Introduction

Rivaroxaban is an oral, direct Factor Xa inhibitor that has been approved for the prevention and treatment of thromboembolic disorders.

Unlike some traditional anticoagulants, routine coagulation monitoring is not required with rivaroxaban owing to its predictable pharmacokinetics and pharmacodynamics. In clinical practice, measurement of rivaroxaban exposure may be used in some circumstances (e.g., prior to urgent surgery).

Studies have indicated that routine clotting assays are not suitable for the quantitative measurement of rivaroxaban exposure, and anti-Factor Xa chromogenic assays have been identified as potential assays for the measurement of rivaroxaban plasma concentrations.

Objective

To evaluate the suitability of anti-Factor Xa chromogenic assays for the measurement of rivaroxaban plasma concentrations (ng/ml) using rivaroxaban calibrators and controls, and to assess the intra-laboratory precision of the measurement.

Methods

Twenty-four centres in Europe and North America were provided with:

- A set of rivaroxaban calibrators containing 41, 209 and 422 ng/ml rivaroxaban.
- A set of pooled human plasma controls containing 20, 199 and 662 ng/ml rivaroxaban. The concentrations of rivaroxaban in the pooled human plasma controls were unknown to the participating laboratories.

The evaluation was carried out over 10 days by each laboratory using local anti-Factor Xa chromogenic assays (Table 1) as well as the centrally provided reagent, a modified STA Rotachrom® assay.

Day-to-day precision and accuracy were evaluated by producing a calibration curve each day and by testing in duplicate three pooled human plasma controls.

The control plasma sample containing the highest concentration of rivaroxaban was diluted with rivaroxaban calibrator containing 5 ng/ml rivaroxaban (1:3 dilution) and re-tested if the measured level was above the highest concentration limit of the calibration curve.

The rivaroxaban concentrations in the three control plasma samples were calculated from linear calibration curves generated using rivaroxaban calibrators by each participating laboratory.

Results

Inter-laboratory precision of the measurements (Table 2):

- Local anti-Factor Xa reagents: the mean rivaroxaban concentrations (measured/calculated) were 17.2 (20 ng/ml), 199 (199 ng/ml) and 656 (662 ng/ml; diluted sample) ng/ml, and the coefficient of variation (CV) was 30.3, 10.9% and 10.0%, respectively.

- Intra-laboratory precision of the measurements (Table 2):

  - Local anti-Factor Xa reagents: the CV was 27.7% (20 ng/ml), 4.0% (199 ng/ml) and 5.8% (662 ng/ml; diluted sample), respectively.

  - Modified STA Rotachrom® method: the CV was 12.3% (20 ng/ml), 5.1% (199 ng/ml) and 5.8% (662 ng/ml; diluted sample), respectively.

  - Median rivaroxaban concentrations in all control plasma samples are shown in Figure 1 (using local reagents) and Figure 2 (using the modified STA Rotachrom® test set-up) for each participating laboratory.

Conclusions

The anti-Factor Xa chromogenic method can be used to assess rivaroxaban exposure (expressed in ng/ml), and the method is suitable for measuring a wide range of rivaroxaban plasma concentrations (approximately 20-660 ng/ml), with the use of rivaroxaban calibrators and controls.

Low rivaroxaban concentrations can be measured with acceptable inter-laboratory precision with the use of a modified anti-Factor Xa method (the modified STA Rotachrom® test set-up).

Further validation of these methods would be helpful in clinical settings.

References