Clofibrate raises human 24 h intragastric acidity but does not affect plasma gastrin concentration

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1 We studied the effects of acute oral dosing with clofibrate (500 mg four times daily) on 24 h intragastric acidity and plasma gastrin concentration in 12 healthy female subjects.

2 The 24 h integrated intragastric acidity rose from 429 mmol l⁻¹ h (95% CI 296–479) before dosing to 527 mmol l⁻¹ h (95% CI 385–664) on the day of dosing (+23%; $P = 0.041$), but no change was observed in the 24 h integrated plasma gastrin concentration: 420 pmol l⁻¹ h (95% CI 282–499) before and 389 pmol l⁻¹ h (95% CI 249–489) during dosing ($P = 0.182$).

3 We conclude that clofibrate has no acute antisecretory effect on the human stomach, and that human gastrin-induced enterochromaffin-like cell proliferation is unlikely with this drug.

Keywords clofibrate intragastric acidity plasma gastrin

Introduction

Phenoxyisobutyrate derivatives (clofibrate, ciprofibrate, bezafibrate) are used as part of the long-term management of hyperlipidaemia. All of these compounds have been shown to have a gastric acid anti-secretory activity in the rat (Eason *et al.*, 1988a,b,c; Lippman & Seekhaler, 1976; Rheault *et al.*, 1982) but not in the mouse or marmoset (Eason *et al.*, 1988c). Ciprofibrate has been shown in the rat to have drug-related proliferative effect on the gastric enterochromaffin-like (ECL) cell, producing in some animals gastric carcinoids (Eason *et al.*, 1988a,c). Clofibrate has not been associated with the development of gastric carcinoids, although one adenoma of the stomach was described in a clofibrate-dosed rat (Svoboda & Azarnoff, 1979).

Gastrin acts as a growth factor for gastric ECL cells (Larsson *et al.*, 1986). Drugs which have an anti-secretory action in the stomach raise the plasma gastrin concentration, and in turn they may induce ECL cell hyperplasia and gastric carcinoids (Arnold *et al.*, 1986; Blom, 1986;

Harleman *et al.*, 1987; Hirth, 1987; Penston & Wormsley, 1987; Strett *et al.*, 1987). A drug-induced rise of plasma gastrin concentration was thought to be the cause of the carcinoids observed in the ciprofibrate-dosed rats (Eason *et al.*, 1988c), rather than a direct effect of the drug.

The objects of the present study were to determine whether clofibrate decreases human intragastric acidity or affects human plasma gastrin concentration.

Methods

Twelve healthy female subjects entered and completed this study. Their median age was 22 years (range 20 to 23 years), their median weight was 65.5 kg (range 50 kg to 78 kg) and their median height was 1.71 m (range 1.6 m to 1.78 m). None of the 12 subjects smoked. Pre-study history and physical examination were unremarkable and no clinically significant ab-

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normality was observed in routine haematology or biochemistry profiles, before or after the study.

This was an open study. The subjects were studied twice; before and during 1 day of oral dosing with clofibrate 500 mg four times daily; one 500 mg capsule was taken at 09.30, 13.30, 18.30 and 22.30 h, respectively.

The subjects were studied using the Royal Free Hospital standard protocol for 24 h studies (Lanzon-Miller *et al.*, 1987). The subjects were admitted to a research ward after an overnight fast. A 10 French gauge Salem Sump nasogastric tube (Argyle Medical) was positioned in the stomach. Aliquots (5–10 ml) of intragastric contents were aspirated hourly throughout the study and the pH of each aliquot measured to the nearest 0.01 pH unit by means of a glass electrode and digital pH meter (Radiometer, Copenhagen). The electrode was calibrated with standard buffers (pH 7.00, 4.01, and 1.09: Radiometer, Copenhagen) before and halfway through each hourly batch of samples.

Every hour from 09.00 to 24.00 h, and 2 hourly thereafter, blood was taken via a venous cannula for assay of plasma gastrin concentration. The blood was collected in lithium-heparin tubes which already contained 0.2 ml aprotinin (Trasylol, Bayer). The tubes were centrifuged immediately, the plasma transferred to plastic tubes and frozen to -20°C . All the plasma samples from each subject were analysed for gastrin in one batch, by radioimmunoassay using antibody GAS 179 in Professor Bloom's laboratory at the Hammersmith Hospital, London (Bryant & Adrian, 1982).

The subjects were ambulant around the ward throughout both studies. The food and environmental conditions for the studies were identical to those used in earlier experiments at the Royal Free Hospital (Lanzon-Miller *et al.*, 1987). The following standard meals were served: breakfast, coffee, lunch, tea, dinner and a bedtime snack at 09.15, 11.15, 13.15, 16.15, 19.15 and 22.15 h, respectively.

Ethical approval

The study was approved by the Ethics Committee of the Royal Free Hospital and written consent was obtained from every subject. Routine safety studies were performed before and after dosing with the clofibrate.

Statistical analysis

Twenty-four hour profiles of intragastric acidity and plasma gastrin concentration were obtained

for every subject on both study days. The significance of median curves of 24 h intragastric acidity or plasma gastrin concentration was assessed using the Kruskal-Wallis analysis of variance. The integrated area under the curve for each individual profile was calculated by the trapezoid rule, with integrated acidity expressed as $\text{mmol l}^{-1}\text{ h}$ and plasma gastrin as $\text{pmol l}^{-1}\text{ h}$. To make these values comparable with single point measurements of either acidity or gastrin, each value should be divided by 23. The significance of the differences between the integrated 24 h values was assessed using the Wilcoxon matched pair signed rank test.

Results

The studies were well-tolerated by all the subjects. No adverse event, either minor or major, was reported by any subject during or after completion of the study.

Intragastric acidity

Figure 1 shows the 24 h median hourly intragastric acidity before and during dosing with clofibrate 500 mg four times daily. Analysis of variance demonstrates no significant difference between the two study days ($0.7 < P < 0.8$).

Figure 2 demonstrates that there was a significant ($P = 0.041$) but small rise (+23%) in the median 24 h integrated intragastric acidity during dosing with clofibrate ($527\text{ mmol l}^{-1}\text{ h}$; 95% CI $385\text{--}664\text{ mmol l}^{-1}\text{ h}$) compared with before dosing ($429\text{ mmol l}^{-1}\text{ h}$; 95% CI $296\text{--}479\text{ mmol l}^{-1}\text{ h}$).

Plasma gastrin

Figure 3 shows the 24 h profiles of median plasma gastrin concentration before and during dosing with clofibrate 500 mg four times daily. There is no significant difference between these curves ($0.95 > P > 0.90$).

Figure 4 demonstrates the individual 24 h integrated plasma gastrin concentrations for all the subjects before (median $420\text{ pmol l}^{-1}\text{ h}$; 95% CI $282\text{--}499\text{ pmol l}^{-1}\text{ h}$) and during dosing with clofibrate 500 mg four times daily (median $389\text{ pmol l}^{-1}\text{ h}$; 95% CI $249\text{--}489\text{ pmol l}^{-1}\text{ h}$). There is no significant difference between the results of the 2 study days ($P = 0.182$).

Discussion

This study demonstrates that clofibrate causes neither a decrease of human intragastric acidity

Figure 1 Median hourly 24 h intragastric acidity profile in 12 healthy female subjects, before (●—●) and during acute dosing with clofibrate 500 mg four times daily (●-----●). B = Breakfast; C = Coffee; L = Lunch; T = Tea; D = Dinner; N = Nightcap.

Figure 2 Twenty-four hour integrated intragastric acidity in 12 healthy female subjects, before and during acute dosing with clofibrate 500 mg four times daily. The figures refer to median values.

nor a rise of plasma gastrin concentration. Thus it appears that the human stomach behaves in the same way as that of the mouse or marmoset (Eason *et al.*, 1988c), and it is unlike that of the rat which does respond to clofibrate-like compounds by a decrease of intragastric acidity and rise of plasma gastrin concentration (Eason *et al.*, 1988a,b,c; Lippman & Seekhaler, 1976; Rheault *et al.*, 1982). The standard dose of

clofibrate (500 mg four times daily) used in this study represented a dose of $31 \text{ mg kg}^{-1} \text{ day}^{-1}$; clofibrate-induced inhibition of gastric acid secretion in the rat was observed when they were dosed with clofibrate 50–500 mg kg^{-1} (Eason *et al.*, 1988c; Rheault *et al.*, 1982). The present study demonstrates a statistically significant 23% rise of 24 h integrated intragastric acidity, which is unlikely to be of clinical significance; long-term placebo controlled studies using clofibrate for the prevention of ischaemic heart disease have not identified an excess risk of peptic ulceration in the treated group (Oliver *et al.*, 1978, 1984).

The subjects chosen for this study were all female—a choice that was made to produce some sexual equality in our experiments, as most studies of gastric function at the Royal Free Hospital, which have often involved the assessment of new chemical entities, have been restricted to male volunteers. It may be relevant that the ECL cell tumours observed after a lifetime of dosing with omeprazole were much more common in female rats (Blom, 1986; Larsson *et al.*, 1986)—a trend that was not observed with studies of clofibrate-like compounds in the rat (Eason *et al.*, 1988c). The values of intragastric acidity before dosing in these 12 females are lower than similar measurements in healthy young men, and the plasma gastrin concentration appears to be relatively (but appropriately)

Figure 3 Median 24 h plasma gastrin concentration profile in 12 healthy female subjects, before (●—●) and during acute dosing with clobifibrate 500 mg four times daily (●-----●). B = Breakfast; C = Coffee; L = Lunch; T = Tea; D = Dinner; N = Nightcap.

Figure 4 Twenty-four hour integrated plasma gastrin concentration in 12 healthy female subjects, before and during acute dosing with clobifibrate 500 mg four times daily. The figures refer to median values.

higher. These observations will be pursued in more extensive comparative experiments in healthy young women and men.

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