Netazepide, a gastrin/CCK₂ receptor antagonist, causes dose-dependent, persistent inhibition of the responses to pentagastrin in healthy subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Gastrin controls secretion of gastric acid and growth of mucosal cells, especially enterocromaffin-like and parietal cells.
- Hypergastrinaemia can be harmful, and there is an unmet clinical need for a gastrin receptor antagonist.
- Nonclinical studies have shown that netazepide is a potent, highly selective and orally active gastrin/CCK₂ receptor antagonist.
- In healthy subjects, single oral doses of netazepide caused sustained dose-dependent increases in 24 h gastric pH, but that effect was mostly lost after repeated dosing, whereas the effect of omeprazole on 24 h gastric pH persisted. However, like omeprazole, netazepide increased 24 h circulating gastrin, consistent with persistent suppression of gastric acid secretion.

WHAT THIS STUDY ADDS

- Despite tolerance to its effect on pH, during repeated dosing netazepide causes persistent inhibition of pentagastrin-induced H⁺ secretion.
- Netazepide is a potential new treatment for acid-related conditions and the trophic effects of hypergastrinaemia.

AIMS

To confirm by means of pentagastrin, a synthetic gastrin agonist, that netazepide is a gastrin/CCK₂ receptor antagonist in healthy subjects, and that antagonism persists during repeated dosing.

METHODS

We did two studies in which we infused pentagastrin (0.6 µg kg⁻¹ h⁻¹ intravenously), aspirated gastric secretion and measured the volume, pH and H⁺ secretion rate of the gastric aspirate. First, we did a double-blind, five-way crossover study (*n* = 10) to assess the effect of single oral doses of netazepide (1, 5, 25 and 100 mg) and placebo on the response to pentagastrin. Then, we did a single-blind, placebo-controlled study (*n* = 8) to assess the effect of the first and last oral doses of netazepide (100 mg) twice daily for 13 doses on the response to pentagastrin.

RESULTS

Netazepide was well tolerated. After placebo, pentagastrin increased the volume and H⁺ secretion rate and reduced the pH of gastric aspirate. Compared with placebo, single doses of netazepide caused dose-dependent inhibition of the pentagastrin response (*P* < 0.02); netazepide (100 mg) abolished the response. After 13 doses, the reduction in volume and H⁺ secretion rate persisted (*P* < 0.001), but the pH effect was mostly lost.

CONCLUSIONS

Netazepide is an orally active, potent, competitive antagonist of human gastrin/CCK₂ receptors. Antagonism is dose dependent and persists during repeated dosing, despite tolerance to the effect on pH. Further studies are required to explain that tolerance. Netazepide is a tool to study the physiology and pharmacology of gastrin, and merits studies in patients to assess its potential to treat gastric acid-related conditions and the trophic effects of hypergastrinaemia.

Introduction

Nonclinical studies have shown that netazepide (YF476) is a potent, selective, competitive and orally active antagonist [1–3] of CCK₂/gastrin receptors [4]. We have shown in healthy subjects that single oral doses of netazepide cause dose-dependent, sustained increases in basal and food-stimulated 24 h gastric pH, consistent with suppression of gastric acid production via antagonism of gastrin receptors [5]. We have also shown that repeated doses of netazepide lead to tolerance to that effect on gastric pH; however, repeated doses increased plasma gastrin, suggesting persistent suppression of gastric acid secretion [6]. Subsequent studies in rodents have also shown that netazepide increases circulating gastrin, via gastric acid suppression and upregulation of the gastrin gene [7–16].

Here we report two more studies in healthy subjects, a single-dose study and a repeated-dose study. The objectives were to confirm that netazepide causes dose-dependent antagonism of gastrin receptors and that antagonism persists during repeated dosing. We used intravenous pentagastrin – a synthetic pentapeptide consisting of β -alanine and the C-terminal tetrapeptide of gastrin – as an agonist to stimulate gastrin receptors [17].

We presented the results of the second study at a meeting of the Clinical Section of the British Pharmacological Society [18].

Methods

We carried out the studies at our facilities in the Central Middlesex Hospital, London, UK, in accordance with the ICH Guideline for Good Clinical Practice and the Declaration of Helsinki. Brent Ethics Committee approved the studies. Subjects gave written informed consent. The studies are registered at ClinicalTrials.gov as NCT01601418 and NCT01601405.

Materials

Ferring A/S (Vanløse, Denmark) supplied capsules of netazepide (1, 5, 25 and 100 mg) and matching placebo. The hospital pharmacy packed and labelled treatments, and randomized subjects to treatment in the single-dose study using sequentially numbered containers. Pentagastrin was supplied by Cambridge Laboratories Ltd (Wallsend, Tyne and Wear, UK) as ampoules of 500 μ g (2 ml)⁻¹.

Study design

Single-dose study The study was double-blind, randomized, single-dose and five-way complete crossover in design. There was 1 week between successive treatments. The protocol required 10 healthy nonsmoking men or women not at risk of pregnancy to complete the study. The

other entry criteria included the following: *Helicobacter pylori* negative (by ¹³C-urea breath test); negative urinary screen for drugs of abuse; negative antibody tests for HIV 1 and 2 and hepatitis B and C viruses; and no medication for the previous 14 days. Subjects fasted from midnight, then at about 08.00 h we passed a nasogastric tube (14 gauge Salem sump tube) to collect gastric aspirate by continuous suction while the subject was semi-recumbent. We confirmed the correct position of the tube by the water recovery test [19].

First, we collected basal gastric aspirate continuously in 15 min epochs for 30 min. Immediately afterwards, the subject took a single dose of netazepide (1, 5, 25 or 100 mg) or placebo by mouth with 150 ml water. We allowed 55 min for absorption of netazepide, after which we collected gastric aspirate for 5 min to empty the stomach. Then, we began an intravenous infusion of pentagastrin (0.6 μ g kg⁻¹ h⁻¹) for 2 h, via a syringe pump. We collected gastric aspirate continuously every 15 min during the infusion to measure the volume, titratable acidity (H⁺ secretion rate) and pH of each sample. Subjects continued to fast until we removed the nasogastric tube at the end of the infusion. We assessed safety and tolerability of treatments by vital signs, ECG, routine safety tests of blood (haematology and biochemistry) and urine (urinalysis) and adverse events.

Repeated-dose study The study was single blind and placebo controlled. The protocol required eight healthy men or women, defined as in the single-dose study, to complete the study. Subjects were resident from Day 0 to 7, and on Day 14. They took the following treatments by mouth: a single dose of placebo on Day 0; netazepide (100 mg) twice daily on Days 1–6; a single dose of netazepide (100 mg) on Day 7; and a single dose of placebo on Day 14. We told all subjects that they would receive placebo on some days, but we did not tell them which days. On Days 0, 1, 7 and 14, we passed a nasogastric tube, collected and analysed gastric aspirate, dosed the subjects and infused pentagastrin as in the single-dose study. Subjects fasted on dosing days as in the single-dose study. We collected blood for plasma netazepide assay before and 1 and 3 h after the morning dose on Days 0, 1, 7 and 14. We assessed tolerability and safety of treatments as in the single-dose study.

Gastric aspirate

In both studies, we collected gastric aspirate via the nasogastric tube into conical flasks primed with a few drops of a silicone antifoaming agent. We used a suction pump to apply continuous negative pressure of 100 mmHg to the nasogastric tube. If necessary, we increased the negative pressure to a maximum of 600 mmHg to clear blockage of the tube by thick mucus. We measured the volume of each collection. We also measured titratable acidity and pH with a pH meter and automatic titrator (Radiometer, Copenhagen, Denmark), which

we calibrated with standard buffers before and after each batch of samples. We used 0.1 M sodium hydroxide as the base, and calculated H^+ secretion rate in micromoles per minute.

Plasma netazepide

We collected blood and separated and stored plasma for netazepide assay by a validated HPLC-MS method [20], as described previously [5].

Sample size

Single-dose study In our previous single-dose, complete crossover study, 10 healthy subjects were enough to show significant differences in 24 h ambulatory gastric pH between netazepide (5, 25 or 100 mg) and placebo [5]. Therefore, we judged that 10 subjects would be enough to detect differences in the response to pentagastrin between single doses of netazepide (1, 5, 25 or 100 mg) and placebo.

Repeated-dose study The number of subjects was determined by feasibility, rather than a power calculation. The results of the single-dose study indicated that eight subjects would be enough to show a significant effect of 13 doses of netazepide (100 mg) vs. placebo on the response to pentagastrin.

Statistics

Single-dose study The primary outcome variable was H^+ content of gastric aspirate during 60–180 min after dosing, expressed as the mean secretion rate during that period, for each subject and each treatment; that method obviated the need for an analysis of repeated measures. When pH was ≥ 7.0 , we set secretion rate to 0. We analysed the results by analysis of covariance (ANCOVA) with factors treatment and subject, using subject- and session-specific basal values (0–30 min after the start of aspiration) as a covariate. We made pairwise comparisons between placebo and each dose level of netazepide with adjustment for multiple comparisons, using the Dunnett–Hsu method.

Repeated-dose study As in the single-dose study, the primary outcome variable was H^+ content of gastric aspirate during 60–180 min after dosing, expressed as the mean secretion rate during that period, for each subject and Day; that method obviated the need for an analysis of repeated measures. We also examined the effect of netazepide on volume and pH of gastric aspirate 60–180 min after dosing. We analysed the results for placebo (Day 0) and the first dose (Day 1) and last dose (Day 7) of netazepide by ANCOVA with factors treatment, subject and Day, using the subject-specific basal values on Day 0 as a covariate. Also, we did pairwise comparisons

between Day 0 and each subsequent Day with adjustment for multiple comparisons, using the Dunnett–Hsu method.

Results

Single-dose study

Subjects Twelve subjects entered the study; one withdrew for personal reasons and another could not tolerate the nasogastric tube. Ten Euroid subjects (six women and four men) completed the study according to the protocol. Their mean age and body mass index were 27.6 years (range 20–42 years) and 24.6 kg m^{-2} (range $19.9\text{--}27.9 \text{ kg m}^{-2}$), respectively.

Basal Before each treatment, H^+ secretion rate was similarly low (Table 1), and volume and pH differed little (Figure 1).

Placebo After placebo, pentagastrin increased the volume and H^+ secretion rate and reduced the pH of gastric aspirate (Table 1 and Figure 1). Compared with basal measurements, mean volume and H^+ secretion rate increased 2.4- and 8-fold, respectively, and mean pH decreased from 2.90 to 1.29 in the epoch 60–75 min after dosing. The increase in H^+ concentration in gastric secretion accounted for a greater proportion of the increase in H^+ secretion rate than did the increase in volume.

Netazepide Single doses of netazepide (1, 5, 25 and 100 mg) inhibited all three measures of the response to pentagastrin in a dose-dependent manner (Table 1 and Figure 1). Netazepide (100 mg) abolished the response. Indeed, netazepide (100 mg) not only reversed the fall in pH, it also increased pH substantially above basal levels. Compared with placebo, all doses of netazepide significantly ($P < 0.02$) reduced the mean H^+ secretion rate (Table 1).

Table 1

Single-dose study: mean (SD; $n = 10$) basal and pentagastrin-induced H^+ secretion rate in gastric aspirate before and after netazepide (1, 5, 25 or 100 mg) and placebo

Dose	Basal (0–30 min before dosing) ($\mu\text{mol min}^{-1}$) Mean (SD)	Pentagastrin (60–180 min after dosing) ($\mu\text{mol min}^{-1}$) Mean (SD)
Placebo	37 (34)	291 (103)
Netazepide (1 mg)	31 (30)	180 (141)**
Netazepide (5 mg)	22 (16)	140 (130)**
Netazepide (25 mg)	22 (34)	67 (66)*
Netazepide (100 mg)	20 (21)	10 (14)*

Asterisks indicate significant difference (* $P < 0.02$ and ** $P < 0.001$) from placebo by ANCOVA, with subject- and session-specific basal value as covariate.

Figure 1

Single-dose study: mean (SD; $n = 10$) basal and pentagastrin-induced volume (A), H^+ secretion rate (B) and pH of gastric aspirate (C) before and after netazepide [1 (—■—), 5 (—▲—), 25 (—×—) or 100 mg (—*—)] and placebo (—◆—)

Safety and tolerability Some subjects reported minor and transient adverse events, mainly sore throat, nausea, loose stools and stomach ache, after both placebo and netazepide. We attributed those adverse events to the nasogastric tube or the pentagastrin infusion. There were no clinically relevant changes in any of the safety assessments.

Repeated-dose study

Subjects Twelve subjects entered the study. None had participated in the single-dose study. Two subjects withdrew on Day 1 because of intolerance to the nasogastric tube, one withdrew for personal reasons, and we withdrew one subject because he proved to have undiagnosed, symptomless achlorhydria at entry to the study. Eight subjects (four men and four women; seven Europid and one Oriental) completed the study according to the protocol. Their

mean age and body mass index were 25.8 years (range 20–44 years) and 21.9 kg m^{-2} (range 18.8–26.1 kg m^{-2}), respectively.

Basal On Days 0, 1, 7 and 14, basal H^+ secretion rates were similarly low, and volume and pH differed little (Table 2 and Figure 2).

Day 0 (placebo) After placebo, pentagastrin increased the volume and H^+ secretion rate and reduced the pH (Figure 2) of gastric aspirate. Compared with basal measurements, mean volume and H^+ secretion rate increased 1.7- and 4.2-fold, respectively, and mean pH decreased from 2.0 to 1.36 in the epoch 60–75 min after dosing. The results were similar to those seen after placebo treatment in the single-dose study.

Table 2

Repeated-dose study: mean (SD; $n = 8$) basal and pentagastrin-induced volume, H^+ secretion rate and pH of gastric aspirate before and after placebo (Days 0 and 14) and before and after the first dose (Day 1) and last dose (Day 7) of 13 doses of netazepide (100 mg) twice daily

	Day	Basal (0–30 min before dosing) Mean (SD)	Pentagastrin (60–180 min after dosing) Mean (SD)
Volume (ml min ⁻¹)	0	2.4 (1.7)	3.8 (1.3)
	1	1.3 (0.7)	0.8 (0.5)**
	7	1.0 (0.5)	1.3 (0.5)**
	14	1.6 (1.2)	3.2 (0.8)
H^+ secretion rate ($\mu\text{mol min}^{-1}$)	0	105 (73)	429 (250)
	1	59 (43)	30 (53)**
	7	41 (38)	51 (40)**
	14	108 (142)	405 (119)
pH	0	2.0 (1.3)	1.4 (0.5)
	1	1.9 (0.5)	4.3 (2.1)**
	7	2.2 (1.2)	1.9 (0.4)
	14	2.0 (1.0)	1.3 (0.4)

Asterisks show significant difference (** $P < 0.001$) from Day 0 by ANCOVA, with subject- and session-specific basal value as covariate.

Day 1 (first dose of netazepide) Compared with placebo on Day 0, the first dose of netazepide (100 mg) abolished all three measures of the response to pentagastrin (Figure 2). The reductions in mean volume and H^+ secretion rate and the increase in pH of gastric aspirate (Table 2) were all significant ($P < 0.05$).

Day 7 (last dose of netazepide) Compared with placebo on Day 0, the last dose of netazepide (100 mg) on Day 7 abolished the increases in mean volume (Figure 2A) and H^+ secretion rate (Figure 2B) of aspirate induced by pentagastrin, as did the first dose on Day 1, but failed to achieve the increase in pH that netazepide caused on Day 1 (Table 2 and Figure 2C). The reductions in volume and H^+ secretion rate (Table 2) were significant ($P < 0.001$), whereas the effect on pH did not differ significantly from placebo.

Day 14 (placebo) On Day 14, 7 days after the last dose of netazepide, the three measures of the response to pentagastrin after placebo were similar to those after placebo on Day 0 (Table 2 and Figure 2).

Plasma netazepide Mean (range) plasma netazepide concentrations (in nanograms per millilitre) at 60 and 180 min after dosing on Day 1 were 118.2 (1.4–302.9) and 18.5 (2.7–34.2), respectively, and on Day 7 were 48.2 (22.3–94.6) and 25.0 (9.2–78.3), respectively.

Safety and tolerability Some subjects reported adverse events after placebo and netazepide, which were similar to

those reported by subjects in the single-dose study. There were no clinically relevant changes in any of the safety assessments.

Discussion

In both studies, which were done in different groups of subjects, basal volume, H^+ secretion rate and pH of gastric aspirate were low on all study days, as would be expected after an overnight fast. Also in both studies, pentagastrin increased the volume and H^+ secretion rate of gastric aspirate and reduced the pH after every dose of placebo. The increase in H^+ concentration in gastric secretion accounted for a greater proportion of the increase in H^+ secretion rate than did the increase in volume. Pentagastrin ($0.6 \mu\text{g kg}^{-1} \text{ h}^{-1}$), which is a submaximal dose, was well tolerated.

In both studies, netazepide was well tolerated, and a single dose inhibited all three measures of the response to pentagastrin. In the single-dose study, netazepide (1, 5, 25 and 100 mg) caused dose-dependent inhibition of the pentagastrin-stimulated increases in the volume and H^+ secretion rate and the reduction in pH of gastric aspirate. Netazepide (100 mg) abolished all three measures of the response to pentagastrin. In the repeated-dose study, the effects of the first of the 13 doses of netazepide (100 mg) were very similar to those of netazepide (100 mg) in the single-dose study. Also, the effects of the last of the 13 doses of netazepide (100 mg) on pentagastrin-stimulated increases in volume and H^+ secretion rate were similar to those of the first dose; but, compared with the first dose, the last dose had much less effect on the pH response to pentagastrin, as in our previous studies, in which we measured pH by the 24 h ambulatory method [6].

Dose-dependent inhibition of the response to pentagastrin by single doses of netazepide is consistent with antagonism of gastrin/CCK₂ receptors. Suppression of pentagastrin-induced increases in volume and H^+ secretion rate of gastric aspirate by repeated doses of netazepide is consistent with persistent antagonism. Those findings support our conclusion that the increase in plasma gastrin after repeated doses of netazepide in our previous studies [6] reflects suppression of gastric acid secretion via antagonism of gastrin receptors and upregulation of the gastrin gene [7–16]. All our findings thus far are in accord with those of nonclinical studies, which have shown netazepide to be an orally active, highly selective and competitive antagonist of gastrin/CCK₂ receptors [1–3] whose action persists after chronic dosing [8, 9].

We allowed 60 min after netazepide dosing before starting infusion of pentagastrin, because that was about the time of maximal plasma concentration in our previous studies [5, 6]. Netazepide concentrations at 60 and 90 min after dosing on Days 1 and 7 in the repeated-dose study were variable, and were only 10–15% of those measured at

Figure 2

Repeated-dose study: mean (SD; $n = 8$) basal and pentagastrin-induced volume (A), H^+ secretion rate (B) and pH of gastric aspirate (C) after placebo on Day 0 (—○—) and Day 14 (—×—), and after the first dose on Day 1 (—□—) and last dose on Day 7 (—△—) of 13 doses of 100 mg netazepide twice daily

similar times after dosing in our previous studies [5,6]. The reason is that for those studies the sponsor supplied what we now know to be a much more bioavailable formulation. Clearly, netazepide is an effective gastrin/CCK₂ receptor antagonist in man, even at low plasma concentrations.

After only 7 days of netazepide (100 mg) twice daily, nearly complete tolerance had developed. That phenomenon resembles the development of tolerance to the effect of netazepide on 24 h ambulatory gastric pH after repeated doses in our previous studies [6]. What might be the mechanism of that tolerance?

Tolerance might reflect a change in a constituent of gastric juice which takes longer to occur than does the immediate effect on acid production and which reduces the buffering capacity of gastric juice. Gastric juice contains many substances apart from hydrochloric acid,

including pepsin, mucus, peptides, amino acids and electrolytes, such as bicarbonate (HCO_3^-) and phosphate. Also, it usually contains saliva and sometimes bile. In man, the buffers of H^+ in gastric juice, which prevent large changes in gastric pH, are mainly HCO_3^- [21], nonpepsin protein [22–24] and phosphate [25]. Pepsin degradation products of nonpepsin protein may also add to the buffering capacity of gastric juice [26]. Nonprotein buffers, especially HCO_3^- , probably play a more important role than do the other buffers [24]. Mucin, the protein of mucus, has little, if any, buffering activity [22].

Various studies have been carried out to assess the mechanisms that control gastric HCO_3^- secretion in humans. Bicarbonate secretion was increased by cholinergic stimulation and reduced by prostaglandin E₂ [27] but was unaffected by pentagastrin [27, 28]. Sham feeding

stimulated gastric HCO_3^- secretion, confirming its central nervous system control via the vagus [29–31]. Bicarbonate is difficult to measure in the presence of acid, and must first be unmasked by suppressing acid production with a histamine H_2 -receptor antagonist (H_2RA) or a proton pump inhibitor (PPI) [32]. Using that method, the rate of secretion of HCO_3^- by the human stomach *in vivo* was equivalent to 10–20% of basal acid secretion [32]. Repeated doses of neither an H_2RA nor a PPI affected HCO_3^- secretion [33]. However, the different methods by which gastric HCO_3^- secretion has been measured in humans have produced discordant results [34]. Nevertheless, the available evidence suggests that gastrin is not directly involved in control of gastric HCO_3^- secretion.

Gastrin, a hormone secreted by G cells in the gastric antrum [17], stimulates gastrin receptors on enterochromaffin-like cells in the gastric mucosa to secrete histamine, which in turn stimulates adjacent gastric parietal cells to secrete acid into the lumen of the stomach. Secretion of gastric acid is mediated by the action of H^+ , K^+ -ATPase (the proton pump) in response to stimulation of histamine H_2 receptors or muscarinic M_3 receptors. There is evidence that parietal cells also express gastrin receptors [35], although their role in acid secretion is uncertain [36]. Gastrin also acts as a growth factor on normal gastric oxyntic mucosa, stimulating enterochromaffin-like and parietal cell growth [17, 37, 38]. Recent studies using knockout mice that either lack the gastrin gene or overexpress it, as well as genomic methods, have revealed that the physiological role of gastrin is far more than regulation of acid secretion [39–41]. Gastrin is pivotal in organizing and maintaining the structure of gastric epithelium. It upregulates various genes, such as histidine decarboxylase, vesicular monoamine transporter type 2, chromogranin A and protein Reg 1A [37], and stimulates paracrine cascades [38], including cytokines, growth factors, such as trefoil factor [42, 43], and prostanoids. Gastric acid secretion is regulated by endocrine, paracrine and neurocrine mechanisms via at least three signalling pathways: gastrin–histamine (stimulation), CCK_1 –somatostatin (inhibition) and the neural network (both stimulation and inhibition). Studies in gene-knockout mice have shown that there is complex interplay among those pathways [36, 44]. Different pathways are suppressed or dominate, depending on the circumstances. It is possible, therefore, that antagonism of gastrin receptors by repeated doses of netazepide led to a switch in control of the buffering capacity of gastric juice in our study.

What might be the impact of the tolerance to gastric pH on the potential therapeutic uses of netazepide? Gastric pH is easy to measure continuously with a nasogastric electrode, and has been widely used as a surrogate clinical end-point in trials of the acid suppressants H_2RA and PPI [45]. A substantial increase in the duration for which pH is ≥ 4 is regarded as essential to heal peptic ulcers or erosive oesophagitis. Given that pH is a logarithmic

scale, the gastric pH may change little despite a large change in H^+ secretion [36, 46]. Furthermore, measurement of gastric pH alone ignores changes in volume. Therefore, the amount of H^+ secreted per unit time is a more sensitive and reliable test of acid suppression than is pH. Repeated doses of netazepide cause persistent blockade of gastrin receptors and could prove a useful treatment for patients with acid-related conditions, such as gastro-oesophageal reflux disease, despite tolerance to the effect on pH. Likewise, netazepide should inhibit the trophic effects of gastrin on parietal and/or enterochromaffin-like cells in the gastric mucosa [17, 37, 38], for example in patients with hypergastrinaemia caused by autoimmune chronic atrophic gastritis [47], Zollinger-Ellison syndrome [47] and prolonged PPI [48–51] or H_2RA treatment [52]. Indeed, in pilot studies in patients with chronic atrophic gastritis and multiple gastric carcinoids secondary to hypergastrinaemia, netazepide reduced the number and size of the tumours and normalized plasma chromogranin A, which increased to pretreatment levels after netazepide was stopped [53, 54]. Chromogranin A is a validated biomarker of increased activity of enterochromaffin-like cells, from which the gastric carcinoids originate.

Many gastrin receptor antagonists have been described [55, 56], but most have had problems with selectivity, potency or bioavailability. Several have been tested in man [57–61], but none has been developed as a medicine. Whether tolerance to the effect on gastric pH is specific to netazepide or a class effect must await studies of other gastrin receptor antagonists.

The design of the single-dose study was ideal; randomized, double blind, placebo controlled, complete crossover and a range of doses. The design of the repeated-dose study – single blind, fixed dose and no randomization – was a compromise, but the methods are robust and the results have face validity.

Conclusions

In healthy subjects, netazepide is an orally active, potent, competitive antagonist of gastrin/ CCK_2 receptors in the stomach. Antagonism is dose dependent, and persists during repeated dosing, despite the reduced effect on pH. Further studies are required to find the mechanism of that reduced effect. Netazepide is a tool to study the physiology and pharmacology of gastrin, and merits studies in patients to assess its potential to treat gastric acid-related conditions and the trophic effects of hypergastrinaemia.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). Netazepide (YF476) came from research by Ferring, Chilworth, England. The James Black Foundation licensed

netazepide from Ferring temporarily in 2001 to sponsor these studies. In 2006, Ferring licensed netazepide to Trio Medicines Ltd, a subsidiary of Hammersmith Medicines Research (HMR), a contract research organization. M.B. and S.W. are directors of HMR and Trio Medicines Ltd, and M.B. owns both companies. Sadly, Sir James Black, who helped design the studies and contributed to the interpretation of the results, died in March 2010.

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