Results of the thrombin time test obtained with two different commercial reagents in real life patients treated with dabigatran

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INTRODUCTION

Limited availability of dabigatran-specific coagulation assay could complicate treatment decisions in emergencies like urgent surgical intervention, or anticoagulation reversal in patients requiring emergent surgery. Thrombin time (TT) test, as extremely sensitive to very low amount of dabigatran, may be elevated even in the presence of clinically insignificant levels of the drug (< 30 ng/mL), although response varies considerably by drug concentration and reagent.

AIM

The aim was to determine TT reagent specific cut off values that might help to rule out relevant drug induced anticoagulation.

METHOD

Ninety citrated plasma samples from 17 patients taking dabigatran due to knee replacement were collected at the Traumatology Clinic, Sestre Milosrdnice University Hospital Center as a part of Croatian Science Foundation research project IP-2016-06-8208, LAB-NOAC. Samples were tested using two different TT reagents, Thromboclotin on Sysmex CS25000 (R1) and Thrombin time on Behring Coagulation System XP (R2), whereas dabigatran concentrations were measured using Innovance DTI assay (all Siemens Healthineers, Germany). Receiver operating characteristic analyses were used to determine sensitivity, specificity and reagent-specific cut off values. Statistical analysis was performed using MedCalc Software, version 11.5.1 (Ostend, Belgium).

RESULTS

Ranges of obtained TT values for R1 and R2 were 15 to >120s, and 12.3 to >150s, respectively. Measured dabigatran concentrations and differences between values are presented in Table 1. R1 and R2 had only moderate linear relationship to dabigatran concentrations: ρ=0.509 (95%CI:0.337-0.649), P< 0.001 and ρ=0.450 (95%CI:0.263-0.604), P<0.001, respectively. Results of sensitivity and specificity for the R1 and R2 at pre-defined and reagent specific TT cut-off values are presented in Table 2.

Table 1. Results of dabigatran concentrations measured with the two different thrombin time reagents in real life patients treated with dabigatran.

	All samples	Characteristics of samples depending on presence of clinically (in)significant dabigatran levels	
N	90	27	63
Concentration of dabigatran (ng/mL)	0 - 466	<30	>30
TT (s) (Thromboclotin reagent/ Sysmex CS25000; R1)	62.8 (43.4 - 96.1)	28.5 (22.7 – 49.9)	97.1 (62.4 – 120.0)
TT (s) (Thrombin reagent/ BCS XP;R2)	50.1 (33.9 -71.1)	25.2 (16.5 – 38.7)	71.0 (62.4 – 120.0)
P	0.304	0.069	0.797

N - number of samples; TT - thrombin time in seconds, results expressed as medians and 95% confidence intervals; P - level of statistical significant difference between R1 and R2 determined by Wilcoxon test

Table 2. Results of sensitivity and specificity for the two different thrombin time reagents (R1 and R2) at pre-defined and reagent specific cut-off values.

Threshold for TT (s)		Sensitivity (%)	Specificity (%)	NPV (%)
Pre-defined cut-off				
R1	19.4	100 (94.2–100.0)	14.3 (4.0-32.7)	100 (39.8–100.0)
R2	21.0	78.3 (65.8 - 87.9)	44.4 (25.5-64.7)	48.0 (27.8–68.7)
Reagent specific cut-off				
R1	19.1	100 (94.2-100.0)	10.7 (2.3-28.2)	100 (39.8–100.0)
R2	13.5	98.3 (91.1 -100.0)	14.8 (4.2 -33.7)	100 (39.8–100.0))

Thromboclotin reagent (R1); Thrombin reagent (R2):specificity and sensitivity are presented as medians and 95% confidence intervals; NPV-negative predictive value given with appropriate 95% confidence interval

CONCLUSIONS

Balanced reagent-specific threshold Thrombin Time assay studied in dabigatran treated patients ensure better sensitivity and negative predictive value for excluding clinically relevant drug concentrations in circulation and might help in emergency situations to support clinical decisions.

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