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Full Length Article

Point of Care Testing (POCT) to assess drug concentration in patients treated with non-vitamin K antagonist oral anticoagulants (NOACs)

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ABSTRACT

Background: Non–vitamin K antagonist oral anticoagulants (NOACs) do not need routine laboratory monitoring but measurement of drug concentration is important in emergency conditions. Specific laboratory tests are not readily available or not implemented in every hospital. Point-of-Care Tests (POCT) may bridge this gap and be used as a bedside solution.

Objectives: Feasibility of POCT to assess plasma levels of dabigatran, rivaroxaban and apixaban.

Patients/methods: Activated Coagulation Time-Low Range (ACT - LR) using a portable Hemochron Signature Elite for dabigatran and prothrombin time (expressed as INR) by Coaguchek XS Pro for rivaroxaban and apixaban were obtained at trough and peak in 136 consecutive patients taking NOACs (70 on dabigatran, 45 on rivaroxaban and 20 on apixaban). Using a paired study design, drug concentrations were concurrently determined by functional specific tests.

Results and conclusions: The correlation between NOACs concentration and the values obtained using the POCTs was high for dabigatran and rivaroxaban (r = 0.80 and r = 0.82, respectively) and low for apixaban (r = 0.21). ACT-LR ≤ 188 s better detected dabigatran levels ≤ 50 ng/ml, with a sensitivity of 87.5% and a specificity of 84.1%. ACT-LR values > 217 s better discriminated value of dabigatran > 200 ng/ml, with a sensitivity of 86.7% and a specificity of 81.4%. INR Coaguchek values ≤ 1.2 better identified patients with rivaroxaban values < 100 ng/ml, with sensitivity of 90%, specificity of 88.5%. This analysis was not possible for apixaban.

Conclusion: In emergency situations POCT use may provide useful immediate information on dabigatran and rivaroxaban concentration.

1. Introduction

Non–vitamin K antagonists oral anticoagulants (NOACs) are widely used in patients with atrial fibrillation (AF) and venous thromboembolism. Currently, four NOACs are available, i.e. a direct thrombin inhibitor (dabigatran etexilate) [1] and three direct Factor Xa (FXa) inhibitors (apixaban, edoxaban and rivaroxaban) [2–4].

The main advantage of NOACs resides in their use at fixed doses without routine monitoring [5]. However, measuring drug concentration may be useful in emergency situations such as active bleeding, urgent surgery, ischemic stroke requiring thrombolysis or drug overdose [6]. Different specific tests are available: diluted Thrombin Time (dTT) and Ecarin Clotting Time (ECT) are considered the tests of choice for the determination of dabigatran concentration [7,8]. On the other hand, a specific calibrated anti Xa assay is recommended for the determination of rivaroxaban, apixaban and edoxaban concentrations [7,8]. These specific tests are not implemented in every hospital and might be time consuming, thus, a readily available drug concentration tool would be worth. The aim of our study was to examine whether an appropriate Point of Care Test (POCT) can provide reliable information about NOACs concentration to get a ready to use information in critical/emergency situations.

2. Methods

2.1. Study design and settings

This is a single centre, paired study design. All consecutive patients starting NOACs (naïve or shifted from classic anticoagulants) followed in an anticoagulation clinic affiliated to a tertiary level university

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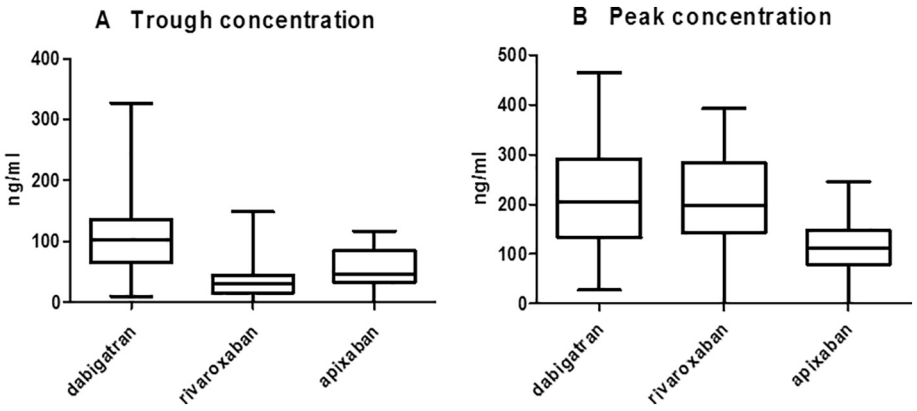

Fig. 1. Trough (A) and peak (B) concentration of dabigatran, rivaroxaban and apixaban.

hospital were included. Patients treated with edoxaban were not included because, at the time of the study, this drug had just been introduced into Italian market. Informed consent was obtained from all patients.

2.2. Sample collection

Blood samples were collected at steady state after a period varying from 2 to 4 weeks since initiation of NOACs therapy. Blood samples were collected at trough level (12 h after intake for dabigatran and apixaban and 24 h for rivaroxaban) and at peak level (2–4 h after drug intake). Blood was drawn with minimal stasis in 0.019 M sodium citrate (9:1) and plasma was obtained after centrifugation at 2000*g* for 10 min and stored at −30 °C until used. A direct finger puncture using a lancing device was used for POCT tests.

2.3. Laboratory tests

The Activated Clotting Time - Low Range (ACT-LR) for the determination of dabigatran activity was obtained with the portable meter Hemochron Signature Elite (Cremascoli & Iris, Milan, Italy). Prothrombin Time (International Normalized Ratio, INR Coaguchek) for the determination of rivaroxaban and apixaban activity was determined with Coaguchek XS Pro (Roche Diagnostics, Monza, Italy). The functional specific tests to obtain the plasma concentration of the three NOACs were Hyphen Hemoclot for dabigatran (modified diluted Thrombin Time, Dasit, Milan, Italy) and Hyphen DiXal for rivaroxaban and apixaban (chromogenic anti Xa, Dasit, Milan, Italy). All these tests were calibrated using commercial plasmas from the same supplier and analysed on Sysmex CA 7000 (Siemens Health Care, Milan, Italy). Activated thromboplastin time (aPTT, Actin FS Siemens) and prothrombin time (PT-INR, Innovin, Siemens) in plasma samples were determined on Sysmex CA 7000 (Siemens Health Care, Milan, Italy).

2.4. Definition of clinically relevant NOACs concentration

A clear definition of therapeutic concentration of NOACs is lacking. In the RELY study the relative risk of ischemic stroke was increased by 50% at dabigatran plasma level of 28 ng/ml while the rate of major bleeding was doubled at a concentration of 210 ng/ml [9]. Concentration of dabigatran < 50 ng/ml, rivaroxaban < 100 ng/ml and apixaban < 10 ng/ml are considered as safe to allow thrombolysis in treatable stroke patients [10]. We analysed the performance of POCT to detect the values < 50 ng/ml for dabigatran and values < 100 ng/ml for rivaroxaban as well as values of dabigatran concentration > 200 ng/ml.

2.5. Statistics

NOACs concentrations obtained by specific tests at trough and at peak concentrations are expressed as median and interquartile ranges. Results obtained by ACT-LR (seconds) and Coaguchek (INR) were compared to NOACs plasma concentration by linear regression analysis. Receiver operating characteristic curve (ROC curve) was used to illustrate the performance of POCT at relevant cut-off points. Sensitivity and specificity, positive and negative predictive values at the defined cut-off points were expressed accordingly.

GraphPad Software (San Diego, CA, USA) was used for statistical analysis and a two-sided p-value ≤ 0.05 was considered as statistically significant.

3. Results

From October 2013 to October 2015, one hundred thirty six consecutive patients were considered and accepted to participate in the study. One patient taking dabigatran was excluded for incorrect timing adherence (drug was taken 24 h before sample collection). Patients taking NOACs were distributed as follows: 70 on dabigatran, 45 on rivaroxaban and 20 on apixaban.

Median trough values were 102 (IQR 65–136.5) ng/ml, 30.5 (IQR 15.5–44.7) ng/ml and 46.5 (IQR 33.5–84.5) ng/ml for dabigatran, rivaroxaban and apixaban, respectively. Median peak values were 206 (IQR 134–292) ng/ml, 198.5 (IQR 142.8–283.3) ng/ml and 111.5 (IQR 79.2–147.8) ng/ml for dabigatran, rivaroxaban and apixaban, respectively (Fig. 1).

Trough and peak values were combined to compute the correlation analysis with POCT results. The linear regression between dabigatran concentration (determined by dTT) and the values obtained using the POCT ACT-LR (seconds) was r = 0.80 (Fig. 2A). The linear regression between rivaroxaban and apixaban plasma levels (determined by anti-Xa assays) and the values obtained using the POCT (INR Coaguchek) were r = 0.82 and r = 0.21, respectively (Fig. 2B and C). The linear regression was also calculated for NOACs concentration and common coagulation tests (aPTT for dabigatran and PT-INR for rivaroxaban and apixaban). Results were r = 0.73, r = 0.76 and r = 0.31 for dabigatran, rivaroxaban and apixaban, respectively.

The evaluation of ACT-LR as diagnostic tool by ROC curve for low and high threshold levels of dabigatran (50 ng/ml and 200 ng/ml) are shown in Figs. 3 and 4.

Area under the curve for ACT-LR using a cut off value of dabigatran of 50 ng/ml is 0.92 (95% CI, 0.861 to 0.958, p < 0.0001), significance level (Fig. 3). ACT-LR ≤ 188 s, better detected dabigatran levels < 50 ng/ml, with a sensitivity of 87.5% and a specificity of 84.1%. Positive predictive value is 41% and negative predictive value is 97%. As shown in Fig. 4, the area under the curve for ACT-LR using a cut-off value of 200 ng/ml is 0.89 (95%CI, 0.821 to 0.933, p < 0.0001). ACT-