Case report

Development of cimetidine resistance in the Zollinger-Ellison syndrome

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SUMMARY A patient with the Zollinger-Ellison syndrome was followed with multiple gastric secretion tests and serum gastrin analyses for six years. During this period cimetidine requirement increased to a daily dose of 8 g, but it reversed spontaneously after two years. The altered cimetidine effectiveness was not associated with reduced oral bioavailability and serum calcium was unchanged. Total serum gastrin was very high at all times, and fractionation of gastrins in serum by gel filtration showed varying proportion of big to small gastrins, but not in a mode which explained the parietal cell resistance to cimetidine.

Patients with the Zollinger-Ellison Syndrome often require high doses of cimetidine to control acid secretion.¹ The reason is in some cases altered bioavailability of cimetidine² and in some the parietal cell responsiveness to cimetidine is for unknown reasons decreased.³ We report a case of Zollinger-Ellison Syndrome which was followed with multiple gastric secretion studies and serum gastrin analyses before and after development of resistance to cimetidine.

Case report

Zollinger-Ellison Syndrome was diagnosed in 1974 in a 29 year old woman. She suffered from severe duodenal ulcer disease with serum gastrin concentrations around 7000 pmol/l and a basal acid output (BAO) in excess of 60 mmol/h. In 1976 treatment with cimetidine was started, and BAO was reduced to below 10 mmol/h after a single dose of 400 mg cimetidine. She was then given 1.6 g of cimetidine daily and was symptom free for the following three years. Repeated studies of acid secretion confirmed that this dose of cimetidine inhibited BAO to below 10 mmol/h. In April 1979, however, duodenal ulcers recurred, and neither symptoms nor acid secretion

could be further controlled by 2 g cimetidine daily. The dose was then increased step-wise to 8.4 g per day. This dose of cimetidine was maintained for the following two years, but could then be gradually reduced to 1.6 g per day with full control of BAO and symptoms.

LABORATORY EXAMINATIONS

Gastric acid secretion and plasma-cimetidine concentrations

A nasogastric tube was placed in the stomach in the morning and gastric aspiration was started 75 minutes after the dose of cimetidine to be tested was swallowed. The first 15 minute aspirate was discharged and gastric contents were then sampled in 15 minute periods for two hours. During this two hour period plasma samples for cimetidine analysis⁴ were taken at 0, 60, and 120 minutes. Corresponding values of the mean acid secretion rate and mean plasma-cimetidine concentration during this two hour period are shown in the Figure. It can be seen that during the years 1976-78 acid secretion was very low at plasma cimetidine concentrations around 2 mg/l after a single dose of 400 mg - that is, the ID₅₀ for cimetidine was less than 1 mg/l. During 1979-81 plasma cimetidine concentrations above 10 mg/l (obtained by single cimetidine doses of 1.0-1.4 g six times daily) were necessary to keep BAO below 20 mmol/h. Linear regression analysis of the data show that the calculated ID₅₀ for cimetidine

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Figure Longitudinal study of gastric acid secretion during cimetidine treatment of a patient with the Zollinger-Ellison Syndrome. The unbroken line indicates the estimated linear correlation of all the data from 1979–81. The broken lines combine results obtained within the same year (★-----★ 1976; ▲-----▲ 1982).

was 9 mg/l in the period 1979–81. In 1982 parietal cell responsiveness to cimetidine was restored with an ID₅₀ below 1 mg/l.

Gastrins in serum

Total serum gastrin concentration was very high at all times. At the time of diagnosis in 1974 it was around 7000 pmol/l and the highest concentration 14 600 pmol/l was seen in 1981 (Table). The distribution between small and large molecular forms of gastrin was measured after fractionation of serum by gel-filtration,⁵ all sera being examined within one month on the same column. The concen-

tration of gastrin in serum and in column eluates was measured with Ab 2604 which measures small and large as well as sulphated and non-sulphated gastrins with equimolar potency.⁶ As the Table shows G 34 was the predominant form of gastrin in blood in 1976–78 and in 1982, coinciding with the quiescent clinical phase with high parietal cell responsiveness to cimetidine. During the years 1979–81, however, when doses of 8 g cimetidine daily were necessary to control acid secretion, small molecular forms of gastrin – that is, G 14 and G 17 constituted the main part. In July 1979 as much as 93% of the serum gastrins was G 17.

Serum calcium

Total serum calcium and albumin were measured regularly and hypercalcaemia did not occur.

Discussion

It is not unusual that Zollinger-Ellison patients have decreased parietal cell responsiveness to cimetidine, often associated with high total serum gastrin concentrations.³ The present longitudinal study of a Zollinger-Ellison patient shows that responsiveness to cimetidine may vary greatly from time to time with no obvious relationship to total serum gastrin. Gel filtration studies showed some variation in the proportion of the different molecular forms of gastrin in blood. It is interesting that the small gastrins constituted the main part at times with cimetidine resistance but this finding does not provide a clue to the changing drug requirement since the acid stimulatory potency of big and small gastrins is similar.⁷

We can, therefore, conclude that this is a case of parietal cell resistance to cimetidine, which cannot be explained by changing serum calcium, parietal cell atrophy, changing total serum gastrin or changing molecular forms of circulating gastrins.

Table Longitudinal study of gastric acid secretion and different molecular forms of circulating gastrin in a patient with the Zollinger-Ellison syndrome

		Year				
		1976–78	1979	1980	1981	1982
ID ₅₀ Cimetidine	mg/l	<1	9	9	9	<1
Serum gastrin, total	pmol/l	7300	9400	13500	14600	12000
Gastrin component I	%	0	2.6	9.3	1.9	3.9
Gastrin 34	%	60.0	19.6	44.1	30.7	65.1
Gastrin 17	%	39.0	72.7	39.7	65.7	31.0
Gastrin 14	%	1.0	5.1	6.9	1.7	0
G 14+G 17	%	40.0	77.8	46.6	67.4	31.0
Total gastrin						

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