Effects of single daily doses of a pyridil-2-tetrahydrothiophene derivative (40749 RP) on 24 hour H^+ activity, nocturnal acid output, gastrin and pepsinogen I profiles in duodenal ulcer patients

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SUMMARY 40749 RP is a pyridil-2-tetrahydrothiophene derivative, belonging to a new class of gastric antisecretory drugs. We compared its effects on gastric secretion with cimetidine. Intragastric acidity, nocturnal acid output, gastrin and pepsinogen-I profiles were measured in patients with duodenal ulcer in clinical remission. A single dose of 100 mg 40749 RP reduced median 24 h gastric acidity as effectively as cimetidine 1000 mg given as four divided doses, 0.63 vs 1.6 mmol/l. Continued treatment with 40749 RP for 10 days reduced the median 24 h gastric acidity even further, to 0.006 mmol/l ($p < 0.001$) and significantly increased fasting concentrations of gastrin and pepsinogen-I ($p = 0.02$). The incremental gastrin secretion to a standard meal was significantly increased after 10 days treatment with 40749 RP when compared with the first day of 40749 RP, or with cimetidine. These results show that 40749 RP exerts a powerful inhibitory effect on gastric acid secretion after a single 100 mg dose, and that this inhibitory effect increases with continued administration.

Histamine H_2 -receptor antagonists in usual dosage achieve a 50 to 70% fall in 24-h H^+ activity and a 70-90% inhibition in nocturnal acid output.¹ After four weeks of cimetidine or ranitidine, about 75% of duodenal ulcers have healed.² After one week of treatment with benzimidazole derivatives, such as omeprazole, the median intragastric 24 h pH is maintained at around 5.30.³ A preliminary clinical trial suggested that appropriate doses of omeprazole will heal nearly all duodenal ulcers.⁴ Potent anti-secretory drugs could also be useful for some patients, particularly those with gastric hyper-secretory states such as the Zollinger-Ellison syndrome.⁵

40749 RP, a pyridil-2-tetrahydrothiophene derivative, is a potent and long acting inhibitor of gastric secretion belonging to a new class of drugs. Dose for dose, 40749 RP is respectively 10 times and 60 times more potent than cimetidine in the inhibition of spontaneous and histamine-stimulated acid secre-

tion in Shay rats.⁶ 40749 RP decreases the acid secretory response to receptor mediated stimuli such as histamine, pentagastrin and carbachol, as well as intracellular stimulation by dibutyl cyclic AMP. This suggests that the compound or one of its metabolites, could act on the H^+/K^+ ATPase transport system.⁷ As the potent antisecretory effect of 40749 RP on pentagastrin stimulated gastric secretion has been confirmed in man,⁸ it was decided to compare the effects of a once daily regimen of 40749 RP with the standard dose of cimetidine (1 g/day) on intragastric acidity, nocturnal acid output, gastrin, and pepsinogen-I (PGN-I) profiles in patients with a history of duodenal ulcers, in clinical remission.

Methods

PATIENTS

Five male patients with endoscopically diagnosed duodenal ulcers in remission were studied. The mean age of the patients was 27.6 years (range 23-36) and average weight 65.2 kg (range 60-70). Four were smokers, all were asymptomatic and none

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were receiving prophylactic treatment before the study. All the subjects gave their informed consent, and the study was approved by the local ethical committee.

PROCEDURE

Using a modification of a technique previously reported⁹ we measured one hour of basal acid output, followed by hourly measurements of gastric pH for 24 h. Nocturnal acid output was measured from 0100 to 0700 h.

The subjects were investigated on three separate occasions: (day 1) cimetidine 200 mg tid and 400 mg nocte, (day 7) during the 1st day of 40749 RP, 100 mg daily given at 7 pm, and (day 17) during the 10th day of 40749 RP treatment, 100 mg daily.

From day 2 to 6, the subjects received no treatment. On the study days, the patients fasted from 1200. From 1800, 5 ml of gastric contents were aspirated hourly and pH measured with a glass electrode. The electrode was calibrated before each batch of measurements. Results were expressed as median hourly H^+ activity and the percentage of samples during which pH was at or below a range of pH values was represented graphically.

Gastric secretions were collected from 1800–1900 by continuous aspiration. On day 1 and day 7, this represents basal secretion whereas on day 17, it represents gastric secretion 23 hours after the last of nine daily consecutive doses of 100 mg of 40749 RP. Nocturnal (0100–0700) gastric secretions were also collected by continuous aspiration. Hourly volume was measured and a sample from each hour of aspiration was titrated with 0.1 mmol NaOH to pH 7 using an automatic titrator and burette. Results were expressed as median hourly acid output.

Dietary and environmental factors were identical on each of the study days.

Venous blood was taken for measurement of

Fig. 1 Median H^+ activity on the different study days.

Fig. 2 Cumulative pH frequency distribution for all drug regimes.

40749 RP and its metabolites, as well as gastrin and PGN-I. 40749 RP and metabolite concentrations were measured by reverse phase HPLC and UV detection. (Details available from authors). Gastrin and PGN-I were measured by radioimmunoassay.¹⁰ 40749 RP and its metabolites were also measured in gastric secretions.

STATISTICAL ANALYSIS

As H^+ activity, acid output, gastrin, and pepsinogen-I concentrations were skew, the data are expressed as median $\pm$ semi-interquartile, and were analysed non-parametrically (Friedman, Wilcoxon). Pharmacokinetic data for 40749 RP and its metabolites were analysed using the Student's *t* test.

Results

The procedures were well tolerated. No side effects were observed. The results of the intragastric acidity measurements on the three study days are shown in Figures 1 and 2; the median values $\pm$ 1 semi-interquartile are shown in Table 1. After 10 days of

Table 1 Median 24 h intragastric acidity during cimetidine 40749 RP treatment

Treatment	Median 24 h H^+ activity (mmol/l) $\pm$ semi-interquartile	Fall in H^+ activity (%)	Median intragastric pH
Cimetidine	1.6 $\pm$ 4.7	—	2.8
40749 RP (day 7)	0.63 $\pm$ 3.95	60.6%	3.2
40749 RP (day 17)	0.006 $\pm$ 0.020	99.6%	5.2

Fig. 3 Pharmacokinetics of 40749 RP and 2 of its main (S-oxide) metabolites on the 1st and 10th day of 40749 RP treatment.

40749 RP, acid is inhibited to a significantly greater degree than after either one day of 40749 RP or cimetidine ($p < 0.001$). Median basal acid output without treatment was 3.15 ± 1.88 mmol/h. Twenty three hours after the last of nine consecutive daily doses of 40749 RP, basal acid output decreased to 0.04 ± 0.48 mmol/h ($p < 0.05$). Overnight acid output was not significantly different on any of the three study days.

Serum concentrations of 40749 RP and 2 of its

main S-oxide metabolites are shown in Figure 3. Mean maximal serum concentrations of 40749 RP and the area under the serum concentration time curve are not significantly different after 10 days treatment than after the first day. The half life of 40749 RP is five to six hours. The serum concentrations and AUCs of the metabolites rose by a factor of 2–3 after 10 days treatment. Their half lives are 25–35 hours. Gastric concentrations of 40749 RP, 10 hours after administration, are similar to those

Fig. 4 Fasting PGN-I and gastrin concentrations before and after 10 days 40749 RP treatment. Lines represent the individual values. Bars represent median concentrations with semi-interquartile shown.

Fig. 5 Variation of gastrin concentrations above the fasting concentration over 12 hours. Baseline represents fasting concentration; each point represents the median value obtained in five subjects.

Table 2 Net secretion of PGN-I and gastrin on the three study days

AUC median ±semi- interquartile	N	Cimetidine	40749 RP Day 1	40749 RP Day 10
ΔGastrin pmol/l	5	175.3±45.9	206.8±54.8	366.1±115.9
ΔPGN-I ng/ml	5	140.4±35.6	48.8±17.9	39.6±222.8

measured in the serum, 0.28 ± 0.24 ng/ml and 0.3 ± 0.1 ng/ml respectively. There was no correlation between either gastric or serum concentrations of 40749 RP and inhibition of gastric secretion.

Pretreatment median fasting concentrations of PGN-I and gastrin are within normal limits for our laboratory.¹⁰ After 10 days 40749 RP the fasting serum concentrations of PGN-I and gastrin increase ($p=0.02$) (Fig. 4). Taking fasting gastrin concentrations as the baseline, the median incremental response (Δ gastrin) is summarised in Figure 5. The net secretion can be deduced from the area under the change in serum concentration curve (Fig. 5). The results of PGN-I and gastrin are shown in Table 2. The incremental gastrin response to a standard meal is long lasting. Significant increases in peak concentration and AUC of gastrin are observed after 10 days 40749 RP treatment compared with the two other study days. These changes were not observed with PGN-I. There were no statistically significant correlations between acid, PGN-I and gastrin secretions.

Discussion

A single dose of 100 mg of a pyridil-2-tetrahydrothiophene derivative (40749 RP) was as effective as cimetidine in decreasing acid secretion. As patients were undergoing three 24 hour study periods it was felt that a fourth study period with placebo would inflict unnecessary discomfort on the subjects. We compared 40749 RP against cimetidine; the effectiveness of cimetidine in blocking acid secretion has been amply shown.¹ It could be argued; however, that our patients had very low levels of acid secretion and that cimetidine was ineffective. The basal acid output before treatment, however, was measured in all subjects and was within normal limits. The median hourly nocturnal acid output on each of the three study days was significantly lower than the pretreatment BAO. Furthermore the BAO measured 23 h after the last

of nine consecutive daily doses of 40749 RP was also significantly lower than the pretreatment BAO.

Inhibition of acid secretion by 40749 RP lasted much longer than its half life and increased with continued treatment. After 10 days, only 5.6% of samples of gastric juice had a pH of less than 3 (range 0–12%). The marked increase in the antisecretory effect is not caused by accumulation of the parent drug as serum concentrations on day 7 and day 17 are similar. The increase in serum concentrations of the two measured metabolites cannot explain the enhanced antisecretory effect as one is inactive whilst the other has only 1/20th the potency of 40749 RP (personal communication). There are several possible explanations to account for this increasing antisecretory activity despite stable serum concentrations and inactive metabolites. Animal studies show that 40749 RP accumulates in gastric mucosa and thus serum concentrations might not accurately reflect the concentration within the parietal cell. It is possible that clearance of 40749 RP from the parietal cell occurs at a slower rate than from the plasma. Although the S-oxide metabolites we measured were inactive, it has been shown, *in vitro*, that they undergo spontaneous transformation to the parent compound.¹¹

In addition to studying acid inhibition by 40749 RP and cimetidine, we also measured the response of gastrin and PGN-I to these two substances. After 10 days 40749 RP, fasting gastrin concentrations rose by 152%. The gastrin response to a standard meal is quite rapid and peaks at 30 minutes. This is in keeping with the findings in normal subjects and patients with duodenal ulcer.^{12, 13} This meal stimulated gastrin secretion is significantly increased after 10 days 40749 RP treatment when major hypochlorhydria is achieved. This is probably because of a combination of higher peak gastrin concentrations and a more prolonged gastrin secretion, lasting about eight hours, caused by the disappearance of acidification of the antrum.¹⁴ Omeprazole, which achieves the same degree of acid inhibition as 40749 RP, has also been reported to increase fasting plasma gastrin concentrations.¹⁵

Fasting PGN-I concentration also increased significantly after 10 days 40749 RP treatment. Similar findings have been reported in healthy volunteers taking omeprazole.¹⁶ The physiological mechanisms underlying these changes in PGN-I are unclear.

The predictable usefulness of 40749 RP in patients with duodenal ulcer and Zollinger-Ellison syndrome was confirmed in clinical studies.^{17, 18} 40749 RP could also be useful in patients not responding to H_2 -antagonists. Although no side effects were observed in our study and none have been reported in man, prolonged administration of high doses of

40749 RP to rats caused neurological toxicity which manifested itself in muscular atrophy of the lower limbs. The clinical implication of this finding remains unclear, but the use of this compound in humans has been discontinued.

Other derivatives of this class of drugs are under development. Because of their cumulative effect secretion studies should be carried out, not only after a single dose, but also after prolonged administration. They promise to be potent, long acting inhibitors of gastric secretion.

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References

- 1 Walt RP, Malè PJ, Rawlings J, Hunt RH, Milton-Thompson GJ, Misiewicz JJ. Comparison of the effects of ranitidine, cimetidine and placebo on the 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer. *Gut* 1981; **22**: 49–54.
- 2 Feely J, Wormsley KG. H₂ receptor antagonists – cimetidine and ranitidine. *Br Med J* 1983; **286**: 695–7.
- 3 Walt RP, Sharma BK, Pounder R, Gomes MFA. Daily oral omeprazole causes 8-000-fold decrease of 24-hour intragastric acidity. [Abstract]. *Gut* 1983; **24**: A497.
- 4 Gustavsson S, Adami HO, Lööf L, Nyberg A, Nyren O. Rapid healing of duodenal ulcers with omeprazole: double-blind dose-comparative trial. *Lancet* 1983; **2**: 124–5.
- 5 Oberg K, Lindstrom H. Reduction of gastric hypersecretion in Zollinger-Ellison syndrome with omeprazole. *Lancet* 1983; **1**: 66–7.
- 6 Derégnaucourt J, Hardy-Houis M. Activités anti-sécrétoire et anti-ulcères du N-méthyl (pyridil-2)-2 tétrahydrothiophène carbothioamide-2 (40749 RP) chez le rat préparé selon la méthode de Shay. *CR Acad Sci Paris* 1982; **294**: 591–4.
- 7 Derégnaucourt J, Hardy-Houis M. Activité anti-sécrétoire du 40749 RP chez le rat préparé selon la méthode de Glosch et Schild. [Abstract] *Gastroenterol Clin Biol* 1983; **7**: 9A.
- 8 Minaire Y, Forichon J, Woehrle R. Inhibition of pentagastrin-stimulated gastric secretion by pyridil-2-tetrahydrothiophene derivative (40749 RP). *Lancet* 1982; **1**: 1179–80.
- 9 Pounder R, Williams J, Milton-Thompson G, Misiewicz JJ. Effect of cimetidine on 24 hour intragastric acidity in normal subjects. *Gut* 1976; **17**: 133–8.
- 10 Griessen M, Malè PJ, Infante F, Jodry H, Loizeau E. Intérêt clinique du dosage du pepsinogène I. *Schweiz Med Wochenschr* 1984; **114**: 1849–51.
- 11 Frydman AM. Rhône-Poulenc Santé Records: *Internal Report* 1983.
- 12 Casthelaz M, Sitavanc L, Griessen M. Le dosage radioimmunologique de la gastrine: caractéristiques d'un antisérum commercial. *Gastroenterol Clin Biol* 1977; **1**: 527–38.
- 13 Taylor IL, Dockray GJ, Calam J, Walter R. Big and little gastrin response to food in normal and ulcer patients. *Gut* 1979; **20**: 957–62.
- 14 Taylor IL. Gastrointestinal hormones in the pathogenesis of peptic ulcer disease. *Clinics Gastroenterol* 1984; **13**: 355–82.
- 15 Howden CW, Reid JL, Forrest JAH. Effect of omeprazole on gastric acid secretion in human volunteers. [Abstract] *Gut* 1983; **24**: A498.
- 16 Festen HPM, Thijs JC, Lamers CBHW, Jansen JMBJ, Pals G, Frants RR, Defize J, Meuwissen SGM. Effect of oral omeprazole on serum gastrin and serum pepsinogen I levels. *Gastroenterology* 1984; **87**: 1030–4.
- 17 Bonfils S, Galmiche JP, Garcia del Risco F, Denis PH, Piat M, Mignon M. Traitement de l'ulcère duodénal par un nouvel antisécrétoire (40749 RP). Résultats endoscopiques, sécrétoires et pH métriques. [Abstract]. *Gastroenterol Clin Biol* 1984; **8**: 12A.
- 18 Bonfils S, Garcia del Risco F, Sauvage M, Mignon M, Vallot TH, Teule M. Efficacité du 40749 RP dans le syndrome de Zollinger-Ellison à brève et longue échéance. [Abstract]. *Gastroenterol Clin Biol* 1984; **8**: 36A.