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The effect of ciprofibrate on gastric secretion in the rat

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Abstract—The potential of ciprofibrate to inhibit gastric secretion has been investigated in the rat. A significant gastric antisecretory effect was observed following a single oral administration of 300 and 500 mg kg^{-1} and following a single intraduodenal dose of 100, 300 and 500 mg kg^{-1}. The toxicological significance of this finding is discussed in the light of a spate of recent publications linking changes in gastric morphology with hypergastrinaemia produced as a secondary effect of inhibition of acid secretion.

Ciprofibrate is structurally related to clofibrate and both compounds have marked hypolipidaemic activity in man and animals following oral administration (Arnold et al 1979; Dvornik & Cayen 1980; Illingworth et al 1982). Several recent publications have revealed that the long-term (two year) administration of inhibitors of gastric secretion is associated with the formation of gastric carcinoid tumours in rodents (Brittain et al 1985; Ekman et al 1985; Jack et al 1985; Langman 1985; Larsson et al 1986).

Ciprofibrate administration produced a low incidence of similar carcinoid tumours in the glandular portion of the stomach in five out of 59 male and one out of 60 female rats after two years (data on file), which prompted our investigation of the antisecretory activity of ciprofibrate.

Many agents including clofibrate (Lippmann & Seethaler 1976; Rheault et al 1982) have been screened for gastric antisecretory effects using the combination of Shay ligation (Shay et al 1954) and single dose administration usually by the oral or intraduodenal route. Lippmann & Seethaler (1976) demonstrated the antisecretory activity of clofibrate over the range 200 to 500 mg kg^{-1} following oral administration (1 h before pylorus ligation). Rheault et al (1982) have confirmed the antisecretory activity of clofibrate in the rat using the intraduodenal and intraperitoneal routes of administration.

In this study we have investigated the effect of ciprofibrate on gastric secretion after single oral and intraduodenal doses to the Shay-ligated rat.

Methods

Male Fischer 344 rats, 150 ± 20 g, were obtained from Charles River Ltd, Manston, Kent, UK. Ciprofibrate (2-[4-(2,2-dichlorocyclopropyl)phenoxyl]-2-methylpropanoic acid) and placebo were administered by intraduodenal injection immediately after ligation of the pyloric sphincter, or by oral administration 1·25 to 1·5 h before ligation.

The secretion of gastric juice was measured using the Shay technique (Shay et al 1954). Food was withdrawn 24 h before measurement of gastric secretion. Under ether anaesthesia, the abdomen of each rat was incised and the pylorus ligated. Four hours later the animals were re-anaesthetized with ether and the stomachs removed before killing. The gastric juice was collected and after centrifugation the pH and volume of samples were measured and acidity titrated with 0·1 M NaOH to pH 7·0 and acid output expressed as μmol h^{-1}.

Animals received ciprofibrate, as suspensions in 0·25% w/w gum tragacanth, at a dosage volume of 5 mL kg^{-1}. Control animals received gum tragacanth alone at the same dose volume. Three treatment levels were used (100, 300 and 500 mg kg^{-1}). There were eight groups in all with five animals allocated to each group. Ciprofibrate was provided as the acid (Sterling-Winthrop Research Centre, Alnwick, UK).

All results were calculated as group mean ± standard deviation. Statistical analyses of the treated groups compared with the control groups, included an analysis of variance followed by the Student's *t*-test.

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Results

The results are presented in Fig. 1.

A dose-related antisecretory effect was established following both oral and intraduodenal administration of ciprofibrate. The dose producing a 50% decrease in volume (ED50) was approximately 400 mg kg^{-1} following a single oral dose and approximately 170 mg kg^{-1} following a single intraduodenal dose. Statistically significant decreases in volume occurred following administration of a single intraduodenal dose of 100, 300 and 500 mg kg^{-1}. In the top dose group intraduodenal administration completely inhibited gastric secretion and therefore no pH or titratable acid determinations could be undertaken. Less pronounced but significant decreases occurred following oral administration of 300 and 500 mg kg^{-1}.

Titratable acid output was significantly decreased in the low and mid dose groups following intraduodenal administration and in the mid and top dose group following oral administration. These changes were associated with a dose-related increase in pH which was significant in the mid dose group following intraduodenal adminstration and in the top dose group following oral treatment.

Discussion

This study has demonstrated that ciprofibrate has the potential to inhibit gastric secretion in the rat following oral or intraduodenal administration. Similar antisecretory activity has been reported for clofibrate (Lippmann & Seethaler 1976; Rheault et al 1982) before this study. This investigation indicates that the antisecretory effect is a common property of this type of hypolipidaemic agent, though the mechanism has not yet been elucidated.

In this study using the pylorus-ligated Shay rat, as an acute model for detecting antisecretory potential, we have demonstrated inhibition of secretion after a single dose over the dose range of 100 to 500 mg kg^{-1}. Subsequent to this experiment, light and electron microscopy has identified morphological changes in the oxyntic cells of the stomach of rats. These changes are consistent with inhibition of acid secretion and have been observed at doses over the range 5 to 20 mg kg^{-1} day^{-1} (data on file).

The potential of ciprofibrate to inhibit gastric secretion in common with other fibrates (Lippmann & Seethaler 1976; Rheault et al 1982) is a significant finding, particularly since a low incidence of gastric carcinoids has been detected in the high dose group (10 mg kg^{-1} day^{-1}) after completion of a two year carcinogenicity study in Fischer rats with this compound (data

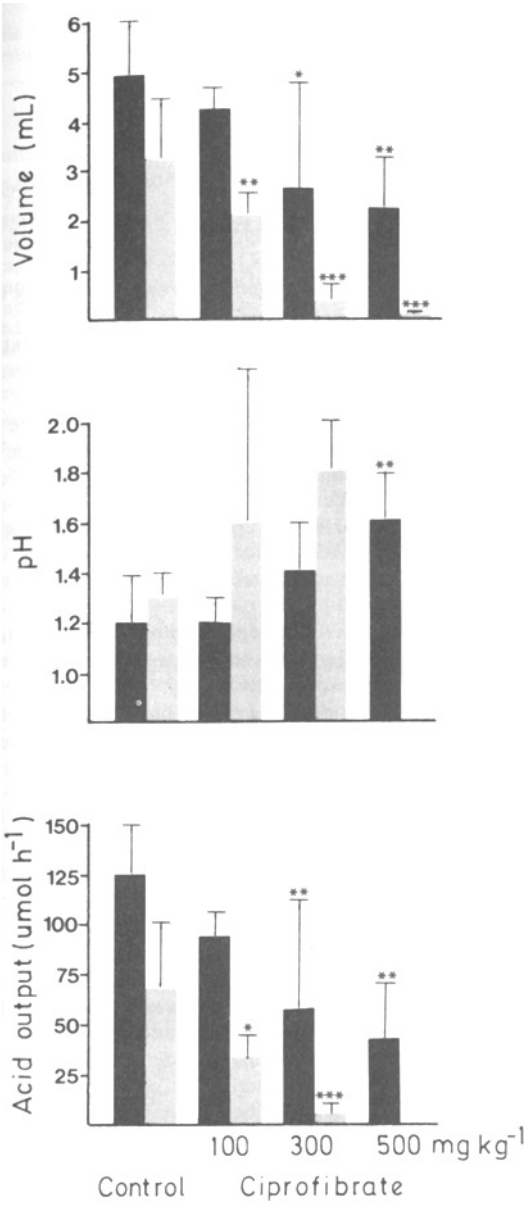

FIG. 1. The effect of ciprofibrate on gastric secretion in the rat following a single oral dose (black columns) and a single intraduodenal dose (grey columns) as measured by the Shay technique. $*P<0.05$, $**P<0.01$ and $***P<0.001$ when compared with control data using Student's *t*-test.

on file). Furthermore, a gastric tumour of similar morphology has been reported in the rat following long term treatment with clofibrate (Svoboda & Azarnoff 1979).

No carcinoids were observed in a two year carcinogenicity study in the mouse with ciprofibrate at the same dose levels used in the rat study. This preliminary communication reports the early findings of an on-going experimental program which is designed to investigate the biochemical basis and significance of the carcinoid tumours which appear to be specific to the rat. Currently the hypothesis under investigation is that long-term inhibition of gastric secretion leads to hypergastrinaemia and long-term morphological changes of the gastric mucosa in rats. These pathological changes would therefore represent an indirect effect of the drug in this species. This hypothesis is consistent with a number of recent publications (Brittain et al 1985; Ekman et al 1985; Jack et al 1985; Langman 1985; Larsson et al 1986). The link between gastric acid secretion, hypergastrinaemia, morphological changes and the species difference in susceptibility to these effects with this group of compounds is being examined.

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