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RESEARCH ARTICLE

Quantity and quality of potential drug interactions with coumarin anticoagulants in the Netherlands

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Abstract
Objective Coumarin anticoagulants are prone to potentially life-threatening drug-drug interactions due to a combination of unfavorable properties. However, real life data on the actual occurrence are scarce. The aim of this study was to quantify and qualify potential drug interactions with coumarin anticoagulants in daily practice.
Methods A cohort study including all users of phenprocoumon or acenocoumarol during the period 1991–2003 in the PHARMO Record Linkage System. All 24 individual drugs and 11 drug groups interacting with coumarins according to central database used in the Dutch pharmacies were considered.
Main outcome measure Frequency and type of potential drug interactions during anticoagulant therapy with coumarins.
Results 48,627 out of 76,455 mainly acenocoumarol-users (64%) were dispensed at least one potentially interacting drug (PID) during anticoagulant therapy. About 35% of these cases were dispensed a (very) strongly interacting drug, whereas 3% were dispensed a contraindicated drug. Antibacterial drugs and NSAIDs (39% and 37% of all users, respectively) were the most frequently dispensed PIDs.
Conclusion Potential drug interactions with coumarins frequently occur in daily practice, confronting two-thirds of patients with an increased risk of bleeding. To a large part, this is attributable to commonly prescribed medication like antibacterial drugs and NSAIDs. This situation substantiates the need for proper monitoring or new anticoagulants with less drug–drug interactions.

Keywords Acenocoumarol · Antibacterial drugs · Anticoagulants · Coumarins · Drug–Drug interactions · NSAIDs · Phenprocoumon · The Netherlands

Impact of findings on practice

- Potential drug interactions occur in two-thirds of patients using coumarins.
- Pincipal interactions concern the commonly prescribed anti-bacterial drugs and NSAIDs.
- The high potential for drug interactions of coumarins puts patients at increased risk of bleeding, and costs time and Money.

Introduction

Coumarin anticoagulants (i.e. acenocoumarol, phenprocoumon and warfarin) are extensively used for the treatment and long-term prevention of thromboembolic diseases [1]. These drugs induce anticoagulation by antagonizing vitamin K, thereby impairing the biologic activity of the vitamin-K dependent coagulation factors (factor II, VII, IX, and X) [2, 3]. Apart from their benefit, coumarin anticoagulants are prone to potentially life threatening drug-drug interactions due to: (i) high protein

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binding; (ii) cytochrome P450 dependent metabolism; and (iii) a narrow therapeutic range [2, 4].

In the Netherlands, a routine screening for potential interactions is implemented in all pharmacies. Before drugs are dispensed to the patients, potential interactions have to be detected by the automated computer system. The entire list of drugs which are supposed to interact with coumarins comprises about 200 different compounds (Z-Index BV, The Hague, The Netherlands, URL: http://www.z-index.nl). Some of these potentially interacting drugs (PIDs) are not allowed to be dispensed to the patient, but should be substituted with another drug. However, the majority of the PIDs can be normally dispensed to the patient after the anticoagulation clinic and/or the patient have been informed (Dutch standard on coumarin interactions; available through the internet via URL: http://www.fnt.nl).

Patients on coumarins who are dispensed a PID, are confronted with an increased risk of bleeding or thromboembolism. In addition, the effectiveness of the interacting drug may be hampered.

Aim of the study

To date, ''real life'' data on the occurrence of potential drug interactions with coumarins are scarce [5]. Therefore, we performed a cohort study to quantify and qualify potential drug interactions with coumarin anticoagulants in daily practice.

Methods

Setting

Data were obtained from the PHARMO Record Linkage System, which includes, among other databases, the drug-dispensing records from community pharmacies and hospital discharge records of more than 1 million community-dwelling inhabitants of 40 demographically defined areas in The Netherlands. For all residents, the computerized drug-dispensing histories contain data concerning the dispensed drug, type of prescriber, dispensing date, dispensed amount, prescribed dose regimens, and the legend duration of use (prescription length). All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification. The hospital records include detailed information concerning the primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). For a detailed description of the database, which is representative for the Dutch population, we refer to previous work [6].

Study cohort

The study population included all users of phenprocoumon (ATC-code B01AA04) or acenocoumarol (ATC-code B01AA07) in the period 1991–2003. No other coumarins are available at the Dutch market. All patients were followed from the first dispensing in the period 1991–2003 until the last dispensing, or the end of follow-up (October 1, 2004), whichever event was earliest.

Potential drug–drug interactions

All 24 individual drugs and 11 drug groups interacting with coumarins according to the current Z-index database, the central database used in the Dutch pharmacies (Z-Index BV, The Hague, The Netherlands, URL: http://www.z-index.nl), were considered for this study. For all PIDs, relevance was classified into five categories according to the Dutch standard on coumarin interactions (available through the internet via URL: http://www.fnt.nl). Category 1 included all contraindicated drugs that very strongly interact with coumarins and may not be used together with coumarins. Category 2 comprised all very strongly interacting drugs for which a substitute is lacking and that necessitate intensive monitoring of anticoagulation. Category 3 included all strongly interacting drugs that preferably are substituted or otherwise necessitate intensive monitoring of anticoagulation. Category 4 encompassed all drugs that moderately or indistinctly interact with coumarins. Category 5 included all drugs that do not influence the intensity of the anticoagulant effect of coumarin anticoagulants, but increase the risk of bleeding by interfering with hemostasis or by their ulcerogenic effect.

To study the frequency of potential drug interactions during anticoagulant therapy with coumarins, treatment episodes of coumarins during follow-up were established for each patient, based on the method of Catalan [7]. In general, a treatment episode is defined as a period of time in which a continuous specific pharmacotherapeutic treatment takes place. Coumarin treatment was considered to be uninterrupted if the gap between the start of two consecutive dispensings was less than 180 days. A treatment episode was measured as the time span between the starting date of the first dispensing and the expiry date of the final dispensing. The latter was set at the average duration time after the last dispensing date. Patients may have had more than one treatment episode of coumarins.

For each PID and PID group, the number of dispensings during a coumarin treatment episode and the number of patients involved was assessed. For frequently occurring PID groups, the individual PIDs within this group were determined. For all patients involved in at least one potential drug-drug interaction (the ''cases''), the number

of different PIDs and the relevance of the exposed potential interaction(s) were determined.

Results

The study cohort included 76,455 users of mainly acenocoumarol in the period 1991–2003 (Table 1). Gender was equally divided, and about two-thirds of the coumarin-users were older than 60 years of age. A quarter of the users had more than 730 days of coumarin treatment during follow-up.

In total, 48,627 patients or ''cases'' (64% of all coumarin-users) were involved in at least one potential drug interaction during anticoagulant therapy. Gender was equally divided, and 75% of the cases was older than 60 years of age (Table 2). Multiple potential drug interactions occurred in more than half of the cases; 5% of the cases were even dispensed eight or more different PIDs. About 35% of the cases were dispensed a (very) strongly interacting drug, that necessitates intensive monitoring of anticoagulation (relevance category 2 and 3). A contraindicated drug (relevance category 1) was dispensed in 3% of the cases.

The most frequently dispensed PIDs during anticoagulant therapy with coumarins were antibacterial drugs and non-steroidal anti-inflammatory drugs (NSAIDs), encompassing nearly 120,000 antibacterial dispensings in 39% of all coumarin-users, and almost 127,000 NSAID-dispensings in 37% of all coumarin-users, respectively (Table 3). The top three potentially interacting antibacterial drugs were amoxicillin, doxycycline, and amoxicillin plus clavulanic acid (dispensed to 13, 13, and 10% of all coumarin-users, respectively). Diclofenac, ibuprofen, and naproxen were the three most frequently dispensed NSAIDs (dispensed to 15, 9, and 7% of all coumarin-users, respectively).

Table 1 Characteristics of users of acenocoumarol or phenprocoumon in the period 1991–2003

Characteristic		Number (N = 76,455)	Percentage of total (%)
Gender	Men	37,767	49.4
	Women	38,688	50.6
Age at start follow-up (in years)	<20	757	1.0
	20–44	8,659	11.3
	45–59	14,343	18.8
	60–74	30,132	39.4
	>74	22,564	29.5
Type of coumarin at start follow-up	Acenocoumarol	68,519	89.6
	Phenprocoumon	7,936	10.4
Number of coumarin treatment episodes during follow-up	1	55,388	72.5
	2	11,958	15.6
	≥3	9,109	11.9
Number of coumarin treatment days during follow-up	≤ 90	26,658	34.8
	91–180	11,253	14.7
	181–365	9,094	11.9
	366–729	8,832	11.6
	≥730	20,618	27.0

Table 2 Demographics and relevance of potential drug interactions during anticoagulant therapy with coumarins in the period 1991–2004

Characteristic		Number of patients (N = 48,627)	Percentage of total (%)
Gender	Men	24,052	49.5
	Women	24,575	50.5
Age at start PID (in years)	<20	242	0.5
	20–44	3,661	7.5
	45–59	8,044	16.5
	60–74	19,135	39.4
	>74	17,545	36.1
Number of PIDs	1	20,260	41.7
	2–4	20,788	42.7
	5–7	5,306	10.9
	≥8	2,273	4.7
Relevance[a]	Category 1	1,574	3.2
	Category 2	1,476	3.0
	Category 3	14,609	30.0
	Category 4	31,846	65.5
	Category 5	28,062	57.7

[a] Numbers do not add up to 100% as patients may have been involved in multiple PIDs of different relevance

PID: potentially interacting drug

Discussion

The results of the present population-based cohort study show that potential drug interactions with coumarins frequently occur in daily practice. About two-thirds of users of acenocoumarol or phenprocoumon (50,000 out of 76,000 users) were dispensed at least one PID. In about one third of these cases, this concerned (very) strongly interacting drugs. The most frequently dispensed PIDs were NSAIDs.

Although, routine screening for potential interactions is implemented at all pharmacies in the Netherlands, a pharmacist may selectively switch off one or more of the interaction-modules. Consequently, some potential drug-drug interactions may remain undetected. This may explain the dispensing of contraindicated drugs (category 1 PIDs) to 3% of the cases and possibly part of the preferably

Table 3 Frequency of potential drug interactions during anticoagulant therapy with coumarins in the period 1991–2004

PID (group)*	ATC-code(s)	Relevance category	Number of dispensings	Number of patients (N = 76,455)	
				n	%
Antibacterial drugs[a]	J01, A07AA	4	119,517	30,022	39.3
NSAIDs[b]	M01A, C01EB03, N02BB02, N02BB04, N02BE51, N02BA, B01AC06, B01AC08, B01AC30	5	126,593	28,364	37.1
Miconazole	A07AC01, G01AF04	1	1,706	890	1.2
Amiodarone	C01BD01	3	35,387	4,238	5.5
Cotrimoxazole	J01EE01, J01EE03	3	7,189	4,087	5.3
SSRIs	N06AB	4	31,078	3,380	4.4
Thyreomimetics	H03A	3	24,052	2,323	3.0
Allopurinol	M04AA01	3	15,943	1,742	2.3
Anti-epileptics (enzyme inducing)	N03AA, N03AB02, N03AF01, N05CA, N05CB02, L02BG01	2	16,206	1,414	1.8
Cimetidine[c]	A02BA01	3	5,152	931	1.2
Fibrates	C10AB	3	8,228	901	1.2
Metronidazole	J01XD01,G01AF01, P01AB01	3	1,246	768	1.0
Thyreostatics	H03B	3	7,125	751	1.0

* The following PIDs or PID-groups each concerned less than 1.0% of the patients: Androgens (A14A,G03B,G03XA01), Azapropazone (M01AX04), Azathioprine (L04AX01), Benzbromarone (M04AB03), Bile acid sequestrants (C10AC), Disopyramid (C01BA03), Disulfiram (N07BB01), Fluconazole (J02AC01-except for single dosages), Griseofulvin (D01BA01), Isoniazid (J04AC01), Itraconazole (J02AC02), Ketoconazole (J02AB02), Mercaptopurine (L01BB02), Non-nucleoside reverse transcriptase inhibitors (J05AG), Phenylbutazone (M01AA01), Propafenone (C01BC03), Protease inhibitors (J05AE), Quinidine (C01BA01), Rifampicin (J04AB02,J04AM02), Rifabutin (J04AB04), Tamoxifen (L02BA01), and Voriconazole (J02AC03)

[a] exclusive cotrimoxazole and metronidazole; [b] Exclusive azapropazone and phenylbutazone; [c] Applies to acenocoumarol only

ATC-code: Anatomical Therapeutic Chemical Classification System - code, WHO Collaborating Centre for Drug Statistics Methodology, ATC/DDD index 2005 (URL: http://www.whocc.no/atcddd)

NSAID: non-steroidal anti-inflammatory drug; PID: potentially interacting drug; SSRI: selective serotonin reuptake inhibitor

substituted category 3 PIDs dispensed to 30% of the cases. Category 3 PIDs may not be avoidable due to, for example, certain patient factors or comorbidity, or lack of prescription alternatives. Unfortunately, we did not have this information. An improved use of the routine screening may reduce the number of PIDs dispensed. It is yet to be expected that this reduction will only be limited.

The study encompassed the period 1991–2003. As mentioned in the methods, the PIDs considered for the study were based on the current interaction database at the time the study was performed (i.e., the 2004 version). The majority of the selected PIDs were already included in this interaction database before 1991 and were available during the whole study period. However, eight out of 24 selected individual drugs (e.g. benzbromarone and disopyramid) and three out of 11 selected drug groups (non-nucleoside reverse transcriptase inhibitors, protease inhibitors and thyreostatics) were included in the interaction database from 1998 or later, and so were only available during the second half of the study period. Consequently, the number of dispensings and patients will be smaller for these drugs. However, our finding that antibacterial drugs and NSAIDs are the most frequently dispensed PIDs is still valid; the number of patients for these two PIDs is much higher than for the other PIDs.

The type of coumarin mainly used by our study cohort was acenocoumarol. In many countries, warfarin is the coumarin of first choice. Potential drug interactions during anticoagulant therapy with warfarin have been shown to be a frequent issue, as well [8, 9]. Among 134,833 patients receiving long-term warfarin therapy, 109,998 (81.6%) were prescribed a concurrent prescription for at least one PID [8].

Given the resemblance in the metabolism of acenocoumarol and warfarin, both types of coumarin are likely to be sensitive to the same PIDs. However, as the CYP2C9 isoenzyme appears to be less important for the clearance of acenocoumarol than for the clearance of warfarin, acenocoumarol may be less sensitive than warfarin [10]. Consequently, the outcome of a drug interaction may be different for acenocoumarol and warfarin.

Patients on coumarins, who are dispensed a PID, are exposed to an increased risk of, mainly, bleeding, or thromboembolism [4]. Bleeding is the most common

complication of anticoagulant therapy. Major or life-threatening hemorrhage during anticoagulant therapy with coumarins has been shown to occur at an estimated rate of 1.1–3.6 per 100 patient-years [11–13]. Concomitant use of other drugs is one of the major determinants of bleeding during anticoagulant therapy [14]. In the present study, antibacterial drugs and NSAIDs were the main PIDs dispensed during coumarin therapy. Antibacterial drugs enhance the anticoagulant effect of coumarins, thereby increasing the risk of bleeding [15]. In a population-based cohort study by Visser et al. use of antibacterial drugs was associated with a 4–20 times increased risk of over anti-coagulation [16]. The risk of major bleeding associated with the use of antibacterial drugs, has been shown to be four to seven times increased [17]. NSAIDs and anti-thrombotic salicylates mainly increase the risk of bleeding by interfering with hemostasis by inhibiting platelet function, or by their ulcerogenic effect [18]. In a previous study, we found a 2–7 times increased risk of major bleeding with the use of NSAIDs during anticoagulant therapy [17]. Although, the risks of major bleeding increase quite strongly in case of concomitant use of antibacterial drugs and NSAIDs, absolute incidence rates are low. Regarding antibacterial drugs an incidence rate of 4.3–7.4 major bleedings per 100 patient-years has been reported. For NSAIDs this rate was 2.4–7.4 per 100 patient-years [17].

In addition to putting patients at an increased risk, the high drug interaction potential of coumarins costs time and money. If at the pharmacy, potential interactions are detected by the automated computer system, actions have to be taken before drugs are dispensed. The necessary action ranges from just informing the anticoagulation clinic and/or the patient, to consulting the prescribing physician for a substitute (Dutch standard on coumarin interactions; available through the internet via URL: http://www.fnt.nl). In addition, the use of a PID may necessitate intensive monitoring by the anticoagulation clinic. This concerned one-third of our cases.

Conclusion

The results of the present population-based cohort study show that potential drug interactions during anticoagulant therapy with coumarins frequently occur in daily practice, confronting about two-third of patients with an increased risk of, mainly, bleeding. To a large part, this is attributable to commonly prescribed medication like antibacterial drugs and NSAIDs. This situation substantiates the need for new anticoagulants with less drug–drug interactions.

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