CORRESPONDENCE

Use of PER977 to Reverse the Anticoagulant Effect of Edoxaban

TO THE EDITOR: New target-specific oral anticoagulants are limited by the lack of a proven reversal agent. PER977 (Perosphere) is a small, synthetic, water-soluble, cationic molecule that is designed to bind specifically to unfractionated heparin and low-molecular-weight heparin through noncovalent hydrogen bonding and charge–charge interactions (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).[1,2] PER977 binds in a similar way to the new oral factor Xa inhibitors, edoxaban, rivaroxaban and apixaban, and to the oral thrombin inhibitor, dabigatran. In thromboelastographic studies and rat-tail–transection bleeding assays, PER977 has been shown to reverse anticoagulation with each of the new oral agents.[1,2] In nonclinical studies, PER977 did not bind to plasma proteins, including albumin, and showed no binding when tested against several common cardiovascular, antiepileptic, and anesthetic drugs. In this study, we assessed the safety, side-effect profile, and effect on anticoagulation reversal of PER977 when administered alone and after a 60-mg dose of the factor Xa inhibitor edoxaban.[3,4]

Pharmacokinetic and pharmacodynamic effects of escalating, single intravenous doses of PER977 (5 to 300 mg) administered alone and after a 60-mg oral dose of edoxaban were studied in a double-blind, placebo-controlled trial involving 80 healthy persons (Fig. S2 in the Supplementary Appendix). The study protocol is available at NEJM.org. Whole-blood clotting time was used to measure the anticoagulant effect of edoxaban and its reversal by PER977. In clinical trials of PER977, whole-blood clotting time showed low variability (interobserver variation, 3.0%) and high reproducibility (intersubject variation, 3.6%), and correlated well with edoxaban plasma concentrations (Fig. S3 in the Supplementary Appendix).

After the administration of edoxaban, the mean whole-blood clotting time increased by 37% over the baseline value (Fig. 1). In patients receiving a single intravenous dose of PER977 (100 to 300 mg) 3 hours after the administration of edoxaban, the whole-blood clotting time decreased to within 10% above the baseline value in 10 minutes or less, whereas in patients receiving placebo, the time to reach that level was much longer (approximately 12 to 15 hours). The whole-blood clotting time remained within 10% above or below the baseline value for 24 hours after the administration of a single dose of PER977. Scanning electron micrographs of clots obtained during measurement of the whole-blood clotting time were analyzed with a computer algorithm to determine the mean fibrin-fiber diameter. Edoxaban anticoagulation significantly reduced the mean fibrin-fiber diameter relative to baseline (from approximately 250 nm to approximately 125 nm, $P<0.001$). The mean fibrin-fiber diameter was restored to normal 30 minutes after administration of PER977 at the same doses that showed reversal by whole-blood clotting time (Fig. S4 in the Supplementary Appendix). There was no evidence of procoagulant activity after administration of PER977, as assessed by measurement of levels of D-dimer, prothrombin fragment 1.2, and tissue factor pathway inhibitor and by whole-blood clotting time. Potentially related adverse events were transient mild perioral and facial flushing and dysgeusia; one person reported a moderate headache. In addition, one person had a moderate muscle cramp and elevation in creatinine phosphokinase levels, events that were not considered to be related to PER977.

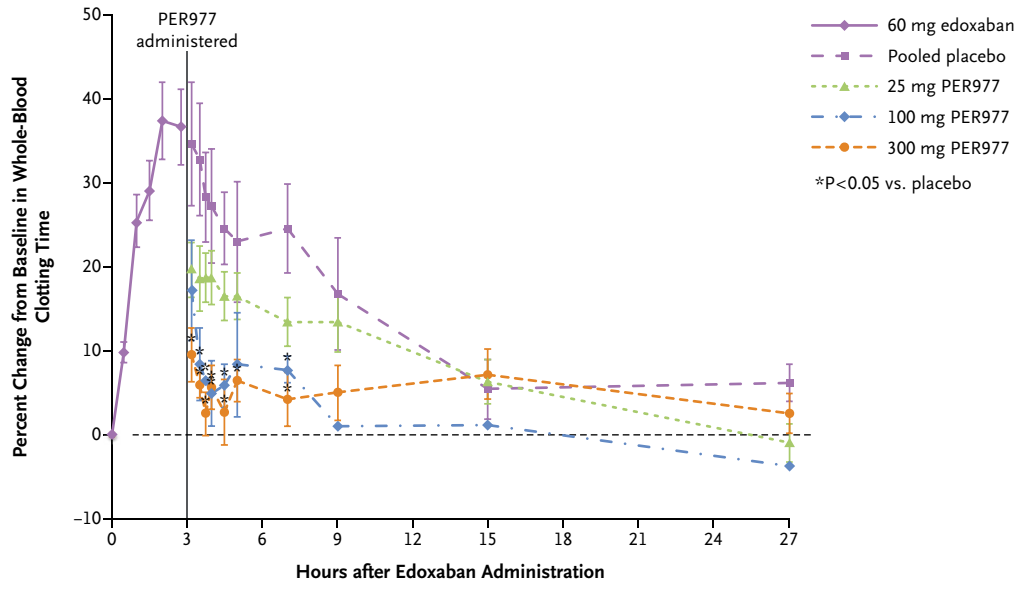

Figure 1. Effect of PER977 on Whole-Blood Clotting Time.

Shown are the mean whole-blood clotting times after administration of a single oral 60-mg dose of edoxaban, followed 3 hours later by a single intravenous dose of 25 mg, 100 mg, or 300 mg of PER977 or placebo.

In this study, baseline hemostasis was restored from the anticoagulated state within 10 to 30 minutes after administration of 100 to 300 mg of PER977 and was sustained for 24 hours. Additional phase 2 clinical studies are ongoing.

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