

Rivaroxaban Calibrator And Control Sets Measuring Rivaroxaban Plasma Concentrations Using The Prothrombin Time

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Background: Rivaroxaban is an oral, direct Factor Xa inhibitor which is marketed in more than 60 countries for the prevention of venous thromboembolism and is under development for the prevention and treatment of arterial and venous thromboembolic diseases. No routine coagulation monitoring is required, but the rivaroxaban plasma concentration might be needed in some cases, i.e. severe overdose or compliance. Variation in the response sensitivity of prothrombin time (PT) reagents to rivaroxaban is well described in the literature and the international normalized ration correction of results can not be used to correct for this variability. **Aims:** This multicentre study evaluated rivaroxaban calibrators and the PT for the measurement of rivaroxaban plasma concentrations. The interlaboratory precision of the measurement of rivaroxaban plasma concentrations (ng/ml) was also evaluated. **Methods:** 20 centres were provided with a set of rivaroxaban calibrators (0, 41, 219 and 430 ng/ml) and a set of unknown rivaroxaban pooled human plasma controls (19, 160 and 643 ng/ml). The evaluation was carried out over 10 consecutive days by each laboratory using its own PT reagent as well as STA[®] Neoplastine CI Plus, Diagnostica Stago. A rivaroxaban calibration curve was produced daily. The day-to-day precision was evaluated by testing in duplicate three plasma controls. The control was diluted and re-tested if the level was above the highest concentration of the calibration curve. **Results:** A large interlaboratory variation (in seconds) was shown for the controls when local PT reagents were used, and their coefficient of variation (CV) was 14 to 30%; but the

results were more consistent when using the same PT reagent with a CV of <6% (with undiluted samples). Expressed in ng/ml, a smaller interlaboratory variation was observed (CV ranging from 2% for the highest to 7.5% for the lowest). In addition, the CV for the 41 ng/ml calibrator with the central reagent was 4.4%, and the results were reliable for concentrations >40 ng/ml and up to 600 ng/ml.

Summary/conclusions: Rivaroxaban measurements may be of assistance when determination of its plasma concentrations is required. The results indicate that the PT expressed in seconds cannot be used to measure rivaroxaban activity in plasma due to the large variation in the sensitivity of different reagents to rivaroxaban; Rivaroxaban concentrations can be measured with acceptable precision by using a rivaroxaban calibration curve with reliable estimation for concentrations >40 ng/ml using both local PT reagents and STA Neoplastine CT Plus. Further validation of these methods in plasma samples obtained from patients with specific clinical events such as hemorrhage, recurrent thromboembolism or suspected overdose.

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