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[1], R Mihić[1], S Šupraha Goreta[2]

[1]Department of Clinical Chemistry, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia

[2]Department of Biochemistry and Molecular Biology, Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia

INTRODUCTION

Direct oral anticoagulants (DOACs) have effect on dilute Russell viper venom screen (dRVVTs) and confirm (dRVVTc) results. Due to high sensitivity of dRVVTs and dRVVTc assays on the presence of all DOACs, it is possible to assume their potential application in exclusion presence of DOACs in circulation.

AIM

To investigate whether normal dRVVT test result expressed as calculated LA ratio (dRVVTs/dRVVTc) can exclude clinically relevant concentration (>30 ng/mL) of DOACs in circulation.

METHODS

DOACs concentrations were measured using commercial assays on BCSXP coagulation 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 estimation of diagnostic accuracy 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. 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 dRVVT result (LA ratio) can´t exclude concentration below 30 ng/mL for dabigatran and apixaban, whereas normal LA ratio could exclude rivaroxaban concentration below 30 ng/mL, as indicated area under curve (AUC) of 0.967, P<0.001.

Table 1. Receiver operating characheristics (ROC) analysis for estimation of diagnostic accuracy at cut-off value of 30 ng/mL for DOACs.

Drug	Drug conc. at FP LA Median (IQR)	Drug conc. at neg. LA Median (IQR)	LA ratio at FP LA Median (IQR)	LA ratio at neg. LA Median (IQR)	AUC (95%CI)	Se (%) (95%CI) at drug conc. >30 ng/mL	Sp (%) 95%CI at drug conc. >30 ng/mL
Dabigatran, n=59 FP LA = 37 Neg. LA= 22	148 (53-250)	101 (19-168)	1.61 (1.47-1.77)	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		P<0.001		P=0.106		
Apixaban, n=28 FP LA = 10 Neg. 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
	P=0.280		P<0.001		P=0.277		
Rivaroxaban, n=70 FP LA = 55 Neg. 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
	P<0.001		P<0.001		P<0.001		

AUC = area under curve; 95%CI = 95% confidence interval; LA = lupus anticoagulant; FP = false positive; Neg = negative; IQR = interquartile range; Se= sensitivity; Sp = specificity, IQR = interquartile range

CONCLUSIONS

Based on the normal dRVVT result expressed as LA ratio, it is not possible to exclude low concentration (<30 ng/mL) of dabigatran and apixaban, whereas normal LA ratio could be potentially useful for excluding low concentration of rivaroxaban.

CONTACT INFORMATION margeticsandra@gmail.com