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BREIF REPORT

Fatal bleeding associated with Rivaroxaban in patient with gastric lymphoma

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ABSTRACT

44-year-old gentleman with history of gastric lymphoma status-post multiple cycles of chemotherapy, atrial fibrillation (AF) and hypertension was brought to the hospital in an unconscious state after a syncopal episode. He was tachycardic in the 130s-140s with systolic blood pressure in the 70s. He was given intravenous fluids and vasopressors. Naso-gastric tube placement brought back blood. Patient was on rivaroxaban for primary prevention of stroke. Patient reported one episode of dark colored stool and was complaining of epigastric discomfort. Gastroenterology was consulted and a pantoprazole drip was started. His creatinine was 4.8, baseline value was 0.9. Esophago-gastro-duodenoscopy showed blood in proximal stomach and tumor mass in distal body of the stomach. No point source was found amenable to endoscopic treatment. Surgical consultation was requested but patient developed cardiac arrest with asystole. Resuscitation attempts failed, and patient died of hemorrhagic shock. Rivaroxaban was approved in November 2011 by the US Food and Drug Administrationfor stroke prevention in non-valvular AF. Thispatient had a score of 1, for hypertension and had gastric lymphoma which increased his bleeding risk. The risk outweighed benefit of anticoagulation, especially with an irreversible agent. Physician education is thus necessary to ensure appropriate patient selection and safety for use of irreversible oral anticoagulants.

Key words: Rivaroxaban, atrial fibrillation, bleeding

Despite the attractive properties of the new oral anticoagulants compared with warfarin, important challenges remain. Rivaroxaban is an oral direct factor Xa inhibitor which was approved in November 2011 by the US Food and Drug Administration for stroke prevention in non-valvular atrial fibrillation (AF).

44-year-old gentleman with a history of gastric diffuse large B-cell lymphoma (DLBCL) status-post multiple cycles of chemotherapy, AF and hypertension was brought to the hospital by emergency medical services in an unconscious state after a syncopal episode. His condition deteriorated and he required endotracheal intubation for airway protection. His skin was found to be mottled and he was tachycardic in the 130s-140s with systolic blood pressure in the 70s. The patient was given intravenous fluid boluses and started on vasopressors. Naso-gastric tube placement immediately brought back bright red blood. The patient was on rivaroxaban for primary prevention of embolic stroke for the last 3 months. His last chemotherapy was one month ago. The patient had one episode of dark colored stool two days earlier and had been complaining of epigastric discomfort. He was admitted to the intensive care unit. An emergent gastroenterology consultation was requested. He was started on pantoprazole drip. His blood work showed elevated creatinine of 4.8, baseline value was 0.9. The esophago-gastro-duodenoscopy showed blood in the proximal stomach and large circumferential tumor mass in the distal body of the stomach with a necrotic center, but no point source was found amenable to endoscopic treatment. Surgical consultation was requested but the patient developed cardiac arrest with asystole. All resuscitation attempts failed and the patient died of hemorrhagic shock.

AF is the most common cardiac arrhythmia and increases the risk of ischemic stroke by a factor of four to five. Accounting for 15% of strokes in persons of all ages. Warfarin reduces the risk of stroke by two-thirds in these patients but has a narrow therapeutic window and requires frequent monitoring and dose changes. It also has multiple drug and dietary interactions. CHADS2 score is used for risk stratification and to guide anticoagulation therapy in patients with AF. CHADS2 is formed by assigning 1 point each for the presence of Congestive heart failure, Hypertension, Age 75 years or older, and Diabetes mellitus and by assigning 2 points for history of Stroke or transient ischemic attack.[1]

Rivaroxaban is an oral direct factor Xa inhibitor which shows peak anticoagulant effect within 2-4 hours after oral administration. The half-life ranges from 5-9 hours in younger patients and goes up to 11-13 hours in older ones. About one-third of the active drug is renally cleared. Thus, the risk of bleeding increases with renal impairment due to drug accu-

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mulation.[2] Also, due to high plasma protein binding (>90%) rivaroxaban cannot be eliminated by hemodialysis.[3]

Unlike warfarin there are no reversal agents available for rivaroxaban yet. Studies in healthy volunteers have shown reversal of prothrombin time prolongation with four-factor prothrombin complex concentrate (PCC) but only laboratory parameters were evaluated in this study, and no bleeding outcomes were measured.[4] Also only three-factor PCCs are available in the United States currently. Caution is required for off-label use of PCCs as thrombotic events have been reported in 1-3% of treated patients.[3]

The ROCKET-AF trial showed the non-inferiority of rivaroxaban to warfarin in preventing stroke in patients with non-valvular atrial fibrillation. The incidence of fatal bleeding was found to be lower in the rivaroxaban group but GI bleeding was higher. The mean CHADS2 score in the trial was 3.[5] and only patients with a score of 2 or more were included.[5] The above mentioned patient had a CHADS2 score of 1, for hypertension. He also had a gastric DLBCL which put him at an increased risk of GI bleeding. In retrospect, the risk of bleeding clearly outweighed the benefit of anticoagulation in this patient, especially with an irreversible agent.

The optimization of the efficacy and safety of these new oral anticoagulants in the community requires better physician education to ensure appropriate patient and dose selection. The lack of an antidote precludes the use of these agents in patients at any increased risk for bleeding.

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