Effect of direct oral anticoagulants on dilute Russell´s viper venom time screen and confirm assays for lupus anticoagulant testing

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BACKGROUND

Direct oral anticoagulants (DOACs) strongly affect a wide variety of specialized coagulation assays. Among them, dilute Russell´s viper venom time screen (dRVVTs) and confirm (dRVVTc) assays, key to the investigation of lupus anticoagulant (LA), are particularly sensitive to DOACs. Thus, results of LA testing could be misinterpreted, mostly due to its false positive identification, in patients treated with DOACs.

AIM

The aim of this study was to investigate the impact of all three DOACs, dabigatran, rivaroxaban and apixaban, on both dRVVTs and dRVVTc assays for LA testing.

MATERIALS AND METHODS

Patients plasma samples:
dabigatran (N = 57); rivaroxaban (N = 58); apixaban (N = 28)

Innovance DTI assay – dabigatran concentration

Innovance anti–FXa assay calibrated with rivaroxaban/apixaban – rivaroxaban/apixaban concentration

LA screening assay
LA confirm assay
LA ratio - LA screen/LA confirm (cut off > 1.37 for positive)

BCSXP coagulation analyzer, Siemens Healthineers reagents, Hyphen Biomed rivaroxaban/apixaban calibrators

MedCalc v11.5.1 statistical analysis

RESULTS

Table 1. Results of dilute Russell´s viper venom time screen (dRVVTs) and confirm (dRVVTc) assays and LA ratio in patients treated with dabigatran, rivaroxaban and apixaban.

DOAC drug	DOAC conc. (ng/mL)		dRVVT screen (LA1) (s)	dRVVT confirm (LA2) (s)	LA ratio (LA1/LA2)
Dabigatran N = 57	142 (84 - 171) 36 - 246		83 (68 - 103) 61 - 109	63 (51 - 72) 44 - 80	1.23 (1.20 - 1.27) 1.19 - 1.27
Rivaroxaban N = 58	118 (22 - 183) 16 -211		66 (50 - 101) 44 - 115	39 (36 - 64) 35 - 70	1.48 (1.23 - 1.90) 1.19 - 1.97
Apixaban N = 28	117 (84 - 204) 80 - 223)		68 (60 - 73) 55 - 73	52 (47 - 59) 42 - 60	1.24 (1.12 - 1.57) 1.09 - 1.58
P	Dabi/Riva	0.813	0.195	0.055	**0.014**
	Dabi/Api	0.460	**0.048**	0.181	0.862
	Riva/Api	0.333	0.931	0.225	**0.039**

Concentrations of all three DOACs were not significantly different among all patients investigated for LA.

LA ratio was significantly higher in patients treated with rivaroxaban compared to patients treated with dabigatran and apixaban.

Proportion of FP LA results was significantly higher in patients treated with rivaroxaban compared to patients taking apixaban (P=0.026).
Proportions of FP results between patients taking dabigatran and rivaroxaban, as well as in those taking dabigatran and apixaban were not significantly different (P=0.307 and P=0.214).
dRVVTs assay is more affected than dRVVTc assay, although significant difference for dRVVTs assay between FP and true negative (TN) results of LA testing was obtained for dabigatran and rivaroxaban, but not for apixaban.
The results of dRVVTc assay showed significant difference between FP and TN for rivaroxaban only.

Table 2. Results of dRVVT screen (LA1), dRVVT confirm (LA2) and LA ratio (LA1/LA2) in patients treated with dabigatran, rivaroxaban and apixaban divided according to LA positive and negative test results.

DOAC drug	DOAC konc. (ng/mL)		dRVVT screen (LA1) (s)		dRVVT confirm (LA2) (s)		LA ratio		Proportion of LA Positive
Dabigatran N = 57	Pos. LA (N = 33)	Neg. LA (N = 24)	Pos. LA	Neg. LA	Pos. LA	Neg. LA	Pos. LA	Neg. LA	33/57 0.56
	166 (100 - 279) 101 - 276	101 (33 – 167) 29 – 187	110 (84 – 134) 84 – 135	68 (58 – 85) 55 - 90	70 (42 – 95) 41 – 95	55 (48 – 69) 44 - 72	1.52 (1.4 – 1.6) 1.4 – 1.6	1.20 (1.2 – 1.3) 1.2 – 1.3	
	P = 0.066		**P = 0.004**		P = 0.242		**P < 0.001**		
Rivaroxaban N = 58	N = 39	N = 19							39/58 0.67
	191 (163 - 255) 122 – 289	49 (6 - 104) 6 – 112	110 (82 - 119) 67 – 123	41 (38 - 46) 38 - 47	61 (56 – 66) 54 – 72	37 (35 - 39) 35 - 39	1.94 (1.7 – 2.0) 1.7 – 2.0	1.15 (1.1 – 1.2) 1.1 – 1.2	
	P < 0.001		**P < 0.001**		**P < 0.001**		**P < 0.001**		
Apixaban N = 28	N = 11	N = 17							11/28 0.39
	177 (122 – 314) 164 – 348	93 (63 – 207) 62 – 216	76 (58 – 109) 63 -88	66 (52 – 70) 53 – 70	46 (35 – 66) 38 – 56	57 (49 – 69) 49 - 68	1.60 (1.6 – 2.0) 1.6 – 1.8	1.10 (0.9 – 1.2) 0.9 – 1.2	
	P = 0.086		P = 0.101		P = 0.152		**P < 0.001**		

All data are presented as median (95%CI) and interquartile range (IQR)

CONCLUSION

dRVVTs assay is the most sensitive test to the presence of all three DOACs. LA testing should not be performed in patients taking DOACs, as these drugs may cause false positive results in high proportion of patients.

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