11 Rebound of Gastric Acid Secretion

11.1 Introduction

Acid Rebound in this document is defined as an increase in gastric acid secretion (basal and/or stimulated) above pretreatment levels following discontinuation of antisecretory therapy. Rebound was initially reported in studies following the use of histamine H_2-receptor antagonists and was thought to be due to increased serum gastrin and/or upregulation of the H_2-receptors. Elevated gastrin levels, or hypergastrinemia, is a secondary effect that occurs during chronic inhibition of gastric acid secretion, such as with long-term antisecretory therapy.[146] In man, gastrin is the primary regulator of gastric acid secretion, which is mediated by histamine released by the enterochromaffin-like (ECL) cell. Increased plasma gastrin stimulates and up-regulates ECL cells to produce and release more histamine to stimulate the parietal cell. In addition, an increase in parietal cell mass may occur with the chronic use of antisecretory agents, and this may be an additional mechanism for increased acid secretion that can occur after discontinuation of therapy. Another possible cause of rebound acid secretion is increased sensitivity to histamine.

Factors associated with acid rebound following antisecretory therapy include duration and dosage of therapy, intragastric pH while on therapy and *H pylori* status.[147]

Long-term acid inhibition with omeprazole may lead to an increase in plasma gastrin levels and ECL or argyrophil cell hyperplasia. It has been suggested that long-term omeprazole therapy may result in acid rebound after therapy is discontinued.[148] However there is no general agreement in the literature whether withdrawal of omeprazole therapy results in acid rebound. It is important to note that the plasma half-life of omeprazole is 0.5 to 1 hour and gastric acid inhibition will occur in the absence of demonstrable blood levels of omeprazole. This is related to inactivation of the proton pumps of the parietal cells. The inhibitory effect of omeprazole is fully reversible upon drug withdrawal. The rate of recovery of gastric acid secretion correlates with the rate of synthesis of new gastric proton pumps.[60] There is evidence that one-third of proton pumps are regenerated within 36 hours with complete regeneration within 72 hours.

This summary provides the following:

- Tabulation and summary of the published literature containing gastric acid secretion data following discontinuation of omeprazole therapy
- Tabulation and summary of the published literature containing gastric acid secretion data following discontinuation of other antisecretory therapy
- Discussion of gastric acid secretion data in *Helicobacter pylori*-positive individuals
- Summary of reports of rebound in the AstraZeneca LP worldwide post-marketing database for omeprazole
- Conclusions regarding the lack of evidence for rebound acid hypersecretion following short-term omeprazole therapy

11.2 Acid Rebound: Preclinical Studies with Omeprazole

Studies in rats and dogs investigated the recovery and potential rebound of acid secretion following cessation of omeprazole treatment after both acute and repeated administration. Several general conclusions may be drawn from these studies. Basal and stimulated gastric acid secretion returned to control levels within a few days after termination of omeprazole treatment regardless of dose level or duration of treatment. In most instances, no rebound above control levels of secretion was observed. In those cases where a rebound effect was noted, supramaximal doses (4-times to 67-times the acute ED_{50} value) were administered for 3 months or more, and the hypersecretion seemed to parallel the general hypertrophy of the gastric mucosa rather than reflect a specific increase in H^+,K^+-ATPase content or alteration in its turnover. Furthermore, either no rebound in basal acid secretion occurred or, if so, it rapidly returned to control levels. Rebound of secretogogue-stimulated acid secretion was more affected, but it too gradually declined from the initial peak. Thus, the results from animal studies suggest that rebound effects after withdrawal of omeprazole therapy are the result of exposures to high doses for prolonged periods, conditions which are not expected to occur during use of omeprazole in an OTC setting.

11.3 Acid Rebound: Clinical Studies with Omeprazole

11.3.1 Short-Term Omeprazole Treatment

Nine clinical studies have addressed the potential for acid rebound hypersecretion after discontinuation of treatment with omeprazole for periods of up to 3 months. Trial measurements, patient characteristics, omeprazole dosages and dosing durations, and times at which follow-up measurements were obtained for these 9 studies are varied. These characteristics for each of the studies are summarized in Table 11.1.

In six studies, there was no evidence to suggest that withdrawal of omeprazole therapy resulted in acid rebound. In a trial by Lind et al., (1983), 6 healthy patients received a single omeprazole dose of 20, 40, 60 and 80 mg. No increase in pentagastrin-stimulated acid secretion was observed at any of the time points between 1 and 14 days post-dosing. No acid rebound was seen following single omeprazole doses in these healthy patients.[149]

A trial by Sharma et al., (1984) investigated the effect of omeprazole 30-60 mg daily administered for 2 weeks on 24-hour intragastric acidity. Nine patients with duodenal ulcer were treated, and measurements were obtained at the end of therapy and at one week and 8 weeks after discontinuation of therapy. At the end of the 2-week treatment period, omeprazole 60 mg daily had decreased 24-hour intragastric acidity by 96%. One week later, 24-hour intragastric acidity was still decreased by 26% compared with pre-treatment values. At 8 weeks post-treatment, 24-hr intragastric acidity values had returned to pre-treatment levels. Thus, no acid rebound was observed after withdrawal of omeprazole therapy in this trial.[150]

Müller et al., (1984) gave 8 healthy patients omeprazole 30 mg daily for 28 days. Basal and pentagastrin-stimulated gastric acid output were measured on Day 15 of therapy and on 1, 3, 5, 7, and 11 days after discontinuation of treatment. One day after treatment discontinuation, mean stimulated acid output was still reduced by 72%. At 11 days post-treatment, acid output had returned to pre-treatment levels. No acid rebound effect on basal or

pentagastrin-stimulated acid secretion was observed after discontinuation of omeprazole treatment.[151]

A double-blind comparative trial in 22 healthy patients by Prewett et al., (1991) assessed the effects of ranitidine (300 mg nightly) and omeprazole (40 mg every morning) on nocturnal intragastric acidity. Assessments were performed prior to and after 25 days of therapy with trial drug and at 3, 6, 9, 12, 15, 18, and 21 days after discontinuation of treatment. There was a significant increase in nocturnal acid secretion with ranitidine at 3 days and 6 days following discontinuation of treatment ($p = 0.01$ and $p = 0.05$, respectively). No rebound hypersecretion was observed following discontinuation of omeprazole treatment.[152]

Bell et al., (1993) gave 30 healthy patients with evidence of gastric acid hypersecretion either omeprazole 20 mg daily, ranitidine 150 mg twice daily or placebo for 4 weeks in a double blind parallel group design trial. Acid rebound was seen on the second day after stopping ranitidine. Pretreatment levels were seen at day 7 after treatment. No rebound was seen at day 1, 7 and 28 after stopping omeprazole.[153]

In an open-label comparative trial by Orr et al., (1992), 17 patients with heartburn were treated for 1 week with either omeprazole 20 mg daily ($n = 8$) or ranitidine 300 mg tid ($n = 9$). Twenty-four hour esophageal pH monitoring was performed at baseline and at 1 day (ranitidine) or 3 days (omeprazole) after stopping treatment. There was no evidence of increased esophageal acid reflux after withdrawal of either trial treatment.[154]

A trial performed by Waldum and colleagues (1996) investigated basal and pentagastrin-stimulated acid secretion before and 14 days after a 90-day treatment period with omeprazole 40 mg daily in 9 patients with reflux esophagitis. Basal and meal-stimulated gastrin release was also evaluated before and during treatment and 90 days after discontinuation of treatment. Histamine and chromogranin A levels in gastric corpus mucosa were determined from biopsy samples prior to and at the end of treatment. The investigator concluded that there was an increase in basal and pentagastrin-stimulated acid secretion 14 days after discontinuation of omeprazole treatment; however, there were no further follow-up data that evaluated the duration of this effect. Upon investigation of the data presented in the manuscript, one sees an increase in basal output ($\geq$ 2 mmol/hr) in only 3 of the 8 patients with data, whereas acid output was virtually unchanged (< 1 mmol/hr change) or decreased in 5 patients. Two of the 8 patients had marked increases in basal output of between approximately 6 and 12 mmol/hr. Pentagastrin-stimulated acid secretion increased in 6 patients (approximately 15-25 mmol/hr) and remained unchanged in 2 patients. During treatment, increases in basal and meal-stimulated gastrin release, serum chromogranin A concentrations, and histamine and chromogranin A concentrations in gastric corpus mucosa were observed. These observations probably reflect an increase in size and number of ECL cells, which is consistent with effects with antisecretory treatment seen by Lamberts (1993). The observed increase in serum chromogranin A probably also reflects increased ECL activity, although there was no significant increase in plasma histamine concentration.[155]

A trial by Gillen et al., (1998) evaluated the possible correlation between acid rebound following withdrawal of omeprazole therapy and intragastric pH and plasma gastrin levels achieved during therapy. Nineteen healthy patients (*H pylori*-negative and asymptomatic) were administered omeprazole 40 mg daily for 8 weeks The maximal acid output was measured at 6 and 16 days

post treatment and was significantly increased compared with baseline at these time points ($p < 0.01$ and $p < 0.003$, respectively). This increase in acid output after stopping therapy was positively correlated with intragastric pH and with gastrin levels during omeprazole treatment, effects that the authors believe are consistent with trophic effects on parietal cells. Further follow-up data were not provided to document the duration of increased acid.[156]

A double-blind, randomized trial was recently performed by Fisher and colleagues (1998) in which 30 healthy patients received treatment with omeprazole 20 mg once daily, ranitidine 150 mg bid, or cisapride 10 mg qid for 12 weeks. Basal and pentagastrin-stimulated acid secretion and serum gastrin levels were measured at the end of treatment (baseline), and at 3 days and 1, 2, and 4 weeks post-treatment. Increases in basal acid secretion were observed 3 days post-treatment with both ranitidine and omeprazole. Acid secretion returned to baseline levels by 1-week post-treatment.[157]

11.3.2 Long-Term Omeprazole Treatment

One trial evaluated the potential for acid rebound following discontinuation of long-term treatment with omeprazole. In a trial by Weinstein and colleagues (1996), 40 patients with Barrett's esophagus received long-term treatment with high-dose ranitidine (n = 7), high-dose omeprazole for ≤ 12 months (n = 10), or high-dose omeprazole for ≥ 24 months (n = 23). Upon withdrawal of treatment, there was a significant increase in pentagastrin-stimulated acid secretion in patients treated with omeprazole. This gastric acid hypersecretion had returned to normal 3 months later, although the exact time that this occurred is unknown since there were no measurements obtained at interim timepoints. These data do demonstrate, however, that the acid rebound seen following discontinuation of long-term omeprazole was reversible and short-lived.[158]

TABLE 11.1
REBOUND — STUDIES WITH OMEPRAZOLE
(PAGE 1 OF 2)

REFERENCE	PATIENTS	TREATMENT, DAILY DOSE(S), DURATION	INTRAGASTRIC ACID MEASUREMENTS	BASELINE ACID SECRETION	TIME TO FOLLOW-UP MEASUREMENT AFTER TREATMENT DISCONTINUATION	POST-TREATMENT ACID SECRETION
Lind et al.[149]	6 healthy patients	O 20, 40, 60, 80 mg (single dose)	P-stimulated acid secretion	Approx. 9 mmol/ 15 min	1, 3, 4, 14 days	No rebound hypersecretion
Sharma et al.[150]	9 patients with duodenal ulcer	O 30-60 mg x 2 wks	24-hour acidity	Mean 24-hr acidity, 38.7 mmol/L	1 week, 8 wks	No rebound hypersecretion
Müller et al.[151]	8 healthy patients	O 30 mg x 28d	Basal and P-stimulated acid output	Basal: mean, approx. 3 mmol/h; P-stimulated: mean, 27 mmol/h	1, 3, 5, 7, 11 days	No rebound hypersecretion
Prewett et al.[152]	22 healthy patients	O 40 mg x 25 d R 300 mg x 25 d	Nocturnal intragastric acidity	Median, 627 mmol-h/L	3, 6, 9, 12, 15, 18, 21 days	No rebound hypersecretion with O; rebound hypersecretion at 3, 6 days with R
Bell et al.[153]	30 healthy patients with gastric acid hypersecretion	O 20 mg x 4 wk R 300 mg x 4 wk Placebo x 4 wk	24-hour acidity and plasma gastrin	Peak acid output > 26 mmol/hr	1, 7, 28 days	No rebound hypersecretion with O at days 1, 7, 28; rebound hypersecretion on day 1 with R

P: PENTAGASTRIN, O: OMEPRAZOLE, R: RANITIDINE, CSP: CISAPRIDE, NR: NOT REPORTED

TABLE 11.1 (Cont.)
Rebound — Studies with Omeprazole
(Page 2 OF 2)

REFERENCE	PATIENTS	TREATMENT, DAILY DOSE(S), DURATION	INTRAGASTRIC ACID MEASUREMENTS	BASELINE ACID SECRETION	TIME TO FOLLOW-UP MEASUREMENT AFTER TREATMENT DISCONTINUATION	POST-TREATMENT ACID SECRETION
Orr et al.[154]	17 patients with heartburn	O 20 mg x 1 wk R 900 mg x 1 wk	24-hour esophageal pH monitoring	NR	1 or 3 days	No rebound hypersecretion
Waldum et al.[155]	9 patients with reflux esophagitis	O 40 mg x 90 d	Basal and P-stimulated acid output	Basal: range, approx. 1-8 mmol/h P-stimulated: range, approx. 20-45 mmol/h	14 days	Rebound basal and stimulated hypersecretion
Gillen et al.[156]	19 healthy patients	O 40 mg x 8 wks	Gastrin-17-stimulated acid output	Median, 34.2 and 36.0 mmol/h	6 days 16 days	Significantly increased acid output 6 and 16 days post-treatment
Fisher et al.[157]	30 healthy patients	O 20 mg x 12 wks R 300 mg x 12 wks Csp 40 mg x 12 wks	Basal and P-stimulated acid output	NR	3 days and 1, 2, and 4 wks	Rebound hypersecretion with O and R 3 days post-treatment
Weinstein et al.[158]	40 patients with Barrett's esophagus	O H-D ≤ 12 mos O H-D ≥ 24 mos R H-D ≥ 24 mos	P-stimulated acid output	NR	3 months	Rebound hypersecretion with O immediately but not 3 mos post-treatment

P: PENTAGASTRIN, O: OMEPRAZOLE, R: RANITIDINE, CSP: CISAPRIDE, NR: NOT REPORTED, H-D: HIGH-DOSE

11.4 Rebound Acid Hypersecretion: Clinical Studies with Other Antisecretory Agents

Nine studies with cimetidine, ranitidine, nizatidine, and famotidine were identified from a literature search on acid rebound with H_2-receptor antagonists (4 with ranitidine were previously cited in Table 11.1 and are included here for completeness). Rebound hypersecretion was demonstrated with each of these agents following discontinuation of therapy. Details of these studies are summarized in Table 11.2.

11.5 *Helicobacter pylori* and Rebound Acid Hypersecretion

The effect of *Helicobacter pylori* (*H pylori*) on gastric acid secretion is variable and may be related to the extent of gastritis present in association with *H pylori* infection. *H pylori*-positive patients with duodenal ulcer have higher basal acid output and maximal acid output than *H pylori*-infected control patients, possibly due to the reduced sensitivity of *H pylori*-infected control patients to gastrin.[159] However, eradicating *H pylori* in patients with duodenal ulcer and high gastric acid secretion may not return acid secretion to normal levels.[160] In *H pylori*-infected controls, an increase in gastric acid secretion can be seen 6 months after eradication and is probably a result of the lack of neutralizing NH_3 produced by the bacteria.[161] The elevated serum gastrin seen with *H pylori* infection may be explained in part by a reduction of somatostatin secretion (and loss of negative feedback inhibition of gastrin) as a result of *H pylori* related antral gastritis.[162]

Gillen et al., suggest that *H pylori* status may influence the development of acid rebound following omeprazole therapy.[147] The authors measured gastric acid secretion 2 weeks after withdrawal of an 8 week course of omeprazole 40 mg daily in 12 healthy *H pylori* negative and 9 *H pylori* positive patients. Gastric acid secretion was elevated in the 12 *H pylori* negative patients but there was a heterogenous response in the 9 *H pylori* positive patients. Some of the *H pylori* patients did not increase their gastric acid.

In the trial by Waldum et al., (1996), 3 of the 9 patients with reflux esophagitis treated with omeprazole were *H pylori*-positive, only 2 of who had post-treatment gastric acid measurements. In one patient, basal and pentagastrin-stimulated gastric acid increased 14 days after discontinuation of omeprazole treatment, while in the other patient, acid secretion was unaffected.[155] In the trial by El-Omar et al., (1996), both *H pylori*-positive and -negative patients had evidence of increased gastric acid 2 days following a 60-day treatment course with ranitidine. Gastric acid secretion returned to normal in both patient groups after 10 days.[163]

H pylori status however may be of little clinical relevance with regard to GERD. Both *H pylori* negative and positive patients with severe GERD have similar recurrence rates and development of esophagitis after stopping omeprazole maintenance therapy.[164]

TABLE 11.2
REBOUND — STUDIES WITH OTHER ANTISECRETORY AGENTS
(Page 1 of 2)

REFERENCE	PATIENTS	TREATMENT, DAILY DOSE(S), DURATION	INTRAGASTRIC ACID MEASUREMENTS	BASELINE ACID SECRETION	TIME TO FOLLOW-UP MEASUREMENT AFTER TREATMENT DISCONTINUATION	POST-TREATMENT ACID SECRETION
CIMETIDINE						
Brown et al.[165]	9 patients with duodenal ulcer	C 1000 mg x 28 days T 800 mg x 28 days	Basal and P-stimulated acid output	Mean basal, 2.06 and 3.69 mEq/hr Mean P-stimulated, 14.55 and 18.60 mEq/hr	2-3 days	Rebound hypersecretion with C
Nwokolo et al.[166]	24 healthy patients	C 800 mg x 35 days F 40 mg x 35 days N 300 mg x 35 days	24-hr and nocturnal intragastric acidity	NR	1 day	Rebound hypersecretion with C, F, N
RANITIDINE						
El-Omar et al.[163]	18 healthy patients (9 *H pylori*-positive, 9 *H pylori*-negative)	R 300 mg x 60 days	Basal and gastrin-releasing peptide-stimulated acid output	Median basal GPP, 3.3 mmol/h Median stimulated, 10.0 mmol/h	2, 10 days	Rebound hypersecretion at 2 days, resolved by 10 days
Prewett et al.[152]	22 healthy patients	O 40 mg x 25 d R 300 mg x 25 d	Nocturnal intragastric acidity	Median, 627 mmol-h/L	3, 6, 9, 12, 15, 18, 21 days	No rebound hypersecretion with O; rebound hypersecretion at 3, 6 days with R
Orr et al.[154]	17 patients with heartburn	O 20 mg x 1 wk R 900 mg x 1 wk	24-hour esophageal pH monitoring	NR	1 or 3 days	No rebound hypersecretion

O: OMEPRAZOLE, C: CIMETIDINE, R: RANITIDINE, T: TRITHIOZINE, N: NIZATIDINE, F: FAMOTIDINE, P: PENTAGASTRIN, CSP: CISAPRIDE. H-D: HIGH-DOSE, NR: NOT REPORTED

TABLE 11.2 (Cont.)
REBOUND — STUDIES WITH OTHER ANTISECRETORY AGENTS
(Page 2 of 2)

REFERENCE	PATIENTS	TREATMENT, DAILY DOSE(S), DURATION	INTRAGASTRIC ACID MEASUREMENTS	BASELINE ACID SECRETION	TIME TO FOLLOW-UP MEASUREMENT AFTER TREATMENT DISCONTINUATION	POST-TREATMENT ACID SECRETION
RANITIDINE						
Fisher et al.[157]	30 healthy patients	O 20 mg x 12 wks R 300 mg x 12 wks Csp 40 mg x 12 wks	Basal and P-stimulated acid output	NR	3 days and 1, 2, and 4 wks	Rebound hypersecretion with O and R 3 days post-treatment
Weinstein et al.[158]	40 patients with Barrett's esophagus	O H-D ≤ 12 mos O H-D ≥ 24 mos R H-D ≥ 24 mos	P-stimulated acid output	NR	3 months	Rebound hypersecretion with O immediately but not 3 mos post-treatment
NIZATIDINE						
Fullarton et al.[167]	8 patients with duodenal ulcer	N 300 mg x 4 wks	Daytime intragastric pH, nocturnal acid output	Median daytime intragastric pH, 1.8 Median nocturnal acid output, 39.4 mmol/h	2 days	Rebound nocturnal hypersecretion
Savarino et al.[168]	17 patients with duodenal ulcer	N 300 mg x 4 wks	24-hr gastric pH	Mean pH approx. 1.7	3 days	No rebound hypersecretion
See Nwokolo et al.[166]						
FAMOTIDINE						
See Nwokolo et al.[166]						

O: OMEPRAZOLE, C: CIMETIDINE, R: RANITIDINE, T: TRITHIOZINE, N: NIZATIDINE, F: FAMOTIDINE, P: PENTAGASTRIN, CSP: CISAPRIDE, H-D: HIGH-DOSE, NR: NOT REPORTED

11.6 AstraZeneca LP Worldwide Post-Marketing Database: Reports of Rebound

In a review of Safe-T-Net, the AstraZeneca LP worldwide post-marketing database, there were 6 physician reports of acid rebound occurring in patients treated with omeprazole. For each of the reports, the omeprazole dosages, durations of dosing, and time after discontinuation of omeprazole therapy at the time of the report are unknown, as are patient details such as demographic characteristics, medical history, concomitant medications, and concurrent illnesses. Thus, no conclusions can be drawn from these patient data regarding acid rebound following discontinuation of omeprazole therapy.

11.7 Summary

- Gastric acid secretion has been shown to return to pretreatment levels after withdrawal of omeprazole therapy, in most studies within 3-5 days following omeprazole dosing.

- Of the nine studies in which patients received short-term omeprazole treatment (≤ 3 months), six studies (Lind et al., 1983; Sharma et al., 1984; Prewett et al., 1991; Müller et al., 1984; Orr et al., 1992; Bell et al., 1993) documented no acid rebound following discontinuation of treatment,[149-154] while three studies (Fisher et al., 1998; Waldum et al., 1996; Gillen et al., 1998a) reported acid rebound.[155-157] In the two latter studies, increased acid secretion was present at 14-16 days post-treatment, but there were no further follow-up data evaluating when acid secretion returned to pretreatment levels. One of these studies showed return to pretreatment levels by 1 week post-treatment.[157]

- In a short-term study utilizing a positive control group (Fisher et al., 1998) in which acid rebound was observed following discontinuation of treatment with omeprazole, rebound hypersecretion was also observed following discontinuation of ranitidine treatment. Acid secretion returned to pretreatment levels within 1 week post-treatment with omeprazole and ranitidine.[157]

- Gastric acid rebound was demonstrated in one long-term trial (Weinstein et al., 1996) with omeprazole (12-24 months); however, the duration of this effect was not fully evaluated. Gastric acid levels had returned to normal when measured 3 months post-treatment.[158]

- Acid rebound has been established with each of the H_2-receptor antagonists, cimetidine, ranitidine, nizatidine, and famotidine, following discontinuation of short-term therapy.

- No conclusions can be drawn from the six reports of acid rebound in the AstraZeneca LP worldwide post-marketing database for omeprazole.

11.8 Conclusions

Although acid rebound has been clearly established with respect to the H_2-receptor antagonists, results from clinical studies are not consistent with respect to the development of acid rebound following discontinuation of omeprazole treatment. The studies showing evidence of acid rebound following withdrawal of omeprazole therapy have mainly included patients taking doses of 40 mg daily for at least 8 weeks of therapy. It appears likely therefore that dosage and duration of therapy may play a role in the development of acid rebound following withdrawal of antisecretory therapy.

Omeprazole intended for over the counter use is not indicated for long term use, and is limited to no more than 10 days of continuous treatment. Based on these data, gastric acid rebound is not a clinically significant concern with short-term omeprazole use.