Dear Sirs,

Rivaroxaban is a novel oral selective potent direct factor Xa (FXa) inhibitor. It is approved for prevention of stroke in non-valvular atrial fibrillation (1), prevention and treatment of venous thromboembolism (2) and deep-vein thrombosis prophylaxis after knee and hip replacement surgery (3). Direct FXa inhibitors limit thrombogenesis via selective inhibition of FXa without requiring cofactors such as antithrombin (4). Rivaroxaban inhibits free FXa and prothrombinase activity as well as clot-bound FXa, thus effectively blocking thrombin generation (5). There is a close correlation between inhibition of FXa activity and rivaroxaban plasma concentration. Thus anti-FXa activity can be measured as a marker for rivaroxaban exposure, reflecting its plasma concentration. The oral bioavailability of rivaroxaban is 80–100% irrespective of food intake; 10 - 20 mg tablets demonstrate dose-proportional bioavailability, but at higher doses, bioavailability decreases as a result of poor solubility (6, 7). Orally administered rivaroxaban is rapidly absorbed, with a Cmax occurring 2-4 hours (h) after ingestion (7). In clinical studies, rivaroxaban has shown no requirement for routine laboratory coagulation monitoring. Up to now, there is little information on patterns of toxicity and toxicokinetics of this substance in human overdose.

A 63-year-old Caucasian male with a history of coronary and hypertensive heart disease, chronic atrial fibrillation, idopathic thrombocytopenia, and chronic vertigo with subsequent falls was brought to the emergency department 2.5 h after ingestion of 1960 mg Rivaroxaban (98 tablets of 20 mg.), 90 mg diazepam, 1 g quetiapine, and 50 mg zolpidem, with a suicidal intent. At admission, he was fully conscious, body temperature 35.9°C, blood pressure 120/90 mmHg, heart rate 90 bpm. The ECG showed atrial fibrillation. Laboratory analysis 2.8 h post-ingestion revealed the known thrombocytopenia at 127 G/l, but normal haemoglobin concentration (141 g/l) and leukocyte count 8.1 G/l; blood chemistry showed a slightly elevated bilirubin at 51 µmol/l (normal <20), lactate dehydrogenase 298 U/l (<265), creatinine kinase 567 U/l (<170) and normal values for electrolytes, liver enzymes; creatinine was 104 µmol/l (<115) with a calculated creatinine-clearance of 85 ml/minute (min) (Cockcroft-Gault). Clotting assays revealed a prothrombin time (PT; RecombiPlasTin 2G, Instrumation Laboratory Company-Bedford, MA, USA) of 66 seconds (s) (normal 9.4–12.5), aPTT (aPTT-SP, Hemosil™, Instrumentation Laboratory) 64 s (normal 25–37), and rivaroxaban quantification with modified chromogenic anti-FXa assay (Biophen DiXaI, HYPHEN BioMed- Paris, France) indicated a very high rivaroxaban plasma level (2010 µg/l), which was confirmed by an HPLC-MS/MS assay (2207 µg/l).

At 3 h after ingestion the patient was treated with oral activated charcoal 1 g/kg, and 4.5 h after ingestion with 2,000 IU (18 units/kg body weight) prothrombin complex concentrate (PCC), a combination of blood clotting factors II, VII, IX, X, as well as protein C and S. We measured haemostatic parameters (PT, aPTT, anti-FXa) every hour until the next morning. Material from every second sample rivaroxaban plasma concentration was evaluated by HPLC-MS/MS. At 7 h after ingestion, the coagulation assay parameters slightly improved (PT 39 s), and rivaroxaban concentration (by anti-FXa assay) had fallen to 1030 µg/l (HPLC-MS/MS: 1106 µg/l). Without further treatment, values 23 h post ingestion were: PT 16 s, aPTT 36 s, and rivaroxaban (anti-FXa assay) 210 µg/l (confirmed plasma concentration 158 µg/l). At 48 h post ingestion we found normalised coagulation parameters (PT 12 s, aPTT 31 s, rivaroxaban (anti-FXa assay) 40 µg/l). No bleeding occurred at any time during the clinical course.

One of the urgent problems in the overdose setting with new or direct oral anticoagulants is how to measure (and monitor, if at all necessary) the effect on the coagulation system. The aPTT is not an option for monitoring rivaroxaban in clinical practice. Mueck et al. showed that the prothrombin time correlates strongly with the plasma concentration of rivaroxaban in healthy trial participants (8). But prothrombin time results vary with different reagents and even with the same reagents, they may differ between centres (9); so the prothrombin time cannot be used to monitor patients on rivaroxaban (10). Measurement of FXa inhibition by anti-FXa assay is a better indicator of plasma concentration of FXa inhibitor drugs than prothrombin time (11), also between centres (9).

In our patient, massive rivaroxaban overdose led to very high rivaroxaban plasma concentrations of over 2200 µg/l, which have never been reported before. In phase II studies of rivaroxaban at total daily oral doses of 5–60 mg, Cmax ranged (mean values) from 40 to 400 µg/l (12). Although bioavailability exhibits saturation kinetics, Tmax was not delayed as compared to 2–4 h in therapeutic doses. From the ingested dose, a higher plasma concentration during peak level was to be expected; thus, the markers observed are in line with the ceiling effect described already at lower doses, thus limiting the risk of bleeding. Elimination of rivaroxaban from plasma occurs with a terminal half-life of 5–9 h in young and 11–13 h in elderly individuals (6); in our patient we found no change to the half-life, and there was no sign of redistribution.

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Comparing rivaroxaban quantification with modified chromogenic anti-FXa assay and analysis with HPLC-MS/MS assay showed a very good correlation even at very high concentrations (Figure 1).

Up to now, there is no available specific antidote to reverse the anticoagulant activity of direct FXa-inhibitors and no prospective data exist about on how to best treat major bleeding or to deal with the overdose of a direct FXa-inhibitor. In this setting, evidence to support the use of PCC, activated PCC (aPCC) or recombinant factor VIIa, is limited to studies in healthy volunteers, animal models and in vitro measurements. For example, in a randomised placebo-controlled trial, Eerenberg et al. (13) showed in healthy, non-bleeding subjects that four-factor PCC at a dose of 50 IU/kg partially reversed the prolongation of the prothrombin time and increased the endogenous thrombin potential in those who received rivaroxaban 20 mg twice daily (a dose not used in daily practice). Zhou et al. showed that administration of PCC, factor VIIa and fresh frozen plasma (FFP) prevent excess intracerebral haematoma expansion in a murine intracranial haemorrhage model associated with rivaroxaban, but at doses not comparable to the clinical setting (14). It is thus uncertain if data from healthy volunteer and animal studies can be extrapolated to patients receiving rivaroxaban. Furthermore, reversal of prolonged coagulation parameters may not correlate with the cessation of bleeding, as we know that even reversal of vitamin K antagonists (VKA) with PCC does not guarantee cessation of VKA-associated intracerebral bleeding (15). Drug absorption may be reduced by administration of oral activated charcoal if given early after drug ingestion (16). So use of charcoal seems reasonable in case of recent, particularly within 1–2 h of ingestion, especially in situation with intentional overdose. Haemodialysis is not an option due to the high plasma protein binding of rivaroxaban, which is around 95%.

In conclusion, an oral overdose of rivaroxaban (1960 mg) may lead to plasma rivaroxaban concentrations >2200 µg/l. In this setting, the administration of a single dose of PCC did likely not improve coagulation parameters. Whether repeated administration would have made a difference remains open. The risk of bleeding seems limited and may depend on other factors than rivaroxaban plasma concentrations alone. There seems to be no need for PCC in rivaroxaban overdoses without bleeding. However, at this time we recommend to evaluate each case on an individual basis.

Conflicts of interest
None declared.

References


