The peroxisome-proliferator ciprofibrate induces hypergastrinemia without raising gastric pH

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The ECL-cell hyperplasia and ECL-cell carcinoids occurring during long-term treatment with ciprofibrate, have been attributed to hypergastrinemia secondary to an inhibitory effect on acid secretion. However, nobody has given any explanation of the mechanism by which ciprofibrate and related phenoxyisobutyrate derivatives inhibit acid secretion. Moreover, the reported inhibition of acid secretion has only been moderate, in contrast to the profound inhibition of acid secretion needed to induce similar ECL-cell changes. To re-examine the effect of ciprofibrate on gastric acidity and serum gastrin, we randomly assigned 33 male Fisher rats into three treatment groups (100 or 20 mg/kg/day of ciprofibrate and control) during a period of 4 weeks. Daily assessments of gastric acidity was done by gastric intubation, using a tube with a diameter of 2.0 mm allowing the introduction of an infant pH-catheter. Measurements were done in all animals 5 days a week. Ciprofibrate did not raise gastric pH. On the contrary, the highest dose increased the acidity. Serum gastrin levels measured in blood taken by vein puncture before the initiation of the drug treatment and on the last day of the 4 week treatment period, revealed a dose-related significant hypergastrinemic effect of ciprofibrate. The slight increase in gastric acidity in the ciprofibrate high-dose group is most likely due to the hypergastrinemia provoked by the drug. This hypergastrinemia is therefore not secondary to an inhibition of acid secretion, but may be due to a direct effect of ciprofibrate on the G-cell. The ECL-cell hyperplasia and the ECL-cell carcinoids, which develop during treatment with peroxisome-proliferators are thus due to hypergastrinemia, which is not secondary to inhibition of acid secretion.

Introduction

Peroxisome-proliferators have a well-known tumorigenic effect on the liver (1). Some of them like phenoxyisobutyrate derivatives (ciprofibrate and other fibrates) also induce hyperplasia of the enterochromaffin-like (ECL*) cell and even tumors from such cells (2,3). Since ECL-cell hyperplasia and ECL-cell carcinoids in the oxyntic mucosa are recognized consequences of hypergastrinemia secondary to profound acid inhibition (4–7), it was natural to postulate that the observed changes of the ECL-cells in the oxyntic mucosa secondary to ciprofibrate treatment, could be due to acid inhibition. Indeed, fibrates have been reported to reduce acid secretion (8,9) and induce hypergastrinemia (2). Therefore, the ECL-cell carcinoids secondary to such treatment have been attributed to an acid inhibitory effect (2,3,9). However, nobody has given any explanation of the mechanism by which fibrates and other peroxisome-proliferators inhibit acid secretion. Moreover, marked ECL-cell hyperplasia and particularly ECL-cell carcinoids in laboratory animals have been reported only after long-term profound acid inhibition whereas the acid inhibitory effect of the fibrates has been reported to be moderate (8,9). Thus, we found it of interest to re-examine the effect of ciprofibrate on gastric acidity and serum gastrin.

Materials and methods

Test substance
Ciprofibrate (2-[4-(2,2-dichlorocyclopropyl)phenoloxyl]-2-methyl propanoic acid) (Modalin, Sanofi/Winthorp, UK) was dissolved in sterile water. Sterile water was used in the placebo group.

Animals and animal management
Male Fisher 344 rats (250 g) (Møllegård, Denmark), were housed in wire-bottom cages at 20°C with a relative humidity of 40–45% and a 12-h light/dark cycle. The Rat and Mouse Diet of B&K Universal Ltd (Hull, UK) and tap water were provided ad libitum. The study was approved by the Animal Welfare Committee of the University Hospital of Trondheim.

Treatment procedures and in vivo intragastric pH measurements in rats
In this study, 33 rats were randomly assigned to three treatment groups (200 or 20 mg/kg/day of ciprofibrate and control). The drug was dissolved in 1 ml of sterile water and administered by gastric intubation in the morning for the first 5 days in the week during a period of 4 weeks.

Dose changes during the project
After the sixth day of medication some deaths due to intoxication occurred in the group receiving 200 mg/kg/day of ciprofibrate, making it necessary to reduce the dose to 100 mg/kg/day from the seventh day.

Determination of intragastric acidity
For the assessment of the effect of ciprofibrate on intragastric pH, a new method for repeated estimation of gastric acidity in the same individual was introduced. This was done by daily gastric intubation, using a special tube with a 2.0 mm inner diameter allowing introduction of a pediatric pH catheter through it (the drug was also administered through the same tube). The equipment used for monitoring the gastric acidity was a pH meter (digitrapper Mark II gold), a pH electrode (pediatric monocrystant model 0012) and a pH catheter (monocrystant anionyin), all from Synectics Medical (Stockholm, Sweden).

On the first day of the week, the pH-estimation was done 5 h after dosing of the drug. On the second day it was measured 4 h after, on the fourth day 2 h after and on the fifth day, 1 h after dosing. On the third day, the estimation was done immediately before administration of the drug.

Loxitidine treatment
The intragastric pH electrode method was validated in 12 other rats: six received the insoluble histamine (H₂) antagonist loxtidine (10) (Glaxo, UK) at 20 mg/day dissolved in 0.5 ml sterile water, and six control rats received water only. Loxitidine or vehicle was given once daily by gastric intubation for 5 days. Intragastric acidity was measured by the pH electrode method 2 h after administration of the drug/vehicle on the fifth day.

Before sacrifice, the animals were given 0.7 ml subcutaneously of a mixture (per ml) of fluanisone 2.5 mg, fenatyl 0.05 mg and midazolam 1.25 mg (Roche, Basel, Switzerland). Blood was then collected by heart puncture and the animals killed by exsanguination.

*Abbreviations: Ciprofibrate, (2-[4-(2,2-dichlorocyclopropyl)phenoloxyl]-2methyl propanoic acid; H₂, histamine; ECL, enterochromaffin-like.
Ciprofibrate induced a dose-dependent hypergastrinemia (Figure 1). The group receiving ciprofibrate 200 mg/kg/day, four of eleven animals died during the first week. Autopsy of these animals did not reveal any definite cause of death, which accordingly was attributed to intoxication. After reducing the dose to 100 mg/kg/day, no mortality was recorded.

The effect of ciprofibrate on gastric acidity
Ciprofibrate did not raise gastric pH (Figure 1). There was, on the other hand, a tendency for a dose-dependent increase in acidity. Thus, the median pH in the ciprofibrate 100 mg/kg/day group was significantly reduced compared with the control group at day 5 (pH 1.7 versus 2.2, P < 0.05), 1.0 versus 2.2 at day 10 (P < 0.01), 1.3 versus 2.2 on day 12 (P < 0.05), and 0.9 versus 1.6 on day 17 (P < 0.05) (Figure 1). In contrast, administration of the H2-receptor antagonist loxetine induced a pronounced inhibition of gastric acid secretion raising the median intragastric pH from 1.95 in the control group to 4.50 in the loxetine group.

The effect of ciprofibrate on serum gastrin levels
Ciprofibrate induced a dose-dependent hypergastrinemia (Figure 2). In the control group, serum gastrin level was 44 ± 4 pmol (mean ± SEM), compared to the low dose group of ciprofibrate (20 mg/kg/day) with 106 ± 6, and to the high dose group of ciprofibrate (200–100 mg/kg/day) with 360 ± 40 pmol. The differences between ciprofibrate treated rats and the controls as well as between the high and low dose ciprofibrate groups were highly significant (P < 0.01).

Discussion
Rather than raising gastric pH, ciprofibrate induced a slight fall at a dose of 100 mg/kg/day. Ciprofibrate also dose-dependently increased serum gastrin. The increased gastric acidity is accordingly most probably due to the hypergastrinemic effect of ciprofibrate. The hypergastrinemic effect may be due to a direct effect on the G-cell. The results of the present study thus confirms that ECL-cell hyperplasia and ECL-cell carcinoids, which developed during treatment with peroxysome-proliferators (3), are caused by hypergastrinemia. However, the hypergastrinemic effect of ciprofibrate is mediated by a hitherto unrecognized mechanism.

The present findings are particulary of interest when discussed in the context of previous reports showing that ciprofibrate induces ECL-cell hyperplasia and carcinoids (2,3). Most studies on hypergastrinemia-induced ECL-cell proliferation have been conducted with methods that induced anacidity and hypergastrinemia, whilst ciprofibrate induces hypergastrinemia with minor changes in gastric acidity. The fact that ECL-cell proliferation occurs also in these experimental circumstances further confirms the central role of hypergastrinemia in growth stimulation. The concomitant anacidity in the models used in many previous studies (4,5) seems to be of minor significance for the ECL-cell growth disturbances. This has a clear parallel to human pathophysiology, since in man ECL-cell carcinoids develop whether hypergastrinemia is accompanied by increased (12) or abolished (13) acid secretion. Ciprofibrate is used in the treatment of hypercholesterolemia, and the effect on serum gastrin may in the long run have negative consequences. Moreover, the combination of ciprofibrate with potent inhibitors of gastric acid secretion, which induce hypergastrinemia by an independent mechanism (4), may in particular cause a great increase in serum gastrin. In conclusion, the present study shows that ciprofibrate induces hypergastrinemia via a mechanism not related to inhibition of gastric acid secretion. How ciprofibrate affects gastrin release needs to be further examined. This is of particular importance since an effect on the release of signal substances from endocrine and paracrine cells, may in fact have relevance for the general tumorigenic effect of these compounds (1).
References


Received on May 19, 1996; revised on July 8, 1996; accepted on July 23, 1996