Effect of Activated Charcoal in Removing Interference in Thrombophilia Assays: Resistance to Activated Protein C, Activity of Coagulation Factor VIII and Antithrombin Activity

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Background: Treatment with direct oral anticoagulants (DOACs) has significant interfering effect on results of many specialized coagulation tests, such as thrombophilia assays, due to possible false negative (FN) or false positive (FP) results.

Aims: To investigate the impact of DOACs (dabigatran, rivaroxaban and apixaban) on thrombophilia assays: resistance to activated protein C (APCR), coagulation factor VIII (FVIII) and antithrombin (AT) activities and to evaluate the efficiency of our own optimized method using activated charcoal (AC) in removing interference.

Methods: DOACs concentrations and thrombophilia assays were firstly determined in native patient plasma samples (total n=65). Secondly, 100 mg of medical AC powder (Jadran Galenski laboratorij, Rijeka, Croatia) was added to 500 µL plasma allowing DOACs adsorption for 10 minutes. Treated samples were centrifuged 20 minutes at 1800xg and all measurements were repeated in supernatant. All assays were performed using commercial methods on BCSXP analyzer (Siemens Healthineers, Germany): Innovance anti-FXa assay with drug specific calibrators for rivaroxaban and apixabann (Hyphen BioMed, France); Innovance DTI assay for dabigatran; ProC Global for APCR; one-stage coagulation assay for FVIII and Innovance Antithrombin for AT activities. Wilcoxon test was used to test differences between pairs of samples. The study was funded by the Croatian Science Foundation as part of the research project IP- 2016-06-8208.

Results: All three DOACs have shown significant and different interfering effect on particular thrombophilia assays evaluated in this study (Table 1), indicating that most of these assays could not be performed in patients on DOACs, and suggesting the effective solution in removing interference by application of procedure with AC (Figure 1). In AC treated samples, concentrations of DOACs were below limit of detection.

Conclusions: AC has been found an effective in vitro agent to overcome effect of dabigatran, rivaroxaban and apixaban on particular thrombophilia assays, confirming potential of AC application before testing in patients treated with DOACs.

Direct oral anticoagulants (DOACs)	DOAC conc. before AC addition Median	DOAC conc. after AC addition Median (95%CI), IQR	APCR normalized ratio Positives < 0.86 (n, ratio)	AT activity (%) Median (95%CI), IQR	FVIII activity (%) Median (95%CI), IQR

	(95%CI), IQR							
			Before AC	After AC	Before AC	After AC	Before AC	After AC
Dabigatran n = 24	120 (86 – 186) 70 – 203	<2.8	23 (0.96)	0 (0)	NA	NA	106 (84 – 121) 76 – 129	161 (150 – 171) 149 – 174
P			<0.001		NA		<0.001	
Rivaroxaban n = 13	168 (33 – 238) 39 – 237	<5.9	11 (0.85)	2 (0.15) both true positives	106 (101 – 123) 101 – 122	95 (85 – 98) 86 – 98	130 (115 – 150) 117 – 150	135 (121 – 152) 121 – 152
P			<0.001		0.001		0.787	
Apixaban n = 28	151 (127-182) 108 -203	<4.1	11 (0.73)	0 (0)	116 (109 125) 107 – 129	94 (90 – 104) 89 – 106	202 (176 – 206) 167 – 206	199 (168 – 206) 159 – 206
P			<0.001		<0.001		0.599	

[Table 1. Results of thrombophilia assays (APCR, FVIII, AT) before and after addition of medical activated charcoal (AC) in patients treated with DOACs]

[Figure 1. Interpretation and recommendation of thrombophilia assays (APCR, AT, FVIII) in patients on DOACs and with activated charcoal application]

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