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Adverse interaction of warfarin and paracetamol: evidence from a post-mortem study

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Abstract

Purpose The aim of the study was to establish the prevalence and nature of potential adverse drug combinations of warfarin in a large post-mortem toxicology database. The concomitant use of warfarin and non-steroidal anti-inflammatory drugs (NSAIDs) was of interest as these drugs have been associated with internal bleeding both in clinical and post-mortem study settings. Another purpose was to obtain facts related to the questioned safety of warfarin-paracetamol and warfarin-tramadol combinations.

Methods The post-mortem database was searched for a 1-year period. All warfarin-positive cases and cases containing interacting drugs, as defined by the SFINX interaction database (Swedish, Finnish, Interaction X-referencing), were included. For controls, all cases containing paracetamol or tramadol were also included, and for each warfarin-positive case, an age-, sex- and alcohol-matched control case was sourced. The contribution of anticoagulant use to the deaths was evaluated from the death certificates based on medico-legal autopsies.

Results In 33% of the 328 warfarin-positive cases, at least one interacting drug was present, and paracetamol was the most abundant, accounting for 49% ($n=53$). When paracetamol and warfarin were detected simultaneously, the number of fatal bleeds was 4.6 and 2.7 times higher compared to paracetamol or warfarin use alone respectively. The presence of an NSAID in combination with warfarin was rare, as only six cases were identified. A majority (66%) of the post-mortem blood samples had a warfarin

concentration below 0.5 mg/l, and for the rest of the cases, the mean concentration was 0.70 mg/l.

Conclusions This study supports the clinical evidence suggesting that warfarin-paracetamol interactions may create significant life-threatening conditions. It also accentuates the significant role post-mortem database research can have in improving drug safety.

Keywords Warfarin · Paracetamol · Adverse drug interaction · Post-mortem · Drug safety

Introduction

Warfarin is a widely used anticoagulant drug that inhibits the vitamin K-dependent synthesis of clotting factors II, VII, IX and X. There are numerous indications for warfarin treatment, but the therapy is challenging as the optimum therapeutic range is narrow and there is wide inter-individual variation in the dose required for suitable anticoagulation [1, 2]. The effect of the treatment is monitored by measuring the international normalised ratio (INR) value, which is calculated from the time of clot formation in vitro. For most clinical indications, the target INR value is 2.0–3.0 [1]. Bleeding is a common adverse drug reaction (ADR) of warfarin therapy, and several risk factors have been identified, such as advanced age, liver disease, alcohol consumption, malignancy, unstable INR and INR values above 3.0 [3–5]. Major bleeding is reported in 0.63% of warfarin users [6]. Gastrointestinal or intracranial haemorrhages due to anticoagulants or NSAIDs are among the most common and fatal ADRs [7].

Warfarin is administered as a racemate. The *S*-enantiomer is five times more potent than the *R*-enantiomer, and the metabolisms of the isomers also differ from each other;

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S-warfarin is metabolised by the hepatic P450 enzyme isoform CYP2C9 (half-life 18–35 h) and *R*-warfarin by CYP1A2 and CYP3A4 (half-life 20–70 h). There are also genetic factors contributing to the response as variation at CYP2C9 and VKORC1 (vitamin K epoxide reductase complex 1) leads to a lower required warfarin dose [8]. Warfarin has a large number of clinically important adverse drug-drug interactions (ADIs) by several mechanisms [9]. CYP2C9, CYP1A2 and CYP3A4 inhibitors may decrease the clearance of warfarin, leading to increased antithrombotic response, while drugs acting as inducers of these enzymes may lead to reduced anticoagulant effect. Drugs such as acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs) can interfere with haemostasis by impairing platelet function. Warfarin therapy is also sensitive to fluctuations in the dietary intake of vitamin K and the use of alternative and complementary medicine [4, 10]. It has been estimated that concurrent use of potentially interacting drugs may result in 3–4.5 times higher risk of bleeding [11].

Although paracetamol has been considered the first-line analgetic for patients on warfarin therapy, case reports describing ADIs have been published and a controversy on the safety of the combination has been raised [12–14]. In several studies, the concomitant use has been reported to result in an increase in INR [15–19]. Contrary to these results, no paracetamol-related increase in INR values was observed in studies on healthy volunteers [20, 21]. As paracetamol is not known to interfere with platelet function like NSAIDs do, other mechanisms for the interaction have been proposed. In an *in vitro* study, NAPQI (the toxic metabolite of paracetamol normally detoxified by cellular glutathione) inhibited the enzymes in the vitamin K cycle [22]. It has also been suggested that decreased CYP2E1 activity due e.g. to aging could reroute the metabolism of paracetamol towards CYP1A2 and CYP3A4, thus leading to competition with *R*-warfarin; furthermore, tissue hypoxia

and hypertension could cause paracetamol to be shunted from glucuronidation towards oxidation via CYP2E1, CYP1A2 and CYP3A4 [23]. In two studies, reduction of functional factor VII has been observed [13, 18].

The current study evaluates the prevalence of warfarin-related ADIs based on a Finnish post-mortem toxicology database and on the related death certificates. It reviewed the use of a comprehensive range of drugs, abused drugs and alcohol combined with bleed findings. The study material, over 6,000 post-mortem cases, represents over 10% of all deaths during a 1-year period. A quantitative analysis method for neutral and acidic drugs in post-mortem blood was developed especially for this study to detect warfarin and NSAIDs with a sufficient sensitivity.

Materials and methods

Subjects

The subjects were autopsied in Finland, and all the toxicological analyses were performed at the Department of Forensic Medicine, University of Helsinki. The study included all warfarin-positive cases that were entered into the laboratory database from 1 February 2007 to 31 January 2008. The samples taken at autopsy were stored in tubes with ~1% NaF or in some cases without the preservative. Only results from femoral venous blood samples were accepted. Altogether 328 warfarin-positive cases were identified from a total of 6,178 cases (5.3%). The characteristics of the study material are summarised in Table 1. For each warfarin-positive case, a control case was obtained by selecting the next matching case in numerical order. The criteria were as follows: same sex, age ± 5 years and, if alcohol was present in the warfarin case, blood alcohol concentration within $\pm 0.5\%$ (otherwise no alcohol was accepted). If drugs included in the study (Table 2) were

Table 1 Characteristics of the study material

Drug finding	Number of cases	Death certificate not available	Male (%)	Female (%)	Age (years) ^a	Positive for alcohol (%)
Warfarin alone	219	5	82	18	69 (11)	35
Warfarin in combination with interacting drug(s)	109	1	61	39	73 (12)	18
Paracetamol alone	300	2	62	38	60 (18)	25
Paracetamol in combination with warfarin	53		66	34	76 (9)	15
+ Other interacting drugs present	7					
Tramadol alone	167	3	74	26	52 (19)	30
Tramadol in combination with warfarin	14		57	43	71 (14)	21
+ Other interacting drugs present	1					
All warfarin-positive cases	328	6	75	25	70 (12)	30

^a Mean \pm standard deviation

Table 2 Number of cases of drugs involving interactions with warfarin

	Class D interactions ^a				Class C interactions ^a								
	LOD (mg/l)	LOQ (mg/l)	2*U (%)	In combination with warfarin cases	All positive cases	Effect on anticoagulation	LOD (mg/l)	LOQ (mg/l)	2*U (%)	In combination with warfarin cases	All positive cases	Effect on anticoagulation	
NSAIDs													
Acetofenac ^{b,c}	3	5	30	0	0	+	Analgetics						
Acetylsalicylic acid ^b	0.3	3	40	3	159	+	Paracetamol ^b	0.1	10	40	53	353	+
Celecoxib ^b	0.5	3	30	0	0	+	Tramadol				14	178	+
Diclofenac ^b	0.1	0.5	30	0	15	+	Others						
Ethodolac ^b	0.1	10	35	0	0	+	Arniodarone				2	33	+
Etoricoxib ^b	0.3	Qualitative		0	6	+	Carbamazepine ^b	0.1	0.3	35	7	153	-
Ibuprofen ^b	0.1	10	30	2	117	+	Citalopram				29	457	+
Indometacin ^b	0.1	0.5	35	0	9	+	Clomipramine				0	12	+
Ketoprofen ^b	0.3	0.3	35	0	23	+	Duloxetine				0	15	+
Ketorolac ^b	3	3	40	0	0	+	Fluoxetine				1	63	+
Mefenamic acid ^b	0.1	3	30	0	0	+	Milnacipran				0	0	+
Meloxicam ^b	5	Qualitative		0	1	+	Paroxetine				2	39	+
Nabumetone ^b	0.1	3	30	0	0	+	Phenazone ^b	0.5	5	40	0	1	-
Naproxen ^b	0.1	10	30	0	65	+	Phenobarbital ^b	0.1	10	30	0	6	-
Nimesulide ^{b,c}	3	Qualitative		0	0	+	Phenytol ^b	0.1	10	35	1	33	+
Parecoxib ^{b,d}	10	10	30	0	0	+	Primidone ^b	0.1	5	40	0	1	-
Phenylbutazone ^{b,e}	0.3	Qualitative		0	1	+	Propafenone				0	0	+
Rofecoxib ^{b,c}	0.1	1	30	0	0	+	Sertraline				3	55	+
Tiaprofenic acid ^b	10	Qualitative		0	0	+	Trimethoprim				6	47	+
Tolfenamic acid ^b	0.1	0.3	30	1	3	+	Venlafaxine				1	86	+
Valdecoxib ^{b,c}	1	3	45	0	0	+							
Others													
Fluonazole				2	39	+	Combinations D+C (cases)				127 (109)		
Fluvoxamine				0	5	+	Warfarin ^b	0.1	0.5	30	328		
Metronidazole				0	0	+							

^a Clinical importance of the interaction classified by the SFINX database [25] from A (probably insignificant) to D (severe)

^b Drugs analysed with the described GC-MS method. For analysis of the remaining drugs, a GC-NPD screening method [42] or a specific LC-MS/MS method was applied

^c No longer marketed at the time of the study

^d Preparation for injections only

^e In veterinary use

detected, the potential control case was discarded. To evaluate the bleeding tendency of paracetamol and tramadol users, all positive cases from the study period were extracted from the database. This yielded 353 and 181 cases for paracetamol and tramadol respectively.

Analysis of acidic and neutral drugs

Sample preparation

For the preparation of calibration and control samples, ethanolic reference standard solutions were carefully evaporated to dryness at 40°C before adding the zero matrix, 1.0 g of bovine blood containing ~1% NaF. Saturated NH₄Cl (500 µl) and the internal standard solution (50 µl of 0.1 mg/ml butalbital-D5 in methanol) were added, and the sample was extracted with ethyl acetate (500 µl) for 5 min. After centrifugation, a 50-µl aliquot was evaporated to dryness in a sample vial at 40°C, 50 µl of MSTFA-TMCS [*N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide: trichloromethylsilane; 99:1] was added to the residue, the vial was capped, and the sample was heated at 85°C for 30 min.

For the plasma/whole-blood ratio experiment, blood samples from two volunteers were drawn into EDTA (H₃) tubes. Aliquots of 1.5 g (for whole blood) and 3 g (for plasma) were transferred into Li-heparin separation tubes and spiked with warfarin (Na) to a final concentration of 1.5 mg/l. The samples were incubated at room temperature for 24 h, the plasma was separated by centrifugation (30 min), and 1.0 g of each sample was taken for extraction.

GC-MS

GC-MS was performed with a 5975 inert XL mass-selective detector coupled to a 6890 N gas chromatograph, equipped with a 7683 injector (Agilent Technologies, Santa Clara, CA, USA) and a DB-5MS (12 m×0.20 mm i.d. with 0.33 µm film) capillary column (Agilent). GC-MS was operated by ChemStation software. Helium was used as a carrier gas at a constant flow rate of 1.5 ml min⁻¹ after pulsed flow injection in a splitless mode (1 µl) for 0.5 min. The injector port temperature was 250°C and the transfer line temperature 300°C. The oven temperature was initially held at 80°C for 0.5 min and then increased by 20°C min⁻¹ to 320°C, which was held for 4 min. The GC-MS analysis was performed by full scan at *m/z* 50–550. The internal standard retention time was locked at 6.40 min (Retention time locking software, Agilent). Spectral data were purified by AMDIS (Automated Mass Spectral Deconvolution and Identification system, version 2.1) [24] and subsequently searched against an in-house library of over 100 compounds and against an extensive commercial library (NIST05). The results, showing spectral match, retention

time and the respective blood concentrations, were summarised in a single CAS number-based table by Deconvolution Reporting Software (Agilent).

Method validation

The method was validated for the quantification of more than 40 drugs, including NSAIDs, antiepileptics, paracetamol and warfarin (Table 2). Four parallel samples were prepared for 10 calibration points in the concentration range of 0.1–100 mg/l. For each compound, three calibration points were chosen on the basis of the therapeutic range. For determining linear range, the acceptance criteria were ±25% in bias and ±20% in precision expressed as coefficient of variation (CV). The limit of detection (LOD) set by AMDIS recognition (match factor 50) and limit of quantification (LOQ) are presented in Table 2. For each compound the extended uncertainty of measurement (2*U) was calculated from precision (calibration samples and three parallels of authentic samples, if available), reproducibility (authentic samples) and accuracy (calibration samples).

Drug-drug interactions

The Swedish, Finnish, Interaction X-referencing (SFINX) is a regularly updated commercial drug interaction database introduced in 2006 [25]. The database classifies two-compound ADIs by their clinical status from probably insignificant (A) to severe (D) and indicates the level of documentation from sparse (0) to well established (4). The database was accessed through the National Library of Health Sciences in Finland. The drugs possessing pharmacokinetic and/or pharmacodynamic interactions with warfarin and present in the laboratory's analysis arsenal were identified, and only the drug combinations classified as the most severe (class D) and the second most severe (class C) were included in the study.

Post-mortem database and death certificates

The case files in the post-mortem database included a forensic pathologist's referral, laboratory analysis results and information extracted from the death certificate issued by a forensic pathologist. The referral contained background information, such as a brief description of the circumstances of death, known medication and the main autopsy findings. The analytical data contained analysis results for alcohols, medicines and drugs of abuse, and occasionally for other substances. Information from the final death certificate included the age and gender of the deceased, the cause of death with contributing factors according to the International Classification of Diseases

(ICD-10) and the manner of death (WHO, World Health Organization). For the cases considered for inclusion in this study, the death certificates were re-evaluated by a forensic pathologist. Only bleeds that were mentioned as the main cause of death were included, and the contribution of anticoagulant use to the death was assessed.

Statistical methods

MINITAB 13.31 was used for statistical analysis. The test for two proportions was used to compare the prevalence and the aetiology of the bleeds between the groups.

Results

Prevalence of interacting drugs

The studied drug interactions are presented in Table 2. At least one interacting drug was present in 33% of all warfarin-positive cases (109 of 328). In 16 cases, there were two interacting drugs and in 1 case three. Paracetamol and citalopram were the most common findings, accounting for 54 cases (49%) and 29 cases (27%) respectively. There were only 6 cases out of 393 NSAID and 328 warfarin-positive cases (1.5% of NSAIDs and 1.8% of warfarin cases) in which the warfarin-NSAID combination was found.

Prevalence of bleeds

The bleeds classified in the available death certificates as the main causes of death are summarised in Table 3. The prevalence of a fatal bleed was 4.6 times higher for the warfarin-paracetamol combination compared to paracetamol alone and 2.7 times higher compared to warfarin alone ($P < 0.05$). The warfarin-tramadol combination compared to tramadol alone and warfarin alone increased the risk 5.9

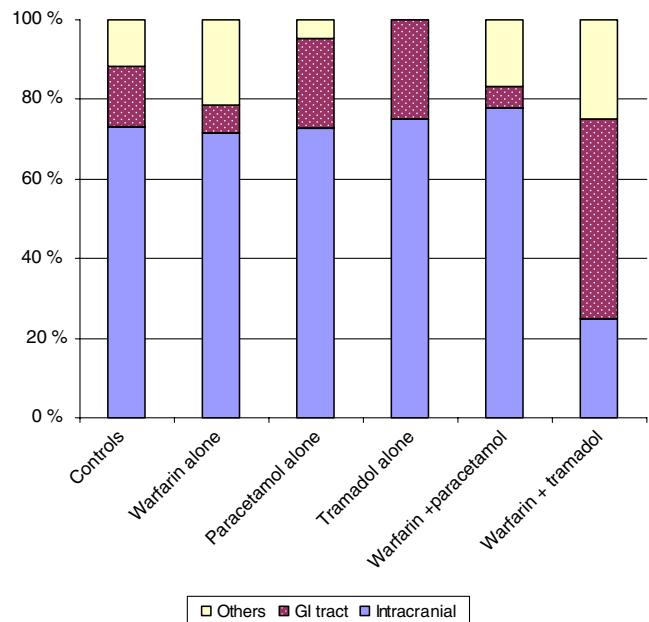


Fig. 1 Location of bleeds

and 2.3 times respectively, but the small number of cases may have skewed the result. There was no statistical difference in the incidence of fatal bleeding between the warfarin-only users, the warfarin control group and the paracetamol-only users. The tramadol-only users had the lowest incidence (4.9%). Even when taking into account the few cases where bleeding was mentioned elsewhere in the death certificate (as an intermediate, immediate or contributing cause of death), the results did not change noticeably (data not shown). There was no statistical difference in the aetiology of the bleeds (spontaneous or traumatic) between the groups. The locations of the bleeds are illustrated in Fig. 1. Intracranial bleeds were the most common, accounting for roughly 70% of the cases, except for the warfarin-tramadol users, but again this could be a consequence of the small number of cases.

Table 3 Number of cases with bleeding as the main cause of death

Drug finding	All cases	Bleeds			Spontaneous bleeds		Traumatic bleeds	
		total	%	$p < 0.05^a$	CASES	%	CASES	%
Warfarin alone	214	27	12.6	••	15	56	12	44
Warfarin control cases	328	27	8.2	••	10	37	17	63
Paracetamol alone	298	22	7.4	••	9	41	13	59
Paracetamol in combination with warfarin	53	18	34.0	••	7	39	11	61
Tramadol alone	164	8	4.9	••	5	63	3	38
Tramadol in combination with warfarin	14	4	28.6	••	3	75	1	25

^a test for two proportions

Post-mortem concentration of warfarin

In the warfarin-positive cases, 66% of the post-mortem blood samples (216) had a warfarin concentration between LOD (0.1 mg/l) and LOQ (0.5 mg/l) and were reported as “positive”. The median concentration for the rest of the samples was 0.70 mg/l (average 0.88 mg/l), and the range was 0.5–6.2 mg/l. The distribution of warfarin between plasma and whole blood was studied *in vitro*. The plasma-to-whole blood ratio was 1.63–2.01.

Discussion

Several studies have been published on warfarin co-prescribed with potentially interacting medication. The number of patients having adverse warfarin co-prescriptions in various settings has been reported to be in the range of 33 to 81.6%, and paracetamol-containing products were often the most common [11, 26–28]. In our study, the prevalence of adverse warfarin-drug combinations was similar (33%), although several drugs possessing serious ADIs with warfarin were not included as they are not of interest to forensic toxicology as such. These drugs included antibiotics, antifungals, antivirals and drugs used in cancer treatment.

NSAIDs are the most commonly used over-the-counter (OTC) drugs after vitamins and mineral supplements in Finland, and they thus have a significant potential to cause ADIs with prescription drugs [29]. Nevertheless, our study indicates that the situation is not alarming: only six cases of warfarin-NSAID combinations were detected during the year. There are no data on whether the NSAIDs in question were OTC or prescribed drugs. This number is much smaller than the results of a prescription study where non-selective NSAIDs were prescribed to 26.3% of warfarinized patients in Scotland [28]. Paracetamol and tramadol were the most popular analgesics among individuals taking warfarin, while selective COX-2 inhibitors were mostly absent from our material. It has been reported that warfarin in combination with selective COX-2 inhibitors poses a similar risk of upper GI haemorrhage as the concomitant use of non-selective NSAIDs [30]. At the time of the study, only celecoxib, etoricoxib and meloxicam were available as prescription medicines (Table 2).

The results of this study imply a significantly elevated risk for an adverse outcome in the simultaneous use of warfarin and paracetamol compared to warfarin alone. Although the mechanism of the interaction is not clear, the safety of paracetamol use among patients on warfarin should be given more serious consideration. The safety of concomitant use of warfarin and tramadol remains unclear due to the small number of cases; the individuals on

tramadol only were also somewhat younger, which may have had an effect on the results (Table 1). Some case reports of warfarin-tramadol interactions have been published [31–33], and a CYP2D6-related mechanism has been proposed [34].

There are few published methods for detecting warfarin post-mortem as the therapeutic effect is normally defined by the INR value [35, 36]. From a forensic standpoint, the presence of warfarin is more essential than the concentration since the correlation of warfarin dosage or concentration with INR is very poor [37]. Determination of warfarin can also be helpful in differentiating non-compliance from anticoagulant resistance. The reference values for therapeutic or normal ranges are usually of clinical origin and given only for plasma or serum. Warfarin is known to be extensively bound to albumin (97%) [38]. In a study on two other highly plasma-bound compounds, diazepam and nordiazepam, the mean plasma/blood ratios were 1.79 and 1.69 respectively [39]. Our experiment with warfarin gave similar ratios (1.63–2.01), which explains why the post-mortem blood warfarin concentrations observed in our cases are generally lower than the therapeutic range given for plasma (1–3 mg/l) [40].

This study supports previous clinical evidence of the significance of the adverse warfarin-paracetamol interaction. To the best of our knowledge, this is the largest dataset on post-mortem warfarin analysis. Furthermore, NSAIDs are rarely included in large-scale drug screening methods despite their potential role in ADRs and ADIs. Routine cause-of-death investigations rarely reveal a serious ADI, although the prevalence of adverse drug combinations in retrospective post-mortem database analysis has been found to approach 1% [41]. A comprehensive post-mortem toxicology database is a valuable resource for ADI research because the proof is based on laboratory analysis, not just prescriptions. The present findings also underline the significance of post-mortem epidemiology in improving drug safety in general.

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