Thrombosis and anticoagulant treatment in special populations
Barco, S.L.

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Successful co-administration of dabigatran etexilate and protease inhibitors ritonavir-lopinavir in a patient with atrial fibrillation

Stefano Barco
Michiel Coppens
Erik-Jan van den Dool
Daan van de Kerkhof
An K. Stroobants
Saskia Middeldorp

The direct oral anticogulant dabigatran etexilate has been approved for the prevention of stroke and systemic embolism in individuals with atrial fibrillation, demonstrating to be safe and effective at the dosages of either 110 or 150 mg twice daily\(^1\). After oral intake, dabigatran etexilate is converted to its active form dabigatran, and hydrolyzed by non-specific ubiquitous esterases\(^2,3\). Dabigatran etexilate, but not dabigatran, is a substrate of the intestinal efflux transporter P-glycoprotein. Phase I studies showed that co-administration of P-glycoprotein inhibitors increases dabigatran bioavailability from 1.5-fold (amiodarone) up to 2.5-fold (ketoconazole)\(^2\). High trough concentrations were associated with an increased risk of bleeding in the phase III RE-LY trial\(^3\).

Human immunodeficiency virus protease inhibitors ritonavir and lopinavir are prescribed in many antiretroviral regimens and ritonavir-mediated Cytochrome P4503A inhibition serves to increase lopinavir bioavailability. Ritonavir is also a strong P-glycoprotein inhibitor interfering with many drugs and it may be expected to increase dabigatran exposure. Therefore, their co-administration requires caution\(^2,3\) and is not recommended in some countries\(^5\). A study conducted by the National Institutes of Health is ongoing to characterize dabigatran pharmacokinetics in combination with ritonavir (NCT01896622).

We present the case of a 64-year-old male on ritonavir/lopinavir requiring periprocedural anticoagulation for atrial fibrillation ablation and with a perceived intolerance to vitamin K antagonists. Routine screening tests were within the normal values. The estimated creatinine clearance was 69 mL/min (Cockcroft-Gault equation) and 80 mL/min/1.73 m\(^2\) (4-variable Modification of Diet in Renal Disease Study equation). Patient's personal history included: human immunodeficiency virus-1 infection (1989), chronic asthma, acute coronary syndrome and paroxysmal atrial fibrillation (2006), and two episodes of suspected transient ischemic attacks three years prior to presentation. CHADS\(2\) and CHA\(2\)DS\(2\)-VASC scores for atrial fibrillation stroke risk were 2 and 3, respectively. He had been treated with vitamin K antagonists since the diagnosis of atrial fibrillation and then switched to nadroparin due to poor International Normalized Ratio control and extreme lethargy, which he ascribed to both acenocumarol and phenprocumon. Co-medications were: ritonavir/lopinavir 400/100 mg twice daily, tenofovir, lamivudine, zidovudine, raltegravir, salmeterol inhalation 25 μg twice daily, metoprolol, carbasalate calcium. Apart from P-glycoprotein inhibitors ritonavir and salmeterol\(^6\), co-medications were not known to exert any relevant P-glycoprotein activity. After careful consideration, dabigatran etexilate was chosen for periprocedural anticoagulation on the basis of efficacy and safety profiles comparable to warfarin\(^7\).
Due to the co-administration of two P-glycoprotein inhibitors, we first prescribed the off-label dose of dabigatran etexilate 75 mg twice daily\(^8\), paralleling the United States recommendation for patients with moderate renal impairment receiving either the P-glycoprotein inhibitor dronedarone or ketoconazole\(^3\). Although no therapeutic range is available, a wide target blood concentration range was derived from the RE-LY trial: 28.2-215 ng/mL for trough, and 52-383 ng/mL for peak concentrations\(^4\).

Dabigatran etexilate intake was scheduled one hour after ritonavir/salmeterol at their expected highest inhibitory influence\(^9\). After five days on dabigatran etexilate, blood samples were taken to generate pharmacokinetic and pharmacodynamic curves at steady state. Blood samples were collected from a peripheral line and centrifuged twice (3,000 g, 15 min, 25°C). The following assays were used: dabigatran plasma concentration (liquid chromatography-mass spectrometry; Acquity UPLC BEH C8 column, Acquity TQ Detector, Waters), diluted thrombin time (Hemoclot, Hyphen BioMed), activated partial thromboplastin time (Actin FS, Siemens Healthcare), thrombin time (Thromboclotin, Siemens Healthcare), and activated clotting time (Hemochron Signature Elite, International Technidyne Corporation). After review of the results and 11-day wash-out period from dabigatran etexilate, the patient was started on the approved dose of 110 mg twice daily and the pharmacokinetic and pharmacodynamic curves were repeated.

Plasma steady state trough values after dabigatran etexilate 75 mg twice daily were 29 ng/mL (liquid chromatography-mass spectrometry), 16 ng/mL (diluted thrombin time), and 33 seconds (activated partial thromboplastin time), while peak values were 96 ng/mL, 109 ng/mL, and 41 seconds, respectively. Thrombin time was greater than 120 seconds at all timepoints (Figure 1, Table 1).

After dabigatran etexilate 110 mg twice daily, plasma steady state trough values increased to 51 ng/mL (liquid chromatography-mass spectrometry), 52 ng/mL (diluted thrombin time), and 35 seconds (activated partial thromboplastin time), while peak values were 89 ng/mL, 113 ng/mL, and 40 seconds, respectively. Time to peak concentration was 2 hours for both doses. Activated clotting time showed substantial agreement with plasma concentrations (Figure 1, Table 1).

Atrial fibrillation ablation was performed after 30 days. The patient has been receiving dabigatran etexilate for six months with no complications reported.
Figure 1. Pharmacokinetic and pharmacodynamic curves of dabigatran etexilate 75 and 110 mg twice daily at steady state

Abbreviations: dTT, diluted Thrombin Time (ng/mL); LC-MS/MS, Liquid Chromatography-Mass Spectrometry/tandem Mass Spectrometry (ng/mL); aPTT, activated Partial Thromboplastin Time (seconds); PT, prothrombin time (seconds).
Table 1. Overview of laboratory tests after dabigatran etexilate 75 and 110 mg twice daily at steady state

<table>
<thead>
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<th>T0</th>
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T0 indicates Time 0 (pre-dose); T1 indicates one hour following the dose of dabigatran etexilate. Abbreviations: dTT, diluted Thrombin Time (expressed in ng/mL); LC-MS/MS, Liquid Chromatography-Mass Spectrometry/tandem Mass Spectrometry (expressed in ng/mL); aPTT, activated Partial Thromboplastin Time (expressed in seconds); ACT, Activated Clotting Time (expressed in seconds).

In our patient, we were uncertain how to safely dose dabigatran etexilate with co-administration of the P-glycoprotein inhibitors ritonavir and salmeterol. The observed dabigatran trough (pre-dose) concentration for the 110 mg twice daily dosage was in line with findings from the RE-LY trial (median 65.9 ng/mL, 10th-90th percentiles: 28.2-155 ng/mL)\(^4\), while dabigatran etexilate 75 mg twice daily resulted in a low trough concentration, that had been associated with a 50% increased risk of ischemic stroke\(^4\).

Although the interpretation of case reports needs caution due to their intrinsic limitations, in this particular patient the measurement of blood concentrations suggests that ritonavir did not cause dabigatran accumulation. Although no true target blood level range has been established thus far, aiming at concentrations typical for RE-LY trial participants provides some reassurance that the observed ischemic stroke and bleeding rates will apply.

REFERENCES

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