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OPINION REVIEW

- 2363 eHealth, telehealth, and telemedicine in the management of the COVID-19 pandemic and beyond: Lessons learned and future perspectives

Giocalone A, Marin L, Febbi M, Franchi T, Tovani-Palone MR

MINIREVIEWS

- 2369 Developing natural marine products for treating liver diseases

Wei Q, Guo JS

ORIGINAL ARTICLE

Case Control Study

- 2382 Analysis of bacterial spectrum, activin A, and CD64 in chronic obstructive pulmonary disease patients complicated with pulmonary infections

Fei ZY, Wang J, Liang J, Zhou X, Guo M

Retrospective Cohort Study

- 2393 Computed tomography perfusion imaging evaluation of angiogenesis in patients with pancreatic adenocarcinoma

Liu W, Yin B, Liang ZH, Yu Y, Lu N

Retrospective Study

- 2404 Epidemiological features and dynamic changes in blood biochemical indices for COVID-19 patients in Hebi

Nie XB, Shi BS, Zhang L, Niu WL, Xue T, Li LQ, Wei XY, Wang YD, Chen WD, Hou RF

Clinical Trials Study

- 2420 Identification and predictive analysis for participants at ultra-high risk of psychosis: A comparison of three psychometric diagnostic interviews

Wang P, Yan CD, Dong XJ, Geng L, Xu C, Nie Y, Zhang S

- 2429 Prognostic significance of peritoneal metastasis from colorectal cancer treated with first-line triplet chemotherapy

Bazarbashi S, Alghabban A, Aseafan M, Aljubran AH, Alzahrani A, Elhassan TA

Observational Study

- 2439 Effect of intraoperative cell rescue on bleeding related indexes after cesarean section

Yu YF, Cao YD

Prospective Study

- 2447 Effectiveness of the combination of workshops and flipped classroom model to improve tube fixation training for nursing students
Wang YC, Cheng HL, Deng YM, Li BQ, Zhou XZ

META-ANALYSIS

- 2457 Mortality in patients with COVID-19 requiring extracorporeal membrane oxygenation: A meta-analysis
Zhang Y, Wang L, Fang ZX, Chen J, Zheng JL, Yao M, Chen WY

CASE REPORT

- 2468 Escitalopram-induced hepatitis: A case report
Wabont G, Ferret L, Houdre N, Lepied A, Bene J, Cousein E
- 2474 Fatal community-acquired bloodstream infection caused by *Klebsiella variicola*: A case report
Long DL, Wang YH, Wang JL, Mu SJ, Chen L, Shi XQ, Li JQ
- 2484 Endoscopic extraction of a submucosal esophageal foreign body piercing into the thoracic aorta: A case report
Chen ZC, Chen GQ, Chen XC, Zheng CY, Cao WD, Deng GH
- 2491 Severe tinnitus and migraine headache in a 37-year-old woman treated with trastuzumab for breast cancer: A case report
Liu YZ, Jiang H, Zhao YH, Zhang Q, Hao SC, Bao LP, Wu W, Jia ZB, Jiang HC
- 2497 Metastatic urothelial carcinoma harboring *ERBB2/3* mutations dramatically respond to chemotherapy plus anti-PD-1 antibody: A case report
Yan FF, Jiang Q, Ru B, Fei XJ, Ruan J, Zhang XC
- 2504 Retroperitoneal congenital epidermoid cyst misdiagnosed as a solid pseudopapillary tumor of the pancreas: A case report
Ma J, Zhang YM, Zhou CP, Zhu L
- 2510 Immunoglobulin G4-related kidney disease involving the renal pelvis and perirenal fat: A case report
He JW, Zou QM, Pan J, Wang SS, Xiang ST
- 2516 Fluoroscopic removal of fractured, retained, embedded Z self-expanding metal stent using a guidewire lasso technique: A case report
Bi YH, Ren JZ, Li JD, Han XW
- 2522 Treatment and five-year follow-up of type A insulin resistance syndrome: A case report
Chen YH, Chen QQ, Wang CL
- 2529 Effective response to crizotinib of concurrent *KIF5B-MET* and *MET-CDR2*-rearranged non-small cell lung cancer: A case report
Liu LF, Deng JY, Lizaso A, Lin J, Sun S

- 2537** Idarucizumab reverses dabigatran-induced anticoagulation in treatment of gastric bleeding: A case report
Jia Y, Wang SH, Cui NJ, Liu QX, Wang W, Li X, Gu YM, Zhu Y
- 2543** Immunoglobulin G4-related disease involving multiple systems: A case report
An YQ, Ma N, Liu Y
- 2550** Daptomycin and linezolid for severe methicillin-resistant *Staphylococcus aureus* psoas abscess and bacteremia: A case report and review of the literature
Hong XB, Yu ZL, Fu HB, Cai ZH, Chen J
- 2559** Isolated scaphoid dislocation: A case report and review of literature
Liu SD, Yin BS, Han F, Jiang HJ, Qu W
- 2569** Dual biologic therapy with ocrelizumab for multiple sclerosis and vedolizumab for Crohn's disease: A case report and review of literature
Au M, Mitrev N, Leong RW, Kariyawasam V
- 2577** Cardiac rehabilitation in a heart failure patient after left ventricular assist device insertion and subsequent heart transplantation: A case report
Yang TW, Song S, Lee HW, Lee BJ
- 2584** Large retroperitoneal atypical spindle cell lipomatous tumor, an extremely rare neoplasm: A case report
Bae JM, Jung CY, Yun WS, Choi JH
- 2591** Hepatocellular carcinoma effective stereotactic body radiotherapy using Gold Anchor and the Synchrony system: Two case reports and review of literature
Masuda S, Tsukiyama T, Minagawa Y, Koizumi K, Kako M, Kinbara T, Haruki U
- 2604** Mantle cell lymphoma with endobronchial involvement: A case report
Ding YZ, Tang DQ, Zhao XJ
- 2610** Fatal systemic emphysematous infection caused by *Klebsiella pneumoniae*: A case report
Zhang JQ, He CC, Yuan B, Liu R, Qi YJ, Wang ZX, He XN, Li YM
- 2616** Takotsubo cardiomyopathy misdiagnosed as acute myocardial infarction under the Chest Pain Center model: A case report
Meng LP, Zhang P
- 2622** Cystic teratoma of the parotid gland: A case report
Liu HS, Zhang QY, Duan JF, Li G, Zhang J, Sun PF
- 2629** Silver dressing in the management of an infant's urachal anomaly infected with methicillin-resistant *Staphylococcus aureus*: A case report
Shi ZY, Hou SL, Li XW
- 2637** Drain-site hernia after laparoscopic rectal resection: A case report and review of literature
Su J, Deng C, Yin HM

- 2644** Synchronized early gastric cancer occurred in a patient with serrated polyposis syndrome: A case report

Ning YZ, Liu GY, Rao XL, Ma YC, Rong L

- 2650** Large cystic-solid pulmonary hamartoma: A case report

Guo XW, Jia XD, Ji AD, Zhang DQ, Jia DZ, Zhang Q, Shao Q, Liu Y

LETTER TO THE EDITOR

- 2657** COVID-19 pandemic and nurse teaching: Our experience

Molina Ruiz JC, Guerrero Orriach JL, Bravo Arcas ML, Montilla Sans A, Escano Gonzalez R

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Editorial Board Member of *World Journal of Clinical Cases*, Nicolae Gica, Doctor, PhD, Assistant Professor, Chief Doctor, Surgeon, Department of Obstetrics and Gynecology Surgery, Carol Davila University of Medicine and Pharmacy, Bucharest 063377, Romania. gica.nicolae@umfcd.ro

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Idarucizumab reverses dabigatran-induced anticoagulation in treatment of gastric bleeding: A case report

Yu Jia, Shao-Hua Wang, Na-Juan Cui, Quan-Xi Liu, Wei Wang, Xue Li, Ya-Mei Gu, Yan Zhu

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Yu Jia, Shao-Hua Wang, Na-Juan Cui, Quan-Xi Liu, Wei Wang, Xue Li, Yan Zhu, Department of Gastroenterology, Hospital of Integrated Traditional Chinese and Western Medicine, Beijing 100039, China

Ya-Mei Gu, Department of General Practice, Tiancun Community Health Service Centre, Beijing 100049, China

Corresponding author: Yan Zhu, MS, Attending Doctor, Department of Gastroenterology, Hospital of Integrated Traditional Chinese and Western Medicine, No. 3 East Yongding Road, Haidian District, Beijing 100039, China. zy815925@163.com

Abstract

BACKGROUND

The drug instructions for dabigatran recommend adjusting the dosage to 110 mg twice daily for patients with bleeding risk, and performing at least one renal function test per year for patients with moderate renal impairment. However, owing to chronic insidiously worsening renal insufficiency, dabigatran can still accumulate abnormally, necessitating therapy with idarucizumab to reverse the anticoagulation due to severe erosive gastritis with widespread stomach mucosal bleeding.

CASE SUMMARY

A 76-year-old woman with a history of atrial fibrillation who took dabigatran 110 mg twice daily as directed to lessen the chance of stroke, was transported to the hospital with hematemesis and melena. Laboratory findings revealed severe life-threatening, blood-loss-induced anemia with a hemoglobin (Hb) level of 41.0 g/L and marked coagulation abnormalities with thrombin time (TT) > 180 s, most likely caused by dabigatran-induced metabolic disorder. Aggressive acid suppressive, hemostatic, and blood transfusion therapy resulted in the misconception that the bleeding was controlled, with subsequent rebleeding. Idarucizumab was administered in a timely manner to counteract dabigatran's anticoagulant impact, and 12 h later, TT was determined to be 17.4 s, which was within the normal range. Finally, the patient had no active bleeding signs and laboratory findings showed an Hb level of 104 g/L and TT of 17.7 s.

CONCLUSION

Renal function, coagulation function, and dabigatran concentration should be regularly monitored in older patients. Proton pump inhibitor and dabigatran coadministration is still controversial in preventing upper gastrointestinal tract

bleeding.

Key Words: Idarucizumab; Dabigatran; Gastric bleeding; Atrial fibrillation; Case report

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Core Tip: The anticoagulatory effect of dabigatran resolves completely after five half-lives, which is approximately 2.5-3.5 d after the last dose for patients with normal renal function. Thrombin time (TT) is sensitive to the effects of dabigatran and can be prolonged even with trivial amounts of the drug. This patient exhibited persistent bleeding in the normal coagulation test (except for TT), possibly due to the anticoagulatory effects of the drug administered 4 days after the last dose for her renal insufficiency. Therefore, idarucizumab was administered for hemostasis, thus stopping the bleeding. This case highlights the importance of regular monitoring of renal function in older patients.

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INTRODUCTION

Dabigatran is an oral direct-acting thrombin inhibitor that was initially approved by the US Food and Drug Administration for the prevention of stroke and systemic embolism caused by nonvalvular atrial fibrillation (AF)[1,2]. It is considered safer and more effective than warfarin and does not require regular coagulation monitoring or dose adjustment, except for those with renal insufficiency (RI), advanced age, and low body weight[3].

However, even long-term dose-adjusted dabigatran therapy in older patients may also increase the risk of major bleeding such as the gastrointestinal (GI) hemorrhage described in this report or cerebral hemorrhage. Idarucizumab was introduced as a dabigatran antidote in December 2015, and its safety and efficacy have been proven in various studies[4]; however, clinical data are still limited, especially in Asians. Here, we report a case of an older Asian woman whose coagulation function was timely and successfully restored by idarucizumab to rescue her from this life-threatening GI bleeding.

CASE PRESENTATION

Chief complaints

On January 26, 2021, a 76-year-old Asian woman was admitted to our hospital with hematemesis and melena, which she had never experienced before and began the previous day.

History of present illness

Four days prior to this reported incident, the patient experienced upper abdominal discomfort and appetite loss without any recognizable precipitating factors.

History of past illness

The patient had a history of AF since 2019, and had been taking dabigatran (110 mg twice daily) to reduce her stroke risk. She had stopped taking dabigatran for at least 4 d before presenting to the hospital. In addition, she had a history of hypertension and coronary atherosclerotic heart disease for > 20 years, type 2 diabetes for > 5 years, and chronic RI (creatinine clearance 30-50 mL/min per 1.73 m²) for 1 year. The present event occurred > 12 years after she underwent surgery for bladder cancer and 7 years after thyroid nodule surgery.

Personal and family history

The patient had no other disease history and relevant family disease history.

Physical examination

On arrival at the ward, the temperature, heart rate, respiratory rate, and blood pressure of the patient

were 36.3 °C, 90 bpm, 18 breaths/min, and 105/80 mmHg, respectively. Her palpebral conjunctiva and complexion were pale, abdomen was soft, and middle and upper abdomen showed slight tenderness. In addition, the bowel sounds of the patient were 6/min.

Laboratory examinations

The routine blood tests of the patient showed a white blood cell count of 6890/ μ L and hemoglobin (Hb) level of 41 g/dL. The coagulation function test showed the following results: thrombin time (TT) > 180 s; activated partial thromboplastin time, 36.2 s; and international normalized ratio (INR), 1.20. The biochemical parameters of the patient were as follows: albumin, 34.6 g/L; blood urea nitrogen, 26.96 mmol/L; and serum creatinine, 251.0 μ mol/L (Table 1). The tumor markers -fetoprotein, carcinoembryonic antigen, cancer antigen (CA)199, and CA125 were all within the normal range. The 13 C urea breath test for detection of *Helicobacter pylori* (*H. pylori*) was negative.

Imaging examinations

Computed tomography of the entire abdomen showed no obvious abnormalities and electrocardiography showed normal sinus rhythm and abnormal ST-T changes. The electronic gastroscopy showed acute erosive gastritis with extensive gastric mucosal bleeding (Figure 1).

FINAL DIAGNOSIS

Acute erosive gastritis with extensive gastric mucosal bleeding was diagnosed using an electronic gastroscope.

TREATMENT

The patient was administered 2 U 400 mL packed red blood cells (PRBCs), a proton-pump inhibitor (PPI), and octreotide intravenously. On day 2, Hb level increased to 67 g/L and the chief complaints were nausea and retching, which appeared to be well controlled; the remaining concern was abnormal coagulation. On the next day, the patient defecated approximately 400 mL black stools with an Hb level, TT, PT and INR of 44 g/L, 121.20 s, 14.2 s, and 1.25, respectively and was immediately administered 2 U PRBCs.

Single doses of idarucizumab (2.5 g) were administered twice *via* intravenous infusion to reverse the effect of dabigatran, and the related commonly encountered adverse reactions such as fever, headache, hypokalemia, and delirium were not observed. Twelve hours later, the TT of the patient was 17.4 s, which was within the normal range. On day 4, she was administered an additional 2 U PRBCs for the third time, without symptoms of hematemesis and melena on the following days.

OUTCOME AND FOLLOW-UP

The patient had no recurrence of AF during hospitalization and her routine stool and occult blood test results were normal. Finally, she was discharged on hospitalization day 14, with Hb level of 104 g/L and TT of 17.7 s.

DISCUSSION

In this study, we presented the case of an older Asian woman whose coagulation function was effectively restored using idarucizumab to reverse the life-threatening GI bleeding experienced following administration of dabigatran. The prodrug of dabigatran, dabigatran etexilate, is rapidly converted to its active form following oral administration. It is an oral non-vitamin K antagonist anticoagulant that acts as a direct reversible and competitive inhibitor of both free and platelet-bound thrombin, thereby affecting the final step of blood clotting[5]. Because of properties such as a short half-life, rapid onset of action, fewer effects on food and drugs, and no INR monitoring requirement[6], dabigatran is deemed a safer and more effective medicine for preventing stroke than some other available agents.

Nevertheless, the elimination of dabigatran is highly dependent on the kidney, through which approximately 85% of plasma dabigatran is excreted, and the process can be prolonged with RI[7]. The RE-LY study demonstrated that dabigatran could reduce all-cause mortality and intracranial hemorrhage, but increased GI bleeding compared with warfarin. The risk of dabigatran-related GI bleeding seems to be evenly distributed between the upper and lower canals (53% *vs* 47%), whereas

Table 1 Laboratory values during hospitalization

Hospital day	Hb (g/L)	TT (s)	PT (s)	APTT (s)	INR	SCr (μmol/L)
Day 1	41	> 180	13.7	36.2	1.20	251
Day 2	67	N/A	N/A	N/A	N/A	N/A
Day 3	44	121.20	14.2	36.3	1.25	229
Day 4	56	17.40	13.1	25.9	1.15	213
Day 5	57	18	12.6	26.0	1.10	202
Day 6	76	N/A	N/A	N/A	N/A	182
Day 8	78	20.90	12.0	28.0	1.04	N/A
Day 10	85	17.70	12.7	29.6	1.11	N/A
Day 14	104	N/A	N/A	N/A	N/A	216

Hb: Hemoglobin (normal concentration: 110-150 g/L); TT: Thrombin time (normal: 14-21 s); PT: Prothrombin time (normal: 9.8-12.7 s); APTT: Activated partial thromboplastin time (normal: 21.1-36.5 s); INR: International normalized ratio (normal: 0.85-1.15); SCr: Serum creatinine (normal: 44-133 μmol/L); N/A: Not available.

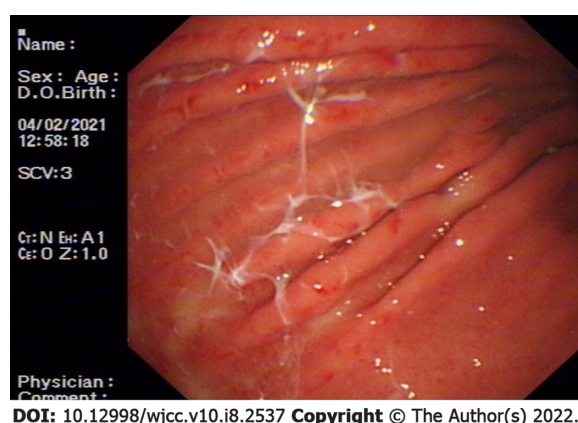


Figure 1 Images of esophagogastroduodenoscopy captured on February 4, 2021 showing erosive and contact bleeding of gastric body mucosal surface.

warfarin-related upper canal bleeding dominated (75% *vs* 25%).

The mechanism by which bleeding is induced remains unclear. One possible theory suggests that the local metabolism of dabigatran etexilate increases the concentration of active dabigatran during transit through the GI tract^{8,9}. Dabigatran-induced GI hemorrhage is also related to age and primarily occurs in patients aged ≥ 75 years.^[10]

H. pylori infection, liver cirrhosis, malignant tumors, genetic factors, history of major bleeding, peptic ulcers, and GI injury such as diverticulosis and intestinal vascular dysplasia can also increase the risk of bleeding^{11,12}. A study showed that coadministration of a PPI and dabigatran not only markedly reduced the risk of upper GI hemorrhage, but also the dabigatran plasma levels in patients with AF^[13].

In this case report, the patient was a 76-year-old Asian woman with a history of AF and concealed progressive RI. She had undergone long-term dabigatran therapy with dose adjustments for 1 year, regular blood coagulation function monitoring, and oral administration of a PPI. The massive hemorrhage from the gastric mucosa was likely induced by prolonged dabigatran excretion because of RI.

Idarucizumab is a humanized monoclonal antibody that specifically and efficiently inhibits the biological activity of dabigatran etexilate. After antibody-antigen binding, it irreversibly neutralizes the anticoagulant effect. The binding affinity of idarucizumab to dabigatran is 350 times higher than that of dabigatran to thrombin, and the reversal effect shows rapid onset and lasts 12 h, which is suitable for life-threatening bleeding, uncontrolled hemorrhage, or emergency surgery in patients administered dabigatran^[14,15]. A single dose of 5 g idarucizumab is reported to be sufficient to reverse the effect of dabigatran etexilate in 98% of patients, and the effect is maintained in most patients for 24 h^[16].

Considering the extensive gastric mucosal bleeding experienced by this patient, endoscopic hemostasis was less efficient. The conventional therapeutic regimen of acid suppression, hemostasis,

and blood transfusion did not achieve hemostasis in this patient and idarucizumab was administered to reverse the effect of dabigatran to rescue her from the second episode of life-threatening bleeding. Subsequently, the patient, whose coagulation function was normalized during hospitalization, was relieved of the symptoms of hematemesis and melena, and her Hb level increased to 104 g/L on day 14. Finally, the patient was discharged in stable conditions.

This study had the following limitations and shortcomings that are worth mentioning. (1) The serum level of dabigatran was not measured because of restricted laboratory conditions; (2) Colonoscopy was not performed because we could not obtain informed consent from the patient; and (3) We were unable to detect any possible intracardiac thrombus caused by AF because the transesophageal echocardiography technique was unavailable.

CONCLUSION

We report a case of safe and successful reversal of dabigatran-induced abnormal coagulation function by idarucizumab. In addition, we provide evidence to support recommendations for regular renal and coagulation function tests and dabigatran concentration monitoring for older patients where clinical conditions permit. This is to ensure that proper dose adjustments of dabigatran are instituted or the drug discontinuation is timely if unpredictable blood loss occurs. As mentioned in the discussion regarding dabigatran-induced GI-bleeding-related factors, especially *H. pylori* infection, there is currently no consensus on the benefits of coadministration of PPIs with dabigatran, which warrants further investigation.

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FOOTNOTES

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Country/Territory of origin: China

ORCID number: Yu Jia 0000-0002-1743-4943; Shao-Hua Wang 0000-0002-9085-5218; Na-Juan Cui 0000-0002-7867-6153; Quan-Xi Liu 0000-0002-6526-2840; Wei Wang 0000-0001-5057-5433; Xue Li 0000-0001-8880-1133; Ya-Mei Gu 0000-0001-7173-1183; Yan Zhu 0000-0001-5906-1412.

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