekday or odd/even days.

occasional consumption affects VKA treatment. Further, it has been proposed that INR elevation might be related to non-compliance or malnutrition.

Excessive use of alcohol was defined as either a statement in the patient chart to the effect that consumption exceeded the recommendations of the Danish National Board of Health (14 and 21 units of alcohol a week for females and males, respectively) *or* the patient chart mentioning alcohol abuse.

Disease

Patient-related factors such as co-morbidity and state of disease have also been shown to be of importance. Conditions related to an increased risk of excessive anticoagulation with readily available information include renal insufficiency, acute illness such as fever or diarrhoea and eating less in general [9-11].

Patients were classified as having a disease influencing VKA treatment if one or more of the following criteria were met:

1) A C-reactive protein (CRP) level ≥ 75 mg/l
2) A patient record notation indicating diarrhoea and/or reduced dietary intake
3) An estimated glomerular filtration rate < 60 ml/min (as calculated by the modification of diet in renal disease (MDRD) formula). Exempt from this were patients with known chronic renal insufficiency as their VKA treatment was expected to have been adjusted accordingly.

Patients with thyroid diseases were not classified as having a disease influencing the VKA treatment. Although patients in the hyperthyroid state are known to have an increased turnover of proteins involved in coagulation, these patients were expected to be in a drug-induced euthyroid state when treated with either thyroid or antithyroid drugs.

Start-up or recent change

It has been demonstrated that initiation of VKA therapy is associated with an increased risk of excessive anticoagulation [11, 12]; however, other studies have questioned this implication [13, 14]. To avoid ruling out a possible reason for excessive anticoagulation, we also included as plausible factors initiation of therapy < 90 days prior to hospitalization and a recent change of dose, which is thought to contribute to a ping-pong effect [15].

Dosage errors

VKA therapy dosing regimens can be complex. It is known that an increase in the complexity of dosing schemes reduces patient compliance [16] and patient satisfaction [17]. A dosing error was considered evident when a notation in the patient chart described a situation where the patient either failed to take the VKA as prescribed or a home nurse provided the patient with a higher dose than prescribed.

Trial registration: not relevant.

RESULTS

We included 100 retrospective and seven prospective admissions (104 distinct patients). The average INR was 9.2, with 22% having a verified bleeding episode (the average INR for bleeding patients was 8.6). The most common indication for treatment was atrial fibrillation. Patients used a median of seven drugs and their median age was 76 years (**Table 1**).

In 86 admissions (80%, 95% confidence intervals 72-87), one (41%) or more (39%) causal events were identified. The more common causes were disease, drug-drug interactions and recent start/dosage changes of the VKA treatment (**Table 2**). The drugs identified as causes of drug-drug interactions entailing excessive anticoagulation are given in **Table 3**; the most common drugs involved were tramadol and paracetamol, although considerable diversity of interactions was identified.

DISCUSSION

We were able to identify a causal event for excessive anticoagulation in the vast majority of included patients,

TABLE 2

Causes of excessive anticoagulation during vitamin K antagonist treatment.

	n
Basic description	
Disease	62
Drug-drug interaction	34
Pharmacokinetic interaction	30[a]
Pharmacodynamic interaction	6[a]
Start-up/recent change	28
Alcohol	12
Dosage error	2
Unknown reason	21
Number of reasons	
1 reason	44
Only disease	26
Only drug-drug interaction	10
Only start-up/recent change	5
Only alcohol	2
Only dosage error	1
2 reasons	32
3 reasons	10

a) The sum of pharmacodynamics and pharmacokinetic interactions is greater than 36 as any patient can experience both.

TABLE 3

Interacting drugs found to be potential causal effects of excessive anticoagulation. The values are number of cases.

Drug	Warfarin	Phenprocoumon	Total
Tramadol	10	1	11
Paracetamol	5	–	5
Fluconazol	4	–	4
Amiodaron	3	–	3
Acetylsalicylic acid	3	–	3
Ciprofloxacin	3	–	3
Ibuprofen	1	1	2
Escitalopram	2	–	2
Sulfamethizol	2	–	2
Other	9	–	9

and roughly half of the patients had more than one causal event.

The primary strength of the study is its use of a standardized, manual data collection which reduces the risk of misclassification. Furthermore, the use of a predefined algorithm for the evaluation of drug-drug interactions makes replication possible in an otherwise complex field of study.

The study has several weaknesses. The evaluation of evidence for drug-drug interactions is always subject to uncertainty which implies that randomized trials often refute claims made in case reports [7]. Patients' kidney status was evaluated from only one plasma creatinine measurement and may therefore well have been declining over a longer period. Lastly, alcohol was included as a potential cause even though evidence in support hereof is limited, and even though it may be a proxy for insufficient nutritional intake and lacking compliance.

The result might be over-estimated as the algorithm used to identify drug-drug interactions used several sources and thereby includes more interactions than if it had relied on a single source. However, the algorithm was designed to be conservative and to avoid the inclusion of too many interactions. The result might be underestimated as not all parameters thought to influence INR or cause bleeding were included. The parameters not included were liver disease and heart failure [14, 18]. Furthermore, the parameters diarrhoea and alcohol use were taken from the medical record and were as such self-reported by the patient. This might lead to underreporting, particularly for alcohol use [19].

The available literature on drug-drug interactions is characterised by limited scientific value because it mostly relies on single patient cases. An example of this is the interaction between warfarin and cranberry which was initially documented by a series of case examples, while a subsequent randomised controlled trial was unable to replicate the drug-drug interaction [20]. This problem is pivotal when working with drug-drug interactions. By comparing four major sources of drug-drug interactions, a British study found that up to 72% of interactions marked at the highest level of significance in one source were not even mentioned in the remaining three sources [6]. This is not only of significance to the result of our study or those of other papers; it also undermines the clinical utility of these resources.

With roughly half of the patients having more than one apparent reason for excessive anticoagulation, it is difficult to point to a single initiative that will significantly reduce the number of admissions due to excessive anticoagulation. The high number of excessive anticoagulation cases attributed to drug-drug interactions calls for better tools to alert prescribers of possible interactions when prescribing medications to patients in VKA treatment. Furthermore, the high number attributed towards states of disease may point to the importance of patient education which emphasizes the need for more frequent INR control during periods of acute disease.

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