Introduction

In recent years, new anticoagulants targeting individual components of the coagulation cascade have been developed. Those that target thrombin and Factor Xa (FXa) seem to be the most promising.1

Objective

To identify a widely available assay (clotting, 0.010 0.15 0.20) that could be used in clinical practice to measure the pharmacodynamic effects of rivaroxaban in special situations.

Effects of the Novel, Oral, Direct Factor Xa Inhibitor Rivaroxaban on Coagulation Assays

Introduction

In recent years, new anticoagulants targeting individual components of the coagulation cascade have been developed. Those that target thrombin and Factor Xa (FXa) seem to be the most promising.1

Methods

Increasing concentrations of rivaroxaban were spiked into citrated pooled human plasma-poor platelet plasma (PPP) – a number of global and matrix clotting assays were performed. In addition, the inhibition of FXa activity was measured, based on chromogenic assays and the fluorogenic thrombin generation test (TGT).

Prothrombin Time

Prothrombin time (PT) was assessed by mixing 50 µL of PPP with 50 µL of STA-PTT® reagent used. International normalized ratio (INR) change during storage (Table 1)

Table 1. Comparison of PT ratio at baseline (fresh) day 0 versus frozen plasma (median values for day 4, 17, 30, and 60) spiked with rivaroxaban.

<table>
<thead>
<tr>
<th>Rivaroxaban (µg/mL)</th>
<th>Fresh</th>
<th>PT</th>
<th>PT</th>
<th>PT</th>
<th>PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.5</td>
<td>1.15</td>
<td>1.19</td>
<td>1.09</td>
<td>1.10</td>
</tr>
<tr>
<td>50</td>
<td>0.7</td>
<td>1.15</td>
<td>1.19</td>
<td>1.09</td>
<td>1.10</td>
</tr>
<tr>
<td>150</td>
<td>1.25</td>
<td>1.19</td>
<td>1.09</td>
<td>1.10</td>
<td>1.05</td>
</tr>
<tr>
<td>450</td>
<td>1.92</td>
<td>1.19</td>
<td>1.10</td>
<td>1.10</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Results

Rivaroxaban increased the dRVVT ratio concentration-dependently (Table 1). A concentration of 0.12 µg/mL rivaroxaban was required to double clotting time.

Thrombin Generation

TGT was assessed by a calibrated automated thrombometer with the Thromboreg® software (Synapse BV, Maastricht, The Netherlands).

Conclusions

Although there is no requirement for routine coagulation monitoring with rivaroxaban, an appropriate coagulation assay should be available.

PT assays using a chromogenic assay are likely to be the most valuable assay for monitoring the pharmacodynamic effects of rivaroxaban in a standardized manner.

References and Disclosures

8. This study was supported by Bayer HealthCare AG and the U.S. and India pharmaceutical 8. and Clinical Pharmacology, C.L.L. (Staging, Asnières, France), Stagco, Innovin 8. and C.H., S.B., and L.M.A., respectively (Stagco, Innovin 8. in France, France, and Stagco, Asnières, France).

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Figure 1. Influence of rivaroxaban on thrombin generation test.

Figure 2. Influence of rivaroxaban on activated partial thromboplastin time (aPTT) with two different cephalins (expressed in ratio versus baseline).

Figure 3. (A) Influence of rivaroxaban on HepTest and (B) dip-tissue factor prothrombinase time (dPT) with two different cephalins (expressed in ratio versus baseline).

Figure 4. Influence of rivaroxaban on the thrombin generation test.

Figure 5. (A) Influence of rivaroxaban on prothrombinase time (PT) and (B) dip-tissue factor prothrombinase time (dPT) with two different thromboplastins (International sensitivity index value in brackets, expressed as ratio versus baseline).

Figure 6. (A) Influence of rivaroxaban on HepTest and (B) dip-tissue factor prothrombinase time (dPT) with two different cephalins (expressed in ratio versus baseline).

Figure 7. Influence of rivaroxaban on the thrombin generation test.

Figure 8. Influence of rivaroxaban on activated partial thromboplastin time (aPTT) with two different cephalins (expressed in ratio versus baseline).

Figure 9. Influence of rivaroxaban on prothrombinase time (PT) and (B) dip-tissue factor prothrombinase time (dPT) with two different cephalins (International sensitivity index value in brackets, expressed as ratio versus baseline).

Figure 10. Influence of rivaroxaban on activated partial thromboplastin time (aPTT) with two different cephalins (expressed in ratio versus baseline).