INTER-INDIVIDUAL VARIABILITY OF PEAK AND TROUGH PLASMA CONCENTRATIONS OF DABIGATRAN, RIVAROXABAN AND APIXABAN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

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SCIENTIFIC RESEARCH INFORMATION Inter-individual variability of both peak and trough plasma concentrations of direct oral anticoagulants (DOACs), dabigatran, rivaroxaban and apixaban, is still insufficiently investigated. Therefore, the aim of our study was to assess inter-individual variability of peak and trough plasma levels of all three DOACs in patients with non valvular atrial fibrillation (NVAF).

METHODOLOGY The study included plasma samples from patients treated with dabigatran (N = 106, 150 mg twice-daily), rivaroxaban (N = 123, 20 mg once-daily) and apixaban (N = 69; 5 mg twice-daily). Blood samples were taken on the same day to obtain both trough (immediately prior the next drug dose) and peak (two hours after drug administration) DOACs concentrations. Both rivaroxaban and apixaban were measured using chromogenic anti-FXa assay (Innovance anti-FXa, Siemens Healthineers, Germany) calibrated with drug specific calibrators (Hyphen BioMed, France). Dabigatran was measured using commercial chromogenic method (Innovance DTI assay, Siemens Healthineers, Germany). All coagulation assays were performed on Behring Coagulation System XP (BCSXP) analyzer (Siemens Healthineers, Germany). Statistical analysis was done using Mann-Whitney test by MedCalc Statistical Software version 11.5.1. The inter-individual variability for trough and peak concentrations was assessed by calculating mean values and standard deviation (SD) for each DOAC concentration measured for all samples. The study was funded as an integral part of the Croatian Science Foundation research project IP-2016-06-8208, entitled New oral anticoagulants: relationship between drug concentration and anticoagulant effect.

FINDINGS

Table 1. Peak and trough concentrations and associated inter-individual variability for dabigatran, rivaroxaban and apixaban in NVAF patients

	Number of measure-ments	Dosing regimen	Measured conc. (ng/mL) Median (95%CI) IQR; range (min.-max)	P	Published expected values* (ng/mL)	Measured conc. mean ± SD (ng/mL)	Inter-individual variability (CV%)
Dabigatran peak	106	150 mg twice daily	138 (109-172) 65-246 (3-473)	<0.001	175 117 - 275	164 ±114	69.6
Dabigatran trough	106		55 (44-68) 21-107 (0-292)		91 61 - 143	74 ±71	95.0
Rivaroxaban peak	123	20 mg once daily	165 (147-189) 118-212 (13-468)	<0.001	249 184 - 343	178 ±89	50.3
Rivaroxaban trough	123		14 (12-16) 9-29 (1-311)		44 12 - 137	34 ±51	149.0
Apixaban peak	69	5 mg twice daily	182 (165-202) 141-226 (56-396)	<0.001	171 91 - 321	188 ±75	40.0
Apixaban trough	69		100 (82-120) 59-136 (10-259)		103 41 - 230	105 ±54	51.0

*Gosselin RC et al . International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. Thromb Haemost 2018;118:437-50

CONCLUSIONS Our study showed a relatively high inter-individual variability for all three DOACs in NVAF patients. The overall inter-individual variability for all three DOACs are lower at peak than at trough plasma concentrations. Further, among all three DOACs, apixaban showed the lowest inter-individual variability for both peak and trough concentrations. Relatively high inter-individual variability of peak and especially for trough concentrations of all three DOACs suggests that single measurement of these drugs not to be sufficient for reliable estimation level of anticoagulation.

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