

Accidental Rivaroxaban Overdose in a Patient with Pulmonary Embolism: Some Lessons for Managing New Oral Anticoagulants

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ABSTRACT: Rivaroxaban is an orally active direct factor Xa inhibitor used to treat venous thromboembolism with approved starting dose of 15 mg twice-daily. We present a case of an accidental overdose in a patient with pulmonary thromboembolism, when the patient received two 150 mg doses of rivaroxaban, instead of 15 mg as prescribed, given 12 hours apart. This error was recognised ten minutes after the second dose, when 50 gm oral activated charcoal was given. Rivaroxaban was stopped and rivaroxaban concentrations, INR, and APTT were monitored. The overdose was uncomplicated and 15 mg twice-daily rivaroxaban was restarted on day two. Apparently unlikely and potentially hazardous dispensing errors do happen. Each oral anticoagulant has a different dosing schedule. In our patient, the prescription for 15 mg twice-daily rivaroxaban was misread as 150 mg twice-daily (a correct dose for dabigatran in atrial fibrillation). Such errors are preventable. Prompt administration of activated charcoal under monitoring of a specific rivaroxaban assay can greatly help management of unusual situations like this one.

KEYWORDS: Rivaroxaban, overdose, anticoagulation

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Introduction

Rivaroxaban is an orally active direct factor Xa inhibitor. It is approved for acute and ongoing treatment of venous thromboembolism (VTE), as well for the prevention of embolic stroke in atrial fibrillation. Rivaroxaban is well absorbed from the gut, maximum factor Xa inhibition occurs after two to four hours, the terminal half-life is 8–12 hours, and approved starting dose for VTE is 15 mg twice daily. Unlike warfarin, there is currently no established way to fully reverse the anticoagulant effect of rivaroxaban in the event of a major bleeding event or overdose.

Case Report

A man in his 50s presented with progressive breathlessness and chest tightness. He occasionally drives long distances, and three years earlier, he was treated for deep vein thrombosis. Physical examination, routine laboratory examinations, and chest X-ray were unremarkable. D-dimer was elevated, and CT pulmonary angiography showed extensive bilateral pulmonary embolism. A thrombophilia screen was negative. Doppler echocardiography was unremarkable and showed no signs of right ventricular strain or elevated pulmonary artery pressure. NT-proBNP was, likewise, within normal limits, confirming no right ventricular strain. Duplex ultrasound

examination of the legs showed deep venous thrombosis involving the right posterior tibial vein.

After initial enoxaparin, the patient received two 150 mg doses of rivaroxaban, instead of the twice daily 15 mg prescribed on the handwritten order. The doses were given by nurses, 12 hours apart at 20:00 on day 0 and 08:00 on day 1. This error was recognized ten minutes after the second dose, when he promptly received 50 g oral activated charcoal. Rivaroxaban was stopped, and rivaroxaban concentrations (measured as chromogenic factor Xa inhibitory activity using rivaroxaban standards),¹ International Normalized Ratio (INR), and Activated Partial Thromboplastin Time (APTT) were monitored (Figs. 1 and 2). The overdose was uncomplicated, and 15 mg twice daily rivaroxaban was restarted on day 2.

Discussion

The immediate response to an accidental drug overdose is to minimize the potential adverse effects. The absence of an approved rivaroxaban antidote left two possible interventions: activated charcoal to reduce continuing drug absorption² and prothrombin complex concentrate infusion to offset excessive factor Xa inhibition.³ Our patient received activated charcoal within ten minutes after the second dose but was not given prothrombin concentrate.

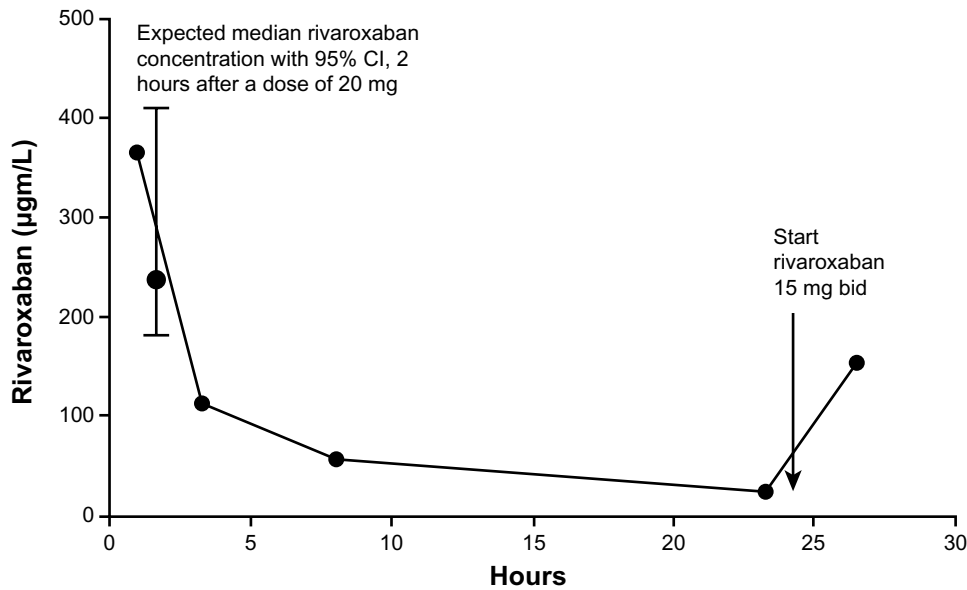


Figure 1. Rivaroxaban concentrations ($\mu\text{g/mL}$) measured after second 150 mg rivaroxaban dose, followed within ten minutes by 50 g activated charcoal, and three hours after first rivaroxaban dose of 15 mg. Expected rivaroxaban concentrations are derived from Mueck et al (Table 3 and Fig. 3).¹

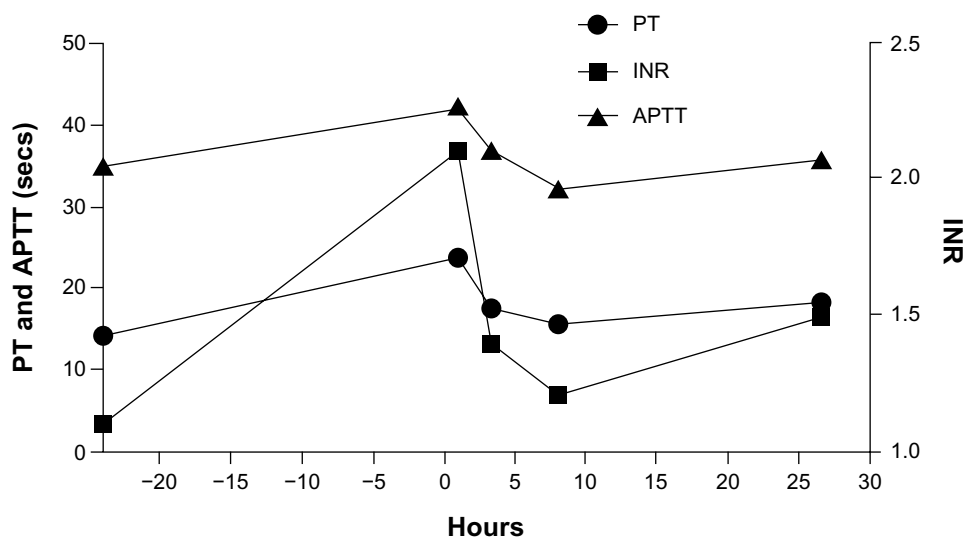


Figure 2. Prothrombin Time (PT), APTT, and INR before rivaroxaban, after the second 150 mg rivaroxaban dose followed within ten minutes by 50 g activated charcoal, and three hours after the first rivaroxaban dose of 15 mg.

The rivaroxaban level one hour after 50 g activated charcoal was within the range expected soon after a daily dose of 20 mg,¹ and then diminished. This suggests that the charcoal had reduced absorption of the second dose. Early activated charcoal reduces the absorption of apixaban (another orally active direct factor Xa inhibitor) by 50%⁴ and may reduce absorption of dabigatran (an orally active thrombin inhibitor).⁵ Recent Australian guidance suggests that activated charcoal should be considered if there is significant bleeding within two hours of taking a new oral anticoagulant.⁶

Our patient did not receive a prothrombin concentrate. He had normal renal function and had low risk of bleeding. The 5–13 hour terminal half-life of rivaroxaban¹ ensures rapid clearance, as was confirmed by rivaroxaban assays. Rivaroxaban concentrations well above the usual therapeutic levels did not cause bleeding in healthy volunteers after twice daily 30 mg or single doses of 80 mg. Prothrombin concentrates in rivaroxaban-treated volunteers improve ex vivo thrombin generation with little effect on prothrombin time and activated partial thromboplastin time and none on factor Xa inhibition, and may have clinical benefit in rivaroxaban-treated patients



with serious bleeding,³ but can have adverse effects. It seemed reasonable to withhold prothrombin concentrate, especially since prompt rivaroxaban assay results were available and the intrinsic bleeding risk was low.

The most important lesson is that apparently unlikely and potentially hazardous dispensing errors do happen. Each “new oral anticoagulant” has its own dosing schedule. In our patient, the prescription for 15 mg twice daily rivaroxaban was misread as 150 mg twice daily (a correct dose for dabigatran in atrial fibrillation). Such errors are preventable. Another message is that prompt administration of activated charcoal and specific rivaroxaban assay can greatly help the management of unusual situations like this one. Fast clearance of rivaroxaban, aided by activated charcoal, underlines the relative safety of this new agent in patients with normal renal function.

Author Contributions

Conceived and designed the paper: DS, AG. Wrote the first draft of the manuscript: DS. Contributed to the writing of the

manuscript: AG. Jointly developed the structure and arguments for the paper: DS, AG. Made critical revisions and approved final version: DS, AG. Both authors reviewed and approved of the final manuscript.

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