# Effect of dexfenfluramine on gastric emptying of a mixed solid–liquid meal in obese subjects

BY MICHAEL HOROWITZ, ANNE MADDOX, JUDITH WISHART, JANE VERNON-ROBERTS, BARRY CHATTERTON AND DAVID SHEARMAN

*Departments of Medicine and Nuclear Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000, Australia*

Recent studies suggest that dexfenfluramine (D-fenfluramine), because of its pure serotonergic effect, may be a more potent anti-obesity agent, associated with fewer side-effects than the racemate DL-fenfluramine. The effect of dexfenfluramine on gastric emptying of a mixed solid and liquid meal was assessed with a double-isotope scintigraphic technique in eleven obese patients. Each subject took a placebo capsule on the morning and evening of the day before, and on the morning of the first gastric emptying measurement. Dexfenfluramine was then taken at a dose of 15 mg twice daily and gastric emptying measurements were performed at 5 and at 29 d after the initiation of active treatment. Dexfenfluramine significantly slowed gastric emptying of the solid meal at both 5 and 29 d when compared with the placebo ($P < 0.05$) and also delayed emptying of solid food from the proximal stomach ($P < 0.01$), but no significant effect on liquid emptying was observed. No significant side-effects were reported and there was a marginal weight loss ($P < 0.005$) during treatment. We conclude that inhibition of gastric emptying may contribute to the efficacy of dexfenfluramine in the treatment of obesity.

Dexfenfluramine: Gastric emptying: Obesity

It has been postulated that the control of appetite is mediated partly through the rate of gastric emptying, and slowing of gastric emptying has been suggested as a means of producing a therapeutic decrease in food intake (Gibbs & Smith, 1978; Booth *et al.* 1986). The efficacy of DL-fenfluramine in the treatment of overweight has been thought to be mediated largely by central serotonergic mechanisms (Blundell & Leshem, 1974), but several workers have demonstrated that DL-fenfluramine inhibits gastric emptying of solid and liquid meals in animals (LeDouarec *et al.* 1966; Davies *et al.* 1983; Booth *et al.* 1986; Robinson *et al.* 1986; Rowland & Carlton, 1984, 1986*a,b,c*), and in a recent study from our group administration of a single oral dose of DL-fenfluramine (40 mg) to obese humans slowed gastric emptying of a solid meal (Horowitz *et al.* 1985). These results suggest that the decreased meal size and prolonged inter-meal interval, which are the characteristic behavioural effects of fenfluramine (Innes *et al.* 1977; Stunkard, 1981), might be directly linked to gastric slowing (Booth *et al.* 1986; Rowland & Carlton, 1986*b*). The observations that in the rat, tolerance to the inhibitory effect of DL-fenfluramine on gastric emptying develops rapidly and in a time-course which closely matches tolerance to the anorectic effects of the drug (Rowland & Carlton, 1984, 1986*b*), and in the rhesus monkey that the anorectic efficacy of DL-fenfluramine is closely related to the extent of gastric slowing (Robinson *et al.* 1986) are consistent with this hypothesis. No studies have, however, assessed the effects of prolonged administration of fenfluramine on gastric emptying in humans.

The D- and L- enantiomers of DL-fenfluramine and their metabolites D- and L-norfenfluramine have distinguishable biological actions, but until recently the majority of

behavioural studies have been conducted using the DL, or racemic mixture. At therapeutic dosage, dexfenfluramine (D-fenfluramine) is a potent and selective serotonergic agonist, by releasing and inhibiting the neuronal re-uptake of serotonin (Garattini *et al.* 1979, 1987), while L-fenfluramine is a less potent serotonergic agonist, and in addition has antidopaminergic properties (Consolo *et al.* 1980; Garattini *et al.* 1987). In animals the effects of dexfenfluramine on food intake are considerably greater than L-fenfluramine (Garattini *et al.* 1979; Hirsch *et al.* 1982). Dexfenfluramine is also more potent than L-fenfluramine in retarding gastric emptying in the rat (LeDouarec *et al.* 1966). These observations suggest that the major action of DL-fenfluramine on food intake is predominantly via the D-isomer, or its metabolite D-norfenfluramine, and provide a rationale for the use of dexfenfluramine alone in the treatment of obesity. Recent studies have now confirmed that dexfenfluramine induces sustained weight loss in obese humans, with a low prevalence of side effects (Finer *et al.* 1985, 1987; Guy-Grand *et al.* 1989).

We have now assessed the effect of acute (5 d) and prolonged (29 d) administration of dexfenfluramine on gastric emptying in obese human subjects and report for the first time a sustained action of this drug on gastric motility.

## SUBJECTS AND METHODS

The studies were performed on eleven randomly selected obese patients (two male, nine female), mean age 36 (range 17–55) years and mean body-weight 132 (range 103–163) kg, who were all more than 40 % in excess of their ideal weight by Metropolitan Life Insurance Company Criteria (range 41–194 kg) (Horowitz *et al.* 1985). All patients were Caucasian, non-smokers, on no medication, without known gastrointestinal disease and had been referred to the Weight Disorders Unit of the Royal Adelaide Hospital. Written informed consent was obtained in all cases and the study was approved by the Ethics Subcommittee of the Royal Adelaide Hospital.

### Study protocol

The study design was a single-blind assessment of the effect of dexfenfluramine on gastric emptying in which each patient was their own control. Each subject was asked to have measurements of gastric emptying performed on three separate days. On the day immediately before the first gastric emptying test each subject took one placebo capsule morning (07.30 hours) and evening (19.30 hours). On the day of the first gastric emptying measurement one placebo capsule was taken at 07.30 hours. Each subject was then asked to take one 15 mg capsule of dexfenfluramine (Adifax, Isomeride; Servier Laboratories Pty Ltd, Gidy, France) morning (07.30 hours) and evening (19.30 hours) for 29 d and the first capsule was taken on the evening after the first gastric emptying measurement. On days 5 and 29 after the commencement of dexfenfluramine, further measurements of gastric emptying were made after administration of 15 mg dexfenfluramine at 07.30 hours. Each gastric emptying test was performed at 10.30 hours after the subject had fasted from 24.00 hours the previous day.

Drug compliance was assessed by tablet counts. On the day of each gastric emptying measurement the patient's body-weight was measured on the same scale. Each subject was asked to notify the investigators immediately of the occurrence of any possible adverse events during the study period and on each study day patients were asked to respond to the following question: 'Have you been aware of any unusual experience or feelings, whilst taking the tablets?' and responses were noted.

### Assessment of gastrointestinal symptoms

Before the performance of each gastric emptying test, gastrointestinal symptoms were assessed by a standard questionnaire (Horowitz *et al.* 1987). 'Gastric' symptoms (anorexia,

Table 1. *Effect of dexfenfluramine 15 mg twice daily on gastrointestinal symptoms in obese subjects*

(Median values and ranges shown in parentheses)

| | | Dexfenfluramine | |
| | Placebo | Day 5 | Day 29 |
| No. of subjects... | 11 | 11 | 9 |
| --- | --- | --- | --- |
| 'Oesophageal' score* | 1 (0–6) | 0 (0–3) | 0 (0–3) |
| 'Gastric' score* | 1 (0–7) | 2 (0–7) | 1 (0–8) |
| Total score | 3 (0–12) | 2 (0–10) | 1 (0–8) |
| No. of bowel actions/week | 7 (2–14) | 10 (7–28) | 10 (7–25) |

\* For details, see below.

nausea, early satiety, upper abdominal discomfort or distention, vomiting, abdominal pain) and 'oesophageal' symptoms (dysphagia, heartburn and acid regurgitation) were scored according to the following scheme: 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). The maximum possible total score for the 'gastric' symptoms was therefore 18 and for the 'oesophageal' symptoms was 9. The number of bowel actions each week, the consistency of bowel actions and the presence or absence of nocturnal diarrhoea and faecal incontinence were also noted. The patient was considered to suffer from constipation if less than three spontaneous bowel actions occurred each week (Horowitz *et al.* 1987).

### Measurement of gastric emptying

Details of this double-isotope test, which measures both solid and liquid gastric emptying simultaneously, have previously been published (Collins *et al.* 1983). The solid meal was 100 g cooked ground beef containing 1·0–1·5 mCi $^{99m}$Tc–sulphur colloid–chicken liver, labelled in vivo. The liquid meal was 150 ml D-glucose (100 g/l) in water labelled with 0·75–1 mCi $^{113}$In diethylene triamine penta-acetic acid (DTPA). The study was performed in the sitting position with the scintillation camera behind the patient. The patient initially ate the solid meal over a 5 min period and then immediately drank the D-glucose solution. Information was collected continuously from the onset of food ingestion and time zero was defined as the time of meal completion. Each study was continued for at least 2 h.

For each frame of the study the radioactivity values in the gastric region-of-interest were corrected for patient movement, radionuclide decay, Compton scatter and gamma-ray (tissue) attenuation (Collins *et al.* 1983). The regions-of-interest for the proximal and distal stomach were also determined by a previously described method in which the proximal stomach is defined as the 'reservoir' area seen for at least the first few minutes after ingestion of the solid meal and a horizontal proximal–distal stomach dividing line is drawn immediately below this region (Collins *et al.* 1988).

From the activity–time curves of solid and liquid emptying (expressed as a percentage of the total meal remaining *v.* time) several variables were derived for subsequent statistical analysis. For the solid component these variables were the lag phase before any food left the stomach, the time for 25 % emptying and the percentage of the meal remaining in the stomach at 100 min. Some patients with delayed emptying did not reach 50 % emptying for the total stomach during the study period and consequently this variable was not used for statistical analysis. For the liquid meal the percentage remaining in the stomach at 10 min after meal completion and the time for 50 % emptying were obtained. The percentage of
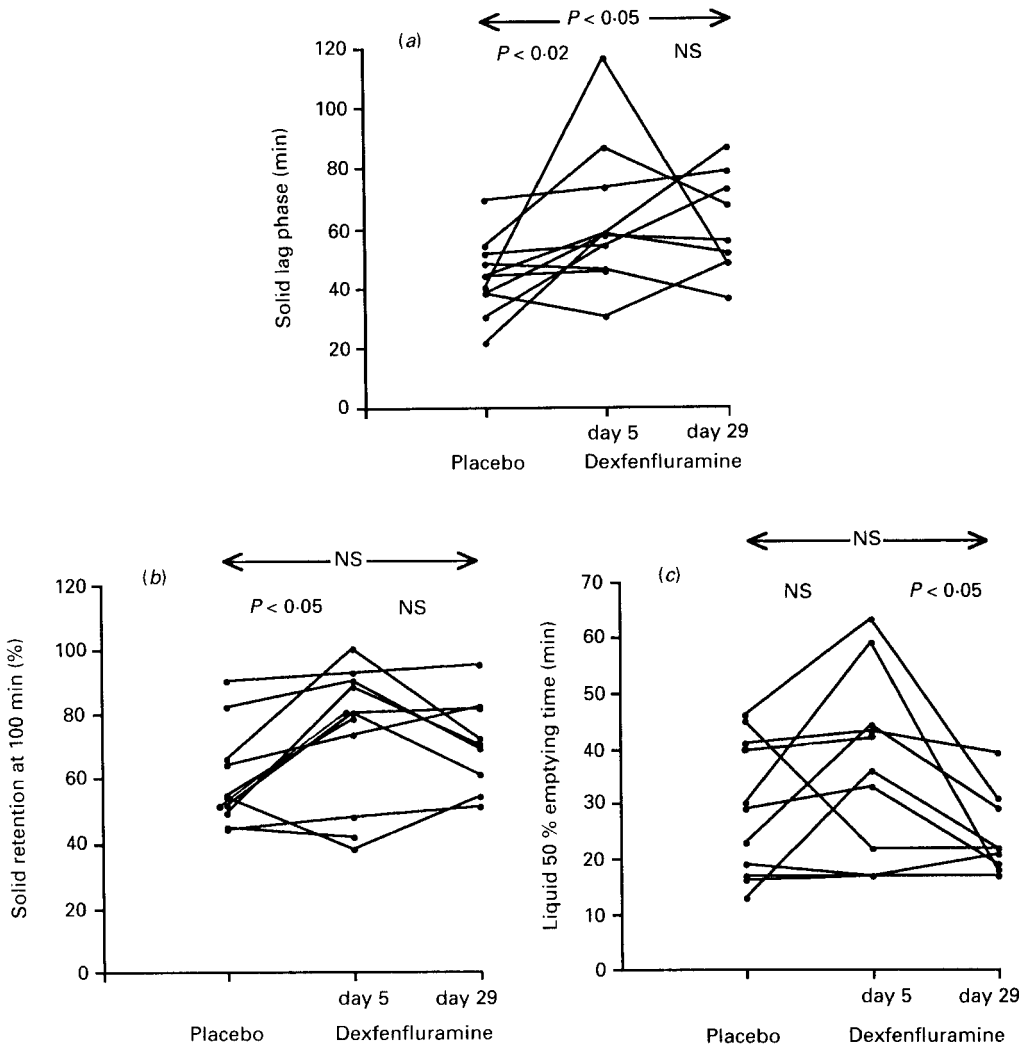
Fig. 1. Effect of dexfenfluramine (15 mg twice daily) for 5 and 29 d on gastric emptying (from the total stomach) in obese subjects of a mixed solid–liquid meal for the: (a) solid lag phase, (b) percentage of the solid meal remaining at 100 min, (c) 50 % emptying time for the liquid meal. For details of procedures, see p. 448. NS, not significant.

the liquid meal remaining at 10 min was used as an index of the early phase of gastric emptying (Horowitz *et al.* 1987). The time for 50 % of the meal to empty from the proximal stomach was calculated for the solid meal and for the liquid meal (Collins *et al.* 1988).

### Statistical analysis

Data were evaluated using the Wilcoxon matched-pairs signed-ranks test. A value of $P < 0.05$ was considered significant in all analyses. Median values and ranges are reported in the text.

## RESULTS

All eleven patients underwent the first two gastric emptying measurements, but only nine of the eleven subjects attended for the third gastric emptying test. Telephone contact confirmed that the two dropouts did not withdraw because of side-effects and the remaining nine patients were assessed as being compliant with medication.

There was a slight, but significant decrease in body-weight between the day of the placebo test and day 29 (median 131 (range 103–163) kg $v$. 130 (range 99–162) kg, $P = 0.004$).

Six patients reported that they were less hungry and five reported excessive tiredness. There was no significant difference in gastrointestinal symptoms between the three study days (Table 1) although on dexfenfluramine there was a non-significant trend ($P = 0.12$) towards an increased frequency of bowel actions each week. Otherwise no adverse events were observed.

Gastric emptying of the solid meal was slower than that of the liquid meal and was characterized by an initial lag phase, before food left the stomach, which was followed by an emptying phase that usually approximated a linear pattern. The emptying curve for liquid was non-linear, with a slope that decreased with time and usually approximated a mono-exponential pattern (Collins $et$ $al.$ 1983). Treatment with dexfenfluramine was associated with a significant slowing of gastric emptying of the solid meal. At 5 d the lag phase ($P = 0.018$), the percentage remaining at 100 min ($P = 0.024$) and the time taken for 25% emptying ($P = 0.01$) were greater than the placebo. On day 29 the lag phase was significantly prolonged ($P = 0.04$) compared with the placebo, but the trends for changes in the percentage of the meal remaining at 100 min and the time for 25% emptying did not quite reach statistical significance ($P = 0.07$ for both). There was no significant difference in variables for solid emptying on day 5 compared with day 29. Dexfenfluramine had no significant effect on variables of liquid emptying, although on day 5 the 50% emptying time for the liquid meal was slower than that for the placebo in eight of the eleven subjects and identical in one subject ($P = 0.36$), and the percentage retention at 10 min was also greater than that with the placebo in eight subjects ($P = 0.076$). Gastric emptying of liquid (50% emptying time) was, however, faster ($P = 0.04$) on day 29 compared with day 5. These results are summarized in Table 2 and Fig. 1.

On the placebo test the proximal stomach 50% emptying times for the solid and liquid meals correlated directly with the amount of the solid meal remaining at 100 min ($r$ 0.70, $P < 0.05$) and the liquid 50% emptying time ($r$ 0.67, $P < 0.05$) respectively. The 50% emptying time for the proximal stomach for the solid meal was slower on day 5 ($P = 0.002$) and on day 29 ($P = 0.008$) compared with placebo (Fig. 2). Dexfenfluramine had no significant effect on the proximal stomach 50% emptying time for the liquid meal. These results are summarized in Table 1 and Figs 1 and 2.

There was no significant correlation between gastric emptying and gastrointestinal symptoms.

## 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 distention theory of post-prandial satiety emphasizes the importance of peripheral factors in appetite regulation and is based on the close association between satiety, stomach distention and the cessation of eating (Gibbs & Smith, 1978). Gastric distention is dependent on the rate of ingestion of food, intragastric pressure and the rate of gastric emptying. It is of interest that several agents which retard gastric

Table 2. *Effect of dexfenfluramine 15 mg twice daily on gastric emptying in obese subjects*

(Median values and ranges shown in parentheses)

| | Placebo 11 | | Dexfenfluramine | | | |
| | | | Day 5 11 | | Day 29 9 | |
| No. of subjects... | Median | Range | Median | Range | Median | Range |
|---|---|---|---|---|---|---|
| Total stomach: | | | | | | |
| Solid | | | | | | |
| Lag phase (min) | 44 | (21–69) | 57* | (30–116) | 55* | (36–86) |
| Retention at 100 min (%) | 54 | (44–90) | 80* | (38–100) | 70 | (51–95) |
| 25% emptying time (min) | 75 | (48–123) | 114* | (60–140) | 86 | (66–142) |
| Liquid | | | | | | |
| Retention at 10 min (%) | 79 | (60–95) | 91 | (64–100) | 76 | (58–90) |
| 50% emptying time (min) | 29 | (13–46) | 36 | (17–63) | 22† | (17–39) |
| Proximal stomach: | | | | | | |
| Solid 50% emptying time (min) | 41 | (2–104) | 67** | (6–138) | 62** | (27–95) |
| Liquid 50% emptying time (min) | 3 | (0–23) | 2 | (0–24) | 4 | (1–10) |

Median values were significantly different from those for subjects when given the placebo: $* P < 0.05$, $** P < 0.01$.

Median values were significantly different from those of day 5 of treatment: $† P < 0.05$.
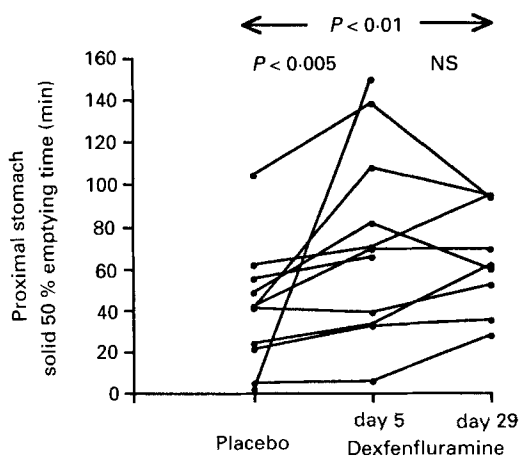


Fig. 2. Effect of dexfenfluramine (15 mg twice daily) for 5 and 29 d on the time-interval for 50% of the solid meal to empty from the proximal stomach in obese subjects. For details of procedures, see p. 448. NS, not significant.

emptying after acute administration, such as salbutamol (Rees *et al.* 1980), L-DOPA (Berkowitz & McCallum, 1980), and cholecystokinin octapeptide (Liddle *et al.* 1986) have been reported to inhibit feeding.

Dexfenfluramine has many physiological effects which could underlie its action on food intake and body-weight. These include gastric inhibition, central anorectic effects and alterations in glucose and lipid metabolism (Booth *et al.* 1986; Even & Nicolaidis, 1986; Rowland & Carlton, 1986b). There is at present a lack of consensus concerning the relative importance of these mechanisms. Our previous study supports a role for inhibition of

gastric emptying in the fenfluramine-induced suppression of feeding observed after acute administration of this drug (Horowitz *et al.* 1985). The slowing of gastric emptying may also be relevant to the interpretation of some of the metabolic effects of fenfluramine on lipid and carbohydrate metabolism (Stunkard, 1981; Even & Nicolaidis, 1986; Rowland & Carlton, 1986*b*).

Dexfenfluramine inhibited gastric emptying of a solid meal and, in contrast to the effect of DL-fenfluramine in the rat (Rowland & Carlton, 1984), this action was maintained for at least 29 d. The slower emptying of the solid meal reflected a prolongation of the lag phase before solid food emptied from the stomach which, at least in part, was demonstrated to be due to a slower redistribution of solid food from proximal to distal stomach. This effect may be mediated by a reduction in fundal tone, as suggested by Robinson *et al.* (1986), but the possibility of an inhibition of the mixing function of the antrum, or changes in pyloric or duodenal motility (Houghton *et al.* 1988) have not been excluded. While the magnitude of the delay in solid emptying was not large (approximately a 25 % prolongation of the lag phase), this may correspond to the 10–20 % reduction of energy intake typically reported in humans (Stunkard, 1981).

The absence of a significant effect of dexfenfluramine on gastric emptying of liquid (particularly at 5 d) may reflect a type 2 error (i.e. due to the relatively small number of subjects that we studied) or the use of a liquid meal of relatively low energy density (Collins *et al.*1983). Previous studies in animals have suggested that DL-fenfluramine may produce greater inhibition of gastric emptying of solid, compared with liquid meals (Rowland & Carlton, 1986*b*). It is, of course, possible that higher doses of dexfenfluramine may modify liquid emptying and there is some evidence that plasma concentrations of fenfluramine correlate with weight loss (Innes *et al.* 1977; Rowland & Carlton, 1986*b*).

The effect of dexfenfluramine on gastric emptying is likely to be mediated by effects on serotonergic mechanisms (Pollock & Rowland, 1981), but it is not clear which of the three types of serotonin receptor (5-HT$_1$, 5-HT$_2$, 5-HT$_3$) that have been characterized (Richardson & Engel, 1986) is important for this effect. Since dexfenfluramine causes the release of serotonin (5-HT) it will have effects on all 5-HT receptors. Previous studies have suggested that central 5-HT$_2$ receptors are not involved in mediating the central anorectic effect of dexfenfluramine, but that central 5-HT$_1$ receptors are of importance (Gibbs & Smith, 1978; Barone *et al.* 1985). The low affinity 5-HT-M receptors located at excitatory receptors on peripheral neurones, which have recently been called 5-HT$_3$ receptors, occur in the enteric nervous system where they control the release of substance P, which activates the smooth muscle cells of the gut wall (Richardson & Engel, 1986). Information obtained in animal and human studies indicates that 5-HT$_3$ receptors may play an important role in the regulation of gastrointestinal motility (Fozard, 1984; Buchheit *et al.* 1985; Costall *et al.* 1986; Akkermans *et al.* 1988). The selective 5-HT$_3$ receptor antagonists ICS 205-930 (Buchheit *et al.* 1985; Akkermans *et al.* 1988), MDL 7222 (Fozard, 1984) and GR 38032 (Costall *et al.* 1986) increase the rate of gastric emptying in animals or humans, or both. There is indirect evidence that fenfluramine releases 5-HT from the gut, because its administration causes ileal contractions which can be blocked by 5-HT antagonists (Mottram & Patel, 1979), although gastric levels of 5-HT are apparently not depleted by fenfluramine (Costa *et al.* 1971). An explanation for the effect of dexfenfluramine on gastric emptying is, therefore, direct stimulation of 5-HT$_3$ receptors in the stomach, but an action on central nervous system control mechanisms is also possible. To date there are apparently no studies of the effects of 5-HT antagonists, either central or peripheral, on gastric inhibition due to fenfluramine to clarify this postulate.

Our study supports the results of other studies demonstrating that dexfenfluramine is generally well tolerated and induces weight loss (Guy-Grand *et al.* 1989; Finer *et al.* 1985, 1987). The symptoms of diarrhoea and tiredness observed by some subjects were mild, but

may have been related to the use of the drug (Finer *et al.* 1985, 1987). Similarly, although we were unable to demonstrate a significant correlation, symptoms such as nausea may relate to delayed gastric emptying. There appears to be a lower prevalence of side-effects with dexfenfluramine compared with the racemic mixture, probably because after a standard dose plasma concentrations of L-fenfluramine are more variable than dexfenfluramine (Finer *et al.* 1987). Steady-state concentrations of dexfenfluramine are usually achieved in normal volunteers within 4 d and are not dependent on body-weight, and the absence of L-fenfluramine does not significantly modify the kinetic variables of dexfenfluramine, or its active metabolite D-norfenfluramine (Caccia *et al.* 1982). Consequently the dosage of 30 mg D-fenfluramine/d used in our study is no greater than the quantity delivered by the lowest recommended dose of DL-fenfluramine (Innes *et al.* 1977; Stunkard, 1981; Finer *et al.* 1985).

The weight loss produced by DL-fenfluramine (and probably also dexfenfluramine (Finer *et al.* 1987; Guy-Grand *et al.* 1989)) in humans, does not continue indefinitely and, characteristically, at about 6 months, a steady-state body-weight is reached, some 10 kg below the initial weight (Innes *et al.* 1977; Stunkard, 1981). This plateau in weight loss has been postulated to reflect a metabolic adaptation to the lower weight, or tolerance to the effect of the drug (Stunkard, 1981), but this problem remains unresolved as there are virtually no long-term studies of the mechanisms of long-term anorexia from fenfluramine, partly due to the rapid development of tolerance in many animal models (Rowland & Carlton, 1986b). While we did not observe any difference in the effect of dexfenfluramine on gastric emptying of the solid meal at 5 d compared with 29 d, the difference in liquid emptying indicates that more prolonged studies are required to confirm that the effect of dexfenfluramine on gastric emptying is maintained. The demonstration in the present study that the effect of dexfenfluramine in slowing gastric emptying of solid food is sustained for 29 d, however, suggests that retardation of gastric emptying may contribute to the efficacy of dexfenfluramine in the treatment of obesity.

## REFERENCES

Akkermans, L. M. A., Vos, A., Hoekstra, A., Roelofs, J. M. M. & Horowitz, M. (1988). The effect of ICS 205-930 (a specific 5-HT$_3$ receptor antagonist) on gastric emptying of a solid meal in normal subjects. *Gut* **29**, 1249–1252.

Barone, D., Luzzani, F., Assandri, A., Galliani, G., Mennini, T. & Garattini, S. (1985). In vivo stereospecific [$^3$H]spiperone binding in rat brain: characteristics, regional distribution, kinetics and pharmacological properties. *European Journal of Pharmacology* **116**, 63–74.

Berkowitz, D. M. & McCallum, R. W. (1980). Interaction of levodopa and metoclopramide on gastric emptying. *Clinical Pharmacology and Therapeutics* **27**, 414–420.

Blundell, J. E. & Leshem, M. B. (1974). Central action of anorexic agents: effects of amphetamine and fenfluramine in rats with lateral hypothalamic lesions. *European Journal of Pharmacology* **28**, 81–89.

Booth, D. A., Gibson, E. L. & Baker, B. J. (1986). Gastromotor mechanism of fenfluramine anorexia. *Appetite* **7**, Suppl., 57 69.

Buchheit, K. H., Engel, G., Mutschler, E. & Richardson, B. (1985). Study of the contractile effect of 5-hydroxytryptamine (5-HT) in the isolated longitudinal muscle strip from guinea-pig ileum. *Naunyn-Schmiedebergs Archives of Pharmacology* **329**, 36–41.

Caccia, S., Ballabio, M., Guiso, G., Rochetti, M. & Garattini, S. (1982). Special differences in the kinetics and metabolism of fenfluramine isomers. *Archives Internationales de Pharmacodynamie et de Thérapie* **258**, 15–28.

Collins, P. J., Horowitz, M. & Chatterton, B. E. (1988). Proximal, distal and total stomach emptying of a digestible solid meal in normal subjects. *British Journal of Radiology* **61**, 12–18.

Collins, P. J., Horowitz, M., Cook, D. J., Harding, P. E. & Shearman, D. J. C. (1983). Gastric emptying in normal subjects – a reproducible technique using a single scintillation camera and computer system. *Gut* **24**, 1117–1125.

Consolo, S., Ladinsky, H., Forloni, G. L., Tirelli, A. S. & Garattini, S. (1980). Comparison of the effects of the stereoisomers of fenfluramine on the acetylcholine content of rat striatum, hippocampus and nucleus accumbens. *Journal of Pharmacy and Pharmacology* **32**, 201–203.

Costa, E., Groppetti, A. & Revuetta, A. (1971). Action of fenfluramine on monoamine stores of rat tissue. *British Journal of Pharmacology* **41**, 57–64.

Costall, B., Kelly, M. E., Naylor, R. J., Tan, C. C. W. & Tattersall, F. D. (1986). 5-Hydroxytryptamine M-receptor antagonism in the hypothalamus facilitates gastric emptying in the guinea-pig. *Neuropharmacology* **25**, 1293–1296.

Davies, R. F., Rossi, J., Panksepp, J., Bean, N. J. & Zolovick, A. J. (1983). Fenfluramine anorexia: a peripheral locus of action. *Physiology and Behaviour* **30**, 723–730.

Even, P. & Nicolaidis, S. (1986). Dextrofenfluramine increases energy cost of muscular effect. *Pharmacology, Biochemistry and Behaviour* **24**, 647–656.

Finer, N., Craddock, D., Lavielle, R. & Keen, H. (1985). Dextrofenfluramine in refractory obesity. *Current Therapeutic Research* **38**, 847–854.

Finer, N., Craddock, D., Lavielle, R. & Keen, H. (1987). Prolonged weight loss with dexfenfluramine treatment in obese patients. *Diabète et Métabolisme* **13**, 598–602.

Fozard, J. R. (1984). MDL 7222: a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors. *Naunyn-Schmiedebergs Archives of Pharmacology* **326**, 36–44.

Garattini, S., Caccia, S., Mennini, T., Samanin, R., Consolo, S. & Ladinsky, H. (1979). Biochemical pharmacology of the anorectic drug fenfluramine: a review. *Current Medical Research Opinion* **6**, 15–27.

Garattini, S., Mennini, T. & Samanin, R. (1987). From fenfluramine racemate to D-fenfluramine. Specificity and potency of the effects on the serotoninergic system and food intake. In *Human Obesity*, vol. 499, pp., 156–166 [R. J. Wurtman and J. J. Wurtman, editors]. New York: New York Academy of Sciences.

Gibbs, J. & Smith, G. P. (1978). The gut and preabsorptive satiety. *Acta Hepatologica-Gastroenterologica* **35**, 413–416.

Guy-Grand, B., Apselbaum, M., Crepaldi, G., Gries, A., Lefevre, P. & Turner, P. (1989). International trial of long-term dexfenfluramine in obesity. *Lancet* **ii**, 1142–1144.

Hirsch, J. A., Goldberg, S. & Wurtman, R. J. (1982). Effect of (+) or (−)-enantiomers of fenfluramine or norfenfluramine on nutrient selection by rats. *Journal of Pharmacy and Pharmacology* **34**, 18–21.

Horowitz, M., Collins, P. J., Tuckwell, V., Vernon-Roberts, J. & Shearman, D. J. C. (1985). Fenfluramine delays gastric emptying of solid food. *British Journal of Clinical Pharmacology* **19**, 849–851.

Horowitz, M., Maddox, A., Harding, P. E., Maddern, G. J., Chatterton, B. E., Wishart, J. & Shearman, D. J. C. (1987). Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetes mellitus. *Gastroenterology* **92**, 1899–1907.

Houghton, L. A., Read, N. W., Heddle, R., Horowitz, M., Collins, P. J., Chatterton, B. & Dent, J. (1988). The relationship of the motor activity of the antrum, pylorus and duodenum to gastric emptying of a solid–liquid mixed meal. *Gastroenterology* **94**, 1285–1291.

Innes, J. A., Watson, M. L., Ford, M. J., Munro, J. F., Stodolant, M. C. & Campbell, D. B. (1977). Plasma fenfluramine levels, weight loss and side effects. *British Medical Journal* **ii**, 1322–1325.

LeDouarec, J. D., Schmitt, H. & Laubie, M. (1966). Etude pharmacologique de la fenfluramine et de ses isomères optiques. *Archives Internationales de Pharmacodynamie et de Thérapie* **161**, 206–232.

Liddle, R. A., Morita, E. T., Conrad, C. K. & Williams, J. A. (1986). Regulation of gastric emptying in humans by cholecystokinin. *Journal of Clinical Investigations* **77**, 992–996.

Mottram, D. R. & Patel, R. J. (1979). Peripheral effects of fenfluramine mediated via the release of 5-hydroxytryptamine. *General Pharmacology* **10**, 441–444.

Pollock, J. D. & Rowland, N. (1981). Peripherally administered serotonin decreases food intake in rats. *Pharmacology, Biochemistry and Behaviour* **15**, 179–183.

Rees, W. R., Clark, R. A., Holdsworth, C. D., Barber, D. C. & Howlett, P. J. (1980). The effect of $\beta$-adrenoreceptor agonists and antagonists on gastric emptying in man. *British Journal of Clinical Pharmacology* **10**, 551–554.

Richardson, B. P. & Engel, G. (1986). The pharmacology and function of 5-HT$_3$ receptors. *TINS* **9**, 424–428.

Robinson, P. H., Moran, T. H. & McHugh, P. R. (1986). The inhibition of gastric emptying and feeding in fenfluramine. *American Journal of Physiology* **250**, R764–R799.

Rowland, N. E. & Carlton, J. (1984). Inhibition of gastric emptying by peripheral and central fenfluramine in rats: correlation with anorexia. *Life Sciences* **34**, 2495–2499.

Rowland, N. E. & Carlton, J. (1986a). Tolerance to fenfluramine anorexia: fact or fiction? *Appetite* **7**, Suppl., 71–83.

Rowland, N. E. & Carlton, J. (1986b). Neurobiology of an anorectic drug: fenfluramine. *Progress in Neurobiology* **27**, 13–62.

Rowland, N. E. & Carlton, J. (1986c). Effects of fenfluramine on food intake, body weight, gastric emptying and brain monoamines in Syrian hamsters. *Brain Research Bulletin* **17**, 575–581.

Stunkard, A. J. (1981). Anorectic agents: a theory of action and lack of tolerance in a clinical trial. In *Anorectic Agents: Mechanisms of Action and Tolerance*, pp. 191–209 [S. Garattini and R. Samanin, editors]. New York: Raven Press.