Br. J. clin. Pharmac. (1985), **19**, 849–851

Fenfluramine delays gastric emptying of solid food

M. HOROWITZ[1], P. J. COLLINS[2], VIRGINIA TUCKWELL[2], JANE VERNON-ROBERTS[3] & [1]D. J. C. SHEARMAN

Departments of [1]Medicine, [2]Nuclear Medicine and [3]Obesity Clinic, Royal Adelaide Hospital, Adelaide, South Australia, Australia

The effect of a single dose of (±)-fenfluramine hydrochloride (40 mg) on gastric emptying of a mixed solid and liquid meal was assessed with a dual isotope scintigraphic technique in eight obese patients. Fenfluramine significantly delayed gastric emptying of solid food (approximately a 15% reduction in the solid linear emptying rate), but had no effect on gastric emptying of liquid.

Keywords fenfluramine gastric emptying obesity

Introduction

The anorectic effects of fenfluramine hydrochloride have been thought to be mediated by central effects on brain serotonergic mechanisms (Blundell & Lesham, 1974). However, the possibility that the satiety effects of fenfluramine in humans could also be mediated in part by peripheral effects has not been investigated. A recent study (Davies *et al.*, 1983) has demonstrated that fenfluramine (5.0 mg/kg intraperitoneally) is a potent inhibitor of gastric emptying in the rat, and that this action is not dependent on a central serotonergic system. We have now assessed the effect of a single oral dose of fenfluramine on gastric emptying in obese human subjects, and demonstrated, for the first time, a significant effect of this drug on gastric motility.

Methods

Eight obese patients, who were greater than 50% in excess of their ideal weight by Metropolitan Life Insurance Company Criteria (three male, five female, mean age 30 years, range 19–38, and mean ± s.e. mean body weight 113 ± 10 kg) were studied after informed consent had been obtained. All patients were non-smokers, on no medication, had no gastrointestinal disease and had been referred to the obesity clinic of the Royal Adelaide Hospital.

In each obese patient gastric emptying was measured at 10.00 h (after the subject had fasted from 24.00 h the previous day) on 2 days separated by a maximum period of 1 week. On each test day the subject was given, in double-blind fashion, a single dose of either oral (±)-fenfluramine hydrochloride 40 mg (Servier Laboratories) or placebo tablets which were identical in appearance and composition, 1 h prior to commencement of the test. Gastric emptying was also measured in 22 control subjects (14 male, eight female, mean age 34 years, range 21–62 and mean body weight 76 ± 2 kg), who were all within 10% of their ideal weight.

Gastric emptying was studied using a previously described and validated dual isotopic scintigraphic technique (Collins *et al.*, 1983) which measures both solid and liquid emptying simultaneously with a single, posteriorly positioned gamma camera. The solid meal was 100 g of cooked ground beef containing 1–1.5 mCi of *in vivo* labelled ^{99m}Tc-chicken liver. The liquid meal was 150 ml of 10% dextrose containing 0.5–0.75 mCi of ^{113m}In-diethylenetriamine-pentaacetic acid (DTPA). From the histograms of solid and liquid emptying (expressed as a percentage of the total meal remaining within the stomach *vs* time) several parameters were derived

Correspondence: Dr M. Horowitz, Department of Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000, Australia

for subsequent statistical analysis. For the solid component these parameters were the lag period (the time between meal consumption and food entering the duodenum), the time for 50% emptying, and the linear emptying rate in %/min. For the liquid component the 50% emptying time and the amount of tracer remaining at 10 min after meal ingestion were obtained (Collins *et al.*, 1983).

The study protocol was approved by the Research Review Committee of the Royal Adelaide Hospital.

Data were analysed using Student's *t*-test for paired and unpaired data.

Results

As previously described (Collins *et al.*, 1983), solid emptying was slower than liquid emptying in all subjects and was characterized by a lag period, before food entered the duodenum, followed by linear emptying. The emptying of liquid was non-linear, with a slope that decreased with time and usually closely approximated a monoexponential pattern.

Treatment with fenfluramine was associated with a significant delay in gastric emptying of solids (50% emptying time, $P < 0.05$) reflecting a slower linear emptying rate ($P < 0.05$) (Table 1). There was no significant change in the lag period for solids. Fenfluramine had no significant effect on parameters of liquid emptying. Gastric emptying of solids was significantly delayed in the obese patients (placebo test), compared to the normal controls (50% emptying time 100 ± 9 *vs* 78 ± 4 min, $P < 0.01$), but liquid emptying was not significantly different (50% emptying time 21 ± 2 *vs* 19 ± 1 min) between the two groups. No side effects were reported by any patient.

Discussion

It seems likely that the long-term regulation of food intake is mediated partly through complex neural and hormonal reflexes resulting from the presence of food in the gastrointestinal tract. The gastric distension theory of post prandial satiety emphasizes the importance of peripheral factors in appetite regulation and is based on the close association between fullness, stomach distension and cessation of eating (Gibbs & Smith, 1978). Gastric distension is dependent on the rate of ingestion of food, intragastric pressure and gastric emptying. Consequently slowing of gastric emptying has been suggested as a therapeutic means of producing anorexia.

(±)-amphetamine inhibits gastric emptying (Bridges *et al.*, 1976), possibly due to anticholinergic effects. The results of our study demonstrate that acute administration of a therapeutic dose of (±)-fenfluramine also significantly delays gastric emptying of the solid component of a mixed solid and liquid meal in obese subjects. The absence of any effect on gastric emptying of liquids suggests that the drug acts by inhibiting antral motility, as the distal stomach is of major importance in controlling the gastric emptying of solid food (Collins *et al.*, 1983). There is some evidence that 5-hydroxytryptamine receptors are involved in the peripheral regulation of gastrointestinal motor function (Ruckebusch & Bardon, 1984), but further studies are required to clarify whether the effect of fenfluramine on gastric emptying is mediated by direct peripheral (serotonergic) or indirect central nervous system mechanisms. The magnitude of the delay in solid emptying was not large (approximately a 15% reduction in the solid linear emptying rate) and the effect may therefore not be of clinical significance. The effects of chronic administration and different doses of

Table 1 Gastric emptying parameters in eight obese patients given oral fenfluramine (40 mg) or placebo. Data are mean values ± s.e. mean.

Parameter	*Placebo*	*Fenfluramine*	P *value*
Solid lag period (min)	43 ± 8	47 ± 8	NS
Solid 50% emptying time (min)	100 ± 9	119 ± 12	< 0.05
Solid linear emptying rate (%/min)	0.92 ± 0.06	0.78 ± 0.08	< 0.05
Liquid 50% emptying time (min)	21 ± 2	23 ± 4	NS
Retention of liquid at 10 min after meal completion (%)	70 ± 3	72 ± 5	NS

NS $P > 0.05$.

fenfluramine would also be of interest.

It is possible that part of the anorectic effect of fenfluramine in humans may be due to delayed gastric emptying.

The moderate delay in gastric emptying of solids in morbidly obese compared to control subjects has previously been reported (Horowitz *et al.*, 1983).

We wish to thank Ms M. Madsen for typing the manuscript.

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(Received January 24, 1985, accepted February 14, 1985)