Pharmacokinetics and pharmacodynamics of roxatidine in patients with renal insufficiency

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- 1 Roxatidine acetate, a new histamine H₂-receptor antagonist, was administered in the evening (75 mg p.o.) to eight patients with renal insufficiency (CL_{CR} 8–17 ml min⁻¹) for 12 days and plasma drug concentrations were measured.
- 2 Ambulatory intragastric pH was monitored following the last dose and values were compared with those on day 1 when all patients received a placebo.
- 3 The terminal elimination half-life (mean ± s.d.) of roxatidine was 10.8 ± 2.4 h and its oral clearance was 178 ± 43 ml min⁻¹.
- 4 During roxatidine treatment gastrin levels increased slightly (median 189 vs 289 ng l⁻¹) and the hyperparathyroid status of the patients was almost normalized (parathyroid hormone levels: median 199 vs 132 ng l⁻¹).
- 5 The mean latency to a gastric pH of at least 4 was 4.3 ± 1.4 h. The duration of action (intragastric pH > 4) was 10.6 ± 3.9 h.
- 6 As in a pilot study with six patients (CL_{CR} ≤ 17 ml min⁻¹) the recommended dosage regimen (75 mg 48 h⁻¹) was unable to maintain gastric pH > 4 for more than 6 h, daily nocturnal intake of 75 mg roxatidine acetate appears appropriate to elevate gastric pH > 4 for a sufficient period of time.

Keywords roxatidine renal insufficiency pharmacokinetics
long-term pH-metry gastrin parathyroid hormone

Introduction

Many patients with renal failure suffer from gastrointestinal symptoms such as loss of appetite, nausea, vomiting, and upper abdominal pain. These symptoms may be caused by gastric and duodenal ulcers, erosions or gastritis [1–3]. Histamine H₂-receptor antagonists are drugs of first choice in the management of acid related diseases [4]. Roxatidine acetate is a new H₂-receptor antagonist, characterized by a novel piperidine and benzole ring structure. In animals and man the acetate is rapidly and completely absorbed from the gastrointestinal tract and converted to roxatidine. Inhibition of gastric acid secretion by roxatidine is comparable with that produced by ranitidine.

The pharmacokinetics of roxatidine have been described in healthy subjects [5–7]. Based on pharmacokinetic data from patients with renal insufficiency (CL_{CR} < 20 ml min⁻¹) a decrease in dose from 150 mg 24 h⁻¹ to 75 mg 48 h⁻¹ or about 40 mg 24 h⁻¹

has been recommended [8–10]. However, 40 mg roxatidine acetate capsules are not available and pharmacodynamic data are lacking.

The present study was designed to assess the pharmacokinetics of roxatidine after multiple dosing (steady state) in patients with renal insufficiency and its effects on intragastric pH. The influence of roxatidine on plasma levels of gastrin and parathyroid hormone was also assessed.

Methods

Patients

Twelve patients (mean age 50 years) with chronic renal insufficiency (mean duration of renal failure

Table 1 Clinical characteristics of the patients studied

Patient Number	Sex	Age (years)	Weight (kg)	Hct (%)	Protein (g l ⁻¹)	CL _{CR} (ml min ⁻¹)	Months of renal insufficiency	Diagnosis
<i>Pilot study</i>								
1	M	45	79	26	72	9	24	IgA-nephritis
2	M	56	56	32	72	11	20	Hypertensive nephrosclerosis
3*	M	40	92	33	70	17	276	Chronic glomerulonephritis
4*	M	47	76	26	64	13	58	Polycystic renal disease
5	F	53	39	32	80	11	60	Interstitial nephritis
6	M	52	74	22	59	9	204	Chronic glomerulonephritis
<i>Main study</i>								
1*	M	48	70	26	64	10	70	Polycystic renal disease
2*	M	40	92	37	75	14	284	Chronic glomerulonephritis
3	M	60	62	36	75	10	27	Interstitial nephritis
4	F	62	74	29	71	8	192	Amyloidosis
5	M	58	73	35	69	17	180	Chronic pyelonephritis
6	M	23	92	26	75	12	24	Interstitial nephritis
7	F	55	59	33	68	8	180	Nephrolithiasis
8	M	62	96	34	70	14	120	Mesangio proliferative glomerulonephritis

*These patients participated in both studies.

123 months; mean CL_{CR} 12 ml min⁻¹) were included in the studies. All gave their informed consent and the protocol was approved by the local Ethics Committee. Patients having had surgery of the gastrointestinal tract and/or with severe liver disease, alcoholism and psychiatric disorders were excluded from the study. Medication affecting the gastrointestinal tract (antacids, H₂-receptor antagonists, prokinetic drugs) was withdrawn 2 weeks prior to the study. Data obtained from a pilot study in six patients suggested that the recommended oral dosage regimen (75 mg 48 h⁻¹) was not sufficient to suppress acid secretion on the second day after administration of roxatidine acetate. Therefore, roxatidine acetate was administered as a 75 mg daily dose to the remaining eight patients. The clinical characteristics of the patients are shown in Table 1. Two patients participated in both studies (patients 3 and 4 of the pilot study and 1 and 2 of the main study, respectively; see Table 1a and b). Adverse effects of the drug were assessed from reports of subjective symptoms and blood biochemistry.

Pharmacokinetic study

In six patients (pilot study) 75 mg roxatidine acetate was administered orally every second day for 12 days; another eight patients (main study) received 75 mg roxatidine acetate every 24 h also for 12 days. All doses were given at 22.30 h.

Venous blood samples were collected prior to the first dose of roxatidine acetate (baseline), on day 7, 11 and 13 prior to the last evening dose to measure trough steady state plasma drug concentrations, and at 2, 10, 17.5, 24, 34 and 41.5 h following the last dose.

All samples were stored at -20° C until assayed by

g.l.c. [11]. The lower limit of determination was 5 ng ml⁻¹. The intra- and inter-day coefficients of variation averaged 1.8% and 4.0%, respectively. Accuracy was within ±10%.

Pharmacokinetic analysis

Compartmental independent pharmacokinetic parameters were evaluated using the TopFit program [12]. The terminal elimination half-life (*t*_{1/2,z}) was calculated from the terminal slope (10–41.5 h). The mean steady state plasma drug concentration (*C*_{av}) was determined from AUC/τ.

Pharmacodynamic assessment

pH monitoring On the first study day, all patients received a placebo single-blind at 22.30 h. Intra-gastric pH was measured following placebo and after the last roxatidine dose using a combined glass electrode (Ingold type 440 M 4, Ingold AG, Urdorf, Switzerland) connected to a portable solid state recorder (DL 70, Schönfeld Messtechnik, Karlsruhe, Germany). The pH measuring unit was calibrated at 37° C using standard buffer solutions of pH 7.0, 4.1 and 1.6. After each run the calibration was repeated to assess the drift of the electrode.

All patients were admitted at 16.00 h for pH-metry having fasted for 3 h. The electrode was placed under fluoroscopy in the gastric corpus (8–10 cm below the cardia). Measurements were started immediately and lasted for 24 h (placebo) or 48 h (multiple dosing of roxatidine acetate). All subjects were ambulatory. The conditions were standardized with respect to timing and composition of meals (dinner at 18.30 h, breakfast at 8.00 h and lunch at 12.00 h).

Water and unsweetened tea could be taken during

meals. No food or liquid was allowed between meals. Normal daily activities were unrestricted. All subjects noted their activities, meals and special events on a diary card.

The pH signals were stored every 5–10 s and the data were transferred to an IBM computer (AT 286) for subsequent analysis [13]. Mean and median pH and inter-quartile ranges were calculated for individuals and groups. For graphical presentation the medians of pH values averaged over 10 min periods were used because pH values are not normally distributed.

The times to reach (latency) and the duration of an intragastric pH > 4 after roxatidine were noted [14].

Hormones

Mean serum gastrin (Becton Dickinson, Orangeburg, New York, USA) and intact parathyroid hormone (PTH (1-84)) (Nichols Institute Diagnostics, San Juan Capistrano, California, USA) concentrations were measured before and after treatment with roxatidine by specific radioimmunoassays. The normal range of serum gastrin was 25–111 pg ml⁻¹ (mean 50 pg ml⁻¹) and the normal range of PTH was 11–54 pg ml⁻¹ (mean 35 pg ml⁻¹).

Statistics

Comparisons were made using the Mann-Whitney-Wilcoxon rank sum test.

Results

Pharmacokinetics

Table 2 summarizes the pharmacokinetic parameters of roxatidine obtained in the main study. During multiple dosing there was a significant difference between the pilot and main study with respect to the minimum steady state plasma drug concentration ($C_{\min}$ 30.0 ± 18.7 vs 126.2 ± 47.7 ng ml⁻¹; $P < 0.002$).

Pharmacodynamics

Gastric pH Figure 1 shows the median 24 h pH values at baseline (placebo) and after treatment with roxatidine in the pilot and main studies. While there was a similar response to roxatidine during the night, daytime acidity was significantly lower in the main study.

Table 3 shows mean gastric pH values after placebo and following the last dose of roxatidine in the pilot and main studies. In both studies the pH values were increased significantly by roxatidine during the night. However, during daytime a significant response was obtained only when the drug was administered every evening. In the pilot study the mean pH during the treatment free interval (second day) did not differ significantly from that of the main study. The same was true for the integral 24 h pH

Table 2 Pharmacokinetic parameters of roxatidine in the subjects of the main study

Subject	$t_{1/2,z}$ (h)	CL_{oral} (ml min ⁻¹)	C_{av} (ng ml ⁻¹)	$C_{\min}$ (ng ml ⁻¹)
1	8.7	202	205	96
2	10.3	227	183	91
3	8.1	206	202	94
4	11.4	141	294	147
5	11.2	145	287	146
6	14.8	182	228	149
7	13.4	107	388	217
8	8.6	215	193	70
Mean ± s.d.	10.8 ± 2.4	178 ± 43	248 ± 71	126 ± 48

data. The onset of action of roxatidine (latency) was 3.5 ± 1.6 h in the pilot study and 4.3 ± 1.4 h in the main study. The duration of maintaining an intragastric pH > 4 was 5.6 ± 1.4 h (pilot study) and 10.6 ± 3.9 h (main study) (see Table 4).

No direct association between the individual pharmacokinetic (AUC or C_{av}) and pharmacodynamic data was apparent. However, the individual, placebo-corrected duration of drug action (time pH > 4) was correlated linearly ($r = 0.66$; $P = 0.026$) with C_{av} .

Hormones The plasma concentrations of gastrin before and after treatment of roxatidine in the pilot and main study are shown in Figure 2. No increase in median gastrin levels was observed in the pilot study (205 vs 148 pg ml⁻¹), but an increase was noted in the main study (189 vs 289 pg ml⁻¹). There was a linear relationship ($r = 0.72$; $P = 0.004$) between gastrin level and the integral 24 h pH response.

Before treatment all patients were hyperparathyroid with a median baseline PTH concentration of 271 ng l⁻¹ in the pilot study and 199 ng l⁻¹ in the main study. After dosage with roxatidine acetate serum PTH levels fell to 220 (pilot study) and 132 ng l⁻¹ (main study), representing 81 and 66% of pretreatment levels, respectively.

No specific side effects were recorded.

Discussion

Our data on the steady state pharmacokinetics of roxatidine in renal impairment are comparable with single dose data published previously by Takabatake *et al.* [8] ($t_{1/2} = 12.1 \pm 1.1$ h; $CL = 85 \pm 9$ ml min⁻¹) and Lameire *et al.* [10] ($t_{1/2} = 14.6 \pm 3.7$ h; $CL = 111.2 \pm 7.5$ ml min⁻¹) who gave 75 and 150 mg roxatidine acetate, respectively.

Hachisu & Yoshida [15] reported that the mean difference in plasma roxatidine concentrations immediately before and after 4.5 h of haemodialysis was 33% and that the post-dialysis concentrations remained above the IC₅₀ value of 64 ng ml⁻¹ [16]. Thus, they concluded, that the optimum dose of oral roxatidine acetate in chronic renal failure patients

Figure 1 Median 24 h gastric pH values in patients with renal insufficiency at baseline (placebo, $\square$) (combined pilot and main study) and after roxatidine acetate treatment in the pilot study (75 mg every other day, —) and in the main study (75 mg daily, ----).

Table 3 pH (mean $\pm$ s.d., 95% confidence intervals for difference from placebo in brackets) in patients after placebo and following the last dose of roxatidine acetate (75 mg given orally at 22.30 h either every second day (pilot study) or daily (main study))

pH values	Placebo (basal) (n = 6)	Roxatidine (pilot study) (n = 6)	Placebo (basal) (n = 8)	Roxatidine (main study) (n = 8)
Evening mean of day 1 (16.00–22.00 h)	2.1 $\pm$ 0.5 (–0.5 to –0.1)	1.8 $\pm$ 0.7 ^b	2.1 $\pm$ 0.4 ^a (1.1–1.5)	3.5 $\pm$ 0.4 ^{a,b}
Night mean of day 1 (22.00–08.00 h)	2.9 $\pm$ 0.7 ^c (1.2–1.8)	4.3 $\pm$ 1.7 ^c	2.8 $\pm$ 0.7 ^d (1.2–1.6)	4.2 $\pm$ 1.2 ^d
Day mean of day 1 (08.00–16.00 h)	2.6 $\pm$ 0.6 (–0.2–0)	2.4 $\pm$ 0.8 ^f	2.5 $\pm$ 0.6 ^c (1.2–1.6)	3.9 $\pm$ 1.0 ^{e,f}
Total mean of day 1 (16.00–16.00 h)	2.6 $\pm$ 0.6 ^g (0.3–0.7)	3.1 $\pm$ 1.7 ^{g,j}	2.5 $\pm$ 0.6 ^h (1.3–1.5)	3.9 $\pm$ 1.0 ^{h,j}
Mean of day 2 (16.00–16.00 h)	—	2.7 $\pm$ 1.4	—	3.0 $\pm$ 0.6

a, b, c, d, e, f, h, j $P < 0.001$; $^g P < 0.01$.

(haemodialysis 2 or 3 times per week) is 3 times 75 mg per week. Using this dosage regimen endoscopic healing rates varied widely from 33 to 100% after 8 weeks of treatment.

In our study, the minimum steady state plasma drug concentration of 30 ± 19 ng ml⁻¹ when 75 mg roxatidine acetate was given every second day was not sufficient for inhibition of gastric acid secretion as confirmed by pH monitoring. Only when this dose was given daily was the trough concentration maintained above the IC₅₀ value [16]. Thus, in patients with renal failure the recommended dosage of 75 mg every other day is not sufficient to suppress acid secretion throughout the dosage interval. A pH of 3.5

or higher is required for 99% elimination of acid equivalents [17]. Therefore, in our study, a pH > 4.0 was selected as an adequate response [14].

In agreement with earlier reports [17–19] no consistent relationship was observed in all individuals between plasma concentrations of roxatidine and the inhibition of acid secretion as assessed by intragastric pH-metry. However, the duration of intragastric pH elevated above 4 units correlated ($r = 0.66$; $P = 0.026$) with the C_{av} of roxatidine. Similarly, Lassman *et al.* [6] found a correlation between the increase in gastric pH (measured in aspirated stomach contents) and the mean plasma concentration of roxatidine.

We have shown previously that patients undergoing

Table 4 Mean ($\pm$ s.d.) integral 24 h pH values, latency and duration of effect after placebo and roxatidine acetate

pH values	Placebo (basal) (n = 12)	Roxatidine (pilot study) (n = 6)	Roxatidine (main study) (n = 8)
Total AUEC (16.00–16.00 h)	3650 $\pm$ 2017	4413 $\pm$ 625 (1128–2316)	5620 $\pm$ 1898 (1047–2075)
Night AUEC (22.00–08.00 h)	1656 $\pm$ 1017	2616 $\pm$ 605 (1006–1672)	2459 $\pm$ 866 (180–1188)
Day AUEC (16.00–22.00 h; 08.00–16.00 h)	1994 $\pm$ 1149	1797 $\pm$ 581* (–103–869)	3161 $\pm$ 1171* (151–1603)
Latency (h)	—	3.5 $\pm$ 1.6	4.3 $\pm$ 1.4
Duration > pH 4 (h)	1.3 $\pm$ 1.2	5.6 $\pm$ 1.4* (3.5–5.9)	10.6 $\pm$ 3.9* (7.6–11.4)

AUEC = area under effect curve (pH units $\times$ min).

All differences from placebo (pilot and main study) were statistically significant ($P < 0.05$).

* $P < 0.05$ (pilot vs main study).

Numbers in brackets are 95% confidence intervals for differences from placebo.

Figure 2 Individual (○) and median (■) gastrin concentrations in patients with renal insufficiency before (day 0) and after (day 13) treatment with roxatidine acetate in a) the pilot study (75 mg every other day) and b) in the main study (75 mg daily).

the onset of action after giving roxatidine acetate is delayed in patients with renal failure.

In agreement with previous studies [21–23] we found elevated and highly variable serum gastrin values in patients with renal insufficiency. Similarly, Ala-Kaila *et al.* [24] reported two different populations in regard to serum gastrin with a cut-off point of 300 pg ml⁻¹ (see Figure 2).

During treatment with omeprazole elevated serum gastrin levels have been reported [25]. However, cimetidine, ranitidine and famotidine have only minimal effects on basal and postprandial serum gastrin concentration [26]. Inoue [27] found no effect of roxatidine on serum gastrin concentration. In contrast to the results of the pilot study we found an increase in the main study which might suggest an upper limit of the therapeutic dosage range.

The effects of cimetidine, ranitidine and famotidine on serum parathyroid hormone (PTH) concentrations are controversial. Some investigators found no inhibition of parathyroid function in hyperparathyroidism after administration of H₂-receptor antagonists [28–30], whereas others reported a decrease in PTH [30–34]. All of these previous studies used non-specific carboxy- and amino-terminal assays for the estimation of PTH in the evaluation of secondary hyperparathyroidism [35]. In contrast, we used a specific and sensitive assay for PTH (1–84). Furthermore, compliance of the patients was confirmed by measuring plasma concentrations of roxatidine. The median levels of PTH (1–84) were decreased in both groups with increasing dose of roxatidine acetate. Therefore, a clinical trial of the use of roxatidine to prevent secondary hyperparathyroidism in patients with renal insufficiency may be warranted. In our study, roxatidine was used only for 2 weeks, which is insufficient to draw conclusions regarding long-term treatment.

haemodialysis have higher acidity and attenuated alkalinisation by food in comparison with healthy subjects [14, 18], and often an abnormal gastric motility can be observed [20]. This may explain why

In conclusion, our data show that dosage adjustments of roxatidine in renal impairment based solely on pharmacokinetic data are not sufficient; pharmacodynamic aspects also have to be considered. Nocturnal intake of 75 mg roxatidine acetate once daily elevated gastric pH > 4 for a sufficient period of time in patients with renal insufficiency. No significant side effects were attributed to roxatidine acetate.

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