The Influence of Prolonged Cimetidine Administration on Serum Gastrin Levels and Gastric Acid Secretion in Rats

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Summary
The correlation between serum gastrin levels and gastric acid secretion during 4 weeks of cimetidine administration (once daily) was investigated. Serum gastrin levels and gastric acid secretion were estimated on the 7th, 14th, 21st and 28th day after cimetidine administration (25 mg.kg\(^{-1}\), intragastrically). At the mentioned time intervals gastric acid secretion stimulated by histamine and pentagastrin was also studied. It was found that on the 14th and 21st day after cimetidine administration serum gastrin levels were significantly elevated. Basal gastric acid secretion after cimetidine administration was significantly decreased at all the observed time intervals. Histamine-stimulated gastric acid secretion was increased on the 14th, 21st and 28th day after cimetidine administration. Hypoacidity was not followed at all time intervals by hypergastrinaemia (only on day 14 and 21 after cimetidine).

Key words
Cimetidine – Gastrin concentration – Gastric acid output

H\(_2\)-receptor antagonists (cimetidine, ranitidine, famotidine) which are potent inhibitors of gastric acid secretion, have proved to be an effective form of treatment of gastric ulceration. It is known that inhibition of acid secretion raises the pH in the gastric antrum. As a result, the antral gastrin content increases and the release of gastrin into the blood is augmented. Many experiment showed that long-term administration of H\(_2\)-receptor antagonists in rats is accompanied by hypergastrinaemia (Halter \textit{et al.} 1978, Tielemans and Willems, 1991). Gastrin is known to be a growth factor for the acid-secreting mucosa. Long-term hypergastrinaemia causes gastric mucosa hyperplasia (Hákanson \textit{et al.} 1986, Hákanson and Sandler, 1990).

The present study was designed to investigate the correlation between gastric acid secretion and serum gastrin levels during four weeks of cimetidine administration. We also compared the influence of cimetidine on acid secretion stimulated by pentagastrin or histamine.

Male Wistar rats of 230–270 g body weight, fed on a standard (Larsen) diet were used. Cimetidine (SIGMA) was given orally (through a gastric tube) in a single dose of 25 mg.kg\(^{-1}\) (dissolved in 0.5 \% methylcellulose, pH 9.0 – prepared with NaOH).

For estimation of the serum gastrin levels and gastric acid secretion rats which had fasted for 24 h were used. Gastrin and acid secretion were determined before cimetidine administration and on the 7th, 14th, 21st and 28th day after daily cimetidine administration. Blood for gastrin determination was taken from the tail vein and the serum gastrin level was determined by means of commercial RIA gastrin test kits (Institute of Radiocology and Utilization of Nuclear Techniques, Košice).

Gastric acid was repeatedly measured in the same rats which were conscious and unoperated according to the previous study (Hagiwara \textit{et al.} 1984). A catheter was introduced into the stomach of fasted rats via the oesophagus. Two milliliters of saline were injected through this tube and about 1.5 ml was rapidly aspirated. Acid in the aspirate was titrated with 0.01 n NaOH after filtration. The acid output was expressed as μEq HCl.ml\(^{-1}\) aspirate. For gastric acid stimulation we used pentagastrin (0.25 mg.kg\(^{-1}\), Acignon VEB.
Fig. 1

Serum gastrin concentration in control rats (C) and after 7, 14, 21, 28-days' cimetidine administration. Mean values ± S.E.M. ++ p<0.01 compared with control rats.

BERLIN - CHEMIE) or histamine (10 mg.kg⁻¹ SIGMA) given subcutaneously. The statistical analysis was performed by Student's t-test.

It can be seen from Fig. 1, that in the group of control rats the serum gastrin level was 243.9 ± 38.9 pg.ml⁻¹. On the 7th day after cimetidine administration the serum gastrin level was 198.7 ± 33.4 pg.ml⁻¹ (which did not differ significantly from the control group). Significantly increased (p<0.01) gastrin levels were observed on the 14th and 21st day after cimetidine administration. On the 28th day after cimetidine administration gastrin levels did not differ from control rats. When studying gastric acid secretion (Fig. 2) we found that basal acid secretion was decreased at all time intervals. The decrease was less pronounced on the 7th and 28th day (p<0.05) that on the 14th and 21st day (p<0.01). Histamine stimulation was followed by a significant increase in gastric acid secretion on the 14th, 21st, and 28th day after cimetidine administration (p<0.01). Pentagastrin stimulation did not alter the gastric acid secretion in rats after cimetidine administration.

Our results have shown that long-term cimetidine administration increases the serum gastrin level on the 14th and 21st day after daily cimetidine administration. This confirms the findings made by other authors, showing that long-term administration of the histamine H₂-receptor antagonists increase gastrin production (Halter et al. 1978, Wallmark et al. 1990, Seensalu et al. 1990). The observation that on the 7th and 28th day after cimetidine administration gastrin levels were not altered suggest a certain time-dependent course of gastrin elevation. On the other hand, we observed gastric acid inhibition without gastrin elevation on the 7th and 28th day. It is conceivable that a feedback relationship, well known in both animal and human studies, is probably not valid during protracted hypoacidity (Lind et al. 1988). Some authors suggest that chronic hypoacidity could lead to increased G-cell activation (Stockbrugger et al. 1977). The resulting hypergastrinaemia could increase the number of gastrin or H₂-receptors by its trophic and up-regulatory effects on the parietal cell (Bertaccini, 1988). Our results have shown that chronic hypoacidity induced by cimetidine increases histamine-stimulated gastric acid secretion. This confirms the findings made by other authors showing that cimetidine and other gastric acid inhibitors increase the sensitivity of parietal cells to histamine (Aadland et al. 1981, Seensalu et al. 1990). Others found, on the contrary, that administration of histamine H₂-receptor antagonists does not increase the sensitivity to histamine (Seensalu et al. 1990, Stables et al. 1990). The mechanism by which cimetidine induces increased sensitivity to histamine remains to be elucidated. Recent studies showed that the sensitivity to histamine is enhanced by gastrin. It is interesting in this context that the increased sensitivity to histamine which we observed on the 14th day after cimetidine administration was not accompanied by hypergastrinaemia. Our finding that long-term administration of cimetidine did not affect the sensitivity to pentagastrin does not agree with previous reports (Aadland and Berstad, 1987).

In conclusion, the present results suggest that long-term cimetidine administration decreases gastric acid secretion. This decrease was not followed by a
significant increase of serum gastrin levels at all the time intervals studied. Long-term cimetidine administration increases histamine-stimulated gastric acid secretion. On the other hand, it has no effect on pentagastrine-stimulated secretion.

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REFERENCES


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