Rivaroxaban, an Oral, Direct Factor Xa Inhibitor, Increases the Thrombolytic Potential of Tissue Plasminogen


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Introduction

- Impaired fibrinolysis is a risk factor for venous thrombosis,1 and potentially also for arterial thrombosis, because it occurs more often in patients who have had a myocardial infarction.
- The risk for developing a venous thrombosis is increased when impaired fibrinolysis is associated with another risk factor, such as the use of hormonal contraceptives, immobilization, and the presence of the Factor V Leiden mutation.
- Impaired fibrinolysis can be due to different causes, which include:
  - Decrease in the production of tissue plasminogen activator (t-PA)
  - Increase in the levels of fibrinolytic inhibitors, such as thrombin-activatable fibrinolysis inhibitor (TAFI)
  - Modification of the clot structure, rendering the clot less accessible to fibrinolytic enzymes.
- Pharmacologic approaches to increasing fibrinolysis are therefore an interesting strategy for prevention and treatment of thromboembolic disorders, and could consist of:
  - Modifying clot structure so that the clot becomes more permeable to fibrinolytic enzymes
  - Decreasing fibrinolytic inhibitor activity, particularly that of TAFI, which prevents the binding of plasminogen to t-PA
  - Rivaroxaban, an oral, direct Factor Xa inhibitor, inhibits thrombus formation and growth in human plasma.2
- Rivaroxaban has recently been approved in the European Union and Canada for the prevention of venous thromboembolism in patients undergoing elective hip or knee replacement surgery.

Methods

- Plasma clots were formed in the absence (control clot) and presence of rivaroxaban at therapeutic concentrations (0.15 and 0.25 µg/mL).
- Clot permeability was evaluated by measuring the flow rate through fibrin clots perfused with N,O-dimethyl formamide in order to obtain a 3D reconstruction of the fibrin network.
- Clot permeability was calculated as the ratio of fibrinogen concentration, fiber diameter, and mass-length ratio.
- The degradation of clots by t-PA was evaluated by measuring the amount of fibrin D-dimer fragments in the eluates of perfused clots
- Rivaroxaban improved t-PA-mediated thrombolysis through a decrease in thrombin generation, two mechanisms were involved: modulation of clot structure, decrease in thrombin generation leads to highly permeable fibrin clots.

Results

- Confluent microscopy showed that clots formed in the presence of rivaroxaban had thinner fibrin and a looser fibrin structure, with larger pores than control clots (Figure 1).
- The modification of the structure of the clot was associated with an increase in the permeation rate.
- The results presented in the table are the mean of five experiments.

Table 1. Physical properties of the clot following clot modification by rivaroxaban

<table>
<thead>
<tr>
<th>Control</th>
<th>Rivaroxaban 0.15 µg/mL</th>
<th>Rivaroxaban 0.25 µg/mL</th>
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</thead>
<tbody>
<tr>
<td>Permeability constant</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>Fibro-meter (µL)</td>
<td>0.84</td>
<td>0.70</td>
</tr>
<tr>
<td>Mass-length ratio (BI/ba)</td>
<td>1.62</td>
<td>2.71</td>
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</tbody>
</table>

- The degradation of clots perfused with a t-PA showed that the modification of the clot structure and increase in clot porosity render clots more susceptible to fibrinolytic enzymes
- In the absence of TM, an increase in fibrinolysis was observed for clots containing 0.15 and 0.25 µg/mL of rivaroxaban added to plasma before clotting; degradation was 3.6- and 3.8-fold higher, respectively, than that of control clots after 90 minutes perfusion with t-PA, as shown by an increased amount of fibrin degradation products (D-dimers) in the eluates of perfused clots.
- In the presence of TM, rivaroxaban still enhanced an increase in fibrin degradation compared with the control, although fibrinolysis was very slightly delayed compared with rivaroxaban alone.
- This experimental system was validated by showing that TM decreased clot degradability in control samples.
- Because the thrombin-TM complex activates TAFI, these results indicate that rivaroxaban indirectly inhibits TAFI activation by inhibition of thrombin generation.

Conclusions

- Rivaroxaban improved t-PA-mediated thrombolysis through a decrease in thrombin generation; two mechanisms were involved:
  - Modification of clot structure, Decrease in thrombin generation leads to highly permeable fibrin clots, composed of thick, loosely woven fibrin strands, which make the clot more accessible to fibrinolytic enzymes
  - Decrease in TAFI activation by the thrombin-TM complex because there is a decrease in the formation of this complex.
- This property of rivaroxaban may contribute to its antithrombotic effects, as demonstrated in clinical studies.

References and Disclosures