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Interference of the new oral anticoagulant dabigatran with frequently used coagulation tests

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Abstract

Background: Dabigatran etexilate is a new oral anticoagulant for the therapy and prophylaxis of venous thromboembolism and stroke prevention in patients with atrial fibrillation. To investigate the extent of interactions of this new anticoagulant with frequently used coagulation assays, we completed a multicenter in vitro trial with Conformité Européenne(CE)-labeled dabigatran-spiked plasma samples.
Methods: Lyophilized plasma samples with dabigatran concentrations ranging from 0.00 to 0.48 µg/mL were sent to the coagulation laboratories of six major Austrian hospitals for evaluation. Coagulation assays were performed under routine conditions using standard reagents and analyzer.
Results: Dabigatran led to a dose-dependent prolongation of the clotting times in coagulometric tests and influenced the majority of the parameters measured. Statistically significant interference could be observed with the prothrombin time (PT), activated partial thromboplastin time (aPTT) and PT/aPTT-based assays (extrinsic/intrinsic factors, APC-resistance test) as well as lupus anticoagulant testing. Even non-clotting tests, such as the colorimetric factor XIII activity assay and to a minor extent the amidolytic antithrombin activity assay (via factor IIa) were affected.
Conclusions: This multicenter trial confirms and also adds to existing data, demonstrating that laboratories should expect to observe strong interferences of coagulation tests with increasing concentrations of dabigatran. This finding might become particularly important in the elderly and in patients with renal impairment as well as patients whose blood is drawn at peak levels of dabigatran.

Keywords: coagulation tests; dabigatran; interference; misinterpretation; new oral anticoagulants.

Introduction

Dabigatran etexilate, a novel oral direct thrombin inhibitor, has been approved for prophylaxis of thromboembolism in patients undergoing total knee or total hip replacement and prevention of stroke in patients with atrial fibrillation. Approval for the treatment of venous thromboembolism is expected soon (1–4). Thus, the use of this drug will soon become widespread and may not only present new challenges for the appropriate monitoring in the case of clinical necessity, but also concerning interference with coagulation-based assays, as in the case for other direct thrombin inhibitors (5, 6). Especially in high-dose use or after blood sampling at the peak level of approximately about 1–4 h after intake of the new anticoagulant, interference of this thrombin blocking agent with coagulation assays will need to be considered (7, 8).

Despite the ongoing debate concerning the need for laboratory monitoring of this new, fixed-dose oral antithrombotic drug (9–12), the extent of the interactions of dabigatran with frequently used coagulation assays is not yet clear. The study group on new oral anticoagulants of the Austrian Society of Laboratory Medicine and Clinical Chemistry completed in vitro experiments during a multicenter pilot trial with the first commercially available, CE-labeled dabigatran-spiked, plasma calibration samples provided by Hyphen Biomed (France), in the following six specialized coagulation laboratories of major Austrian hospitals: the central laboratories of Medical University Vienna, Municipal Hospital Hietzing-Rosenhügel (Vienna), Clinic St. Pölten, General Hospital Linz, Clinic Wels-Grieskirchen and Medical University Innsbruck. The aim of this study was to evaluate the extent of

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interference of dabigatran with frequently used coagulation tests in clinical laboratories.

Materials and methods

Lyophilized plasma calibration and control samples were obtained from Hyphen BioMed, Neuville sur Oise, France. Calibration and control samples derived from a pool of healthy persons were spiked with dabigatran (active moiety of the prodrug), checked by HPLC and were kindly donated by CoaChrom Diagnostica, Vienna, Austria. The CE-labeled calibrator and control samples showed dabigatran concentrations of 0.00, 0.10, 0.24 and 0.48 µg/mL, respectively. They were shipped to the central laboratories of six major hospitals in Austria to be analyzed parallel by all laboratories and for all tests listed in Tables 1 and 2 under routine conditions. Equal volumes of the 0.00 µg/mL and the 0.10 µg/mL calibrators were mixed to obtain a concentration of 0.05 µg/mL dabigatran. Coagulation assays (clotting, chromogenic and immunologic) were performed under routine conditions with a single measurement using reagents and analyzers representative of those utilized in Austrian coagulation laboratories.

Reagents were provided by the following vendors: Siemens Healthcare Diagnostica Products GmbH, Marburg, Germany (SIE); Hyphen Bio-Med, Neuville sur Oise, France (HYP); Pentapharm, Basel, Switzerland (PEN); Life Diagnostics, Clarkston, GA, USA (LD); Technoclone, Vienna, Austria (TEC); Instrumentation Laboratory SpA, Milano, Italy (IL); Diagnostica Stago, Asnieres, France (STA); and CoaChrom Diagnostica, Vienna, Austria (COA). As the reagents for frequently used "screening tests" might be of special interest, they are also listed below.

For measuring prothrombin time (PT) we used Thromborel S (SIE), Innovin (SIE), Normotest (TC), and RecombiPlasTin 2G (IL). Activated partial thromboplastin time (APTT) was assessed with Pathromtin SL (SIE), Actin FS (SIE), and SynthASil (IL). Functional fibrinogen tests were MultifibrenU (SIE), Fibrinogen Reagent (TC), STA Fibrinogen (STA) and Fibrinogen C XL (IL). Antithrombin (AT) via F Xa was measured with Innovance Antithrombin (SIE), and Hemosil Liquid Antithrombin (IL), whereas AT via F IIa was assessed using Berichrom AT III (SIE), and STA AT-III (STA). The APC-resistance tests were Coatest APC-R (COA), Pefakit APC-R FV Leiden (PEN), and Hemoclot Quanti V-L (HYP).

The analyzers used included the following: ACL-Top and ACL Elite-pro (IL), BCS and BCS (SIE) with clot detection by light scatter and STA-R Evolution (STA) with mechanical clot detection.

Medians and 25th and 75th percentiles of the calibration samples with increasing dabigatran concentrations (0.0, 0.05, 0.10, 0.24 and 0.48 µg/mL, respectively) were calculated from the different coagulation tests. To determine statistical significance, the Kendall's W coefficient of concordance (KW) and the Kendall rank correlation coefficient (Kendall's tau coefficient) as non-parametric hypothesis tests were calculated to measure the association between dabigatran concentration of the calibrator plasma samples and the coagulation test results from the different centers (13). An overall p-value <0.05 and a Kendell-Tau rank correlation coefficient >0.4 were considered as statistically significant; the Bonferroni correction of the levels of significance was applied for multiple comparisons (14). SPSS 18 was used for all statistical analyses.

This study is an in vitro trial, using commercial, CE-labeled calibration plasma samples. Thus, no ethical approval or informed consent was needed.

Results

Dabigatran led to a dose-dependent prolongation of the clotting times in the PT and aPTT coagulometric tests and thus

Table 1 Significantly influenced coagulation tests.

Analyte	Influence of different concentrations of dabigatran in plasma				
	0.0 µg/mL	0.05 µg/mL	0.10 µg/mL	0.24 µg/mL	0.48 µg/mL
PT, %	69.0 (68/74)	63.0 (59/64)	54.0 (52/64)	41.5 (40/42)	28.0 (23/29)
INR, -	1.22 (1.2/1.2)	1.3 (1.3/1.3)	1.44 (1.4/1.5)	1.7 (1.6/1.8)	2.42 (2.4/2.4)
aPTT, s	43.0 (39.1/45.9)	57 (54.8/62.2)	76 (64.8/83.4)	90.2 (89/108)	131.5 (107.5/147.5)
Fib/Clauss <50U IIa, mg/dL	232.0 (217/239)	203.3 (174/218)	205.0 (187/222)	200.9 (158/221)	110.6 (78/121)
AT (IIa), %	94.2 (91/97)	99.4 (97/102)	97.3 (97/98)	113.2 (107/119)	123.3 (118/129)
F II, %	87.0 (82/91.5)	74.1 (72.6/78.1)	68.15 (63.7/73.5)	54 (50.6/58.5)	34.1 (33.1/35)
F V, %	74.8 (72/82)	69.3 (64/70)	72.2 (68/74)	54.8 (52/58)	42.2 (36/44)
F VII, %	80.0 (78/85)	76.0 (74/78)	78.0 (71/78)	63.0 (60/69)	62.0 (52/64)
F X, %	79.6 (75/80)	70.9 (68/75)	69.0 (67/69)	59.0 (58/63)	47.0 (43/55)
F VIII, %	64.45 (59/65.2)	41 (38/43.6)	28.85 (27.5/32.9)	12 (8.3/17)	4.0 (2/5.5)
F IX, %	72.3 (68/77)	47.7 (44/57)	33.8 (30/34)	11.9 (8/15)	5.2 (3/6)
F XI, %	69.0 (66/74)	48.4 (40/50)	29.8 (25/34)	9.4 (8/11)	5.0 (3/5)
F XII, %	91.0 (79/94)	63.0 (57/64)	54.0 (36/58)	31.0 (28/39)	16.7 (14/25)
F XIII Act, %	104 (94/118)	80.2 (79.6/80.6)	68.95 (67.5/81.5)	36 (30/38.3)	15 (15/17.6)
Prot. S clotting, %	66.0 (61/71)	116.0 (92/140)	150.0 (144/156)	250 (242/258)	>250
dRVVT Screen, s	44.4 (44/51)	81.2 (78/90)	99.1 (91/118)	147.0 (140/168)	>180
dRVVT Confirm, s	38.0 (38/38)	57.6 (57/59)	68.5 (67/72)	97.5 (96/99)	140.0 (136/150)
dRVVT Standard ratio	1.2 (1.1/1.2)	1.3 (1.3/1.5)	1.3 (1.3/1.5)	1.5 (1.4/1.6)	>1.5
dRVVT Normalized ratio	1.1 (1.1/1.1)	1.3 (1.2/1.3)	1.3 (1.3/1.4)	1.4 (1.4/1.4)	>1.5

Results of significantly influenced coagulation tests with increasing concentrations of dabigatran in plasma. Given values are median vs. 25th and 75th percentile (in brackets). Significance was defined for p (Kruskal-Wallis) <0.05 and relevant coherence for τ (Kendell-Tau rank correlation coefficient) >0.4, respectively.

Table 2 Analytes that were not significantly influenced by dabigatran.

Analyte	Influence of different concentrations of dabigatran in plasma				
	0.0 µg/mL	0.05 µg/mL	0.10 µg/mL	0.24 µg/mL	0.48 µg/mL
Fib/Clauss >50U IIa, mg/dL	266.0 (252/280)	249.5 (247/252)	245.5 (237/254)	259.0 (251/267)	260.0 (251/269)
free Prot. S, %	66.0 (66/70)	70.0 (39/71)	73.0 (72/74)	66.0 (66/68)	67.0 (66/69)
AT (Xa), %	95.0 (89/95)	92.3 (90/93)	91.0 (89/93)	98.7 (91/105)	98.0 (94/110)
vWF-Ag, %	76.6 (74/77)	72.0 (70/74)	69.0 (67/71)	70.0 (68/73)	68.9 (68/71)
vWF:RCo, %	55.0 (55/58)	57.0 (53/58)	57.0 (56/59)	55.0 (54/57)	54.0 (54/57)
Prot. C act.(amidol), %	88.0 (84/92)	87.0 (85/91)	88.0 (85/89)	59.0 (83/90)	87.0 (85/87)
Plasminogen (amidol), %	87.5 (85/90)	85.0 (83/86)	82.0 (81/83)	88.5 (86/91)	87.5 (85/90)

No statistically significant influence with increasing concentrations of dabigatran in plasma was seen for the following coagulation tests. Given values are the median vs. 25th and 75th percentile (in brackets). Significance was defined for p (Kruskal-Wallis) <0.05 and relevant coherence for τ (Kendell-Tau rank correlation coefficient) >0.4, respectively.

influenced the majority of the parameters measured (Table 1). The different origin of various thromboplastins (rabbit, bovine, human, recombinant) used as activators in prothrombin time assays accounts for large inter-laboratory variabilities. In an attempt to limit this variation in Austria and other few countries PT results are analyzed and given as percentage activity instead of seconds or ratio (patient-to-normal) clotting times. There is, however, no evidence that the percentage activity is effective to abrogate the between-thromboplastin variability.

As a pilot experiment, a dabigatran calibrant set from another production lot with concentrations of 0.04, 0.12, 0.25, 0.30 and 0.50 µg/mL dabigatran was previously evaluated and provided comparable results (data not shown), confirming the data of Lindahl et al. concerning five routine coagulation tests (8).

Reagents purchased from different manufacturers showed different responses toward the concentrations of dabigatran used for the experiments presented herein, probably due to their different formulations. Pooling of data obtained by using reagents from different companies seems therefore to be causative for the relatively high variation of the results presented. This is in line with findings by Lindahl et al., who clearly demonstrated that the extent of dabigatran interference with fibrinogen measurement is dependent on the formulation of reagents used (8). A phenomenon similar to the abovementioned is also well known from external quality assurance trials, when lyophilized samples are sent out to various laboratories working with different brands of reagents.

The functional fibrinogen (Clauss) assays in our trial tended to show falsely decreased results (Table 1) with dabigatran levels >0.24 µg/mL when reagent-thrombin concentrations below 50 U/mL were used (reagents by Siemens Healthcare and Instrumentation Laboratory), whereas reagents with a higher thrombin concentration (Technoclone and Diagnostica Stago) produced less affected results (Table 2).

Statistically significant interference with increasing clotting times and decreasing factor activities, decreasing PT-levels (%) and increasing International Normalized Ratio (INR) could be demonstrated in the PT and aPTT as well as in the PT- and aPTT-based assays, such as extrinsic and intrinsic coagulation factors. Misinterpretation of the diagnosis "lupus anticoagulant" and "APC-resistance" (false-positive results) resulted when calculating the standard dilute Russell Viper Venom Time (dRVVT)-Ratio and APC-resistance ratio of plasma samples due to increasing clotting times with dabigatran concentrations >0.05 µg/mL and 0.20 µg/mL, respectively (Table 1). Normalization of dRVVT results against a reference plasma pool and calculation of a "normalized" ratio is recommended in the revised ISTH-guidelines for lupus anticoagulant detection (15). Although normalization of dRVVT data led to lower ratios in our study, the conversion failed to correct the false-positive lupus anticoagulant test results in plasma samples containing dabigatran at concentrations higher than 0.05 µg/mL (Table 1).

Thrombin-dependent, non-clotting tests, such as the colorimetric factor XIII (F XIII) activity assay which showed markedly decreased values, and to a minor extent the amidolytical AT activity assay via factor IIa, which tended to show falsely increased activities, were also influenced (Table 1). As to be expected, immunologic von Willebrand-factor antigen (vWF-Ag), free Protein S and other thrombin-independent assays (amidolytic activities of plasminogen, protein C or AT via Xa) were less affected than other assays or not affected at all by dabigatran (Table 2).

Discussion

Dabigatran-etexilate, the prodrug of dabigatran, is a potent, small, non-peptide molecule that inhibits both free and clot-bound thrombin by binding to the active site of the thrombin molecule. Because of its high polarity, the drug is not orally available. After oral administration of dabigatran-etexilate it is rapidly hydrolyzed by non-specific ubiquitous esterases (16, 17). Thus, the production of inhouse dabigatran spiked plasma samples is hindered. Therefore, in our trial, we used the first CE-labeled, lyophilized calibration samples, spiked with HPLC-controlled concentrations of dabigatran (18).

The use of spiked plasma samples instead of plasma samples collected after in vivo administration of dabigatran is a limitation of our study. Nevertheless, we believe that improved stability for shipping of test samples, better standardization and traceability outweighs this "limitation" of our trial. This is also corroborated by findings of the German study group

by Lindhoff-Last et al., who evaluated the impact of the anti Xa inhibitor rivaroxaban in ex vivo coagulation samples (19) as well as by results presented by a Swiss study group using spiked plasma samples (20).

At peak level, 2 h after oral administration of 100 mg dabigatran etixilate, the plasma dabigatran concentration was approximately 0.07 µg/mL (mean of six healthy participants) and following intake of 200 mg, plasma dabigatran was 0.12 µg/mL (21). The non-inferiority trial involving patients with acute venous thromboembolism compared oral dabigatran administered at a dose of 150 mg twice daily with warfarin, whereas the trial in patients with atrial fibrillation used two fixed doses of dabigatran of 110 mg or 150 mg twice daily (2, 3). Because renal excretion is the predominant elimination pathway and because dabigatran is a substrate for the efflux transporter P-glycoprotein (P-gp), a reduced dose of dabigatran etexilate is recommended not only in patients with moderate renal insufficiency or in the elderly, but also after coadministration of amiodarone, which is a suspected P-gp inhibitor (17, 21). Additionally, trough levels (before intake of the next dosage) showed varying dabigatran concentrations from 0.03 µg/mL to 0.23 µg/mL (7). Thus, clinical laboratories must expect interference in frequently used coagulation assays due to increased dabigatran levels when blood is drawn 2–4 h after drug intake and anytime plasma samples are obtained from elderly patients or those with renal impairment, who showed two to three times higher dabigatran concentrations in plasma samples compared with patients of normal renal function (4).

Our study showed that even very low concentrations of dabigatran not only increased the clotting times of dRVVT, but also the standard and normalized ratios of the dRVVT screening assay and the dRVVT confirmatory assay – a dRVVT with a high concentration of phospholipids – in such a way that the resulting values would generate *false-positive interpretations* for the presence of an lupus anticoagulant.This phenomenon has already been described with the thrombin inhibitors argatroban and lepirudin (5).

Furthermore, our results demonstrated that even very low levels of dabigatran, such as 0.05 and 0.10 µg/mL, induced false results for F VIII, IX, XI and XII activities when using the standard predilution of the patient plasma sample to be analyzed of 1:5. Together with an incorrect dRVVT ratio, these false results are problematic in laboratories when a prolonged aPTT prompts secondary investigations, such as dRVVT and factor analysis because the dabigatran therapy of the patient was not reported to the laboratory.

Interestingly, even F XIII activities showed markedly decreased values with increasing concentrations of dabigatran. Although the F XIII activity assay provided by Siemens is not a clotting but a colorimetric assay, the first step of the reaction involves the activation of F XIII to F XIIIa and is thrombin dependent. Only after this occurs can F XIIIa cross-link a specific peptide substrate to glycine ethyl ester, thereby releasing ammonia, which is then determined via decrease of NADH by monitoring the absorbance at 340 nm (22). This example shows that one must be aware that the interference of dabigatran with laboratory tests is not limited to the obvious clotting assays.

The authors do not advocate the use of thrombin-insensitive test systems (such as immunologic assays) to avoid interference with the new antithrombotics – this would result in the total loss of functional sensitivity in coagulation testing. The option to evaluate a coagulation parameter, if available, with a second, dabigatran-insensitive test or the use of two different predilutions for factor analysis might sometimes be medically indicated, but very costly.

The Austrian study group on new oral anticoagulants therefore recommends drawing blood for coagulation assays from patients receiving dabigatran etexilate (e.g., before major surgery) after dabigatran has been discontinued for at least 2–5 days (23, 24). If discontinuation is not possible, blood for routine clotting assessments, such as the PT, aPTT and fibrinogen assays, should be sampled *before* the next intake of dabigatran (trough level, i.e., 12 or 24 h after the last oral administration of dabigatran etexilate) to avoid maximum diagnostic interference at the peak level of the antithrombotic activity. Specialized coagulation laboratories should be able to determine quantitative dabigatran levels in suspected plasma samples with specific tests, such as the hemoclot dilute thrombin assay, which can be calibrated with the CE-labeled standard set used in this study.

To minimize risky misinterpretations or costly secondary investigations, it is *mandatory* that the clinical laboratory be informed of the dabigatran medication of the patient if coagulation analyses are ordered.

Conclusions

The present in vitro multicenter trial is confirming and contributes to previously published data (7, 8), demonstrating that laboratories must expect interferences from increasing dabigatran plasma levels with frequently ordered coagulation tests. This might become apparent especially in the elderly patients, those with renal impairment or during co-administration of drugs like amiodarone. These findings emphasize the importance of providing information concerning the patient's anticoagulation regimen to the clinical laboratory to avoid misinterpretation or costly secondary laboratory investigations.

Addendum: authors contributions

W.-M. Halbmayer and G. Weigel contributed equally to this work. They designed the study and wrote the manuscript.

W.-M. Halbmayer is the head of the study group, initiated and organized the study and prepared the manuscript.

W.-M. Halbmayer, P. Quehenberger, J. Tomasits, A.C. Haushofer, G. Aspöck and M. Schnapka-Köpf were responsible for the laboratory experiments at the different laboratories. A.C. Haushofer is the president of the Austrian Society of Laboratory Medicine and Clinical Chemistry and gave birth to the study group.

L. Loacker collected the laboratory data and was responsible for Tables.

A. Griesmacher initiated and organized resources for professional statistics and wrote parts of the manuscript.

G. Göbel performed statistical analyses and discussed the statistical results.

All authors have read and approved the final manuscript.

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Conflict of interest statement

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