

Adverse drug reaction

Medication-induced oesophageal injury leading to broncho-oesophageal fistula

N A McAndrew, M W Greenway

Summary

Medication-induced oesophageal injury is one of the least recognised side-effects of oral medication and, in contrast to other oesophageal pathologies, is rarely considered in the differential diagnosis of chest pain. We describe a case of medication-induced oesophageal injury with a rare complication in which the diagnosis was not considered until the characteristic features were demonstrated at endoscopy.

Keywords: adverse drug reaction; acemetacin; oesophageal ulceration

Medication-induced oesophageal injury is oesophageal injury caused by the local and systemic action of medications. The contribution of medications to gastro-oesophageal reflux and oesophageal *Candida*, for example, and the harm caused by dissolved pill contents in the refluxed fluid are well appreciated. However, doctors may be less aware of the injuries that can be caused by retention of pills in the oesophagus, injuries that were first reported in 1970 as a side-effect of oral potassium.¹

Case report

A 77-year-old woman presented in 1997 with a 3-week history of dyspnoea, a productive cough, and right-sided pleurisy. She had been troubled with recurrent chest infections for the previous 5 months. Systemic enquiry elicited a history of retrosternal burning pain radiating through to her back immediately following food.

Medical history included a partial thyroidectomy, myocardial infarction, left pleural effusion, sigmoid colectomy and colostomy following a perforated sigmoid diverticulum, and rheumatoid arthritis. She had been admitted to hospital in 1994 with left-sided pleuritic chest pain that was diagnosed as musculoskeletal chest pain and at that time gave a history of oesophageal discomfort on swallowing. Oesophageal reflux was diagnosed on clinical grounds, aspirin stopped and omeprazole started. Other medication at that time was piroxicam gel, acemetacin, verapamil, prothiaden and co-amilofruse. Medication on current admission was co-amilofruse 5/40 mg od, verapamil 40 mg bid, prednisolone 7.5 mg od (a short-term prescription), acemetacin 60 mg tid, meptazinol 200 mg bid, omeprazole 40 mg

od, dothiepin 75 mg nocte, ferrous sulphate 200 mg od, and temazepam.

She was pyrexial, in atrial fibrillation with a ventricular rate of 110 beats/min, blood pressure of 140/110 mmHg, normal heart sounds and moderate ankle oedema. Examination of her chest revealed bilateral basal crackles. There was a midline abdominal scar and colostomy. Chest X-ray showed bilateral upper lobe consolidation. Pneumonia and left ventricular failure were diagnosed. Verapamil, prednisolone and acemetacin were stopped. Digoxin, frusemide and augmentin were commenced with a good initial clinical and radiological response. Echocardiogram demonstrated left ventricular impairment but no valvular heart disease and a normal left atrium. Endoscopy revealed two large discrete mid-oesophageal ulcers. Biopsies showed erosive oesophagitis. Medication-induced oesophageal injury was diagnosed.

Subsequently, the patient complained of choking after taking oral fluids. Fluoroscopy demonstrated a fistula connecting the left main



Figure 1 Barium swallow demonstrating broncho-oesophageal fistula and contrast within the left lower lobe

Department of Health
Care of the Elderly,
Glan Clwyd Hospital,
Rhyl, Denbighshire
LL18 5UJ, UK
N A McAndrew
M W Greenway

Correspondence to
Dr N A McAndrew,
Llandough Hospital, Penlan
Road, Penarth, CF64 2XX,
UK

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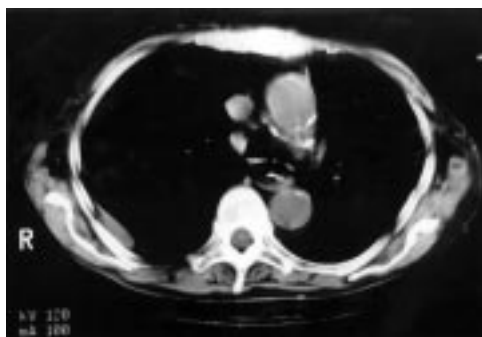


Figure 2 CT scan of the thorax showing thickening of the posterior wall of the oesophagus at the level of the main bronchus

bronchus and oesophagus at the level of the aortic arch (figure 1). Nasogastric feeding was instituted. At bronchoscopy the bronchial end of the fistula was not visualised and no malignant lesion seen. Three sputum samples were negative for malignant cells. Computed tomography (CT) scan of the thorax showed thickening of the posterior wall of the oesophagus at the level of the carina but no evidence of malignancy and no lymphadenopathy (figure 2).

A barium swallow carried out 6 weeks after admission showed persistence of the fistula. Repeat endoscopy revealed only one small oesophageal ulcer. This improvement was thought to be due to withdrawal of the medication responsible. Despite this, persistent respiratory infections eventually proved fatal. Post-mortem showed no evidence of malignancy and histology demonstrated an inflammatory type fistula. Cause of death was bronchopneumonia.

A Yellow Card report was sent to the Committee on Safety of Medicines (CSM)/Medicines Control Agency (MCA).

Discussion

Medication-induced oesophageal injury is characterised by odynophagia or dysphagia and the onset of retrosternal pain may be sudden, exacerbated by swallowing, and can occur soon after ingestion of the medication. Risk factors are detailed in box 1.² The passage of tablets can be delayed in the middle and lower oesophagus in the region of anatomical narrowing of the oesophagus where it passes close to an enlarged left atrium, the left main bronchus and the aortic arch. Adhesions following thoracic and cardiac surgery limit the ability of the oesophagus to be displaced by surrounding structures which will then compress rather than displace it. The mechanism of injury is unclear, although the formation of an acid solution by tablets may be important. Whilst the list of medications causing oesophageal injury is extensive,² some of the more common ones are listed in box 2. Complications include oesophageal ulcers and strictures but more serious complications have been reported (box 3).

Risk factors for medication-induced oesophageal injury

- tablet size, shape and coating
- increasing age
- previous thoracic surgery
- left atrial enlargement
- ingestion of medication whilst supine
- ingestion of medication without liquid

Box 1

Drugs causing medication-induced oesophageal injury

- doxycycline
- other tetracyclines
- potassium chloride
- NSAIDs
- ferrous sulphate
- quinidine
- alendronic acid

Box 2

Complications of medication-induced oesophageal injury

- oesophageal ulceration
- stricture formation³
- haemorrhage⁴
- oesophageal perforation⁵
- mediastinitis⁶
- fistula formation⁷

Box 3

Which medication(s) caused our patient's lesions is unclear but, based on previously published cases, acemetacin, ferrous sulphate, prednisolone, and possibly even verapamil are candidates.² Acemetacin seems the most likely causative agent: its duration of prescription encompasses the period when symptoms were first reported in 1994, it was continued until her last admission, and healing of the ulcers occurred after its withdrawal. Verapamil is another candidate for the same reasons. Up to 10% of reported cases of medication-induced oesophageal injury have been associated with non-steroidal anti-inflammatory drugs (NSAIDs), including five with indomethacin which is closely related to acemetacin, although none have been reported with acemetacin itself. There is only one reported case with a calcium channel blocker and that was with nifedipine. Furthermore, approximately one-third of complications of medication-induced oesophageal injury are associated with NSAIDs, a disproportionately high number.² Ferrous sulphate and prednisolone were also considered possible causative agents in our patient as there have been 12 published cases with ferrous sulphate or succinate and six with corticosteroids. However, in our case both were recent prescriptions, neither was being taken in

Learning points

- medication-induced oesophageal injury is rarely included in the differential diagnosis of chest pain
- it is not a difficult diagnosis to make and is easily treated
- if left untreated or undiagnosed it can lead to complications

Box 4

1994 and they thus seem unlikely to be responsible.

The manufacturers of acemetacin have received no other reports of acemetacin causing medication-induced oesophageal injury (personal communication, Merck Pharmaceuticals, West Drayton, UK). Similarly, the CSM/MCA has not received any reports of oesophageal ulcer or perforation associated with either acemetacin or verapamil through the Yellow Card Scheme, although there has been one fatal report of 'oesophageal ulcer and septicaemia' in association with prednisolone (personal communication, CSM).

If a definitive diagnosis of medication-induced oesophageal injury is required, endoscopy is the most sensitive technique, with double contrast barium swallow a less sensitive alternative. Withdrawal of the offending medication and symptomatic treatment will produce resolution of symptoms in most cases in 7–10 days. If the medication responsible needs to be continued then substitution of a liquid preparation, taking medication with plenty of fluid, and avoiding ingestion of tablets whilst supine or immediately prior to retiring to bed

may all be of benefit. Similar advice appears in the British National Formulary (BNF) in relation to alendronic acid, a bisphosphonate used in the treatment of postmenopausal osteoporosis.⁸ This follows the report in 1996 of a series of 199 patients experiencing medication-induced oesophageal injury following ingestion of alendronate sodium, of which 51 had severe or serious reactions including 22 with oesophageal ulcers.⁹ The injuries caused by alendronate appeared severe compared with those induced by other medications and the frequency sufficiently high to warrant a specific warning in the BNF and a modification to the prescribing information to include the following contraindication: "abnormalities of oesophagus and other factors which delay emptying (eg, stricture or achalasia)".

The history and endoscopy findings in our patient were characteristic of medication-induced oesophageal injury and it seems likely that the ulcers represented one end of or were closely associated with the fistula. The thickening of the posterior wall of the oesophagus seen on the CT scan is suggestive of a chronic process and it is possible that her symptoms in 1994 represented the start of this process. These features, the histology consistent with an inflammatory type fistula, and the endoscopic demonstration of healing after withdrawal of certain medications, lead us to suggest that the fistula was a complication of medication-induced oesophageal injury.

Although this case demonstrates a rare complication of medication-induced oesophageal injury, it serves to highlight a more common problem which is entirely avoidable and which may pass undiagnosed or misdiagnosed in many patients.

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