Dabigatran Reversal in a Patient With End-Stage Liver Disease and Acute Kidney Injury

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Dabigatran, a direct thrombin inhibitor and one of the new class of direct oral anticoagulants, is increasingly used in preference to warfarin because of its efficacy and ease of administration. However, because the drug is cleared by the kidneys, it can accumulate in plasma and increase the risk for bleeding in patients with decreased kidney function. We report a patient with end-stage liver disease who developed life-threatening hemorrhage and acute kidney injury while taking dabigatran, 150 mg, twice daily. Although the patient received idarucizumab, an anti-dabigatran antibody fragment used as an antidote, hemostasis could not be achieved. Administration of vitamin K, fresh frozen plasma, desmopressin, octreotide, and pantoprazole did not arrest bleeding or affect coagulation parameters, and it was not possible to establish vascular access for hemodialysis. In patients with end-stage liver disease, who are at increased risk for both bleeding and acute kidney injury, dabigatran should be prescribed cautiously and at decreased dose.

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Am J Kidney Dis. 71(1): 137-141. Published online May 24, 2017.

doi: 10.1053/j.ajkd.2017.03.025

Introduction

Dabigatran is one of a class of new direct oral anticoagulants used as an alternative to warfarin for stroke prophylaxis in patients with nonvalvular atrial fibrillation. Dabigatran, a direct thrombin inhibitor, is more efficacious than warfarin and easier to administer, but when first available, it had no antidote in cases of severe bleeding.[1] Idarucizumab, a humanized monoclonal antibody fragment, was subsequently developed to bind dabigatran and rapidly reverse its anticoagulant effect.[2]

In healthy individuals, the half-life of dabigatran is 8.3 hours, and >80% of the drug is excreted in urine.[3] Although pharmacokinetic data have not been obtained in patients with acute kidney injury (AKI), in those with end-stage renal disease, the half-life of dabigatran is prolonged to 34 hours and drug exposure (measured by plasma concentration-time area under the curve [AUC]) is increased by nearly 7-fold.[4] This prolonged dabigatran exposure with decreased kidney function may render idarucizumab less effective in patients with AKI who require anticoagulation reversal.

We report a patient with end-stage liver disease (ESLD) who was treated with dabigatran and experienced life-threatening bleeding during an episode of AKI. Idarucizumab was used to reverse dabigatran activity, but the benefit of the antidote was transient because the patient was unable to excrete dabigatran. In patients at risk for AKI, such as those with ESLD, the risks and benefits of dabigatran should be considered carefully.

Case Presentation

Clinical History and Initial Laboratory Data

A 71-year-old man with a history of ESLD from alcohol abuse and atrial fibrillation receiving dabigatran, 150 mg, twice daily presented to an external facility with a report of nausea and vomiting for several days. Aside from ESLD with nonbleeding esophageal varices and atrial fibrillation, the patient's medical history was notable for transient ischemic attack, insulin-requiring type 2 diabetes, hypertension, hyperlipidemia, and benign prostatic hypertrophy. Initial laboratory data were notable for serum urea nitrogen level of 45 mg/dL; serum creatinine level of 4.8 mg/dL, increased from a recent baseline of 0.9 mg/dL; and international normalized ratio (INR) of 4. Other laboratory data are shown in Table 1. An ultrasound of the abdomen revealed ascites, findings compatible with liver cirrhosis, and kidneys of normal size and echogenicity without hydronephrosis. Although dabigatran treatment was discontinued on admission and fresh frozen plasma (FFP) and vitamin K were administered, the patient subsequently developed hematemesis.

The patient was transferred to our institution on hospital day 3. Blood pressure was 140/66 mm Hg, heart rate was 95 beats/min, and oxygen saturation was 93% on room air. Upon arrival to the intensive care unit, he developed hemoptysis and hypoxia requiring intubation. Continuous bleeding was noted in the endotracheal tube, orogastric tube, and urinary catheter. Octreotide

Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

Table 1. Laboratory Data

	Baseline	Days 1-2	Day 3	Day 4	Day 5	Reference Range
Prothrombin time, s	19.2	45	44.7	41	31.2	12.1-14.5
INR	1.62	4.00	4.82	4.38	3.36	
PTT, s		110	105	76.7	56.5	22-36
Fibrinogen, mg/dL				147	194	200-450
White blood cells, $\times 10^3/\mu L$	3.8	6.9	3.8	4.9	8.9	3.8-10.6
Hemoglobin, g/dL	13.3	13.6	10.4	8.2	7.3	13.5-17
Platelets, $\times 10^3/\mu L$	69	100	48	50	45	150-450
Sodium, mmol/L	141	135	130	131	135	135-145
Potassium, mmol/L	4.3	4.4	4.8	5.0	5.3	3.5-5
Chloride, mmol/L	106	100	95	97	98	98-111
Bicarbonate, mmol/L	29	19	19	19	18	21-35
SUN, mg/dL	8	52	79	86	97	10-25
Creatinine, mg/dL	0.71	5.31	7.94	8.31	9.05	<1.13
ALT, IU/L	47	192	87			<40
AST, IU/L	52	236	136			<35
Albumin, g/dL	3.2	2.3	3			3.2-4.6
Bilirubin (total), mg/dL	0.8	3.7	3.4			<1.2
Alkaline phosphatase, IU/L	246	288	154			<140
Lactate (whole blood), mmol/L			2.8	3.0	3.6	0.4-1.8

Note: Baseline values were obtained 2 to 4 months prior to the current presentation. Data for hospital days 1 and 2 were obtained from the outside hospital. In the case of multiple values per day, the mean is reported.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PTT, partial thromboplastin time; SUN, serum urea nitrogen.

and pantoprazole infusions and vitamin K, 10 mg, intravenously were given at the time of arrival in an attempt to arrest bleeding. Because of ongoing hemorrhage with worsening AKI (Table 1), desmopressin, 0.3 μg/kg, was administered intravenously 14 hours after arrival. Because of recent dabigatran exposure, idarucizumab, 5 mg, was administered intravenously 18 hours after arrival.

Albumin, saline, and midodrine were prescribed as presumptive treatment for type 1 hepatorenal syndrome, and broad-spectrum antibiotics were administered empirically for sepsis.

Additional Investigations

Urinalysis showed blood (200 cells/μL), bilirubin 100 μmol/L, urobilinogen 8 U/dL, albumin > 300 mg/dL, and glucose 100 mg/dL (previous urinalyses showed glucose only). Urine microscopy revealed red blood cells obscuring the entire visual field (3,678 cells/high-power field). Urine output decreased from 1.5 mL/kg/h on admission to 0.3 mL/kg/h within the first 12 hours. No antinuclear, antinuclear cytoplasmic, or anti–glomerular basement membrane antibodies were detected by serologic testing. Diagnostic paracentesis gave negative results for spontaneous bacterial peritonitis, and ascites fluid and blood cultures also yielded negative results.

Administration of FFP had no effect on INR or partial thromboplastin time (PTT). Administration of idarucizumab improved these parameters within 3 hours, but the benefit lasted less than 8 hours (Fig 1).

Diagnosis

AKI due to anticoagulant nephropathy or type 1 hepatorenal syndrome and uncontrolled hemorrhage due to dabigatran toxicity.

Clinical Follow-up

The patient's hemorrhagic complications worsened, including hematuria, hemoptysis, and bleeding from the gastrointestinal tract and venipuncture sites. By hospital day 4, in addition to these measures, 7 units of FFP, 2 units of packed red blood cells, and one 6-pack of platelets had been transfused. Because of refractory coagulopathy and diffuse hemorrhage, he was unable to undergo esophagogastroduodenoscopy or hemodialysis catheter placement. The patient's family expressed his wishes to forego aggressive resuscitative measures, and he died on hospital day 5.

Discussion

Of the commercially available direct oral anticoagulants, dabigatran is the only direct thrombin inhibitor and it blocks the rate-limiting step in the clotting cascade.[5] Compared with rivaroxaban and fondaparinux, dabigatran is the most potent inhibitor of thrombin generation in patients with ESLD.[6] The medication is administered orally as the prodrug dabigatran etexilate, which is completely metabolized to the active dabigatran by the liver, even in patients with moderate hepatic impairment (Child-Pugh classification B).[7] Dabigatran is eliminated mainly by the kidneys (>80%), and plasma clearance