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Adding Herbal Products to Direct-Acting Oral Anticoagulants Can Be Fatal

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ABSTRACT

Direct-acting oral anticoagulants (DOACs) are used to prevent and treat systemic and cerebral embolisms in patients with non-valvular atrial fibrillation (NV-AF). The use of DOACs with herbal products without consulting healthcare professionals increases the possibility of drug–herb interactions and their adverse effects. An 80-year-old man on dabigatran with a known history of NV-AF presented with a 1-day history of haematemesis and black stool which began 3 days after he had started taking a boiled mixture of ginger and cinnamon. The patient was hypotensive and treated as a case of gastrointestinal bleeding and haemorrhagic shock. Despite continuous aggressive resuscitation measures including administration of a reversal agent for dabigatran, we were unable to control bleeding and the patient died within 24 hours. The interaction of ginger and cinnamon with dabigatran led to fatal bleeding.

LEARNING POINTS

- Direct-acting oral anticoagulants (DOACs) are frequently prescribed for patients with non-valvular atrial fibrillation.
- Combining herbal products (ginger and cinnamon) with DOACs can be fatal.
- Physicians should alert patients and caregivers about dangerous combinations and interactions.

KEYWORDS

Ginger, cinnamon, dabigatran

INTRODUCTION

In January 2019, the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) recommended direct-acting oral anticoagulants (DOACs) rather than warfarin in patients with non-valvular atrial fibrillation (NV-AF)[1].
The use of herbal products has become increasingly popular, especially in combination with conventional medicines and usually without the advice of a healthcare professional[2,3]. However, it is difficult to predict the pharmacokinetic and/or pharmacodynamic interactions when herbal products, such as ginger and cinnamon, are combined with DOACs. Here we present a case where self-administration of ginger and cinnamon together with dabigatran in an 80-year-old man caused fatal bleeding.

CASE DESCRIPTION

An 80-year-old male patient with a 4-year history of chronic NV-AF, type 2 diabetes mellitus and a history of dyslipidaemia presented to the emergency department with general weakness, nausea, vomiting of blood-tinged material, vague abdominal pain and black stool of 1 day's duration. He denied fever or diarrhoea. His regular medications included dabigatran 110 mg twice daily for 4 years to prevent thromboembolic events, metformin 1,000 mg twice daily and insulin glargine 20 units at night. The last dose of dabigatran was on the morning of presentation. There were no previous episodes of bleeding or decreases in haemoglobin since dabigatran was started 4 years previously. No new medications had been administered recently. The patient denied alcohol or tobacco consumption. However, he mentioned the recent use, without physician counselling, of 200 ml of a boiled mixture of ginger and cinnamon twice daily for 3 days before presentation to hospital.

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Physical examination was remarkable for overweight (body mass index 28 kg/m^2), skin pallor, irregular tachycardia (115–125 bpm), tachypnoea (respiratory rate of 28/minute), low blood pressure (80/60 mmHg) and dry oral mucosa. His oxygen saturation was 94% on room air. Cardiovascular examination was remarkable for irregular tachycardia, chest examination was normal, and abdominal examination revealed mild tenderness all over the abdomen. His extremities were cold. Digital rectal examination showed melena. The remainder of the examination was unremarkable.

On presentation, the patient had a haemoglobin (Hb) of 8 g/dl (normal 13.5–17 g/dl), haematocrit (Hct) of 24% (normal 45–52%) microcytic hypochromic anaemia, reticulocyte index >2, platelet count of 600,000 (normal range 150,000–450,000/l), International Normalized Ratio (INR) of 1.9 (normal INR 1.1 or less), and activated partial thromboplastin time (aPTT) of 45 sec (normal 30–40 sec). His blood glucose level was 142 mg/dl (normal 70–140 mg/dl) and kidney function was normal (eGFR 90 ml/min/1.73 m^2, estimated by CKD-EPI). Serum sodium was 140 mEq/l, serum potassium was 4.5 mEq/l, and a liver function test was normal.

As the history and clinical picture were suggestive of gastrointestinal bleeding with an element of haemorrhagic shock, resuscitation measures were started in the emergency department with administration of intravenous fluid and the patient was moved to the intensive care unit. He later developed severe haematemesis after which the trachea was intubated and the patient was mechanically ventilated. Packed red blood cell transfusion was started.

As the patient had taken his last dose of dabigatran 110 mg on the morning of admission, idarucizumab, a reversal agent of dabigatran, was administered (5 g intravenously according to protocol). Urgent upper endoscopy was performed and showed diffuse haemorrhage of the mucosal membrane with fresh blood and blood clots in the oesophagus, stomach and duodenum; no definite ulcers or oesophageal varices were identified. The resuscitation measures were continued with intravenous fluid (crystalloid and colloid) and blood products, but bleeding persisted with fresh blood from the nasogastric tube. Haemorrhagic shock continued despite volume replacement (fluid and blood) and vasopressor support, and the patient died within 24 hours.

The history of recent combination of herbal products (ginger and cinnamon) with DOACs (dabigatran) and the presence of diffuse haemorrhage of the mucosal membrane of the upper gastrointestinal tract raised the possibility of a herb–drug interaction leading to severe gastrointestinal bleeding.

DISCUSSION

Atrial fibrillation (AF) is a very common cardiac arrhythmia and the main cause of thromboembolic complications such as ischaemic stroke[4]. NV-AF is defined as AF in the absence of moderate to severe mitral stenosis or a mechanical heart valve. The 2019 AHA/ACC/HRS update on AF recommends DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) over warfarin in NV-AF (class I, level A evidence)[1].

For many years herbal products have been generally considered safe and have become increasingly popular especially in combination with conventional medicines and are used usually without consultation with a healthcare professional[2,3]. No studies have investigated the co-administration of herbal medicines with dabigatran, rivaroxaban, apixaban or edoxaban[5]. Patients and physicians are generally unfamiliar with herb–drug interactions and consequently underestimate and under-report the side effects of such combinations.

Ginger and cinnamon are frequently used herbal products. There are two main types of cinnamon: Ceylon cinnamon (also known as 'true' cinnamon) and cassia cinnamon, the most commonly used and generally referred to as 'cinnamon'. Cassia cinnamon is considered a rich source of coumarin. Each teaspoon of cassia cinnamon contains approximately 5 mg of coumarin, while Ceylon cinnamon only contains trace amounts of the compound[6]. Oral anticoagulants (like warfarin) are derived from coumarin, which inhibits the synthesis of vitamin K and prevents the formation of blood clots.

Verma et al. showed that 5 g of ginger in two divided doses consumed with a fatty meal significantly inhibited platelet aggregation in healthy males[7]. Ginger is also a strong P-glycoprotein (P-gp) inhibitor and has been reported to significantly reduce the P-gp-mediated efflux of dabigatran[8] and consequently increase drug concentration. Dabigatran etexilate is a substrate for the efflux transporter P-gp, which means that concomitant administration of a P-gp inhibitor (for example ginger) will increase dabigatran concentration.

In our case, the self-administered boiled mixture of ginger and cinnamon twice daily for 3 days before presentation to hospital with diffuse mucosal haemorrhage of the upper gastrointestinal tract and the absence of any new medications raised the high possibility of a dabigatran–herbal product interaction causing severe gastrointestinal bleeding.

Cinnamon and ginger taken together with dabigatran will increase dabigatran concentration and also supply a second oral anticoagulant (coumarin) in addition to dabigatran, thus significantly increasing the risk of bleeding.

CONCLUSION

Co-administration of cinnamon/ginger with dabigatran is unsafe and can lead to fatal gastrointestinal bleeding, and should be discouraged.

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