CASE REPORT

Uncontrollable haemorrhage following dabigatran prophylaxis

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SUMMARY

An 88-year-old man, on dabigatran anticoagulation after a total hip replacement 1 week before admission, presented with acute abdominal pain associated with malaena and haematemesis. After examination and investigation, he was found to have a perforated viscus and underwent laparotomy. The perforation was surgically repaired, but the patient suffered from a massive haemorrhage during the operation, requiring intensive care admission postoperatively. The patient subsequently deteriorated despite aggressive treatment and died several days later.

BACKGROUND

This is a case of massive haemorrhage following routine venous-thromboembolic (VTE) prophylaxis, with a reduced dose of a new anticoagulant, dabigatran, in a patient with concurrent gastrointestinal and renal problems. As dabigatran has no antidote, and as its effects cannot be reliably measured using standard clotting tests, this case highlights the need for extra vigilance in its administration.

CASE PRESENTATION

An 88-year-old man was referred to accident and emergency by his general practitioner with a suspected acute abdomen. The history revealed acute onset epigastric pain in the week prior to admission, with episodes of malaena and haematemesis. Medical history of note included stage 3 renal failure, benign prostatic hypertrophy and dyspepsia, which was being treated with lansoprazole. Prior to this acute admission the patient had been living at home with his wife and mobilising independently. A week before presentation the patient had had a total hip replacement. The operation and post-operative period were uneventful and he was discharged the next day on dabigatran 150 mg a day for VTE prophylaxis. On this acute admission, the patient's dabigatran was changed to dalteparin, as per local VTE protocols.

On examination, the patient had signs of an acute abdomen.

INVESTIGATIONS

A contrast CT of the abdomen and pelvis confirmed a perforated viscus with evidence of free air and fluid within the abdomen.

Haematology and biochemistry results on admission showed mild anaemia and neutrophilia, thrombocytosis, raised C reactive protein (CRP) and a raised lactate dehydrogenase. Electrolyte abnormalities were in keeping with the patient's renal

impairment (see table 1). A clotting screen was not taken on admission.

TREATMENT

Emergency laparotomy was carried out. The perforation was successfully identified and closed; however, blood loss during the operation exceeded 3000 mL. The intraoperative clotting results were severely deranged, with an international normalised ratio (INR) greater than 12 (see table 1). While in theatre, the patient received 3500 IU of Octaplex (a complex of coagulation factors II, VII, IX, X and proteins C and S), 4 units of fresh frozen plasma (FFP), 4 units of red blood cells (RBCs), 1 g of tranexamic acid and 20 mL of 10% calcium gluconate. Owing to the extent of his coagulopathy, the patient was left with an open, packed abdomen and transferred, intubated and ventilated, to the intensive care unit (ICU). Over the next few days the patient received a further 4 units of FFP, 6 units of RBCs and 1 unit of platelets. Inotropic support, as well as continuous venovenous haemodiafiltration (CVVHDF), was also initiated.

OUTCOME AND FOLLOW-UP

The patient returned to theatre the next day, where the abdomen was closed and abdominal drains inserted. He then returned to ICU for further management including intermittent positive pressure ventilation, inotropic support and CVVHDF. He also received further blood products over the following days. Unfortunately his condition continued to deteriorate and he died.

DISCUSSION

Dabigatran is a relatively new anticoagulant drug licensed for primary prevention of VTE events in adults who have had elective total knee replacement or elective total hip replacement surgery. It is also licensed for the prevention of stroke and systemic embolism (SSE) in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors.¹

Dabigatran acts by directly inhibiting thrombin and not by depleting clotting factors.² As thrombin is involved in the final common pathway of the clotting cascade, dabigatran acts as a very effective anticoagulant.

The benefits of dabigatran over older anticoagulants, such as warfarin, are that it has a rapid onset of action and does not require therapeutic monitoring. As such, it is gaining increasing popularity. However, it is important to note that dabigatran

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Table 1 Series of haematology and biochemistry results during patient admission

	On admission	Intraop (emergency laparotomy)	10 h postoperation	16 h postoperation	1 h post-CVVHDF commencement (24 h postoperation)	5 h post-CVVHDF commencement (28 h postoperation)	4.5 days postoperation	Normal values
Haemoglobin (g/dL)	12.4	6.1	8.9	10.0	9.3	8.7		13–18.1
INR		>12.0	3.6	3.8	3.4	2.6		
APTT (s)		138.0	89.9	92.7	87.5	77.5		22–36
APTT ratio		5.1	3.3	3.4	3.2	2.8		0.8–1.4
Prothrombin time (s)			33.6	35.0	31.7	24.8		8.5–13
Clauss fibrinogen (g/L)		1.7						2–4
Thrombin time (s)							266.0	14–20
Mean cell haemoglobin (pg)	32.1	32.5	32.6	31.7	31.7	31.6		26.9–32
White cell count ($\times 10^9$)	8.6	1.3	3.1	5.0	7.0	7.5		3.7–11
Neutrophils	8.0	1.2	2.9	4.7	6.6	7.0		1.7–7.5
Red blood count ($\times 10^9$)	3.86	1.89	2.73	3.14	2.93	2.75		4.3–6
Platelets	572	143	130	156	151	144		150–450
Haematocrit (L/L)	0.370	0.179	0.250	0.288	0.266	0.253		0.39–0.501
C reactive protein (mg/L)	68		171	230		314		0–5
Sodium (mmol/L)	131		140	140		141		136–145
Potassium (mmol/L)	5.1		4.0	4.8		4.96		3.5–5.1
Urea (mmol/L)	14.5		17.7	18.9		13.2		3.2–7.4
Serum creatine (μ mol/L)	180		243	276		201		63–111
Bicarbonate (mmol/L)			19.0	18.0		20.0		22–29
eGFR (mL/min/1.73 m ²)	29		20	18		25		
Total protein (g/L)	72		52	53		44		64–83
Albumin (g/L)	38		24	24		18		35–50
Alanine transferase (U/L)	43		22	23		20		10–35
Alkaline phosphatase (U/L)	102		54	58		50		40–150
Total bilirubin	33		93	89		59		3.4–20.5
Lactate dehydrogenase (U/L)	339							125–243

APTT, activated partial thromboplastin time; CVVHDF, continuous venovenous haemodiafiltration; eGFR, estimated-glomerular filtration rate; INR, international normalized ratio.

has no known antidote and is eliminated unchanged through the urine, requiring dose-reduction in known cases of renal impairment. For this reason, guidelines from the Medicines and Healthcare products Regulatory Agency (MHRA) contraindicate dabigatran for use in patients with severe renal impairment (creatinine clearance <30 mL/min), and it is advised that the dose should be reduced in patients with moderate renal impairment (creatinine clearance 30–50 mL/min). Similar precautions exist with patients over the age of 75.¹

A series of blood results relating to the patient's admission are shown in table 1. Although INR is not sensitive to dabigatran,³ it is interesting that during primary surgery, the patient's INR was recorded to be greater than 12.0. The activated partial thromboplastin time (aPTT) and aPTT ratio were also markedly raised signifying just how pronounced the patient's coagulopathy was. It is important to note that the intraoperative blood results show that the patient was neutropenic. This could have been due to a combination of sepsis with secondary coagulopathy because of dabigatran or to dabigatran alone. Alternatively, he could have developed a rare acquired coagulopathy. Although platelet levels were low, disseminated intravascular coagulation was excluded as fibrinogen levels were effectively normal.

As dabigatran does not lead to the depletion of clotting factors, their administration, in cases of dabigatran toxicity, is not anticipated to be very effective, and is only recommended as a last resort when other supportive measures and attempts at bleeding control have failed.² The ineffectiveness of these

measures was proven in this case as the patient remained massively coagulopathic after the administration of clotting factors during his primary surgery.

Evidence suggests that haemodialysis may be effective in removing approximately 60% of dabigatran.² However, haemodialysis was not available on site and so, after consultation with haematologists, the patient was started on CVVHDF 24 h post primary laparotomy in an attempt to reduce the levels of dabigatran. The patient's clotting function did improve while he was on CVVHDF (see table 1), but without analysis of the dialysate, there was no evidence that dabigatran was definitely removed.

Laboratory coagulation tests are best used as qualitative assessments in measuring the contribution of dabigatran to a bleeding event.² aPTT is used primarily for its negative predictive value, that is, if normal, it suggests that little anticoagulant activity is present. A mild increase in aPTT can be associated with clinically significant levels of dabigatran although the test becomes increasingly insensitive at higher levels of dabigatran, such as in overdose. A normal thrombin time (TT) rules out significant levels of dabigatran and is sensitive to the effects of therapeutic levels of the drug. It is less useful in overdose and is best used as a sensitive test to ensure the absence of dabigatran.³ It is important to note that this patient had a markedly increased TT of 266 s (normal range: 14–20 s) 4 days post primary surgery.

Problems of uncontrollable bleeding following dabigatran administration have been highlighted in a number of case reports from Japan in which patients receiving dabigatran for SSE suffered fatal haemorrhages.¹ These patients were over the

age of 75, had renal impairment, additional risk factors for bleeding and received a 'low' dose of dabigatran (220 mg/day). Half of these patients were also reported to have severe renal impairment. As a result of these reports, the advice for dabigatran prescribing has been strengthened by the MHRA to reiterate the need for regular, careful tests of renal function,¹ and for the need to monitor for signs of anaemia and bleeding—with a recommendation of dose reduction or cessation of treatment if renal impairment or bleeding occurs.^{1–4} The Ministry of Health, Labour and Welfare in Japan, where 81 cases of serious side effects, including gastrointestinal bleeding, have been reported since the launch of dabigatran, has also called for patients to be informed about how to look for signs of dangerous bleeding, such as bloody stools, and to inform their physicians immediately if such signs occur.⁴

It is important to note, however, that abnormal bleeding is a well-recognised adverse effect of any anticoagulant, and that all patients who are at increased risk of bleeding require close monitoring. However, the problem with dabigatran lies in its irreversibility, and whereas other anticoagulants, such as warfarin, can be reversed,⁵ such a safety net does not exist with dabigatran. Although it is wise to use any anticoagulant with caution in patients with concurrent gastric irritation, it may be prudent to contradict dabigatran in such cases when other reversible anticoagulants are available.

We believe that dabigatran directly influenced this patient's case by worsening his coagulopathy and therefore complicating an already life-threatening surgical emergency. Chronic renal failure became acute on chronic as the result of peritonitis, thus increasing the anticoagulant activity of dabigatran. In addition, the patient already had symptoms of dyspepsia prior to his hip replacement. He may have had duodenal erosion or an ulcer and the dabigatran may have directly led to duodenal perforation.

This case highlights the need for extreme caution in the use of this drug at all in elderly patients with moderate renal impairment and gastrointestinal symptoms. Stressing the need for physicians to closely monitor renal function in these patients, and for patients to recognise signs of bleeding, is vital. Dabigatran may be considered advantageous over older anticoagulants as it may increase compliance, and therefore treatment efficacy, due to the perceived reduction in venepuncture tests to monitor clotting factors, hence delivering a more comfortable experience for the patient. However, where regular renal function tests are required, regular venepuncture will be necessary, thereby removing the convenience conferred by dabigatran. Therefore, with no antidote and no truly sensitive method of monitoring this

drug currently available, we would advocate that an alternative anticoagulant such as low-molecular weight heparin is used in such patients, adjusting the dose according to the renal function of the patient.

Learning points

- ▶ Mild to moderate renal impairment may be enough to increase dabigatran to toxic levels.
- ▶ Even lower doses of dabigatran, as recommended by the guidelines, may cause complications in those with coexisting bleeding risks or gastrointestinal problems.
- ▶ There are currently no clotting tests reliable enough to monitor dabigatran anticoagulation.
- ▶ Alternative anticoagulants to dabigatran should be considered in patients with any risk factors for increased bleeding (eg, renal failure).

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REFERENCES

- 1 Medicines and Healthcare products Regulatory Agency. Dabigatran (Pradaxa): risk of serious haemorrhage—need for renal function testing [web page online]. *Drug Safety Update* 2011;5:A2. <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137771> (accessed Feb 2013).
- 2 University of Utah Health Care Thrombosis Service. Dabigatran (Pradaxa) principles and guidance for the reversal of effect and management of life threatening or major bleeding [pdf online]. The University of Utah Health Care 2011. http://healthcare.utah.edu/thrombosis/newagents/TS.Dabi_Bleeding.pdf (accessed Feb 2013).
- 3 University of Utah Health Care Thrombosis Service. Dabigatran (Pradaxa) laboratory monitoring overview [pdf online]. The University of Utah Health Care 2011. http://healthcare.utah.edu/thrombosis/newagents/TS.Dabi_lab.monitor.pdf (accessed Feb 2013).
- 4 Wood S. Deaths prompt dabigatran safety advisory in Japan [article online]. *theheart.org*. [Clinical Conditions>Arrhythmia/EP>Arrhythmia/EP] 2011. <http://www.theheart.org/article/1264365.do> (accessed Feb 2013).
- 5 Baker RI, Coughlin PB, Salem HH, et al. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis [journal online]. *Med J Aust* 2004;181:492–7. <https://www.mja.com.au/journal/2004/181/9/warfarin-reversal-consensus-guidelines-behalf-australasian-society-thrombosis-and> (accessed Feb 2013).

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