Gastrointestinal bleeding in a patient on multiple medications including edoxaban

Introduction

Edoxaban is an oral factor Xa inhibitor which was found to be non-inferior to the vitamin K antagonist warfarin for stroke prevention in atrial fibrillation in the manufacturer-sponsored ENGAGE AF-TIMI 48 trial (Giugliano et al, 2013). Like other direct oral anticoagulants, edoxaban is expected to have fewer drug–drug interactions than vitamin K antagonists. This article reports a patient with gastrointestinal bleeding who was taking multiple medications including edoxaban.

Discussion

Most probably, this patient's bleeding was caused by edoxaban. Before starting edoxaban, he had neither gastrointestinal problems nor anaemia, despite having polymorbidities and taking multiple medications. After cessation of edoxaban, anaemia did not recur, although the bleeding site and edoxaban levels were not assessed.

Elderly patients on edoxaban seem more prone to gastrointestinal bleeding: in the ENGAGE AF-TIMI 48 study, patients ≥75 years taking edoxaban suffered more frequently from gastrointestinal bleeding than those taking warfarin (Kato et al, 2016). This might be the result of the active anticoagulant being present in the gut. Whereas vitamin K antagonists have 99% bioavailability and unabsorbed vitamin K antagonists are inactive, edoxaban, like other direct oral anticoagulants, is partially excreted in the faeces as an active drug (Bathala et al, 2012).

Bleeding might be promoted by drug–drug interactions. Edoxaban is a substrate of the P-glycoprotein efflux-transporter system and is metabolized by the cytochrome P450 isoenzymes 3A4 (CYP3A4) and 2J9 (CYP2J9) (Parasrampuria et al, 2016). Among the patient's drugs, amiodarone inhibits P-glycoprotein, CYP3A4 and CYP2J9 activity. In healthy subjects, edoxaban levels increased by 40% when concomitantly administered with amiodarone (Mendell et al, 2013). In ENGAGE AF-TIMI 48, amiodarone-treated patients had an increase in non-major bleeding (Steffel et al, 2015). Edoxaban levels were measured in 6780 of the 14 069 patients and were higher in amiodarone-treated patients (Steffel et al, 2015).

It is unknown whether leflunomide and methotrexate have contributed to bleeding since no data are available about drug–drug interactions. However, leflunomide can potentiate the effect of warfarin and inhibit platelet aggregation (Lim and Pande, 2002). Applying the drug interaction probability scale to the current patient and his comedication gives a score of 5, indicating a probable drug–drug interaction (Horn et al, 2007).

While drug–drug interactions of vitamin K antagonists can be easily revealed by deviations in the international normalized ratio, drug–drug interactions of direct oral anticoagulants are more difficult to detect (Cuker et al, 2014). Measurements of anticoagulant activity in edoxaban-treated patients are, so far, not standardized (Douxfils et al, 2016). Measurement of direct oral anticoagulant plasma levels is not available in routine care. Thus drug–drug interactions will be only detected if a complication – either bleeding or thromboembolism – occurs. Studies of drug–drug interactions of direct oral anticoagulants would be much easier if tests to measure the plasma level of direct oral anticoagulants were available. Independent data about drug–drug interactions of direct oral anticoagulants are needed.

Professor Claudia Stöllberger, Physician, 2nd Medical Department, Krankenanstalt Rudolfstiftung, A-1030 Wien, Austria

Dr Peter Pommer, Physician, Fachklinik Allgäu, Pfronten, Germany

Correspondence to: Professor C Stöllberger (claudia.stoellberger@chello.at)

CASE REPORT

A 76-year-old man was admitted complaining of weakness and black stools for several days. He had a 1-year history of chronic obstructive pulmonary disease, a 5-year history of seropositive rheumatoid polyarthritis treated with methotrexate and leflunomide, an 8-year history of arterial hypertension, a 27-year history of peripheral arterial occlusive disease with percutaneous dilatation of the right femoral artery at 52 years of age and an 8-year history of type 2 diabetes. He had a history of 50 pack/years of cigarettes and stopped smoking 3 weeks before.

Ten weeks before this admission, atrial fibrillation was diagnosed, edoxaban 60 mg/day was initiated and successful electrical cardioversion carried out. Amiodarone was initiated 4 weeks later because of recurrent atrial fibrillation. Two weeks before the current admission, he was hospitalized because of heart failure. A further cardioversion was carried out. Anticoagulant therapy with edoxaban 60 mg/day was continued. Laboratory findings showed anaemia (*Table 1*) but no cause was looked for.

At the time of this admission the patient was taking edoxaban 60 mg/day, indacaterol 85 µg/day and glycopyrronium 43 µg/day, ramipril 2.5 mg/day, bisoprolol 5 mg/day, amiodarone 200 mg/day, metformin 1000 mg/day, torasemide 25 mg/day, pantoprazole 20 mg/day, leflunomide 20 mg/day, methotrexate 15 mg/week and colecalciferol 10 000 IU/week.

Physical examination was normal, except for pale skin. His weight was 63 kg with a body mass index of 19.9 kg/m^2. Blood pressure was 80/50 mmHg. The electrocardiogram showed atrial fibrillation with 107 beats/min, low voltage and repolarization abnormalities.

Blood tests showed that he was still anaemic (*Table 1*) so he received five units of packed erythrocytes. Gastroscopy revealed haemorrhagic erosions of the gastric mucosa, but no bleeding source. Colonoscopy showed blood in the colon and several diverticula. Bleeding from a diverticulum was suspected as the cause of his blood loss. Anticoagulant therapy was stopped, after which anaemia did not recur. He was discharged after 4 weeks in a rehabilitation clinic. At discharge his electrocardiogram showed sinus rhythm.

Table 1. Laboratory findings

Parameter (normal range)	First admission	Second admission	Current admission
Creatinine mg/dl (<1.2)	0.71	0.94	1.2
Creatinine clearance* ml/min	79	60	47
Potassium mmol/litre (3.5–5.5)	4.4	3.86	4.8
Sodium mmol/l (135–145)	131	142	133
Haemoglobin g/dl (14–18)	13.1	8.7	3.6
Erythrocytes /pl (4.4–6.0)	3.99	2.87	1.24
Haematocrit % (38–52)	40.1	27	12
Thrombocytes /nl (140–400)	165	236	207
International normalized ratio	1.16	1.3	1.6
Activated partial thromboplastin time sec (20–40)	45	42	41.4
Alanine aminotransferase U/litre (0–30)	24	14	19
Bilirubin mg/dl (0.3–1.2)	0.9	NM	0.8
Total protein g/litre (35–52)	NM	NM	24.9

**estimated according to the Cockcroft–Gault formula. NM = not measured*

Conclusions

Care should be taken if direct oral anticoagulants are prescribed to patients taking multiple medications, especially if they include drugs which affect P-glycoprotein, CYP3A4 or CYP2J9. If a patient develops anaemia during anticoagulant therapy, either with a direct oral anticoagulant or a vitamin K antagonist, the bleeding source should be sought and the need for anticoagulant therapy should be reassessed. BJHM

LEARNING POINTS

- The influence of multiple medications on the safety and efficacy of edoxaban, an oral factor Xa inhibitor, is unknown.
- Gastrointestinal bleeding often occurs during anticoagulant therapy without a definite bleeding source.
- Co-medication with drugs known to inhibit P-glycoprotein, or the cytochrome enzymes CYP3A4 or CYP2J9, might increase serum levels of edoxaban and thus increase the bleeding tendency.
- Care should be taken if direct oral anticoagulants are prescribed to patients taking multiple medications, especially if any medications are known to inhibit P-glycoprotein, CYP3A4 or CYP2J9 activity.

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