CASE REPORT

Pradaxa-induced esophageal ulcer

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SUMMARY

Pradaxa (dabigatran) is a direct thrombin inhibitor approved for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. We describe a case of esophageal ulceration associated with Pradaxa administration in a 75-year-old man. The patient reported difficulty swallowing and a burning sensation after taking his first dose of Pradaxa. An esophagogastroduodenoscopy (EGD) revealed linear ulcerations in the mid-esophagus. Pradaxa was held beginning the day before the EGD. The patient reported that his pain and difficulty swallowing resolved on stopping Pradaxa. Pradaxa is formulated with a tartaric acid excipient to reduce variability in absorption. We hypothesise that the capsule lodged in the patient's esophagus and the tartaric acid may have caused local damage resulting in an esophageal ulcer. It is important to educate patients on proper administration of Pradaxa, to decrease the risk of this rare, but potentially serious adverse event.

BACKGROUND

Pradaxa (dabigatran) is a direct thrombin (Factor IIa) inhibitor; in 2010, it was Food and Drug Administration (FDA) approved for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). Pradaxa, along with two other new direct-acting oral anticoagulants (referred to collectively as the Novel Oral Anticoagulants, or NOACs), Xarelto (rivaroxaban) and Eliquis (apixaban), and the older drug, warfarin, are first-line options recommended for patients with AF at high risk of stroke by the American Heart Association and American College of Cardiology.¹ Pradaxa offers several advantages compared with warfarin therapy, including no routine laboratory monitoring required, fewer drug-drug interactions and no known dietary interactions. Potential disadvantages of Pradaxa include higher rates of gastrointestinal bleeding and dyspepsia, also, there is no antidote to reverse Pradaxa's effects.^{1 2}

We describe a case of esophageal ulceration associated with Pradaxa administration. In December 2014, we completed a comprehensive systematic electronic search of the published literature in PubMed using the MESH terms 'dabigatran', 'Pradaxa', 'esophageal disease/esophageal ulcer', 'rivaroxaban' and 'apixaban'. We also searched Medwatch and the Clin-Alert Database. This is the first rigorous case report using the Naranjo probability scoring method to assess causality. Despite the paucity of published literature regarding this serious potential adverse drug event (ADE) from Pradaxa, it appears to have been previously

recognised.³⁻⁶ The package label for Pradaxa was revised in December 2013 to include esophageal ulcer as an adverse event identified in postmarketing surveillance.^{7 8} Administration instructions were also updated to say it 'should be taken with a full glass of water'. The New Zealand Medicines and Medical Devices Safety Authority also issued an alert warning in 2013, describing cases of esophageal ulcer from Pradaxa that have been reported to the manufacturer.⁸ This safety alert indicated that these cases primarily occurred in one of three patient clusters: (1) those using an incorrect administration technique by breaking open the capsule, (2) those who developed gastroesophageal reflux disease (GERD) and (3) those who had swallowing difficulties or experienced the capsule sticking in their throats, many of whom either took the drug with little or no water or lay down shortly after taking the drug. The patient we describe in our case report falls into this third category. He reported not taking dabigatran with a full glass of water, his symptoms began shortly after taking dabigatran and resolved shortly after discontinuing the drug.

CASE PRESENTATION

A 75-year-old man with newly diagnosed atrial flutter was started on Pradaxa 150 mg capsule by mouth twice daily to decrease his risk for stroke and systemic embolism. His CHA₂DS₂-VASc score was 2 due to being aged 75 years or older, and indicating the need for anticoagulation per current guidelines.¹ Pradaxa was chosen over warfarin due to patient preference and convenience, as he travels out of the country frequently and it would be burdensome to keep up with routine laboratory international normalised ratio monitoring, required with warfarin therapy.

The patient filled his Pradaxa prescription on 24 September 2014. He called his primary care physician on 1 October 2014 and reported that he had difficulty swallowing since eating breakfast the prior morning. He stated that he began having symptoms after his first dose of Pradaxa. The patient, on 20 October 2014, stated, "The first morning I took it, I was in great pain. I must not have swallowed enough water to pass it through the esophagus to the stomach..."

INVESTIGATIONS

The patient was referred for an esophagogastroduodenoscopy (EGD) due to difficulty swallowing, with a burning sensation from his throat to his esophagus. The patient also reported that he felt as if something was stuck in his throat. On 6 October 2014, the patient called his doctor and reported

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painful swallowing while eating a banana. His primary care doctor prescribed omeprazole to alleviate symptoms until his EGD. On 8 October 2014, the patient explained that he was not getting any relief of his symptoms. He continued to take Pradaxa as prescribed. He took his last dose of Pradaxa on 19 October 2014, prior to his EGD on 20 October 2014. The EGD revealed linear ulcerations, which were biopsied, in the mid-esophagus, 33 cm from the incisors. The rest of the esophageal mucosa was normal. The esophageal biopsies were benign with no signs of infection or pre-cancerous changes. Biopsies were also taken from the stomach due to gastric body 'cobblestoning'. Gastric cobblestoning is a characteristic radiological appearance of the intestinal mucosa with uniform nodules, due to submucosal involvement or oedema, and looks similar to a road paved with 'cobbled' stones.⁹ Stomach biopsies revealed *Helicobacter pylori*, which was treated with amoxicillin, levofloxacin and omeprazole.

The gastrointestinal doctor suspected that a Pradaxa capsule had lodged into the esophagus, causing the ulcers.

OUTCOME AND FOLLOW-UP

On 10 October 2014, it was reported that the patient felt a lot better after stopping the Pradaxa. His pain and difficulty swallowing resolved after he discontinued the medicine. Therefore, the patient elected to switch to warfarin instead of retrying Pradaxa.

DISCUSSION

We are the first to utilise the Naranjo Scale to assess the causality of Pradaxa in relation to a patient's esophageal ulcer. The Naranjo Scale is a validated tool useful for determining the probability of whether an adverse reaction is due to a drug rather than the result of other factors.¹⁰ The Naranjo Score for this case was 7, indicating that it was probable that this adverse event was related to taking Pradaxa. This score was arrived at as there are previous reports of esophageal ulcers related to Pradaxa administration (1 point), the patient's symptoms occurred after the first dose (2 points), symptoms improved on Pradaxa discontinuation (1 point), there were no other clear risk factors for developing esophageal ulcers (2 points) and the adverse event was confirmed by objective evidence (1 point). *H. pylori* is known to cause stomach ulcers, but we found no evidence suggesting that *H. pylori* is a risk factor for esophageal ulcers.¹¹

Pradaxa (active ingredient: dabigatran) is formulated as a capsule, with several pellets inside containing tartaric acid, to reduce variability in absorption.¹² The presence of this tartaric acid excipient has been suggested as the explanation for significantly higher rates of dyspepsia with Pradaxa compared to warfarin (11.3% vs 5.8% in the RELY Trial).² We hypothesise that the capsule may have lodged in the patient's esophagus and, as it dissolved, the tartaric acid may have caused local damage to the esophagus, resulting in an ulcer. Among the NOACs, this

adverse drug reaction appears to be unique to Pradaxa. There were no case reports of esophageal ulcer found for Xarelto or Eliquis, nor is there any mention of esophageal ulcer or the need to take these medications with a full glass of water in their package labels.

Learning points

- ▶ Pradaxa is formulated with a tartaric acid excipient to reduce variability in absorption, which may potentially cause irritation and side effects.
- ▶ It's important to educate patients on proper administration of Pradaxa to decrease the risk of side effects
- ▶ Patients should take Pradaxa with a full glass of water and not break, chew or open the capsule.

Contributors MW and PS identified the case report, interpreted the data and revised the manuscript.

Competing interests None declared.

Patient consent Obtained.

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