3 Pathophysiology and Pharmacology

3.1 Pathophysiology of Heartburn

This section provides a brief overview of the current understanding of the pathophysiology of heartburn, including the inter-relationships between gastric acidity, esophageal acidity, and heartburn severity. This information, in conjunction with the clinical pharmacology of Ome, will be useful in understanding the clinical trial results from the OTC Ome-Mg program.

Heartburn is a symptom described as substernal discomfort that is frequently upward-moving and accompanied by a burning or painful feeling. The typical OTC heartburn consumer frequently attributes his/her heartburn to a variety of factors, generally in combination, but most commonly foods and beverages.[2] Regardless of its etiology, the common causative factor in development of heartburn symptoms is exposure of the esophagus to gastric acid. Agents that reduce the acidity of the refluxate are efficacious in reducing heartburn symptoms. This has been the cornerstone of heartburn treatment and prevention for the past many years of OTC antacids and H_2RA (Histamine-2 Receptor Antagonists) availability.

Episodes of heartburn generally self-resolve within 3–5 hours after onset, although symptoms return just as often within a few hours. A series of recently published abstracts illustrate the temporal and quantitative relationships between gastric acidity, esophageal acidity, and heartburn severity in a series of small studies that evaluated meal-induced heartburn in a typical OTC population.[17-19]

There is substantial variability in sensitivity to esophageal acid exposure among those subjects with meal-induced heartburn.[19] This variation in esophageal acid sensitivity suggests substantial variation in the extent to which heartburn is experienced and reported. In turn, the high degree of variability in time and sensitivity of heartburn development relative to esophageal acidity contributes to the high degree of variability seen in symptomatic relief trials.

3.2 Clinical Pharmacology of Omeprazole

Omeprazole (Ome) is a PPI that inhibits gastric acid secretion by irreversible specific inhibition of the H^+/K^+ ATPase enzyme at the secretory surface of the gastric parietal cell. Ome itself, as well as its circulating metabolites, is inactive with regard to suppression of gastric acid secretion. In order to exert an effect, Ome must enter the acidic compartment of the parietal cell.[20] In this very acidic environment, Ome (a weak base) is protonated and transformed to the active sulphenamide inhibitor. This protonation and conversion can only take place at a significant rate at pH<2. Only the acidic milieu of the parietal cell in the gastric mucosa meets this requirement; proton pumps in other locations (i.e., the colon and kidney) are not sufficiently acidic to promote protonation to the active form of the drug. This accounts for the very specific action of Ome.

Omeprazole is metabolized by two different cytochrome P450 (CYP) isoforms, CYP2C19 (responsible for about 80% of the total metabolism) and CYP3A4.[21,22] There is a small subset of

the population that lacks CYP2C19 (approximately 15% of Asians and 3% of Caucasians) and are known as "slow" metabolizers who still metabolize Ome but at a slower rate.[23] However, even at this slower rate, the plasma half life is <2 hours.

Omeprazole is completely absorbed after oral administration. Food, antacids, and H_2RAs have no clinically meaningful influence on the extent of Ome absorption.[21,24,25] Ome bioavailability after a 20 mg single dose is approximately 40%, indicating a significant first-pass effect. The bioavailability of Ome after repeated dosing is increased to about 60% at steady state due to the inhibition/saturation of its own metabolism.[26] Approximately 95% is bound to plasma protein. The plasma elimination half-life ($t_{½}$) of less than 1 hour shows a rapid elimination of the drug, and the absence of Ome in the urine or feces indicates complete metabolism.

Ome-Mg dissociates rapidly in water to form Ome and magnesium: a 10.3 mg dose of Ome-Mg is the same as a 10 mg dose of Ome and a 20.6 mg dose of Ome-Mg is the same as a 20 mg dose of Ome (Table 3.1). Ome-Mg tablets have a similar bioavailability profile to the commercially available Ome capsules during fasting conditions and can be administered irrespective of food intake.

TABLE 3.1
RATIOS OF GEOMETRIC MEANS AND 95% CONFIDENCE INTERVALS FOR AUC_0
SUBJECTS WITH COMPLETE PHARMACOKINETIC DATA (N=30)

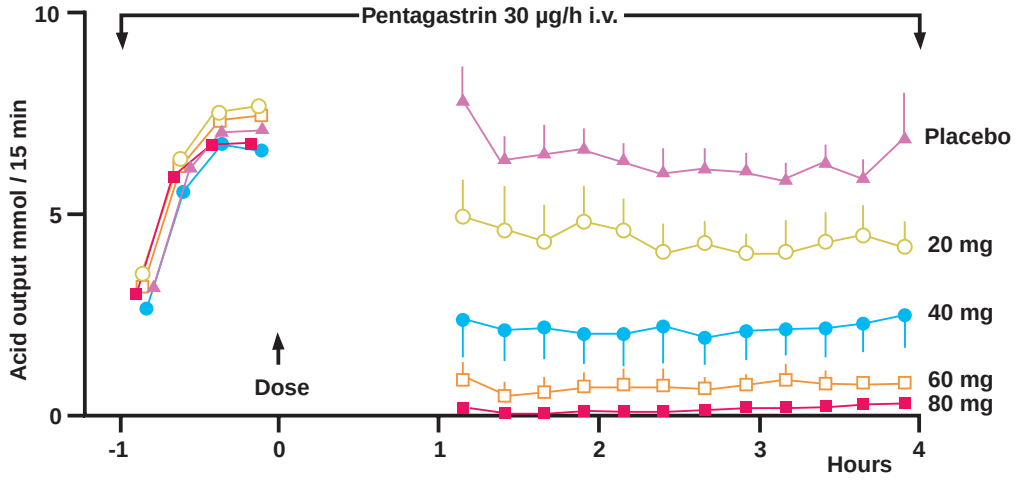
			95% CONFIDENCE LIMITS FOR RATIO		
TREATMENTS[a]		**RATIO OF GEOMETRIC MEANS**	**LOWER LIMIT**	**UPPER LIMIT**	**PAIRWISE COMPARISON *P*-VALUES**
Ome-Mg 2x10 to Ome 20	(X) (Y)	1.001	0.941	1.064	0.985
Ome-Mg 20 to Ome 20	(X) (Y)	1.042	0.980	1.108	0.188
Ome-Mg 2x10 to Ome-Mg 20	(X) (Y)	0.960	0.903	1.021	0.193

[a] For each pair of treatments, the ratios and confidence limits represent X/Y.

3.2.1 Inhibition of Gastric Acid Secretion

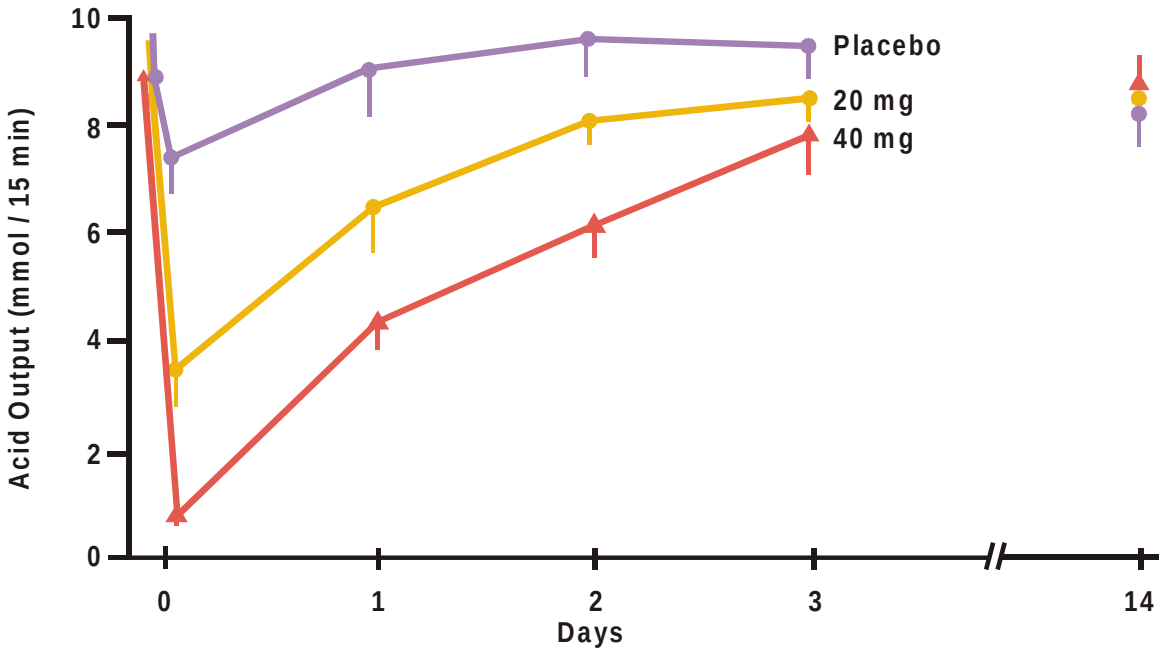
Following a single oral dose of 20 mg–80 mg Ome suspension in buffered sodium bicarbonate, pentagastrin-stimulated gastric acid secretion is rapidly and dose-dependently inhibited (Figure 3.1).[27] Ome begins to have an effect on gastric acid secretion as soon as 1 hour. Other studies have shown that Ome dose-dependently inhibits basal acid secretion, as well as acid secretion induced by other stimuli, such as histamine, modified sham-feeding, and peptone, with a similar efficiency.[28,29] This finding was expected, because Ome acts at the final step in the acid secretion process and therefore inhibits gastric acid secretion equally effectively and independent of stimulus.

FIGURE 3.1
EFFECT OF SINGLE ORAL DOSES OF OMEPRAZOLE SUSPENSION ON PENTAGASTRIN STIMULATED GASTRIC ACID SECRETION IN HEALTHY SUBJECTS (N=6)



Both 20 mg and 40 mg single doses of Ome produced a marked inhibition of gastric acid secretion 2 hours after dosing, and the degree of acid inhibition then gradually decreased over the next 3 days (Figure 3.2).[27] With the 20 mg dose, inhibition was not significantly different from placebo by Days 3 and 4. A 40 mg dose of Ome displayed a small but statistically significant inhibition of acid secretion at Day 3, but by Day 14 returned to baseline levels. The inhibitory effect of Ome lasts longer than circulating plasma levels. The return of acid output to baseline level is linear in contrast to the exponential elimination of drug from plasma.

FIGURE 3.2
DURATION OF ACTION OF TWO DIFFERENT SINGLE ORAL DOSES OF OMEPRAZOLE SUSPENSION ESTIMATED BY REPEATED MEASUREMENTS OF PENTAGASTRIN STIMULATED GASTRIC ACID SECRETION IN HEALTHY SUBJECTS (N=6)



The effect of repeated daily doses of Ome on gastric acid secretion has been studied in both healthy subjects and duodenal ulcer patients in order to find a clinically relevant dose.[30,31] Each dose of Ome (5 mg, 10 mg, 20 mg, 30 mg, or 40 mg) was given to the patients in a randomized order for 5–7 days, to stabilize the inhibitory effect of each dose. In two studies, pentagastrin-stimulated gastric acid secretion was measured 6 hours and 24 hours after the last dose (Figures 3.3 and 3.4).[30,31]

FIGURE 3.3
INDIVIDUAL VALUES FOR PERCENTAGE REDUCTION OF PENTAGASTRIN STIMULATED GASTRIC ACID SECRETION MEASURED BOTH 6 AND 24 HOURS AFTER THE 5TH DOSE OF OMEPRAZOLE IN HEALTHY SUBJECTS (N=8)

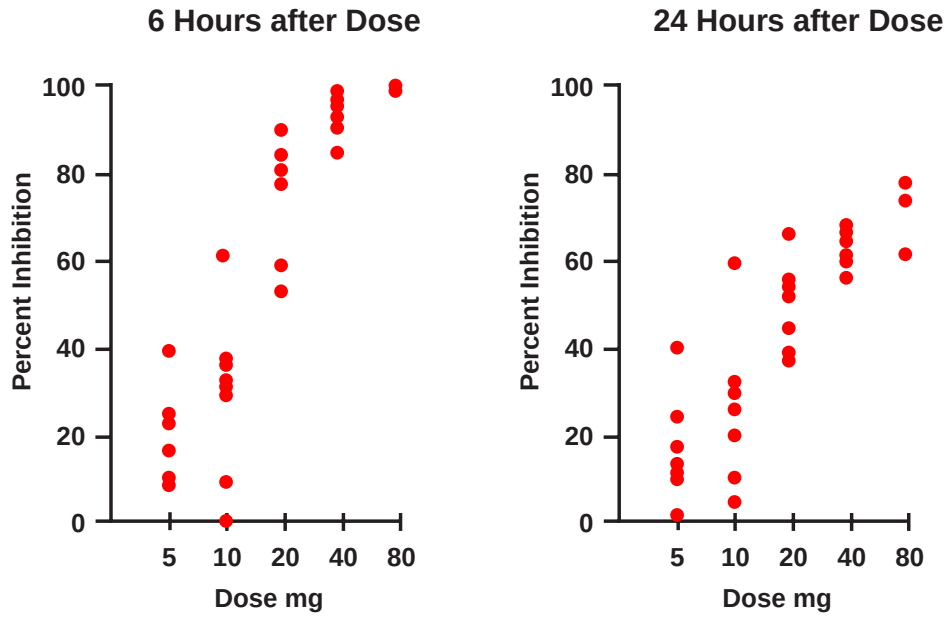
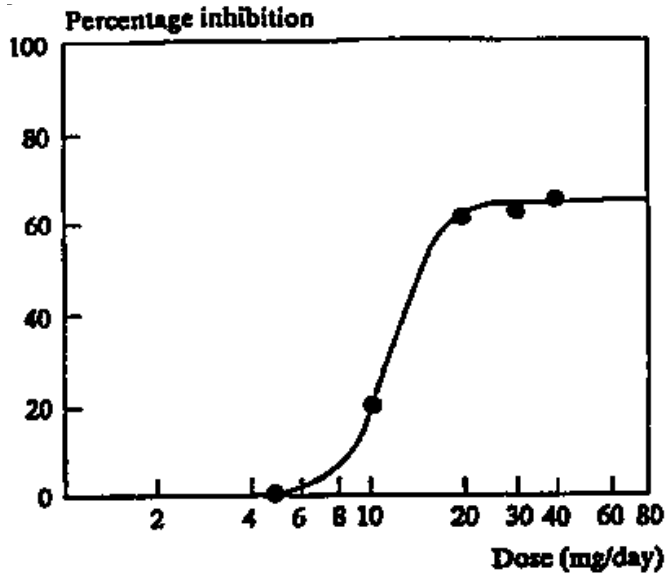


FIGURE 3.4
DOSE RESPONSE CURVE FOR REPEATED ONCE DAILY DOSES OF OMEPRAZOLE.



Each Point Represents Reduction in Mean Peak Acid Output in Healthy Subjects (n=6).
The Curve is Obtained by Using an Extended Least Squares Non Linear Regression Analysis

It was observed that once daily treatment with 5 mg Ome for 5 days produced a minimal effect, while a 10 mg dose of Ome did not produce a consistent inhibition of gastric acid secretion in all patients. The variation in effect for the 10 mg Ome was substantial, ranging from 0% to 40% inhibition at 24 hours after the last dose. With five daily doses of 20 mg and 40 mg, there was a reduction of pentagastrin-stimulated acid secretion of approximately 36% to 67%, 24 hours after the last dose (Figure 3.3). A daily dose of 20 mg to 40 mg Ome produces a marked and more consistent inhibition than the lower doses, but not a complete blockade of gastric acid secretion over the 24-hour dosing interval. On the basis of these results, 5 mg was not considered any further as a possible dose for OTC use.