Evaluation of pirenzepine on gastric acidity in healthy volunteers using ambulatory 24 hour intragastric pH-monitoring

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SUMMARY The effect of pirenzepine on 24 hour intragastric acidity was studied in 10 healthy volunteers using ambulatory 24 hour intragastric pH-monitoring in a double blind crossover study. Tests were performed on the seventh day of ingestion of either placebo, 75 mg pirenzepine or 150 mg pirenzepine per day. The drugs were given at two doses at 8.30 am and 8.30 pm. Mean nocturnal hydrogen ion activity during placebo treatment was $68 \text{ mmol/l} \pm 9 \text{ SEM}$ and was reduced by 75 mg (26%, $p < 0.01$) and 150 mg of pirenzepine (36%, $p < 0.01$), respectively. Mean diurnal hydrogen ion activity was $32 \text{ mmol/l} \pm 6 \text{ SEM}$ and was not significantly reduced ($p > 0.1$) by either dose of pirenzepine (4% and 12% respectively). Thus, the effect of pirenzepine on intragastric acidity is small, even with high doses of the drug, and becomes apparent only during the night.

Clinical studies have shown that pirenzepine, a selective antimuscarinic compound,^{1,2} is superior to placebo in the treatment of duodenal ulcer disease.³ The drug has been shown to reduce gastric volume secretion,^{4,5} but the effect of chronic ingestion on gastric acidity has not been evaluated in man. The aim of the present study was therefore to evaluate the effect of a high and a low oral dose of pirenzepine on 24 hour gastric acidity in healthy subjects. Gastric pH was monitored by means of continuous electrode measurements which has been validated in our laboratory.⁶ The day to day reproducibility of the method was tested in a series of repeat measurements during placebo treatment.

Methods

SUBJECTS

Ten healthy volunteers (six men, four women, median age 25 years) participated in the study. Informed consent was obtained in all cases, and the protocol was approved by the local ethical committee.

Gastric pH was measured by miniature glass electrodes (Radiometer Copenhagen GK282C)

connected to a pH meter with digital read-out (Metrohm E 602, $T^{\circ}: 37^{\circ}\text{C}$) and an analogical recorder (Tarcan W+W, chosen speed: 12 cm/h). Before and after each 24-hour test, the electrodes were calibrated with commercial buffer solutions (Ingold pH 7, pH 4.01 and pH 1.679). The precision of the electrodes was excellent: the drift at the end of the recorded periods was negligible – that is, < 0.1 pH unit, pH values during final calibration being as follows (mean $\pm$ SD, $N = 37$ experiments): 6.98 ± 0.07 , 4.03 ± 0.06 , 1.66 ± 0.08 for the three buffer solutions, respectively.

The electrodes were positioned in the gastric corpus under fluoroscopical control. The measuring tip was situated 10 cm below the cardia. The pH values were continuously recorded on a writer which was mounted on a trolley. During the tests, the volunteers could move around the ward. Measurements began at 8.30 am after a 12 hour fast and lasted for 24 hours. Subjects had three standardised meals (breakfast at 9 am, lunch at 12 noon, and dinner at 6 pm). The total energy content was 8014 kJ. Subjects were allowed to drink tap water *ad libitum* but had to record water intake.

The two doses of pirenzepine and placebo were administered according to a double blind cross over protocol. The three separate seven day treatment periods were at least one week apart. Pirenzepine

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was administered by mouth in daily doses of either two times 37.5 mg or two times 75 mg, taken at 8.30 am and 8.30 pm. Seven of the 10 volunteers performed a second placebo test under identical conditions. The pH recording was performed on the seventh day of each treatment period. Blood samples for a pirenzepine radioimmunoassay were taken at 8 am, 2 pm and 8 pm on the day of the pH metry. The assay detected pirenzepine at concentrations of 1 nanogram per millilitre.⁷

EXPRESSION OF RESULTS

Separate calculations were performed for the day period (8.30 am to 8.30 pm), the night period (8.30 pm to 8.30 am) and the whole 24 hour period. pH values were read every 10 minutes from the printout and converted to hydrogen ion activity.⁸ Statistical comparisons were made using two-way analysis of variance⁹ of hydrogen ion activity. In threshold curves, the time period during which the intragastric pH was above a certain pH value was expressed in per cent of a 24 hour time period.¹⁰

Results

REPRODUCIBILITY

Mean 24-hour H⁺ activity of seven volunteers was similar in two separate placebo tests (Table).

STUDY COMPLIANCE

All subjects tolerated the pH recording well. Two volunteers taking 150 mg of pirenzepine complained

of a dry mouth. No other side effects of pirenzepine were noticed.

EFFECT OF PIRENZEPINE ON INTRAGASTRIC ACIDITY

The mean hydrogen ion activity is shown in the Figure (upper graph). Individual values for day and night times are given in the Table. As compared with placebo, the mean 24 hour H⁺ activity was reduced by 19% and 29% under the two regimens of 75 and 150 mg of pirenzepine, respectively ($p < 0.001$). The reduction of intragastric H⁺ activity during the day time was not significant (4% and 12% respectively, $p > 0.10$). During the night time, the reduction was statistically significant (26% and 36% respectively, $p < 0.001$). A dose of 150 mg of pirenzepine per day was more effective than a dose of 75 mg, but the difference was only significant ($p < 0.05$) at night. The pH threshold curves as shown in the figure are similar with placebo and with the two doses of pirenzepine for the whole 24 hour period (lower graph).

SERUM PIRENZEPINE CONCENTRATIONS

The plasma concentrations of pirenzepine correlated well with the ingested doses (mean $\pm$ SEM, ten subjects): with placebo, they were always under the limit of detectability of the method; with pirenzepine 75 mg/d, the plasma concentrations were 27 ± 3.7 , 34 ± 5.5 and 26 ± 2.7 ng/ml at 8 am, 2 pm and 8 pm respectively; with pirenzepine 150 mg/d, the corresponding values were 53 ± 4.3 ,

Table Individual mean hydrogen ion activities (mmol/l) for day time (8.30 am–8.30 pm) and night time (8.30 pm–8.30 am)

Subject (no)	Placebo				Pirenzepine			
	Day		Night		Day		Night	
	Test 1	Test 2	Test 1	Test 2	75 mg	150 mg	75 mg	150 mg
1	28	31	78	59	35	31	76	63
2	42	31	115	121	48	23	103	75
3	61	65	57	56	25	32	26	36
4	15	25	43	34	13	19	21	25
5	61	52	67	65	48	58	43	46
6	23	31	68	62	20	25	54	46
7	35	43	46	35	34	31	30	22
8	23	—	74	—	46	24	65	49
9	18	—	105	—	16	9	58	57
10	17	—	28	—	24	24	27	13
Mean (1–10)	32	—	68	—	31	28	50	43
SEM (1–10)	6	—	9	—	4	4	8	6
Mean (1–7)	38	40	68	62				
SEM (1–7)	7	5	9	11

Figure Upper graph: Twenty four hour hydrogen ion activity (mmol/l) during treatment with pirenzepine 75 mg/d, pirenzepine 150 mg/d or placebo. Each point is the mean H⁺ activity of 10 healthy subjects. Each bar is the standard error of the mean (SEM). For the sake of clarity, we display only one value every 30 minutes, and the SEM when feasible. Lower graph: pH threshold curves. Mean $\pm$ SEM of ten volunteers. Each point shows the time (expressed in percent of a 24 hour period) during which pH was above a given threshold. For example, pH was above 2 during 27.5% of the 24 hour period (corresponding to 6 hours and 36 minutes) when the subjects were treated with placebo. Placebo: —●—. Pirenzepine 37.5 mg twice daily: —○—. Pirenzepine 75 mg twice daily: —■—.

72±9.0 and 50±4.6 ng/ml respectively. No correlation was found between the effect of pirenzepine on acidity and the serum concentrations.

Discussion

In the present study we have evaluated the effect of long term administration of pirenzepine on gastric acidity using a new method of continuous intragastric pH-metry. We have recently validated this method⁶ and its good reproducibility was again shown in repeat placebo tests in seven volunteers (Table).

Hydrogen ion activity during placebo treatment was, on average, 30–40 mmol/l during the day and much higher – that is, 60–70 mmol/l, at night. Similar findings were reported by others.¹¹ Pirenzepine had only a small effect on intragastric pH. Even a high dose of 150 mg which may cause anticholinergic side effects, reduced nocturnal acidity by only 36% and had no measurable effect on diurnal acidity. It is surprising that such a small reduction of acid concentration may be sufficient for the acceleration of ulcer healing. It might be argued that the effect of pirenzepine decreases over time and might be higher on the first than on the seventh day of treatment. Pirenzepine is, however, given to ulcer patients at a fixed dose during several weeks. Thus, the effect seen in the present study is more representative of what happens in a clinical setting than in studies where the drug is given only on one day. It might further be argued that pirenzepine may reduce gastric volume output even in the absence of an effect on hydrogen ion activity^{4,5} and that this volume effect may, on its own, reduce duodenal bulb acidity. Pirenzepine has, however, also been shown to accelerate gastric ulcer healing.¹² Therefore, it is uncertain whether there is a direct relationship between the extent of secretory inhibition and therapeutical efficacy of a drug. Future studies with drugs which almost completely inhibit acid production^{13,14} will shed more light on this point. In all other circumstances slightly 'tipping the balance' might be as effective as a strong inhibitory effect.^{15–17} Low dose antacid regimen, which has an effect on acidity comparable to that of pirenzepine,¹⁸ has been recently shown to have an effect similar to that of cimetidine in duodenal ulcer treatment.¹⁹ Therefore, long term secretory tests are useful for the characterisation of antiseecretory drugs, but it is difficult to predict from the results to what extent the drug accelerates ulcer healing.

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