Oesophageal candidiasis after omeprazole therapy

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Abstract

Oesophageal candidiasis was diagnosed incidentally at endoscopy in two patients receiving omeprazole therapy. There were no other predisposing factors for the development of candidiasis. The infection was resolved rapidly by anti-candidal therapy and by stopping omeprazole. These findings suggest that gastric acid secretion and physiological reflux of acid into the oesophagus may play a protective role in preventing candida infection.

Case reports

CASE 1

A 63 year old man presented with a symmetrical distal polyarthritis and a positive rheumatoid factor (titre 1/640). In 1965 he had undergone vagotomy and pyloroplasty for a duodenal ulcer, and in 1979, after an endoscopically diagnosed stomal ulcer, was begun on maintenance H₂ receptor antagonist therapy (cimetidine 400 mg at night) – that is, 12 years before the onset of rheumatoid arthritis. The arthritis was treated with intramuscular gold injections and non-steroidal anti-inflammatory drugs (diclofenac, 75 mg twice daily), and omeprazole (20 mg at night) was empirically substituted for cimetidine. One month after beginning omeprazole he developed new epigastric pains, prompting endoscopy. Extensive, confluent oesophageal candidiasis was seen from 27 cm onwards (and confirmed histologically) but no stricture was evident and the rest of the study was normal. Omeprazole treatment was stopped, cimetidine recommenced, and the candidiasis was treated with nystatin (500 000 IU four times daily) and fluconazole (50 mg daily). Four weeks later his symptoms had entirely settled and repeat endoscopy showed no residual candidiasis. Random oesophageal biopsy specimens showed no tumour. Further investigations showed normal peripheral blood leukocyte and differential counts, normal glucose and calcium metabolism, negative autoantibody screen (including anti-centromere antibodies), and antibodies to HIV were not detected. At no time had the patient received steroids, antibiotics, or antimetabolites. Four months after recommencement of cimetidine the patient remained well and endoscopically free of candidiasis.

CASE 2

A 77 year old man presented with a haematemesis. Endoscopy showed a deep gastric ulcer on the lesser curve; the oesophagus was normal. He was treated with omeprazole (40 mg daily). At repeat endoscopy six weeks later the ulcer was

entirely healed. Patches of candidiasis were observed in the lower third of the oesophagus and confirmed histologically. This was successfully treated with nystatin (500 000 IU four times daily). The patient also suffered from chronic obstructive airways disease and used a beclomethasone inhaler (200 µg twice daily). No other risk factors for oesophageal candidiasis were identified.

Discussion

The H⁺-K⁺-ATPase inhibitor omeprazole is a highly effective therapy for acid-peptic disease of the gastrointestinal tract¹ and has a favourable safety profile.² However, concern has been expressed that its virtual abolition of intragastric acidity³ may predispose treated individuals to enteric infection.⁴

The suggestion that gastric acid has a protective effect against gastrointestinal infection is not a new one.⁵ A critical examination of the clinical and experimental data⁶ is most suggestive for the non-typhoid salmonellosis and cholera, as these infections occur more frequently in achlorhydric individuals. The temporary hypochlorhydria induced by omeprazole may therefore be expected to predispose to these infections.⁴ In healthy volunteers receiving omeprazole, Sharma *et al.*⁷ showed a temporary increase in intragastric bacterial counts but isolated no new pathogenic species. A single case of recurrent salmonella enteritis concurrent with repeated courses of omeprazole therapy for oesophagitis has recently been reported.⁸

It is unclear whether gastric acid protects against candidal infection. There have been occasional reports of local or systemic candidiasis complicating therapeutic interventions producing hypoacidity, for example after partial gastrectomy,⁹ vagotomy,¹⁰ and therapy with H₂ receptor antagonists for peptic ulcer¹¹⁻¹³ or as prophylaxis.¹⁴ Acid suppression and an increase in the gastroduodenal pH are believed to favour candidal overgrowth, but the factors which initially permit colonisation of the gut by *Candida* and promote its pathogenic action are not clear. In addition to reduced gastric acid secretion, impaired gastric motility, and reduced oesophageal clearance may be relevant.^{9,10} Depression of cell mediated immunity in acute hepatic failure may have contributed to the cases of systemic candidiasis during prophylactic cimetidine therapy reported by Triger *et al.*¹⁴ Interestingly, all three patients were incidentally noted at autopsy to have oesophageal erosions or ulcers infected with *Candida*. The possibility that H₂ receptor antagonist therapy contributed to the development of candidiasis in case 1 cannot be entirely refuted, but the circum-

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stantial evidence is very much against it, namely the 12 symptom free years on cimetidine before omeprazole therapy, the onset of new symptoms after omeprazole was started, and the absence of recurrence of candidiasis after reintroduction of cimetidine. The previous vagotomy, by producing a degree of hypomotility, may have been contributory.¹⁰

By inference, the virtual abolition of gastric acid secretion caused by omeprazole might be expected to produce similar complications. We have not been able to locate any previously published reports of candidal infection during omeprazole therapy, although two cases have been reported to the drug manufacturers (Astra Pharmaceuticals International Drug Surveillance Unit, Sweden) and one to the Committee on Safety of Medicines. Astra also have a small number of reports of candidiasis detected by random oesophageal biopsy specimens during trials of omeprazole in patients with refractory reflux oesophagitis.

Oesophageal pH monitoring has shown that reflux of gastric acid occurs in asymptomatic subjects such that the oesophageal pH is less than 4 for up to 5% of the time. Omeprazole has been shown to be more effective than cimetidine in increasing the pH of the gastro-oesophageal refluxate in patients with oesophagitis, and in some patients abolishes acid reflux altogether.¹⁵ Our observation of oesophageal candidiasis after omeprazole therapy raises the possibility that physiological acid reflux may have a protective role against candidal infection.

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