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Reversal of dabigatran by intraosseous or intravenous idarucizumab in a porcine polytrauma model

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Abstract

Background: Idarucizumab is licensed to reverse dabigatran in life-threatening haemorrhage. Establishment of venous access can be challenging, and the intraosseous (IO) route is a potentially life-saving alternative. In this study, we compared the efficacy and safety of IO or intravenous (i.v.) idarucizumab for dabigatran reversal in a porcine polytrauma model.

Methods: Male pigs (n=21) received oral dabigatran etexilate (30 mg kg^{-1} bid) for 3 days. On the 4th day, animals received dabigatran infusion and were randomised 1:1:1 to receive IO saline (control), i.v. idarucizumab (60 mg kg^{-1}), or IO idarucizumab (60 mg kg^{-1}), or animals were included in a sham group (n=7). Study treatment was administered after polytrauma and the animals were monitored for 240 min, or until death. Coagulation status was monitored by thromboelastometry, thromboelastography, and thrombin measurements.

Results: Total blood loss was lowest in sham animals [521 (52) ml, P<0.01 *vs* all other groups], and comparable in the two idarucizumab groups [IO: 1085 (102) ml *vs* i.v.: 1142 (125) ml], and highest in the control group [4065 (557) ml, P<0.001 *vs* all other groups]. Survival to 240 min was 100% in the sham group and both idarucizumab groups, and 14% in the control group. IO and i.v. idarucizumab promptly normalised global coagulation assays and thrombin generation. Thromboelastography showed a strong correlation between dabigatran concentrations and R-time (R^2=0.90 and 0.89) in idarucizumab-treated animals.

Conclusions: Intravenous and intraosseous idarucizumab were comparable for reversing dabigatran in a porcine trauma model. Dabigatran reversal could be monitored using fully automated thromboelastography.

Keywords: anticoagulants; idarucizumab; dabigatran; intraosseous; thromboelastography

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Editor's key points

- Dabigatran, a thrombin inhibitor, is increasingly used in patients with a risk for thromboembolic events, but increases the risk for bleeding in trauma settings.
- Intravenous administration of an antidote of dabigatran, idarucizumab, is frequently prohibited because of difficult i.v. access, and intraosseous idarucizumab administration might be a life-saving alternative.
- In a porcine polytrauma model, the efficacy and safety of intraosseous and i.v. idarucizumab administration for dabigatran reversal were comparable.
- Idarucizumab administration to reverse dabigatran may be considered as an alternative route in case of acute life-threatening haemorrhage.

Direct oral anticoagulants (DOACs) are effective alternatives to warfarin in primary and secondary prophylaxis of thromboembolic conditions. Clinical data indicate that DOACs are at least as effective as vitamin K antagonists for stroke prevention in patients with atrial fibrillation, with reduced rates of life-threatening bleeding.[1] Despite the therapeutic benefits, as with all anticoagulants, DOACs are associated with a risk of bleeding complications. Patients with trauma-related bleeding or a need for urgent invasive surgery may require emergency reversal of DOAC therapy.

Idarucizumab is a specific reversal agent for the direct thrombin inhibitor (DTI) dabigatran. It binds exclusively to dabigatran with high affinity, providing rapid reversal of anticoagulation without affecting the coagulation cascade.[2] Preclinical and clinical studies have shown that idarucizumab is efficacious and well tolerated in emergency reversal of dabigatran.[3–8]

During life-threatening haemorrhage and shock, attaining vascular access for administration of haemostatic therapy can be challenging because of hypovolaemia and peripheral vasoconstriction. Additional complications may include obesity, peripheral oedema, damaged vascular structures, and traumatic amputations. Intraosseous (IO) administration may enable difficulties of vascular access to be avoided, and has been endorsed in trauma guidelines.[9] However, evidence supporting IO administration of haemostatic agents is limited.[10–14] It may be questioned whether the large molecular size of idarucizumab might limit transportation from the bone marrow to the plasma, and whether the antibody structure remains intact during this process.

In this study, we investigated the efficacy and safety of IO *vs* i.v. administration of idarucizumab for dabigatran reversal in a lethal porcine polytrauma model. We also investigated fully automated thromboelastography as a tool for monitoring dabigatran and its reversal by idarucizumab.[15,16]

Methods

Animals and ethics

The study was performed in 28 male German landrace pigs with mean bodyweight 43.2 kg [standard deviation (SD): 3.7 kg]. Permission was granted by the government office for animal care and use (Landesamt für Natur, Umwelt und Verbraucherschutz, Recklinghausen, Germany), and the study was performed in compliance with German legislation governing animal studies and the Animal Research: Reporting of in vitro Experiments (ARRIVE) guidelines. Before surgery, male German landrace pigs from a disease-free barrier breeding facility were housed in ventilated rooms and allowed to acclimatise to their surroundings for a minimum of 7 days. Animals were fasted overnight before surgical procedure, with water allowed *ad libitum*. Examination by a veterinarian ensured that the animals were in good health.

Dabigatran administration and idarucizumab preparation

Dabigatran etexilate was given to 21 animals, orally twice daily for 3 days (30 mg kg^{-1} bid), with the last dose administered 12 h before surgery. Placebo was given to the remaining seven animals (sham group). For 12 h before surgery, all pigs were fasted and provided with water. Methods for anaesthesia and surgical preparation were as described previously.[17] Dabigatran (1 mg ml^{-1}; Boehringer Ingelheim, Biberach, Germany) was infused at a rate of 0.77 mg kg^{-1} h^{-1} for 30 min and 0.2 mg kg^{-1} h^{-1} for 60 min. Sham animals received saline infusion. Before trauma, dabigatran-treated animals were randomised 1:1:1 (using sealed envelopes) to receive: IO placebo (crystalloid solution), i.v. idarucizumab (60 mg kg^{-1}), or IO idarucizumab (60 mg kg^{-1}). Idarucizumab (Praxbind®, Boehringer Ingelheim) was formulated in Tween® 20 buffer (25 mM acetate, 220 mM sorbitol, and 0.2% polysorbate 20; Sigma-Aldrich, St Louis, MO, USA) at a concentration of 44 mg ml^{-1} (osmolality 270–330 mOsm kg^{-1}). Study treatment in the sham group was placebo (saline infusion).

Injury phase, intervention and follow-up

A captive bolt gun (Schermer Stunner Model MKL, Karl Schermer and Co., Karlsruhe, Germany) was used to induce a right midshaft femur fracture with concomitant soft-tissue injury in all animals including the sham group. This was followed by a reproducible, pressure-controlled blunt liver injury, as described previously.[18] Immediately after trauma, IO access was established using an Arrow® EZ-IO® Vascular Access Driver under sterile conditions at the proximal tibial plateau. Correct positioning was confirmed by aspiration of bone marrow, and it was then flushed with 20 ml crystalloid solution (Sterofundin®, Braun, Melsungen, Germany).

Five minutes after injury, crystalloid solution was administered, with an initial bolus (25 ml kg^{-1} over 5 min) followed by infusion of 40 ml kg^{-1} h^{-1} for 2 h, and subsequently 20 m kg^{-1} h^{-1} until completion of the experiment.

The abdomen was reopened 12 min after liver injury to measure blood loss (intraperitoneal blood was suctioned into a pre-weighed container). A pre-weighed gauze was then applied as hepatic packing. At 15 min post-trauma, study treatment was administered by the investigator who was unaware of the study arm of each animal.

Haemodynamic values, including cardiac output, pulmonary artery pressure, pulmonary wedge pressure, central venous pressure, and arterial pressure were monitored throughout the study. Blood samples were collected after dabigatran infusion and at 12, 30, 60, 120, and 240 min after trauma. Details of tests performed on blood samples are provided in the Supplementary material. Animals surviving for 240 min were euthanised. The abdomen was reopened immediately after death and the inferior vena cava was clamped. Total blood loss was calculated by weighing