

Is Low Molecular Weight Heparin-Calibrated Chromogenic Anti-Xa Assay Suitable for Assessing Anticoagulant Effect of Apixaban in Adolescents?

L. Čelap¹, S. Margetić¹, R. Mihić¹, J. Obuljen², I. Linarić², J. Leniček Krleža²

¹University Hospital Centre Sestre Milosrdnice, Department of Clinical Chemistry, Zagreb, Croatia,

²Children's Hospital Zagreb, Department of Laboratory Diagnostics, Zagreb, Croatia

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Background: Although clinical application of apixaban does not require coagulation monitoring, there are clinical situations in which measurement of drug concentration should be performed. Anti-activated factor Xa (anti-FXa) inhibition methods for all anti-FXa drugs are based on the same principle, so there are attempts to evaluate potential clinical application of heparin-calibrated anti-FXa assay as an alternative method for direct FXa inhibitors.

Aims: To assess whether commercial low molecular weight heparin (LMWH)-calibrated anti-FXa assay can be used for assessing anticoagulant effect of apixaban in adolescents.

Methods: LMWH-calibrated anti-FXa method (Innovance heparin, Siemens Healthineers, Germany) was used for measurement of LMWH anti-FXa activity. Innovance heparin (Siemens Healthineers, Germany) calibrated with apixaban calibrators (Hyphen BioMed, France) was used for quantitative determination of apixaban concentration. Agreement between LMWH and apixaban calibrated anti-FXa assays was tested using kappa statistics whereas receiver operating characteristics (ROC) analysis was performed for LMWH therapeutic range. The study was funded by the Croatian Science Foundation as part of the research project IP-2016-06-8208.

Results: In 36 plasma samples of 11 adolescents (13-22 years), concentrations of apixaban ranged from 20 ng/mL to 267 ng/mL (median 94 ng/mL). LMWH anti-FXa activity ranged from 0.11 to 1.50 (upper LMWH measuring range) (median 0.68 IU/mL) (Table 1).

	Median (95%CI) IQR
Apixaban concentration (ng/mL)	94 (69 – 107) 52 – 136
LMWH anti-FXa activity (IU/mL)	0.68 (0.47 – 0.85) 0.28 – 1.00

[Table 1. Results of apixaban concentration and low molecular weight heparin (LMWH) activity in paired samples in adolescents]

Inter-rater agreement analysis showed poor agreement ($\kappa=0.16$; 95%CI – 0.0327 to 0.3386) between therapeutic range of LMWH-calibrated anti-FXa activity and clinically relevant apixaban concentrations (>30

ng/mL) (Table 2). ROC analysis showed that only apixaban concentrations between 57 and 121 ng/mL could be expected with certainty within therapeutic range for LMWH anti-FXa activity. Cut-off value for LMWH anti-FXa activity for apixaban concentrations < 30 ng/mL is 0.12 IU/mL.

LMWH therapeutic range 0.4 – 1.1 IU/mL	Apixaban <30 ng/mL	Apixaban >30 ng/mL	Number (ratio)
< 0.4	2	8	10 (0.28)
0.4 -1.1	0	19	19 (0.53)
>1.1	0	7	7 (0.19)
Kappa = 0.16 95%CI = -0.0327 to 0.3386	2	34	36

[Table 2. Results of agreement between therapeutic range for LMWH anti-FXa activity and apixaban concentration at cut-off value of 30 ng/mL.]

Conclusions: LMWH anti-FXa activity assay is not appropriate method for quantitative estimation of apixaban concentration and should not be used as an interchangeable method. Quantitative measurement of apixaban concentration should be performed in all clinical situations.

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