The effect of domperidone on oesophageal emptying in diabetic autonomic neuropathy

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- 1 Oesophageal emptying of solids was studied with a scintigraphic technique in 12 patients with insulin dependent diabetes complicated by autonomic neuropathy and in 22 control subjects.
- 2 In the diabetics the acute and chronic effects of oral domperidone on oesophageal emptying and symptoms of heartburn and dysphagia were assessed.
- 3 The number of swallows required to clear the oesophagus in the diabetics (median 9.5, range 2–30) was significantly greater ($P < 0.001$) than in normal controls (median 2, range 1–14).
- 4 Domperidone did not increase solid oesophageal emptying in diabetic patients either after acute or after chronic administration.

Keywords domperidone oesophageal emptying diabetes

Introduction

Oesophageal motor dysfunction, characterised by a reduction in the primary peristaltic wave with frequent spontaneous contractions has been demonstrated in patients with diabetes mellitus by manometric and radiological techniques (Vix, 1969; Silber, 1969; Mandelstam *et al.*, 1969; Vela & Balart, 1970; Horgan & Doyle, 1971; Stewart *et al.*, 1976; Hollis *et al.*, 1977). Oesophageal dysfunction is relatively common in diabetes mellitus, may be asymptomatic and is often associated with peripheral neuropathy (Hollis *et al.*, 1977). The treatment of oesophageal disorders in diabetics is often unsatisfactory.

We have used a radionuclide technique to measure oesophageal emptying (Maddern *et al.*, 1984) in diabetic patients with autonomic neuropathy and assessed the acute and chronic effects of oral domperidone on oesophageal emptying and symptoms of dysphagia and heartburn in these patients.

Methods

A control group of 31 normal volunteers (median age 33, range 19–62 years) 11 males, 20 females who were non-smokers, on no medication and with no evidence of gastrointestinal disease was studied.

The diabetic group comprised 12 patients (six male, six female), median age 43 years (range 21–61), who were ambulant outpatients, had insulin dependent diabetes for at least 10 years and were subsequently demonstrated to have autonomic neuropathy, as assessed by abnormal cardiovascular reflex tests. All had other complications of diabetes mellitus including nephropathy, retinopathy and peripheral neuropathy. All were non-smokers and were not taking medications known to affect gastrointestinal motility. Informed consent was obtained in all cases and the study was approved by the Research Review Committee of the Royal Adelaide Hospital.

All diabetic patients underwent: (a) a subjec-

tive assessment of symptoms of dysphagia and heartburn, (b) an objective assessment of autonomic nerve function by standard non-invasive physiological methods, (c) assessment of the acute and chronic effect of domperidone on oesophageal emptying.

(a) Assessment of symptoms of dysphagia and heartburn

Patients were evaluated by a standard questionnaire for symptoms of dysphagia and heartburn. They were scored as 0 = none, 1 = mild (symptom could be ignored if the patient did not think about it) 2 = moderate (symptom could not be ignored, but did not influence daily activities), 3 = severe (symptom influenced daily activities). Delayed oesophageal emptying due to organic obstruction was excluded by upper gastrointestinal endoscopy.

(b) Objective assessment of autonomic nerve function

Parasympathetic function was evaluated by the heart rate variation (R-R interval) during deep breathing and the immediate heart rate response to standing (30:15 ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. All patients were required to have abnormal results on both tests of parasympathetic function, according to criteria outlined by Ewing & Clarke (1982).

(c) Measurement of oesophageal emptying

The solid bolus test has been reported previously (Maddern *et al.*, 1984). The bolus is prepared by cooking a 100 g mince beef 'hamburger' to which is added 1.6 mCi ^{99m}Tc macro-aggregated albumin. A 10 g disc is then cut from the 'hamburger'. The subject undergoes an overnight fast and is seated upright with the gamma camera positioned posteriorly. The subject swallows 5 ml of water following which the meat is chewed into a bolus. The subject is then asked to swallow the bolus and instructed to swallow every 15 s on command. Cricoid movement is monitored during the performance of the test to ensure that no additional swallows are taken. The test is continued until the bolus is seen to enter the stomach or until 30 swallows have been carried out.

Oesophageal emptying was measured once in each control subject. In each diabetic subject three oesophageal emptying tests were performed. Two initial oesophageal emptying tests were separated by a maximum period of 7 days.

One hour before each test, patients were given 40 mg of domperidone orally or placebo in double-blind fashion. All patients then received domperidone (20 mg three times a day, 30–60 min prior to meals). The third oesophageal emptying test was performed 60 min after the administration of 40 mg domperidone orally, after each patient had taken domperidone for 35–51 days (median 38). Symptoms of dysphagia and heartburn were recorded again at this time. Drug compliance was assessed by tablet counts at each visit.

Statistical methods

Data were evaluated using the Wilcoxon matched pair signed rank test and the Spearman rank correlation coefficient (r_s).

Results

The symptom of dysphagia was present in five of 12 patients prior to treatment (median score 2, range 2–3). After treatment with domperidone for 37–51 days it was present in four patients (median score 1.5, range 1–2). Heartburn was initially present in six patients (median score 1.5, range 1–3) and following treatment only two patients complained of heartburn, one severe, the other mild. Neither of these changes was statistically significant. Two of the four diabetic patients with oesophageal emptying outside the normal range on the placebo test complained of dysphagia, the same two also describing heartburn. Oesophageal emptying was significantly slower ($P < 0.001$) in the placebo treated diabetic group compared to the controls (Figure 1). Oesophageal emptying did not alter significantly in the diabetics, either after acute or after chronic administration of domperidone.

After acute administration of domperidone oesophageal emptying was unchanged in each of the four patients who had results outside the normal range on the placebo test. In one other patient oesophageal emptying was also outside the normal range. After chronic administration of domperidone oesophageal emptying was outside the normal range in four of the 12 patients (Figure 2). No side effects were reported by any patient.

Discussion

Tests measuring oesophageal radionuclide transit using liquid or solid food boluses are non-invasive and relatively simple to perform.

Figure 1 Oesophageal emptying values obtained for controls and diabetic patients. The line dividing each group represents the median value.

Recent evidence suggests that they are as sensitive as manometric techniques in detecting oesophageal dysfunction in diabetes mellitus (Russell *et al.*, 1983) and other oesophageal motility disorders (Maddern *et al.*, 1984; Tolin *et al.*, 1979; Blackwell *et al.*, 1983). Our findings of a marked delay of oesophageal emptying in four of the 12 diabetics studied (of which two were asymptomatic) is consistent with this. The use of a solid food bolus may be more appropriate than liquid in the detection of clinically significant abnormalities of oesophageal emptying, as patients usually complain of solid food dysphagia.

The aetiology of the oesophageal dysfunction in diabetes mellitus may be a vagal neuropathy (Hollis *et al.*, 1977). The use of prokinetic drugs such as metoclopramide and bethanechol in the treatment of disordered oesophageal motility (and the resulting delayed emptying) has been suggested and supported by objective evidence of increased contractile activity in the oesophagus after their administration (Hollis *et al.*, 1977). However although manometric studies

Figure 2 Oesophageal emptying values for diabetic patients after placebo, oral domperidone 40 mg and 37–51 days of chronic domperidone (20 mg three times a day). The line dividing each group represents the median value.

may demonstrate objectively that increased motor activity occurs after such pharmacological intervention, this may not correlate with increased emptying.

Domperidone is a new gastrokinetic drug which is a potent peripheral dopamine antagonist like metoclopramide but lacks cholinergic activity and does not cross the blood-brain barrier, consequently neurological side effects are rare. Reports (Bron & Massih, 1980; Pozzessere *et al.*, 1982; Brogden *et al.*, 1982; Horowitz *et al.*, 1984) have indicated that domperidone is effective in a variety of gastrointestinal disorders.

This study demonstrates that domperidone does not improve oesophageal emptying of a solid bolus in a group of patients with diabetic autonomic neuropathy. Four of the 12 patients studied had oesophageal emptying values outside the normal range on the placebo test and in all of these oesophageal emptying was unchanged after acute administration of domperidone. It therefore appears unlikely that domperidone will increase oesophageal emptying of a solid bolus in diabetic patients with either clearly abnormal or normal oesophageal function. Our results show a trend towards improve-

ment in the symptoms of heartburn and dysphagia after treatment, but the number of patients is small, the changes are not statistically significant and a placebo control was not included. The same dose of oral domperidone has previously been demonstrated by our group to increase both solid and liquid gastric emptying in these patients (Horowitz *et al.*, 1984). It therefore appears likely that the oesophageal

emptying disorder in diabetics is more resistant to treatment with prokinetic drugs than delayed gastric emptying.

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