# Scientists develop antidote to new anticoagulants

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(Medical Xpress)—Anticoagulants have saved the lives of those at risk for heart attack or stroke. However, because they prevent blood clotting, they can be dangerous to patients who suffer traumatic injuries or who require urgent surgery. Doctors use Vitamin K as an antidote to the commonly prescribed blood-thinner Warfarin. Scientists at Portola Therapeutics, a South San Francisco pharmaceutical company, have successfully tested an antidote to two next-generation anticoagulants. The study appears in the March 3 online issue of *Nature Medicine*.

In the last several years, scientists have developed anticoagulants that are more effective than Warfarin, the most commonly prescribed blood thinner in the U.S. Two of these new anticoagulants, Eliquis (apixaban) and Xarelto (rivaroxaban), which the FDA recently approved, work by inhibiting factor Xa, an enzyme that plays an essential role in the blood clotting process. Unfortunately, until now, there has been no specific antidote to factor Xa inhibitors. This makes their use a problem for the small percentage of patients taking the drugs who find themselves at risk of hemorrhaging.

Uma Sinha and her colleagues at Portola created a recombinant protein, PRT064445, that can reverse the effect of factor Xa inhibitors. PRT064445, a modified version of recombinant factor Xa, does not contribute to blood clotting. However, because it mimics factor Xa, factor Xa inhibitors bind to it.

The Portola researchers were able to use PRT064445 to reverse the

effects of Eliquis and Xarelto in human plasma. They also found that PRT064445 acts as an antidote to betrixaban, an experimental Xa factor inhibitor.

PRT064445 restored normal clotting in rabbits given Xarelto and in rats given two forms of heparin, an older, injectable blood thinner.

Meanwhile, Boehringer Ingelheim, the maker of Pradaxa (dabigatran), a factor IIa inhibitor, is involved in phase 1 testing of its own antidote to this next-generation blood thinner.

Perosphere, a startup pharmaceutical company based in Mount Kisco, New York, has developed an antidote, PER977, which reverses the activity of a broader range of anticoagulants: the new factor Xa and factor IIa inhibitors, as well as some forms of heparin.

Solomon Steiner, Perosphere's chief executive, says it is important for an antidote to be effective against a wide range of anticoagulants, as emergency room patients may not know which blood thinners they are taking.

Another advantage of PER977 is, unlike biologics such as PRT064445, it is stable at room temperature because it is a synthetic small molecule. According to Sasha Bakhru, chief technology officer at Perosphere, this means emergency personnel can keep PER977 in solution in an ambulance.

**More information:** A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa, *Nature Medicine* (2013) doi:10.1038/nm.3102

**Abstract**
Inhibitors of coagulation factor Xa (fXa) have emerged as a new class of

antithrombotics but lack effective antidotes for patients experiencing serious bleeding. We designed and expressed a modified form of fXa as an antidote for fXa inhibitors. This recombinant protein (r-Antidote, PRT064445) is catalytically inactive and lacks the membrane-binding γ-carboxyglutamic acid domain of native fXa but retains the ability of native fXa to bind direct fXa inhibitors as well as low molecular weight heparin–activated antithrombin III (ATIII). r-Antidote dose-dependently reversed the inhibition of fXa by direct fXa inhibitors and corrected the prolongation of ex vivo clotting times by such inhibitors. In rabbits treated with the direct fXa inhibitor rivaroxaban, r-Antidote restored hemostasis in a liver laceration model. The effect of r-Antidote was mediated by reducing plasma anti-fXa activity and the non–protein bound fraction of the fXa inhibitor in plasma. In rats, r-Antidote administration dose-dependently and completely corrected increases in blood loss resulting from ATIII-dependent anticoagulation by enoxaparin or fondaparinux. r-Antidote has the potential to be used as a universal antidote for a broad range of fXa inhibitors.