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<b>TITLE OF CASE</b>
Upper gastrointestinal haemorrhage associated with cholinesterase inhibitor use
<b>SUMMARY</b>
<p>An 86 year old man was admitted with a 3 day history of melaena and syncope. He was haemodynamically compromised and anaemic on presentation. His only past medical history was mild Alzheimer’s Disease diagnosed 6 months prior. For this, he was on donepezil, a cholinesterase inhibitor (ChEI), with a recent dose increase 3 months ago. After fluid resuscitation with packed red cells, an endoscopy was performed which showed an acute duodenal ulcer. This was treated with high dose proton pump inhibitor. He recovered well and was discharged on donepezil. In view of other absent risk factors of upper gastrointestinal haemorrhage, donepezil was the likely causative agent. ChEIs is associated with frequent side effects and increased hospitalisation due to central and peripheral increase in acetylcholine. With this case report, we review the literature of side effects related to ChEIs, where the mechanisms of action, complications and appropriate management are discussed.</p>

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## BACKGROUND

The National Institute of Clinical Excellence (NICE) of United Kingdom recommends the use of cholinesterase inhibitors (ChEIs) as a pharmacological agent in the multipronged approach in managing Alzheimer's Disease, the most common form of dementia.[1] ChEIs are currently licensed for patients with mild to moderate Alzheimer's Disease,[1] where it requires specialist input with regular cognitive and behavioural assessments to assess efficacy. With the incidence of dementia steadily rising to a projected 40% over the next 12 years,[2] coupled with improved diagnostics, care bundles and organisation of specialist teams, general physicians and practitioners would be encountering ChEIs at a greater frequency. Our case report highlights a patient who suffered an upper Gastrointestinal haemorrhage (UGIB) on a ChEI, donepezil, in the absence of any other risk factors for peptic ulcer.

## CASE PRESENTATION

An 86 year old man was referred to the Acute Medicine Unit by his General Practitioner (GP) with a history of dark stools and dizziness on standing for three days, having had a syncopal episode in front of the surgery that morning. His past medical history included mild Alzheimer's disease. He had started donepezil approximately five months prior to presentation, initially taking 5mg once a day, with the dose increased to 10mg once a day three months after. There was no other significant past medical or gastrointestinal disease history. Apart from donepezil, he was not on any other regular medication. In particular, there was no recent use of non-steroidal anti-inflammatory (NSAID), over-the-counter medication or alcohol consumption. He lived alone with help from the family.

On examination, the patient's GCS was 14/15. He was afebrile. Despite a lying blood pressure (BP) of 75/35, he was not tachycardic, with a regular pulse rate of 90 beats per minute. The GP surgery recorded a lying BP of 117/64, with an unrecordable BP on standing, indicating a significant postural drop. His respiratory rate was 24 breaths per minute, with oxygen saturations of 98% on air. His abdomen was soft, with some epigastric tenderness, but no rebound tenderness. Digital examination of the rectum confirmed melaena, with soft stool present in the rectum.

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An erect chest radiograph showed no free air under the diaphragm. His electrocardiogram showed a normal sinus rhythm. His blood tests were consistent with an upper gastrointestinal bleed (UGIB); the haemoglobin was 75 g/L (normal values 130 – 170 g/L), urea was raised at 21.6mmol/L (normal values 1.7 – 7.1 mmol/L), and creatinine normal. Electrolytes and liver enzymes were within the normal range. The patient's Blatchford Score was 14 (Table 1). The case was discussed with the on-call gastroenterologist shortly after arrival, who felt that the most important issue was to optimise his resuscitation prior to endoscopy. He was resuscitated with crystalloid immediately and subsequently transfused with three units of packed red cells. He was haemodynamically stable overnight. His immediate post-transfusion haemoglobin was 95g/L.

At endoscopy the following morning an acute duodenal ulcer approximately 1cm in diameter was located in the inferior bulbar region. The Forrest Classification at time of endoscopy was IIc, with no blood seen in the stomach. There was no visible vessel and no active bleeding. Hence, no endoscopic intervention was needed. A rapid urease test was negative, indicating *Helicobacter pylori* infection was unlikely.

## INVESTIGATIONS

As above – blood results and gastroscopy result in Case Presentation

## DIFFERENTIAL DIAGNOSIS

A differential diagnosis would be UGIB secondary to a uraemic gastropathy, pathology sometimes associated with patients with chronic kidney disease (CKD). However, we are able to exclude CKD as the patient's estimated glomerular filtration rate (eGFR) was 75ml/min/1.73m<sup>2</sup> 4 months ago. Also, he had a normal Creatinine then and on admission.

Other common causes of anaemia include B12, Folate and Iron deficiency states. The patient's blood results for this were normal. The thyroid function tests 6 months prior were normal. These are shown in Table 2. His blood count differentials did not suggest a haematological malignancy.

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Common causes for an UGIB include esophageal disease such as esophagitis, perforation or UGI malignancy. In this case, the diagnosis was achieved by an Oesophago-gastro duodenoscopy.

## TREATMENT

The patient was commenced on oral lansoprazole 30mg twice a day for 6 weeks.

## OUTCOME AND FOLLOW-UP

The length of stay in hospital under the Gastroenterologists was 8 days, mainly due to a worsening of the patient's mobility and cognitive function associated with the hypotensive shock. There was no further melaena and the haemoglobin remained stable throughout the admission. He was discharged on donepezil and high-dose lansoprazole.

In the absence of any other identifiable cause for the development of this patient's ulcer, we have reported a suspected adverse event of donepezil causing a significant UGIB through peptic ulceration to the Medicines and Healthcare products Regulatory Agency (MHRA).

## DISCUSSION

Alzheimer's Disease is the most common form of dementia, accounting for 62% of dementias in the UK.[2] The link between acetylcholine, cognitive decline and its role in Alzheimer's Disease was greatly studied in the 1970s through animal and post-mortem brain studies.[3] This gave rise to ChEIs. Donepezil is a 2<sup>nd</sup> generation ChEI, where it is a selective reversible non-competitive inhibitor of acetylcholinesterase, reducing breakdown and hence increasing levels of the neurotransmitter acetylcholine at the central and peripheral cholinergic synaptic clefts.

A Cochrane review of mainly industry-sponsored trials has suggested that donepezil has significant cognitive benefits.[4] However two independent studies were unable to demonstrate significant clinical benefit, although either the number of participants[5] or the duration of treatment[6] limited these studies.

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There are significant side effects associated with ChEI use, as shown by excess numbers of patients discontinuing treatment: 16-43% of patients in treatment groups versus 0-33% in placebo groups.[4] These side effects are mostly attributed towards unwanted cholinergic effects. In a Canadian population matched case-control study, the risk of hospitalisation for bradycardia doubled in ChEI users. In this group, ChEI was often restarted on discharge, and the authors felt that clinicians failed to appreciate its cardiovascular toxicity.[7] Moreover, in a separate cohort study, ChEI users were more likely to suffer neurocardiogenic syncope and syncopal related events such as hip fractures.[8] Interestingly, this cholinergic effect of donepezil may potentially explain why our patient did not have a compensatory tachycardia despite a very low systolic BP.

Due to the cholinergic innervation of the GI system, the side effects of GI disturbances are observed among ChEI users, where nausea, vomiting and diarrhoea pre-dominate as adverse events.[4] The MHRA Yellow Card system has received 30 reports of gastrointestinal haemorrhage in patients taking donepezil, including 4 fatalities,[9] although the nature of these spontaneous reports means that we cannot be certain of a causal link between drug and suspected reaction. 38 cases of duodenal, gastric or peptic ulcers were also reported to MHRA, including 2 fatalities.[9] A recent retrospective population-based cohort study based on healthcare administrative claims databases reported on the relative frequency of UGIB in patients with dementia on ChEIs compared to matched nonusers.[10] More than two thirds of the ChEI users were on donepezil. Although no statistically significant association was found between UGIB and ChEI usage, it was noted that 34.4% of ChEI users were already on a gastro-protective agent, and there was no ability to capture data such as disease severity, length of hospital stay or background gastrointestinal pathology.

Our patient had no other risk factors for a peptic ulcer. The biological plausibility of donepezil causing GI ulceration could be due to its ulcer promoting effect through increased acid production, which is partly controlled by cholinergic vagal fibres. Only one case report has reported recurrent UGIB due to a gastric ulcer following ongoing donepezil use.[11] In our case, ulcer formation could have coincided with a recent upward dose titration of donepezil.

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A physician has to be wary when starting patients on ChEI, where cautious administration of ChEIs is advised in patients who have a previous history of severe liver disease, peptic ulcer disease and current alcoholism. Patients were excluded from donepezil trials if they had 'uncontrolled gastrointestinal diseases'. Galantamine trials specifically excluded patients with active peptic ulcer disease and rivastigmine trials excluded patients with a peptic ulcer in the preceding 5 years.[4]

ChEI associated side effects presents a dilemma for general physicians. Firstly, there is no available guidance to manage these side effects, in particular peptic ulcers. In this case the ChEI was continued with the addition of a gastro-protective proton pump inhibitor (PPI). However, it is usual for NSAIDs to be stopped after a significant UGIB. Perhaps ChEIs should be discontinued until ulcer healing has been confirmed.

Whether there is a role for the universal use of PPI for primary prevention of ulcer formation is debatable. For NSAIDs, in patients who are at high risk of developing NSAID related GI adverse events, such as patients above the age of 65 years old, starting a PPI is recommended.[12]

Patients placed on donepezil are likely to have a high risk factor profile towards GI disturbances. However, donepezil is much less widely used than NSAIDs, and the level of risk does not appear to be as high. We would be reluctant to recommend universal use of PPIs, given that PPIs have been associated with increased risk of *Clostridium difficile* infections and fractures.[13] Hence, a case-by-case approach should be adopted.

Not only do we have to be vigilant about side effects, we also have to recognise the issues of polypharmacy and drug interactions with ChEIs in a vulnerable elderly population. This could prove challenging to manage. Indeed, a retrospective cohort study found that patients with dementia on ChEIs had an increased risk of receiving an anticholinergic drug to manage urinary incontinence, which would in fact oppose each other's pharmacological action.[14]

In conclusion, this case report has highlighted a significant and potentially life-threatening side effect of ChEIs and we have prompted discussion of their management. It is important for

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secondary care providers and General Practitioners to have regular communications with ChEI users under their care and their caregivers and family members, discussing and evaluating the benefits and risks associated with this class of drugs at regular intervals.

## LEARNING POINTS/TAKE HOME MESSAGES

- The usage of cholinesterase inhibitors (ChEIs) is likely to increase due to recent NICE recommendation and the medical communities' higher vigilance towards an early diagnosis of dementia. General and acute physicians are likely to see more patients on ChEIs.
- This case report exemplifies one of the potentially significant adverse events associated with ChEI use.
- It is important to recognise patients that are of higher risk of developing ChEI-related side effects.
- There is a need for guidance for managing ChEI-related side effects. Cessation of ChEI after a peptic ulcer or admission with cardiac syncope should be considered.

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## TABLES

Table 1. Glasgow-Blatchford Score of patient

On Admission	Score
Blood Urea (mmol/l)	4
21.6	
Haemoglobin (g/dl) for men	6
75	
Systolic Blood Pressure (mmHg)	3
75	
Other markers	
Presentation with melaena	1
Presentation with syncope	1
Total Glasgow-Blatchford Score	15

Table 2. Patient's blood results on admission

Investigation	Normal range	Units	result
Ferritin	23 - 300	ug/L	136
Vitamin B12	130 - 1100	ng/L	230
Folate	2.7 - 15.0	ug/L	2.9
Free T4	8 - 21	pmol/L	12
TSH	0.35 - 3.5	mU/L	1.25
WCC	4.0 - 10.0	10 <sup>9</sup> /L	10.6
Neutrophils	2.0 - 7.0	10 <sup>9</sup> /L	8.87
Lymphocytes	1.0 - 3.0	10 <sup>9</sup> /L	0.92
Monocytes	0.2 - 1.0	10 <sup>9</sup> /L	0.76
Eosinophils	0.02 - 0.5	10 <sup>9</sup> /L	0.02
Platelets	150 - 410	10 <sup>9</sup> /L	173
Globulin	21 - 35	g/L	25
C-reactive protein	0 - 10	mg/L	2

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