Unrestricted prescription of dabigatran: Is it safe in a resource-limited setting

Sir,

A 71-year-old grossly underweight male (about 52 kg), on dabigatran (110 mg twice daily) for paroxysmal atrial fibrillation, was admitted to our intensive care unit (ICU), with hemorrhagic shock following lower gastrointestinal bleeding. He was bedridden for past 3-months following right middle cerebral artery stroke and was on tracheostomy. He had recently undergone radical cystectomy with ileal conduit for bladder malignancy. His other comorbidities include hypertension and a history of stable coronary artery disease. He was also on aspirin, levetirecetam, and atorvastatin.

He was resuscitated with crystalloids, four units of packed red blood cells, and brief period of noradrenaline infusion. Six units of fresh frozen plasma were also transfused empirically (questionable benefit). Initial laboratory investigations showed hemoglobin: 5.7 g/dl, activated partial thromboplastin time: 49 s, international normalized ratio: 2.3, thrombin time >60 s (report received only after 4 days), and normal platelet count and hypoalbuminemia 2.1 g/dl. Hemodialysis was planned at the beginning but it took another 6 h in family counseling (and Nephrologist!), to arrange a dialysis machine, and finally start the dialysis (12-h after last dabigatran dose). In the following 24 h he continued to have deranged coagulation parameters and intermittent bleeding per rectum (albeit hemodynamically stable) requiring further transfusion. Colonoscopy showed diverticular disease with large ulcers and active ooze [Figure 1]. At 36-h in the ICU, he suffered cardiac arrest with monitor showing ventricular tachycardia. Repeat electrocardiogram done post-resuscitation showed new ST-segment elevation in anterior leads [Figure 2]. When explained, family refused further treatment and decided to take him home. On a telephonic follow-up 2 weeks after his discharge from the ICU, he was alive with apparently no change in his preadmission cognitive state.

Reversal agent to dabigatran, that is, a neutralizing monoclonal antibody aDabi-Fab is limited to research setting.[1] Some of the measures suggested to stop dabigatran-induced bleeding[2] are either not available in

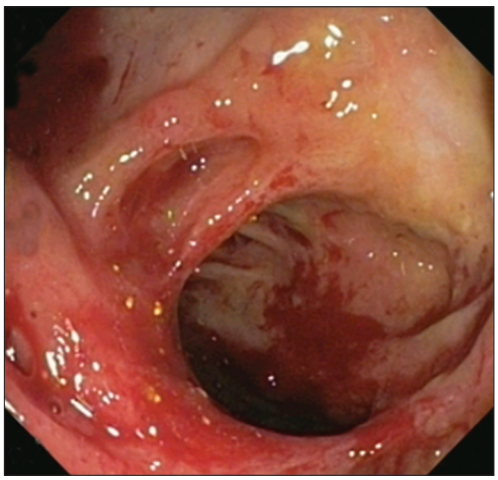

Figure 1: Bleeding colonic diverticular ulcer

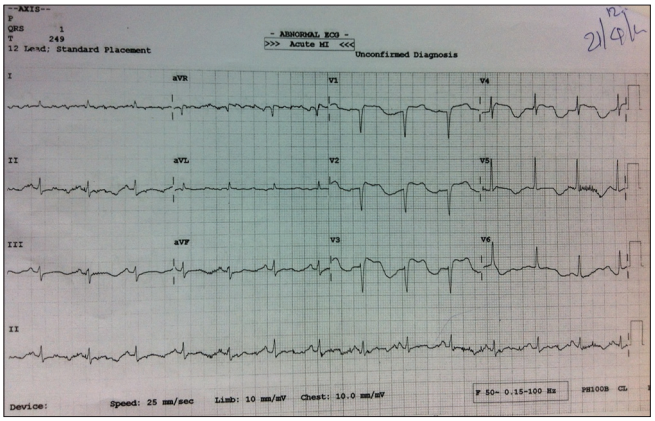

Figure 2: Electrocardiogram (ECG) showing ST elevation in the anterior leads

many developing countries, for example, prothrombin complex concentrates including factor eight inhibitor bypassing activity or are not widely accessible, for example, hemodialysis or continuous venovenous hemofiltration.

Data regarding safety of dabigatran in elderly and underweight patients is sparse. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, largest study conducted on dabigatran, average weight of dabigatran treated patients in the 110 and 150 mg group was 82.9 and 82.5 kg, respectively; with only a sixth of patients having weight below 73 kg.[3] It is highly unlikely that RE-LY trial data can be extrapolated and used in an underweight patient like the present case. In a review of 78 bleeding episodes identified during an audit in Australia and New Zealand, advanced age was identified as one of the factors contributing to bleeding risk and this was compounded further by the presence of impaired renal function (common in elderly) and low body weight (<60 kg).[4] Bleeding risk in these frail elderly patient was not completely mitigated by dose reduction.[4]

In RE-LY trial, compared to warfarin, dabigatran was associated with a small but significant increase in the rate of myocardial infarction (MI).[3] In a recent meta-analysis of seven randomized control trials (n = 30,514), association of dabigatran with a higher risk of MI or acute coronary syndrome was confirmed further.[5] Till cardiac risk of dabigatran is further investigated, clinicians should apply caution in prescribing the drug to high-risk patients.[5]

Current case illustrates the limitations of prescribing dabigatran in resource-limited setting and a need for appropriate prescriber education program to restrict complications of therapy.

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