

## Current Status of Acid Pump Antagonists (Reversible PPIs)

Wilhelm Wurst<sup>a</sup> and Manfred Hartmann

*Byk Gulden Pharmaceuticals, Konstanz, Germany*

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The introduction of H<sub>2</sub>-receptor antagonists in the mid-1970s provided, for the first time, acceptable medical therapy for acid-related diseases. Their short duration of action and single receptor targeting, however, limited satisfactory treatment of patients. Today the control of gastric acid secretion can be effectively achieved by direct inhibition of the H<sup>+</sup>, K<sup>+</sup>-ATPase. Inhibition of the proton pump suppresses acid secretion independent of the route of stimulation. Two classes of drugs are able to inhibit the proton pump. First, the substituted benzimidazoles (proton pump inhibitors [PPIs]), which, due to their pKa of about 4, accumulate in the acidic secretory canaliculus of the stimulated parietal cell. Following conversion to a cationic sulfenamide, they react with cysteines on the extracytoplasmic face of the H<sup>+</sup>, K<sup>+</sup>-ATPase subunit. Second, acid pump antagonists (APAs) acting by K<sup>+</sup>-competitive and reversible binding to the gastric proton pump, which is the final step for activation of acid secretion in the parietal cell.

One possible class of APAs are imidazopyridines. BY841 was selected from this class and is chemically a (8-(2-methoxycarbonylamino-6-methyl-phenylmethylamino)-2,3-dimethyl-imidazo [1,2-a]-pyridine). In pharmacological experiments such as pH-metry in the conscious, pentagastrin-stimulated fistula dog, BY841 proved to be superior to both ranitidine and omeprazole by rapidly elevating intragastric pH up to a value of 6. The duration of this pH elevation in the dog was dose-dependent.

As was predicted by the above-mentioned dog model, available clinical phase I data confirm dose-dependent pharmacodynamics of BY841 in man. Using both acid output and continuous 24-hr pH measurements, a pronounced antisecretory effect of BY841 has been found. Actually, a single 50 mg oral dose of BY841 immediately elevated intragastric pH to about 6. Higher doses caused a dose-dependent increase in duration of the pH-elevation, without any further increase in maximum pH values. Twice daily administration was more effective than once a day administration of the same daily dose. With both regimens, the duration of the pH-elevating effect of BY841 further increased upon repeated daily administration. This demonstrates lack of tolerance development, the latter being a well-known disadvantage of H<sub>2</sub>-receptor antagonists. In comparison with the standard dose of omeprazole, BY841 administered at a dose of 50 mg or 100 mg twice daily is markedly more effective on Day one of treatment, and both doses are at least as potent as omeprazole following repeated daily administration.

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### INTRODUCTION

The introduction of H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs)<sup>b</sup> about 20 years ago provided, for the first time, acceptable effective medical therapy for acid-related diseases. However, due to their single receptor targeting, the acid-suppressing effect can be overcome by stimulation via other pathways. Further shortcomings in patient treatment were development

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<sup>a</sup>To whom all correspondence should be addressed: W. Wurst, M.D., M.Sc., Byk Gulden, Byk-Gulden-Str. 278467 Konstanz, Germany. Tel: 49-7531-84-2252; Fax: 49-7531-84-2474.

<sup>b</sup>Abbreviations: H<sub>2</sub>RA, H<sub>2</sub>-receptor antagonist, PPI, proton pump inhibitor; APA, acid pump antagonist; AUC, area under the curve; PSAO, pentagastrin-stimulated acid output.

of tolerance and short duration of action combined with poor control of daytime acid secretion.

The development of substituted benzimidazoles, the so-called proton pump inhibitors (PPIs) markedly improved the treatment of acid-related diseases. PPIs act by covalent binding to the final step of gastric acid secretion, the gastric  $H^+$ ,  $K^+$ -ATPase. Hence, in contrast to  $H_2$ RAs, suppression of intragastric acidity may not be overcome by stimulation via any pathway. In general, the PPIs are weak base pro-drugs that accumulate only in the acidic secretory canaliculus of the secreting parietal cell. There they are activated by acid to cysteine-reactive sulphenamides. The PPIs have a short serum elimination half-life of about one hour, but their covalent binding provides a long-lasting inhibition of acid secretion. On the other hand, steady-state inhibition is reached only after 48 to 72 hours on once daily dosing when a balance is struck between inhibition of active pumps and *de novo* synthesis of new pumps.

The development of another class of compounds targeting the  $H^+$ ,  $K^+$ -ATPase tries to combine the advantages of both PPIs and  $H_2$ RAs. These new drugs act by competing with  $K^+$  on the outer surface of the enzyme. Due to their reversible binding to the proton pump, they are called acid pump antagonists (APAs). They are active in the absence of acid secretion and bind to specific sites in the membrane domain of the  $H^+$ ,  $K^+$ -ATPase. This prevents  $H^+$  ion transport. Treatment with APAs should thus provide a more rapid elevation of gastric pH than is found with PPIs, and the elevation of pH should be greater than with oral PPIs at least as long as the APA is present in blood above threshold. Further prolongation of the acid-suppressing effect might be caused by high affinity of the drug to the enzyme, and tolerance is not to be expected.

Therefore, APAs should provide excellent control of intragastric pH, hence faster symptom remission and perhaps better clinical results in gastric acid-related diseases, symptom relief and in combination therapy for *Helicobacter pylori* eradication.

APAs represent, apart from additional chemical structures, imidazopyridines (e.g., BY841) or quinolines (e.g., BY067/SK&F96067, BY574/SK&F97574), a great variety of which have been tested pharmacologically. Based on preclinical and clinical phase I data, BY841 has been chosen for further development and is currently in Phase II. This publication summarizes the data obtained so far for BY841, with particular focus on phase I clinical trials.

## PRECLINICAL

The gastric  $H^+$ ,  $K^+$ -ATPase of the parietal cell extrudes protons from the cytoplasm into the extracytoplasmic space in exchange for potassium, which is absorbed into the cytoplasm. It belongs to the class of P-type ATPases. They are so-named because of the phospho-enzyme intermediate that is formed during the hydrolysis of ATP. In order to keep the reaction cycle ongoing, the enzyme has to be dephosphorylated by potassium from the extracytoplasmic face of the pump. Due to the comparable molecular size, ammonium can mimic potassium in activating the sodium, as well as the proton pump. If ammonium is derivatized, leading to compounds with nitrogen containing heterocycles (imidazopyridines, quinolines), inhibitors of the enzyme are obtained. The main characteristics of these inhibitors are the competition for the  $K^+$ -binding at the proton pump and the reversibility of this binding (i.e., inhibition of the enzyme). The latter can be demonstrated by dilution experiments. Due to these properties, compounds of this type are so-called acid pump antagonists (APAs). The structural differences between the proton pump and the sodium pump allow  $K^+$ -competition by the APA at the proton pump only, whereas the inhibition of the sodium pump is low and seems to be non-competitive (data not shown). SCH28080 (Schering) was the first APA in preclinical and clinical development followed by the choline derivatives BY067 and BY574.

**Table 1. IC<sub>50</sub> values for proton pump and sodium pump at 1 mM K<sup>+</sup>.**

	Proton pump ( $\mu\text{M}$ )	Sodium pump ( $\mu\text{M}$ )
BY067	1.9	60
BY574	1.5	95
BY841	0.04	63

W.A. Simon, unpublished data.

**Table 2. Inhibition of acid secretion ED<sub>50</sub> values after i.v. administration.**

	Ghosh Schild Rat (mg/kg)	Heidenhain Pouch Dog (mg/kg)
BY067	1.1	0.10
BY574	0.7	0.04
BY841	0.1	0.03

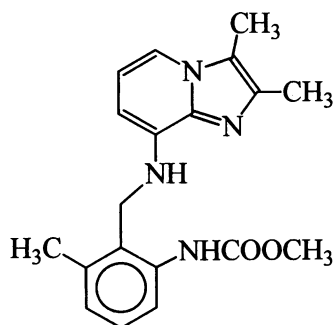
S. Postius, R. Riedel, unpublished data.

The inhibitory potency of antisecretory compounds is expressed in terms of their IC<sub>50</sub> values (i.e., the concentration of agent required to cause a 50 percent inhibition). Thus, as can be seen from Table 1, BY841 has the lowest IC<sub>50</sub> value and is therefore the most potent of the three compounds. The ratio of the IC<sub>50</sub> values for the sodium vs. the proton pump as an index for the selectivity was at least one order of magnitude greater for BY841 than for BY067 and BY574. Hence, BY841 has the greatest selectivity for the proton pump (Table 1).

In both screening models, the pentagastrin-stimulated Ghosh Schild Rat and the histamine stimulated Heidenhain Pouch Dog, BY841 proved to be the most potent compound (Table 2, for methods see [1]).

pH-metry in the conscious and fasted pentagastrin-stimulated fistula dog (for methods, see [2]) BY841 proved to be superior to both ranitidine [3] and omeprazole by rapidly elevating intragastric pH up to values of about 6 even after a single oral dose of about 10 mg/kg. The duration of this pH elevation in the dog was dose-dependent [3]. In this experimental model, BY841 was also more effective than ranitidine in suppressing carbachol-stimulated acid secretion.

Due to its unique pH profile and potency, BY841 was chosen for further clinical development. Its chemical structure is shown in Figure 1.

**Figure 1: Chemical structure of BY841.**

## PHASE I CLINICAL TRIALS WITH BY841

### *Materials and Methods*

All study protocols were approved by independent ethics committees, and written informed consent by each volunteer was obtained prior to the start of the study.

In pH-metry studies, intragastric pH was continuously recorded over 24 hours using a DL70 recorder (Schönfeld Datentechnik, Karlsruhe, Germany) and Ingold glass electrodes M440 (Ingold, Urdorf, Switzerland).

#### *Study 1: Single increasing oral doses, pH-metry*

Healthy male subjects ( $n = 18$ ) were admitted to the study and divided into three groups of six subjects each. Their age ranged from 23 to 42 years (median: 27.5) and their body weight, from 65 to 86 kg (median: 73).

Each subject was given two single oral doses of BY841 in increasing order with interposed placebo administration. There was a wash-out period of at least one week between two consecutive treatment days.

- Group 1: 10 mg, 20 mg, interposed placebo
- Group 2: 50 mg, 100 mg, interposed placebo
- Group 3: 200 mg, 400 mg, interposed placebo

Groups 1, 2 and 3 received treatment in that order and only after completion of the treatment in the preceding group.

Safety and tolerability were assessed by vital signs, ECG, clinical laboratory and adverse events. In Groups 2 and 3, intragastric pH was continuously recorded over 24 hours.

#### *Study 2: Single increasing oral doses, pentagastrin-stimulated acid output (PSAO)*

Healthy male subjects ( $n = 18$ ), aged 18 to 44 years (median 32) with body weight of between 61 and 97.5 kg (median 79.5) were divided into three groups of six subjects each. Each subject was given two single oral doses of BY841 in increasing order with interposed placebo administration. There was a wash-out period of at least one week between two consecutive treatment days.

- Group 1: 10 mg, 20 mg, interposed placebo
- Group 2: 50 mg, 100 mg, interposed placebo
- Group 3: 200 mg, 400 mg, interposed placebo

Groups 1, 2 and 3 received treatment in that order and only after completion of the treatment in the preceding group.

Safety and tolerability were assessed by vital signs, ECG, clinical laboratory and adverse events. Gastric acid output was assessed using the aspiration technique. A gastric tube was inserted into the stomach, and its correct position was checked by the water recovery method. Gastric acid secretion was stimulated by a continuous i.v. infusion of pentagastrin (Peptavlon®, ICI, UK) at a rate of 0.6  $\mu\text{g}/\text{kg}/\text{hr}$ , and gastric content was aspirated and collected in 15-min aliquots from two to five hours post-dose. The volume of the 15-min samples was measured and the  $\text{H}^+$  concentration was determined by titration with 0.1 N NaOH up to a pH of 7. pH was measured by use of a pH meter (Radiometer Copenhagen). Acid output was calculated. Blood was withdrawn and BY841 serum concentrations were analyzed by HPLC.

### *Study 3: Repeated oral once-daily and twice-daily doses, pH-metry*

Healthy male subjects (n = 8), aged 19 to 41 years (median 35), with body weights of between 65 and 96 kg (median 76) underwent the following two treatment periods of nine days each in randomized order:

#### Once-daily treatment:

- Day -2 and -1: Placebo once daily
- Day 1 to 7: 200 mg BY841 (in the morning)

#### Twice-daily treatment

- Day -2, -1: Placebo bid
- Day 1 to 7: 100 mg BY841 twice daily (in the morning and evening)

There was a wash-out period of at least two weeks between the treatment periods.

Safety and tolerability were assessed by vital signs, ECG, clinical laboratory and adverse events. Intra-gastric pH was continuously recorded over 24 hours on Day -2 (placebo) as well as on Day one and Day seven of both treatment periods. Blood was frequently withdrawn on Days one and seven of both periods and serum concentrations were analyzed by HPLC.

### *Study 4: repeated oral twice-daily doses vs. omeprazole, pH-metry*

In a randomized single-blind three-period crossover study, 12 healthy male volunteers, aged 22 to 41 years (median 29), with body weights of between 62 and 97 kg (median 83.5), completed the following treatment periods of seven days each:

- 50 mg BY841 twice daily (in the morning and in the evening)
- 100 mg BY841 twice daily (in the morning and in the evening)
- 20 mg omeprazole in the morning, placebo in the evening

Medication was filled in identical hard gelatin capsules. There was a wash-out period of at least one week between consecutive treatment periods.

Safety and tolerability were assessed by vital signs, ECG, clinical laboratory and adverse events. Within one week before the start of the first treatment period, the subjects underwent a baseline pH-metry. On Days one and seven of each treatment period, intra-gastric pH was continuously recorded over 24 hours.

#### *Analytics*

Serum concentrations of BY841 were measured by a validated and specific reversed phase gradient HPLC using fluorescence detection. Workup of samples was performed off-line by liquid-liquid extraction. The limit of quantitation was 0.005 mg/l.

#### *Statistics*

All data were evaluated descriptively by calculating mean/median values and profiles. The pharmacokinetic characteristics area under the curve (AUC) and  $t_{1/2}$  were evaluated using standard methods [4].

## **RESULTS**

### *Pharmacodynamics*

**Study 1:** A single oral dose of 50 mg produced a rapid and steep increase in intra-gastric pH. Within 30 to 60 min, pH values of about 6 were reached. Increasing the dose

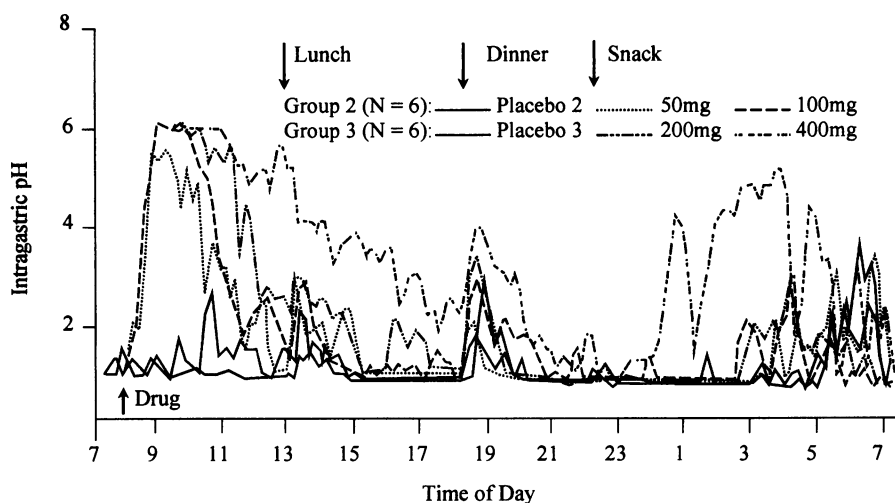


Figure 2. Median intragastric pH profiles in healthy male volunteers following single oral doses of BY841 (n = 6/dose).

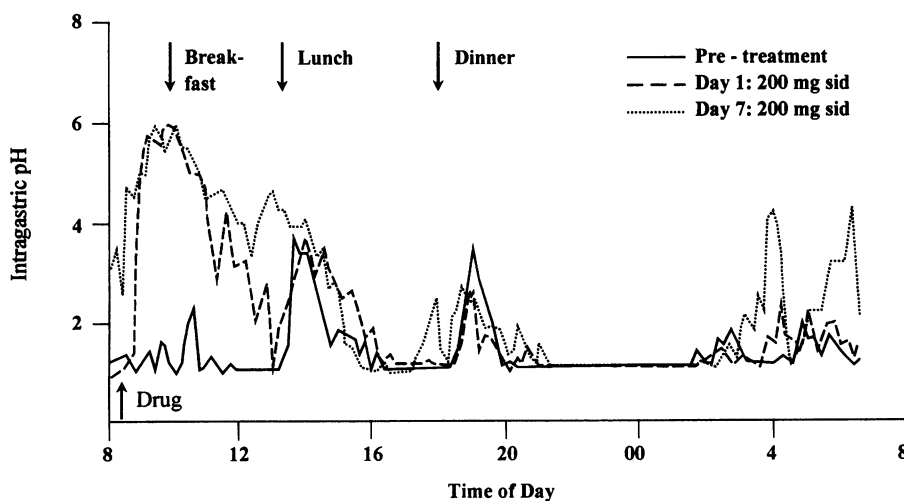


Figure 3. Median (n = 8) intragastric pH profiles in healthy male volunteers on the first and seventh day of treatment with 200 mg BY841 once a day.

led to a prolongation of the pH elevation without further increase in maximum pH values ([5], Figure 2).

**Study 2:** Single oral doses produced a dose-dependent inhibition of PSAO. Inhibition was nearly complete at doses of 200 mg or 400 mg. Inhibition of the secreted volume paralleled that of acid output, but to a lesser extent ([6], Table 3).

**Study 3:** Intake of 100 mg both in the morning and in the evening rapidly raised intragastric pH. The effect of the evening dose lasted longer than that of the morning dose. On Day one, the effect of 200 mg was superior to that of 100 mg, however, on Day seven there

**Table 3. Mean percent inhibition of PSAO and volume following single oral doses of BY 841 (n = 6 subjects each dose).**

		Percent inhibition vs. placebo	
		PSAO	Volume
Group I	10 mg	11	12
	20 mg	27	26
Group II	50 mg	54	22
	100 mg	62	47
Group III	200 mg	97	73
	400 mg	100	91

was nearly no difference between the 100 mg morning and the 200 mg dose. The evening dose of 100 mg produced a marked elevation of pH throughout the night even after the first dose. In contrast, the 200 mg dose administered once daily in the morning showed nearly no effect on nighttime pH. Thus, twice daily administration is more effective than once a day administration of the same daily dose. With both treatment regimens, the effect, particularly during the day, increased upon repeated dosing, the increase being more pronounced with twice daily dosing ([7], Figures 3 and 4).

**Study 4:** In comparison to baseline values, both doses of BY841, 50 mg twice daily and 100 mg twice daily, markedly elevated intragastric pH and prolonged percent of time of  $\text{pH} \geq 4$  even on Day 1. In contrast, only minor effects were observed with 20 mg omeprazole once daily (Figure 5). Repeated daily administration led to an increase in suppression of intragastric acidity with all three treatment regimens. On Day 7, the effect of 50 mg and 100 mg BY841 twice daily was at least comparable to that of 20 mg omeprazole once daily (Table 4, Figure 6).

#### Pharmacokinetics

**Study 2:** BY841 was rapidly absorbed. Maximum serum concentrations were attained between 0.5 and 1.5 hr following administration (Figure 7). Median  $C_{\text{max}}$ - and AUC-values increased with dose and ranged from 0.2 to 1.9 mg/l ( $C_{\text{max}}$ ) and from 0.3 to 4.1 mgxh/l (AUC) for the doses 20 to 400 mg. BY841 was eliminated monophasically from serum. Its serum elimination half-life was short, median values ranging from 1.1. to 1.7 hours.

**Table 4. Median 24-hr pH and median percent of time of  $\text{pH} \geq 4$  (n = 8).**

	Treatment	Day 1	Day 7
Median pH		Baseline: 1.5	
	50 mg twice daily	1.1	3.1
	100 mg twice daily	2.6	2.7
	20 mg omeprazole	1.5	2.5
Median percent of time $\text{pH} \geq 4$		Baseline: 8.9	
	50 mg twice daily	18.9	28.8
	100 mg twice daily	29.4	29.3
	20 mg omeprazole	9.2	24.7

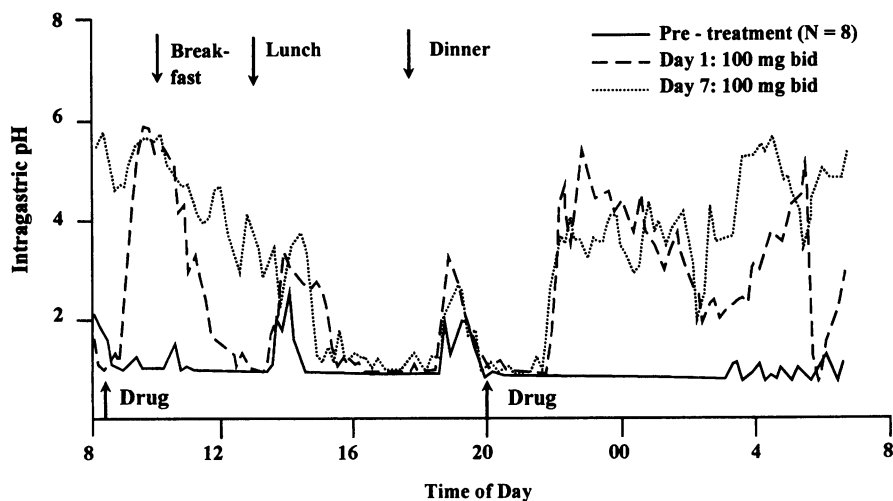


Figure 4. Median ( $n = 8$ ) intragastric pH profiles in healthy male volunteers on the first and seventh day of treatment with 100 mg BY841 twice daily.

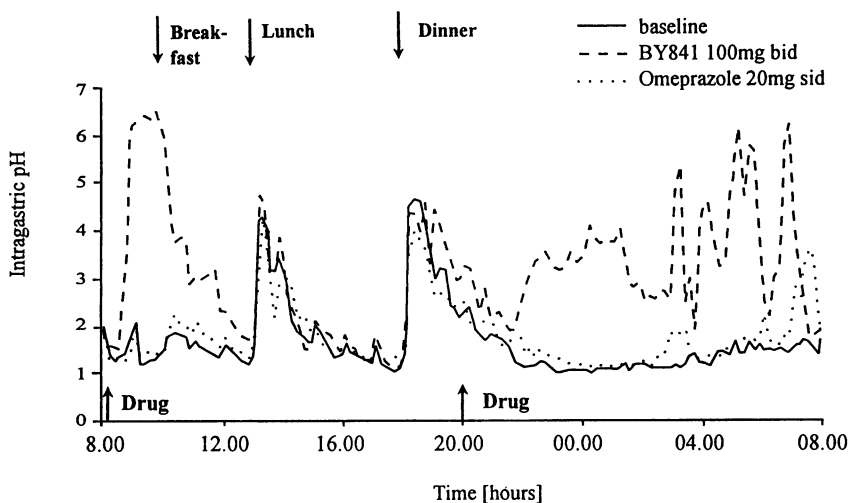
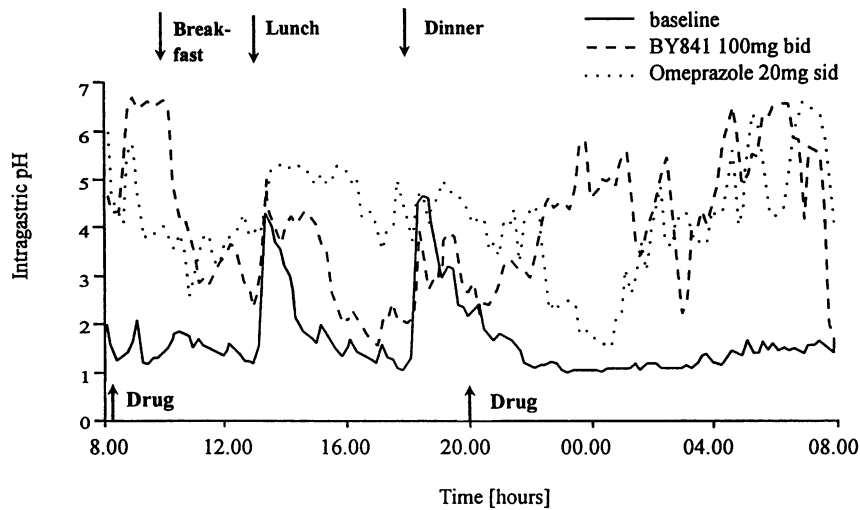


Figure 5. Median ( $n = 8$ ) intragastric pH profiles in healthy male volunteers baseline and on the first day of treatment with 100 mg BY841 twice daily and omeprazole 20 mg once daily.

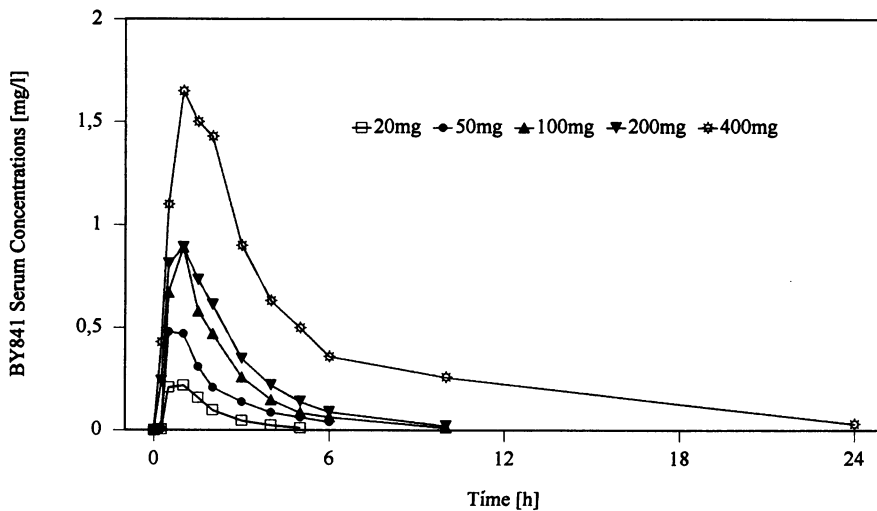
**Study 3:** Following repeated oral doses of either 100 mg twice daily or 200 mg daily, AUC-values of BY841 on Day seven were slightly to moderately increased compared to the values obtained on Day one for both dosing schemes (Figure 8).

AUC and  $C_{max}$  of BY841 were higher following a 200 mg than one 100 mg dose, although the increase was less than dose-proportional.  $T_{1/2}$  and  $t_{max}$  seemed to be independent of the dose. The elimination half-life of BY841 was unchanged following repeated doses at either dose level.





**Figure 6.** Median ( $n = 12$ ) intragastric pH profiles in healthy male volunteers baseline and on the seventh day of treatment with 100 mg BY841 twice daily and omeprazole 20 mg once daily.



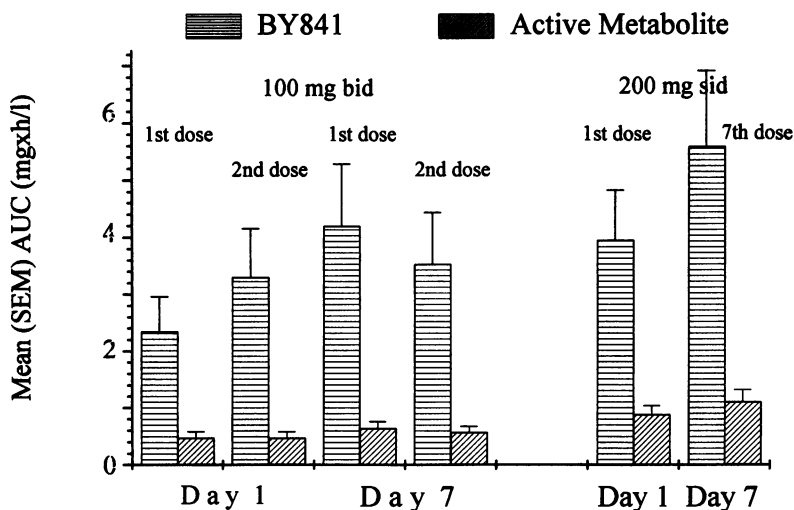
**Figure 7.** Mean ( $n = 6$  each dose) serum concentration-time profiles of BY841 following single oral doses of BY841 in healthy male volunteers.

#### *Safety and tolerability*

In all the above-mentioned phase I trials, BY841 was well-tolerated. There were no clinically relevant changes in vital signs, ECG or laboratory parameters.

### DISCUSSION

The acid pump antagonist BY841 proved to be a potent antisecretory drug in man by rapidly increasing intragastric pH up to values of about 6 even with a single oral dose of 50 mg. Higher doses caused a dose-dependent increase in duration of this pH elevation,



**Figure 8.** Mean AUC of BY841 on Day 1 and Day 7 of treatment with 100 mg twice daily and 200 mg once daily BY841 in eight healthy male subjects.

without any additional increase in maximum pH values. Twice a day administration was more effective than once daily morning administration of the same daily dose. The duration of the pH-elevating effect of BY841 further increased upon repeated daily administration. This demonstrates lack of tolerance development, the latter being a well-known disadvantage of H<sub>2</sub>RAs (8).

As known from the literature (9), omeprazole shows low efficacy after the first dose with increasing antisecretory effect to steady-state conditions upon repeated, once-daily administration. In this intraindividual comparison to the standard dose of omeprazole both doses of BY841, 50 mg twice daily and 100 mg twice daily, were markedly more effective on Day one of treatment. Both doses proved to be as effective as omeprazole with regard to median pH and percent of time at pH  $\geq$  4 following repeated daily administration.

In duodenal ulcer, the pH threshold for optimal healing is 3 (10). Similar criteria apply for gastric ulcer where the duration of treatment is important and the model of pH 3 holds good at eight weeks (11). For gastro-esophageal reflux disease the critical threshold for intragastric pH is 4 at eight weeks (12). Hence, BY841 at a dose of 50 mg or 100 mg twice daily should be at least as effective in treatment of patients as the standard dose of omeprazole. However, BY841 is markedly more effective in suppressing intragastric acidity during the first days of treatment, a shortening of the healing time and an even more rapid pain relief may be expected.

BY841 was rapidly absorbed. C<sub>max</sub> and AUC increased with increasing dose in the dose range 20 to 400 mg. Its serum elimination, half-life was short and unchanged upon repeated administration. Slightly increased AUC-values upon repeated administration corresponded with an increase in the pharmacodynamic effect.

As to *H. pylori* eradication, administration of BY841 in combination with one antibiotic should result in high and predictable pH values of about 6 in particular during the period when maximum serum concentrations of the antibiotic are achieved. Profound acid suppression seems to have a synergistic effect on *H. pylori* eradication (13). Whether dual

therapy with BY841 and one antibiotic therefore improves *H. pylori* eradication remains to be investigated in clinical trials.

Further advantages are that an acid pump antagonist such as BY841 is acid-stable and hence, does not have to be protected from gastric acid by enteric coating. It acts irrespective of the activation state of the proton pump. The latter also means that a resting parietal cell is inhibited and can not be subsequently stimulated to secrete acid.

In conclusion, BY841 is unique among the acid-suppressing drugs because it combines the advantages of both H<sub>2</sub>RAs and proton pump inhibitors and should therefore further improve the therapy of acid-related diseases.

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