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증 례

급성신손상으로 인해 발생한 dabigatran 독성

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Dabigatran Toxicity Secondary to Acute Kidney Injury

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Dabigatran is the first oral direct thrombin inhibitor approved by the US Food and Drug Administration (FDA) for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Because dabigatran is excreted mainly by the kidneys, serum levels of dabigatran can be elevated to a supratherapeutic range in patients with renal failure, predisposing to emergent bleeding. We describe the case of a 66-year-old man taking dabigatran 150 mg twice daily for atrial fibrillation and cerebral infarction who presented with hematochezia and disseminated intravascular coagulation. Laboratory evaluation showed a hemoglobin level of 6.3 g/dL, platelets of 138,000/mm^3, activated partial thromboplastin time (aPTT) of 10?s, and an international normalized ratio (INR) of 8.17. Colonoscopy showed a bleeding anal fissure. Hemostasis was provided by hemoclips and packed red blood cells and fresh frozen plasma were transfused. Since then, there was no further hematochezia, however, bleeding including oral mucosal bleeding, hematuria, and intravenous site bleeding persisted. At presentation, his serum creatinine was 4.96 mg/dL (baseline creatinine, 0.9 mg/dL). Dabigatran toxicity secondary to acute kidney injury was presumed. Because acute kidney injury of unknown cause was progressing after admission, he was treated with hemodialysis. Fresh frozen plasma transfusion was provided with hemodialysis. At 15 days from admission, there was no further bleeding, and laboratory values, including hemoglobin, partial thromboplastin time, and prothrombin time were normalized. He was discharged without bleeding. After 2 months, he undergoes dialysis three times per week and no recurrence of bleeding has been observed.

Key Words: Dabigatran, Acute kidney injury, Disseminated intravascular coagulation, Hemodialysis

Introduction

Warfarin remains the standard anticoagulant for ischemic stroke prevention in patients with atrial fibrillation, deep vein thrombosis and pulmonary thromboembolism. Because the anticoagulant effects of warfarin vary from individual to individual, optimizing warfarin dosage in individual patients can be difficult[1)]. Dabigatran is the first oral direct thrombin inhibitor approved by the US Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation[2)]. Because the anticoagulant effects of dabigatran are more predictable than those of warfarin,

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dabigatran has begun to replace warfarin. Because dabigatran is excreted mainly via the kidneys, it may accumulate in patients with impaired renal function[3]. Safety concerns have been raised because there is no effective therapy to reverse dabigatran-induced coagulopathy[4,5]. We describe a case of gastrointestinal bleeding and disseminated intravascular coagulation in a patient with supratherapeutic dabigatran concentrations secondary to acute kidney injury.

Case

A 66-year-old man presented to the emergency department with hematochezia. He had been taking dabigatran 150 mg twice daily for atrial fibrillation and cerebral infarction for a year. His past medical history included chronic liver disease, diabetes mellitus, hypertension, and cerebral infarction. Four weeks earlier, his serum creatinine was 0.9 mL/dL, with estimated glomerular filtration rate (eGFR) of 84.1 mL/min.

The patient had a heart rate of 37 beats per minute and blood pressure of 114/50 mmHg. Laboratory evaluation revealed a hemoglobin level of 6.3 g/dL, platelets of 138,000/mm^3, activated partial thromboplastin time (aPTT) of 10 s, and an international normalized ratio (INR) of 8.17. A coagulation factor assay showed factor V of 41%, factor X of 48% and factor XI of 3%. A liver function test showed albumin of 1.9 g/dL, total bilirubin of 0.2 mg/dL, aspartate aminotransferase of 20 IU/L, and alanine aminotransferase of 22 IU/L.

Colonoscopy revealed anal fissure bleeding and hemostasis was provided by hemoclips. He was also treated with packed red blood cells and fresh frozen plasma (FFP). Since then, he suffered no further hematochezia. However, other bleeding, from the oral mucosa, urinary tract, and intravenous sites, persisted. Furthermore, laboratory values including hemoglobin, aPTT, and PT, did not recover. At the time of presentation, his blood urea nitrogen was 40.4 mg/dL and serum creatinine was 4.96 mg/dL, with an eGFR of 12.3 mL/min. The patient' s bleeding and elevated aPTT and INR were believed to be attributable to dabigatran overdose resulting from acute kidney injury.

Because an acute kidney injury of unknown cause was progressing after admission, on hospital day 7, hemodialysis was started. Daily hemodialysis was provided and FFP transfusion was continued. At 15 days from admission, no bleeding was observed. Laboratory values, including hemoglobin, aPTT, and INR had normalized, but the acute kidney injury had not resolved. The patient was discharged without bleeding. After 2 month, he dialyzes three times per week and no recurrence of bleeding has been observed.

Discussion

Oral anticoagulation is important for preventing stroke and other systemic thromboembolic diseases in patients with atrial fibrillation. Warfarin has been the 'classical' oral vitamin K antagonist for decades. Its narrow therapeutic index and multiple drug interactions are disadvantages of warfarin. Dabigatran is a novel oral direct thrombin inhibitor approved by the US FDA for stroke prophylaxis in non-valvular atrial fibrillation[2].

Dabigatran is absorbed across the gastrointestinal wall by p-glycoprotein and rapidly converted to the active form by esterase. Although the bioavailability of dabigatran is low (6~7%) compared with other factor Xa inhibitors, its plasma concentration reaches a peak level in 1.25~1.5 h, allowing a more rapid onset of action than vitamin K antagonists[3]. One of the major benefits of dabigatran compared with warfarin is its more predictable pharmacokinetic profile. The absorption is constant and has less individual variability[6]. Thus, patients taking dabigatran do not require frequent drug level monitoring. Furthermore, dabigatran is not metabolized by cytochrome P450 enzymes, so has fewer drug interactions than warfarin[3]. Because of its rapid onset, bridging with heparin is also not needed.

However, there are still some problems associated with using dabigatran. One major concern is the absence of a clear antidote to reverse its action. Although the bleeding rate associated with dabigatran is not higher than with oral vitamin K antagonist[3], once bleeding occurs, it can be life-threatening.

Thus, concerns about the safety of dabigatran have been raised. FFP and prothrombin complex concentrate (PCC) can provide factors for activating thrombin but their role is limited in the bleeding associated with dabigatran, a direct thrombin inhibitor. Otherwise, recombinant factor VIIa (rfVIIa) can be helpful because it promotes thrombin formation directly through the activation of factor X[7]. In several case reports, the effects of these agents for the reversal of other direct thrombin inhibitors have been conflicting[1]. Previous animal studies suggest that PCC may reverse effects of dabigatran, whereas no benefit was observed with rfVIIa[8,9]. These results do not correspond with a report that PCC did not normalize coagulation assays in healthy volunteers receiving dabigatran[10]. It is difficult to interpret the results of these studies as they apply to the practice setting. The results of animal model studies may not correspond to human models, and markers used in studies may not correlate with clinical results.

The risk of bleeding associated with dabigatran increase in patients with renal impairment. More than 80% of absorbed dabigatran is excreted via the kidney so the dabigatran concentration is dependent on renal function. In patients with normal renal function, the half-life of dabigatran is 13 h, but this increases to 18 and 27 h in patients with moderate and severe renal failure, respectively[3]. Thus, dabigatran is not recommended for patients with severe renal dysfunction, a creatinine clearance of ‹30 mL/min. In a most recent report, patients with major bleeding event under dabigatran were older, had a lower creatinine clearance, and took aspirin or nonsteroidal anti-inflammatory agents[11].

Hemodialysis can be effective in the treatment of dabigatran toxicity by enhancing dabigatran clearance, even in patients with normal kidney function. Two small prospective pharmacokinetic studies have been reported, evaluating the effects of hemodialysis in non-bleeding ESRD patients receiving a single[12] or three doses of dabigatran[13]. The studies consistently reported that hemodialysis could remove dabigatran. The extraction ratio was 6168% and serum dabigatran concentration was reduced by up to 60% with 4 h of high-flux hemodialysis[13]. In previous case reports of patients with bleeding related with dabigatran who were treated with hemodialysis, serum level of dabigatran fell dramatically during hemodialysis. The half-life of dabigatran was shorter during hemodialysis than without it. Intermittent hemodialysis was more effective than continuous renal replacement therapy[14], likely because higher attainable blood and dialysate flow rates could be provided during intermittent hemodialysis. The large volume of distribution of dabigatran leads to a rebound effect following hemodialysis[13], but this may be corrected by prolonging the duration of intermittent dialysis, multiple intermittent dialysis, or continuous renal replacement therapy.

Weitz. et al.[15] proposed an algorithm for management of bleeding episodes in patients treated with dabigatran (Fig. 1). For moderate-to-severe bleeding, the serum creatinine level and creatinine clearance should be measured to estimate the half-life of dabigatran. The aPTT and/or Hemoclot (if available) should also be determined. Diuresis should be maintained and transfusion support is needed. With severe or life-threatening bleeding, FEIBA (Anti-Inhibitor Coagulant Complex), PCC, rfVIIa and hemodialysis should be considered. But these recommendations are based on limited nonclinical data only. Thus, it is difficult to apply this algorithm to clinical setting.

Moderate hepatic failure, Child Pugh Score B or less, has not been shown to significantly affect drug levels[16]. However, coagulation factors cannot be supplied sufficiently in patients with chronic liver disease, impairing hemostasis. Our patient received 3~4 unit of FFP every day. Although PT and aPTT did not recover after FFP transfusion, we consider that FFP transfusion had some benefit on coagulopathy with chronic liver disease.

Dabigatran has many advantages including its rapid onset, more predictable drug levels, and fewer drug-drug interactions than warfarin. However, supratherapeutic range drug levels resulting from renal dysfunction may lead to life-threatening bleeding and no effective antidote is available. Physicians should be aware of renal status in patients on dabigatran.

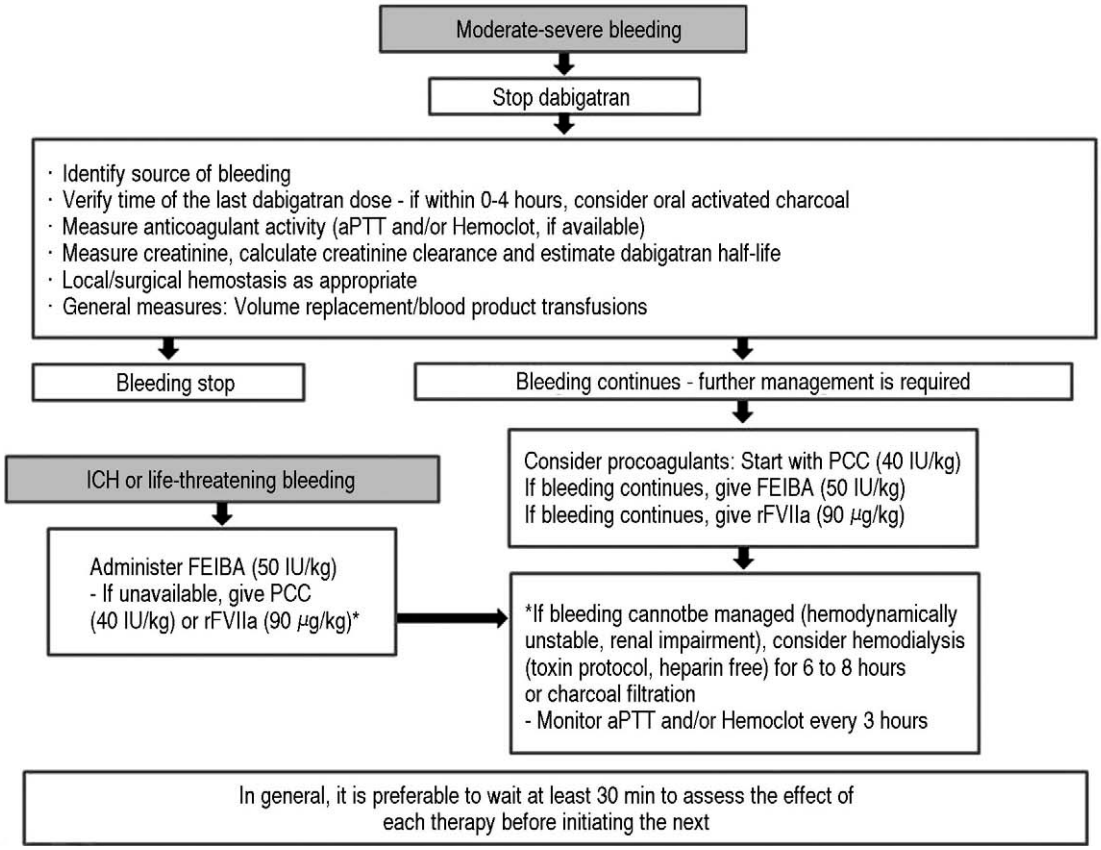

Fig. 1. Proposed algorithm for management of moderate-to-severe bleeding and life-threatening bleeding episodes in patients treated with dabigatran. * Recommendations are based on limited nonclinical data only. FEIBA indicates Factor Eight Inhibitor Bypassing Activity; PCC: prothrombin complex concentrates (nonactivated), rFVIIa: recombinant activated factor VII. Moderate-to-severe bleeding indicates a reduction in hemoglobin ≥2 gd/L, transfusion of ≥2 U of red cells, or symptomatic bleeding in critical area (ie, intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intraarticular, or pericardial bleeding). Life-threatening bleeding indicates symptomatic intracranial bleed, reduction in hemoglobin ≥5 gd/L, transfusion of ≥ 4 U of red cells, hypotension requiring inotropic agents, or bleeding requiring surgical intervention.

Although hemodialysis is effective in removing dabigatran, standard dialysis duration may not remove sufficient amounts of dabigatran. Further study is required to determine the best treatment protocol for dabigatran-related bleeding.

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