

Oesophageal ulcer caused by warfarin

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Summary: Oesophageal injury is a well recognized complication of certain oral medications but warfarin has not been implicated previously. We present a case of an oesophageal ulcer occurring in a patient with mitral regurgitation taking warfarin, and demonstrate a delayed oesophageal tablet transit time.

Introduction

Oesophageal injury is a well recognized complication of certain oral medications.¹⁻³ To date, over 200 cases of drug-induced oesophageal injury have been reported,⁴ but this almost certainly represents a minority of cases. The most common presenting symptoms of drug-induced oesophageal injury are retrosternal pain, odynophagia and dysphagia. In one study haematemesis occurred in four out of 127 cases.¹ Table I summarizes preparations which have been reported to cause oesophageal injury. Oral anticoagulants have not been implicated previously. We report a case of an oesophageal ulcer occurring in a patient with mitral regurgitation taking warfarin.

Case report

A 58 year old woman presented with a 6-hour history of an acute onset, severe interscapular pain which had woken her at night. Three hours after the onset of pain the patient vomited partially digested food then 20 minutes later vomited approximately 200 ml fresh blood. She had a past history of rheumatic fever. Four weeks prior to admission she presented with a transient ischaemic attack causing temporary dysphasia and was commenced on warfarin. The patient generally took these approximately 2 hours before bed-time, sometimes, but not always, with a drink, but occasionally forgot and (as on the night of admission) took them at bed-time. She was on no other medication. There was no history of peptic ulcer disease. On examination she was not shocked and there was no abdominal tenderness.

Investigation revealed that she was over-

anticoagulated (prothrombin time 168, control 13 seconds). No cause for poor anticoagulant control was apparent and she was given parenteral vitamin K, two units of fresh frozen plasma and the warfarin stopped. She did not require blood transfusion and she was commenced on intravenous ranitidine.

Upper intestinal endoscopy the next day revealed a mid-oesophageal ulcer with overlying blood clot. The lower third of the oesophagus, stomach and duodenum were normal. Ranitidine was continued orally. Repeat endoscopy 10 days later confirmed a longitudinal mid-oesophageal ulcer measuring 10 cm × 1 cm, extending from 25 to 35 cm from the incisor teeth; the lower oesophagus (35 to 40 cm) being normal. Multiple biopsies showed ulceration of the squamous epithelium with marked active submucosal inflammation and no evidence of malignancy.

Two-dimensional, coloured and Doppler echocardiography revealed mitral valve prolapse with a degree of regurgitation and a slightly dilated left atrium (4.1 cm) and left ventricle. Barium swallow confirmed the oesophageal ulcer but showed no motility disorder.

The patient made an unremarkable recovery and endoscopy 24 days later showed the ulcer to have healed completely. Ranitidine was stopped and she has not been recommenced on warfarin.

Oesophageal tablet transit time was measured 2 months after endoscopic confirmation of healing. This was established by administration of a barium sulphate tablet similar in size (8 mm diameter), shape and total weight (500 mg) to the implicated 5 mg warfarin tablet. Tablet transit time supine was over 30 minutes and 150 ml water did not result in passage of the tablet which lodged at approximately the level of the left atrium. The patient was not aware of the retained tablet within the oesophagus. Transit time standing was 3 seconds.

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Table I Drugs implicated in oesophageal injury

<i>Commonly reported</i>	<i>Occasionally reported</i>	<i>Anecdotal reports</i>
Emepromium bromide	Clindamycin	Erythromycin
Tetracyclines	Lincomycin	Penicillin
Potassium chloride	Naftidrofuryl	Tinidazole
Quinidine	Alprenolol	Ascorbic acid
Ferrous sulphate	Phenobarbitone	Digoxin
Indomethacin and aspirin	Theophylline	Paracetamol
		Phenylbutazone
		Fluouracil
		Estramustine phosphate
		Carbachol
		Cimetidine

Discussion

Warfarin is a weak acid with a pH of 5.0. It forms a water soluble salt, warfarin sodium, which is used in warfarin tablets BP. The pH range of a 1% solution of warfarin sodium is 7.2 to 8.3. Dissolution of warfarin tablets is slow at 70% dissolution in 45 minutes. Warfarin-induced oesophageal ulceration has not been described previously, though it has been reported to cause ulcerative stomatitis and small intestinal ulceration (Committee on Safety of Medicines, communication).

The retention of tablets in the oesophagus can be prolonged beyond 5 minutes in over 50% of subjects with an apparently normal oesophagus and in over 70% of subjects with abnormal oesophageal motility.⁵ Drug-induced oesophageal injury may occur in an

otherwise normal oesophagus, with no evidence of gastro-oesophageal reflux, motility disorder or external compression. However, in the case of some preparations, notably potassium chloride, oesophageal damage has been reported almost exclusively in the presence of left atrial enlargement with consequent oesophageal compression.⁶

The case for warfarin being the cause of the ulcer is strong and that for a bleeding diathesis remote. The patient had taken the tablet on going to bed that night, had woken up with pain, then vomiting which clearly preceded the haematemesis. The oesophageal ulcer was at the site of the enlarged left atrium and tablets were shown radiologically to lodge in this site for over 30 minutes when tablet transit was assessed 2 months after healing of the ulcer. The bleeding ulcer coagulated readily and spontaneously and no transfusion was required. There was no other bleeding diathesis. Furthermore, it is unlikely that the ulcer was of peptic origin or a Mallory-Weiss tear as the lower third of the oesophagus and gastro-oesophageal junction were entirely normal. She was on no other medication and the ulcer healed rapidly on cessation of therapy.

The incidence of tablet-induced oesophageal injury can be reduced by administration with meals or a cupful of water, and remaining in the standing posture for at least 90 seconds. Administration should be avoided immediately before bed-time and care should be taken in patients with mitral valve disease and left atrial enlargement, a scenario frequency encountered in patients on bed rest in a coronary care unit! Finally, lower oesophageal ulceration is usually assumed to be of peptic origin, but drug-induced damage should always be considered.

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