Does Normal Diluted Russell Viper Venom Time Test Result Can Exclude Concentrations of Direct Oral Anticoagulants below 30 ng/mL?

S. Margetić[1], *I. Ćelap*[2], *R. Mihić*[2], *S. Supraha Goreta*[3]

[1]University Hospital Center Sestre Milosrdnice, Department of Clinical Chemistry, Zagreb, Croatia, [2]University Hospital Center Sestre milosrdnice, Department of Clinical Chemistry, Zagreb, Croatia, [3]Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia, Department of Biochemistry and Molecular Biology, Zagreb, Croatia

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Background: Direct oral anticoagulants (DOACs), i.e. dabigatran, rivaroxaban and apixaban, have strong effect on dilute Russell viper venom screen (dRVVTs) and confirm (dRVVTc) test results. Therefore, it is possible to assume potential application of these assays in exclusion of DOACs presence in circulation.

Aims: To investigate whether normal dRVVT test result expressed as calculated lupus anticoagulant (LA) ratio i.e., dRVVTs/dRVVTc, can exclude clinically relevant concentration (>30 ng/mL) of DOACs.

Methods: DOACs concentrations were measured using commercial assays on BCS XP analyzer (Siemens Healthineers, Germany): Innovance heparin (Siemens Healthineers, Germany) calibrated with specific calibrators (Hyphen BioMed, France) for rivaroxaban and apixaban; Innovance DTI assay (Siemens Healthineers, Germany) for dabigatran. LA ratio was calculated from measured dRVVTs and dRVVTc tests with commercial LA1 Screening and LA2 Confirmation reagents using original protocols (Siemens Healthineers, Germany). Differences between groups were tested using Kruskal-Wallis test. Receiver operating characteristics (ROC) analysis was performed for diagnostic accuracy estimation at cut-off value of 30 ng/mL for each DOACs. The study was funded by the Croatian Science Foundation as part of the research project IP- 2016-06-8208.

Results: LA ratios showed significant differences between false positive (FP) and true negative (TN) LA results (P< 0.001) for all three DOACs (Table 1). Among patients with FP and TN results of LA, concentrations of DOACs were significantly different for rivaroxaban only (P< 0.001). ROC analysis confirmed that normal LA ratio result can´t exclude concentration below 30 ng/mL for dabigatran and apixaban (area under curve (AUC=0.625, P>0.05), whereas normal LA ratio could exclude rivaroxaban concentration below 30 ng/mL, AUC=0.967, P< 0.001 (Table 1).

Conclusions: Based on the normal dRVVT result (LA ratio), it is not possible to exclude low concentration of dabigatran and apixaban. On the contrary, normal dRVVT (LA ratio) could be potentially useful for excluding low concentration of rivaroxaban.

DOAC drug	Drug conc. in false positive LA results Median (IQR)	Drug conc. in neg. LA results Median (IQR)	LA ratio in false positive LA results Median (IQR)	LA ratio in negative LA results Median (IQR)	AUC (95% CI)	Sensitivity % (95%CI) at drug. conc. > 30 ng/mL	Specificity % (95%CI) at drug. conc. > 30 ng/mL

Dabigatran n = 59 False positive LA = 37 Neg. LA = 22	148 (53-250)	101 (19 -168)	1.61 (1.41 – 1.77)	1.24 (1.19 – 1.29)	0.625 (0.489 – 0.747)	86.5 (71.2 – 95.5)	31.8 (13.9 – 54.9)
P	0.111		<0.001		0.106		
Apixaban n = 28 False positive LA = 10 Negative LA = 18	171.5 (82 – 202)	91 (56 – 208)	1.59 (1.54 – 1.80)	1.14 (1.01 – 1.24)	0.625 (0.423 – 0.799)	90.0 (55.5. – 99.7)	11.1 (1.4 – 34.7)
	0.280		<0.001		0.277		
Rivaroxaban n = 70 False positive LA = 55 Negative LA = 15	194 (122 – 286)	14.3 (8 – 22)	1.80 (1.50 – 1.99)	1.20 (1.10 – 1.28)	0.967 (0.894 – 0.995)	92.7 (82 – 98)	80.0 (51.9 – 95.7)
	<0.001		<0.001		<0.001		

[Table 1. Receiver operating characteristics (ROC) analysis for excluding direct oral anticoagulants at cut-off of 30 ng/mL]

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