

## Histamine<sub>2</sub>-receptor antagonists: Rapid development of tachyphylaxis with repeat dosing

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### Abstract

Histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) are available over-the-counter (OTC) for the treatment and prevention of heartburn, but more than occasional, single-dose use can lead to rapid development of tachyphylaxis. The aim of this review is to assess the published evidence regarding the development of tachyphylaxis with repeat usage of H<sub>2</sub>RAs. PubMed and SCOPUS were searched across all years to identify clinical studies that examined the development of tachyphylaxis with repeated dosing of H<sub>2</sub>RAs. Although a single (first) dose of an H<sub>2</sub>RA can be effective for controlling gastric acid and preventing or relieving food-related heartburn, numerous studies confirm that tachyphylaxis, also known as tolerance, is consistently detected at the first time point assessed after the first dose, including the second day and/or second dose. Even if symptom relief is achieved with an H<sub>2</sub>RA, it may be due to desensitization of the esophagus to acid exposure, potentially providing symptom relief without significantly decreasing esophageal acid exposure. When recommending OTC drugs for treatment of frequent heartburn, clinicians should be aware of the potential for rapid development of

tachyphylaxis in patients who use H<sub>2</sub>RAs for 2 or more consecutive days. Even if symptom relief is achieved, it may be due to desensitization of the esophagus to acid by the H<sub>2</sub>RA, potentially providing symptom relief without significantly decreasing esophageal acid exposure. Other strategies, such as an OTC proton pump inhibitor, may be needed to optimize management of frequent heartburn.

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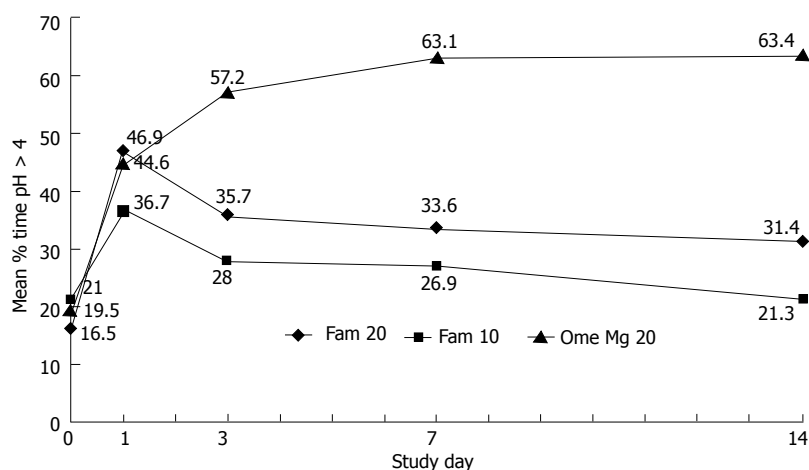
**Key words:** Histamine<sub>2</sub>-receptor antagonist; Tachyphylaxis; Tolerance; Gastric pH

**Core tip:** Histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) are available over-the-counter (OTC) for the treatment and prevention of heartburn, but recommendations for use should be limited to those with infrequent heartburn. A single dose of an H<sub>2</sub>RA can be effective for controlling gastric acid and preventing or relieving heartburn, but tolerance (tachyphylaxis) develops rapidly, and is evident by the second day/second dose. Even if symptom relief is achieved, it may be due to desensitization of the esophagus to acid by the H<sub>2</sub>RA, potentially providing symptom relief without significantly decreasing esophageal acid exposure. For frequent heartburn ( $\geq 2$  d/wk), an OTC proton pump inhibitor should be considered.

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### INTRODUCTION

Heartburn is a common complaint<sup>[1-4]</sup>. In a recent review



**Figure 1 Famotidine vs omeprazole for 14-d gastric acid control.** Mean percentage of time gastric pH > 4 across 14 d of dosing in subjects with frequent heartburn<sup>[14]</sup>. Famotidine (Fam) 10 mg or 20 mg was dosed twice a day. Omeprazole (Ome Mg 20) was dosed once a day (omeprazole-magnesium 20.6 mg). Gastric pH was assessed for 24-h on day 0 (baseline) and dosing days 1, 3, 7 and 14. Both famotidine doses showed a rapid decline in gastric acid control by dosing day 3, followed by a more gradual decline across 14-d of dosing. Omeprazole showed similar gastric acid control to famotidine 20 mg on dosing day 1, with an increase in gastric acid control over the first several days, followed by a sustained effect across 14-d of dosing (reprinted with permission<sup>[14]</sup>).

of 29 published studies, the range of prevalence for experiencing heartburn at least once per week was estimated at 18%-28% in North America, 9%-26% in Europe, 3%-8% in East Asia, 9%-33% in the Middle East, 12% in Australia and 23% in South America<sup>[5]</sup>. More than 50 million Americans experience frequent heartburn, defined as occurring at least 2 d a week<sup>[2]</sup>. The majority of adults with frequent heartburn have consulted a healthcare provider<sup>[6]</sup>, but they primarily rely on over-the-counter (OTC) heartburn remedies to manage their symptoms. Therefore, it is important that healthcare providers understand the benefits and limitations of different heartburn remedies.

The mainstay of pharmacologic therapy for frequent heartburn is acid suppressive therapy<sup>[7]</sup>. All OTC heartburn therapies may provide a benefit when taken as directed, but there are important differences among the available therapies. Antacids act to rapidly but transiently neutralize acid that has refluxed into the esophagus<sup>[8]</sup>. Histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) slow gastric acid production by competitively and reversibly binding to one of the pathways for stimulation of acid production, the H<sub>2</sub> receptors on parietal cells<sup>[9,10]</sup>. H<sub>2</sub>RAs act relatively quickly, with gastric pH rising within 30 min of a single dose, and have a longer duration of action (up to 10 h) than antacids<sup>[9,11]</sup>. Proton pump inhibitors (PPIs) suppress acid production by binding to and inhibiting the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme system ("proton pump", the final step in acid production) at the secretory surface of the gastric parietal cell<sup>[11,12]</sup>. PPIs inhibit gastric acid secretion by all known stimuli and are more potent anti-secretory agents than H<sub>2</sub>RAs<sup>[11-14]</sup>. Proton pump inhibitors have a slower onset of action (1-2 h), but exhibit comparable 24-h acid control to H<sub>2</sub>RAs on dosing day 1, and reach peak effect after several days, providing sustained acid suppression throughout the 14 d course of therapy (Figure 1)<sup>[14-16]</sup>.

Owing to their pharmacodynamic profiles, both antacids and OTC H<sub>2</sub>RAs are indicated for on-demand therapy when relief of an existing episode of heartburn is desired<sup>[8-10,17]</sup>. An OTC H<sub>2</sub>RA can also be useful for preventing symptoms that are associated with eating food or drinking beverages that cause heartburn<sup>[9,10]</sup>. Both ant-

acids and H<sub>2</sub>RAs are indicated for a maximum of 14 d of therapy, after which consumers with persisting symptoms should seek advice from a physician<sup>[9,10,17]</sup>. In contrast, the OTC PPIs are indicated to treat frequent heartburn (occurring 2 or more days weekly), and are indicated for once daily use every day for 14 d, with a repeat 14-d course every 4 mo<sup>[12,13]</sup>. As with antacid and OTC H<sub>2</sub>RAs, consumers with symptoms persisting beyond 14 d are encouraged to consult a physician. Any patient presenting with "alarm" symptoms (*e.g.*, dysphagia, odynophagia, bleeding, weight loss, anemia)<sup>[6]</sup> may have a more serious condition and should be referred to a physician for further evaluation. With the availability of OTC acid-suppressive therapies, it is important for health professionals to appreciate the strengths and weaknesses of these agents in order to help guide effective consumer-directed management of heartburn.

## RESEARCH

We conducted a comprehensive search of PubMed and SCOPUS scientific databases across all years to identify clinical studies that examined the development of tachyphylaxis with repeated dosing of H<sub>2</sub>RAs. The terms "histamine receptor antagonist", "H<sub>2</sub>RA", "tachyphylaxis", "tolerance", "intra-gastric pH", "gastric acid" and "heartburn" were used to identify clinical studies. Additionally, the reference section of each identified publication was explored for publications not identified in the PubMed and SCOPUS searches. Published clinical studies that assessed intra-gastric pH and/or gastric acid production following multiple days of dosing of an H<sub>2</sub>RA were included, and data regarding H<sub>2</sub>RA dose, timing of dosing, sample size, gastric acid production and/or intra-gastric pH were extracted and examined.

## RESULTS

Fifteen publications, reporting a total of 18 clinical studies, were identified for this review, and the details of these studies are summarized in Table 1. With repeated doses of an H<sub>2</sub>RA, tachyphylaxis was consistently observed by the first time period tested after the initial dose, includ-

**Table 1** Intra-gastric pH studies demonstrating histamine<sub>2</sub>-receptor antagonists<sup>1</sup> tachyphylaxis

Ref.	Design	Treatment regimen	Dosing duration	n	Days pH recorded	Tachyphylaxis observed
Wilder-Smith <i>et al</i> <sup>[38]</sup> , 1990	OL	Famotidine 40 mg QD	28 d	14	1, 14, 28	Day 14
	R, PC, DB, crossover	Ranitidine 300 mg QID	7 d	10	1, 7, 28	Day 7
		Ranitidine 300 mg QHS	21 d			
	R, PC, DB, crossover	Ranitidine 300 mg TID	14 d	14	1, 14	Day 14
Ranitidine 300 mg QHS					Day 14	
Smith <i>et al</i> <sup>[39]</sup> , 1990	R, PC, crossover	Famotidine 40 mg QD	28 d	13	0, 1, 14, 28	Day 14
	R, PC, crossover	Ranitidine 300 mg QID	7 d	13	1, 8	Day 8
		Ranitidine 300 mg QHS	21 d			Day 8
Nwokolo <i>et al</i> <sup>[24]</sup> , 1990	R, OL	Cimetidine 800 mg QD	29 d	48	0, 1, 15, 29	Day 15
		Nizatidine 300 mg QD				Day 15
		Famotidine 40 mg QD				Day 15
		Ranitidine 150 mg BID				Day 15
		Ranitidine 150 mg QD				Day 15
		Ranitidine 300 mg QD				Day 15
Nwokolo <i>et al</i> <sup>[40]</sup> , 1991	R, DB, PC	Ranitidine 150 mg QHS	5 mo	17	1, 29, 57, 85, 113, 141	Day 29
		Ranitidine 150 mg prn				Day 29
Wilder-Smith <i>et al</i> <sup>[23]</sup> , 1992	R, PC, blinded, crossover	Ranitidine IV 0.25 mg/kg per hour	6 d	10	1, 6	Day 6
		Ranitidine IV by pH-feedback, up to 800 mg/24 h				Day 6
		Ranitidine 300 mg PO QID				Day 6
Merki <i>et al</i> <sup>[31]</sup> , 1993	R, PC, crossover	Ranitidine IV ≤ 600 mg/24 h, pre/post 300 mg QD for 9 d	9 d	11	1, 9	Day 9
Merki <i>et al</i> <sup>[30]</sup> , 1994	R, DB, crossover	Ranitidine IV, ≤ 576 mg/24 h	3 d	12	1, 3	Day 3
		Omeprazole IV, ≤ 288 mg/24 h				Not observed
Hurlimann <i>et al</i> <sup>[22]</sup> , 1994	R, DB, parallel	Ranitidine 150 mg QID	14 d	28	1, 2, 7, 14	Day 2
		Omeprazole 40 mg QD				Not observed
Lachman <i>et al</i> <sup>[41]</sup> , 2000	OL	Ranitidine 150 mg QID	5 d	28	1, 5	Day 5
Komazawa <i>et al</i> <sup>[20]</sup> , 2003	R, crossover	Ranitidine 150 mg BID	14 d	7	1, 14	Day 14
		Famotidine 150 mg BID				Day 14
Hsu <i>et al</i> <sup>[15]</sup> , 2004	R, OL	Cimetidine IV 1200 mg/24 h	5 d	80	1, 2, 3, 4, 5	Day 2
		Ranitidine IV 200 mg/24 h				Day 2
		Omeprazole IV 40 mg BID				Not observed
Miner <i>et al</i> <sup>[14]</sup> , 2006	R, PC, crossover	Famotidine 10 mg BID	14 d	31	1, 3, 7, 14	Day 3
		Famotidine 20 mg QD				Day 3
		Omeprazole 20 mg QD				Not observed
Shimatani <i>et al</i> <sup>[25]</sup> , 2007	R, OL, crossover	Famotidine 20 mg BID	15 d	8	1, 8, 15	Day 8
		Omeprazole 10 mg QD				Not observed
		Famotidine 10 mg				Day 8
Fändriks <i>et al</i> <sup>[16]</sup> , 2007	R, crossover	Omeprazole 20 mg	8 d	8	1, 8	Day 8
		Famotidine 10 mg				Not observed
Ono <i>et al</i> <sup>[15]</sup> , 2008	R, crossover	Ranitidine 150 mg BID	10 d	7	-1, 1-7, 11-12	Day 2
		Rabeprazole 20 mg QD			(no dose 8-10)	Not observed

<sup>1</sup>Includes only histamine<sub>2</sub>-receptor antagonists marketed in the United States. All doses were administered orally unless specified otherwise. BID: Twice daily; HS: Bedtime; IV: Intravenous; OL: Open-label; PC: Placebo-controlled; PRN: As needed; QD: Daily; QID: Four times daily; QHS: Every bedtime; R: Randomized.

ing the second day/second dose<sup>[14-16,18-32]</sup>. This effect was reported over a wide range of doses of H<sub>2</sub>RAs, including both prescription and OTC doses, and occurred regardless of route of administration (oral and IV). This phenomenon has been observed under both fasting and fed conditions, and in various populations, including healthy subjects, patients with gastro-esophageal reflux disease, and post-surgical patients. While the mechanism for H<sub>2</sub>RA tachyphylaxis remains speculative, it may involve the up-regulation of parietal cell receptors for other mediators of acid secretion (*i.e.*, acetylcholine, gastrin), the sensitization of H<sub>2</sub> receptors, the impairment of inhibitory neurohormonal control of acid secretion, and/or an alteration in receptor turnover after chronic competitive inhibition<sup>[19-21]</sup>.

In a study assessing the gastric acid control of OTC doses of an H<sub>2</sub>RA, 31 healthy adults with frequent heartburn (occurring ≥ 2 d/wk) underwent 24-h gastric pH monitoring over a 14-d period while taking famotidine 10 mg twice daily, famotidine 20 mg twice daily, or omeprazole 20 mg once daily, in a double-blind, 3-period crossover fashion<sup>[14]</sup>. As depicted in Figure 1, the mean percentage of time gastric pH > 4 was at its highest level on dosing day 1 for both doses of famotidine, then decreased on subsequent days of continued dosing, consistent with H<sub>2</sub>RA tachyphylaxis reported previously with prescription doses<sup>[20,22-24]</sup>. A similar loss of H<sub>2</sub>RA antisecretory effect has been reported in other studies examining OTC doses of famotidine (versus omeprazole; Table 1)<sup>[16,25]</sup>. In contrast to H<sub>2</sub>RAs, PPIs do not exhibit

tachyphylaxis, but rather show similar efficacy to H<sub>2</sub>RAs on dosing day 1, then increase in effectiveness over several days before reaching a sustained plateau effect for the duration of dosing (Figure 1)<sup>[14-16,18,22,25-29]</sup>.

Tachyphylaxis to H<sub>2</sub>RAs does not appear to be progressive, as studies have typically demonstrated no further reduction in antisecretory effect after the initial loss of potency is detected<sup>[21-23]</sup>. In one of the longest studies assessing H<sub>2</sub>RA tolerance, Nwokolo *et al.*<sup>[24]</sup> demonstrated no further reduction in acid inhibitory efficacy from 1 to 5 mo of dosing in 17 healthy patients taking ranitidine 150 mg nightly. However, once tachyphylaxis to an H<sub>2</sub>RA has developed, increasing the dose does not appear to be effective in overcoming the loss of anti-secretory effect<sup>[29,30]</sup>. Merki *et al.*<sup>[31]</sup> found that the tolerance observed with ranitidine infusion could not be overcome by individual pH-regulated titrated doses of ranitidine of more than 500 mg/24 h, even after three days of treatment.

The physiologic effect of tachyphylaxis has been found to persist for 3 d after H<sub>2</sub>RA dosing is discontinued. In one study, ranitidine was dosed twice daily for 7 d, dosing was stopped for 3 d, and then dosing was resumed for 3 d<sup>[15]</sup>. Tachyphylaxis was evident by day 2 of dosing in the first period, and the physiological effects of tachyphylaxis were still evident (decreased response to the H<sub>2</sub>RA) when dosing was re-initiated after the 3-d hiatus<sup>[15]</sup>. This study showed that it took longer than 3 d to recover the beneficial effects of an H<sub>2</sub>RA once tachyphylaxis had occurred, supporting that only occasional, isolated doses of an H<sub>2</sub>RA provide the maximum benefit of the drug.

## CLINICAL IMPLICATIONS OF H<sub>2</sub>RA TACHYPHYLAXIS

Although prospective data evaluating the clinical relevance of H<sub>2</sub>RA tachyphylaxis for patients with frequent heartburn are limited, decreasing gastric acid production is the accepted mechanism of action for H<sub>2</sub>RAs, studies have demonstrated a link between gastric acid suppression and heartburn relief<sup>[32,33]</sup>, and the percentage of time that the gastric pH is > 4.0 over a 24-h period is frequently used as a surrogate marker for the clinical efficacy of acid suppressive therapies<sup>[14,34,35]</sup>. If tachyphylaxis is a class effect for H<sub>2</sub>RAs that significantly decreases acid control starting the second day/second dose, why do some frequent heartburn sufferers appear to achieve symptom control with daily dosing? A 2004 study sought to determine if daily doses of ranitidine decreased esophageal sensitivity to chemical and/or mechanical stimulation<sup>[36]</sup>. Eighteen patients who experienced functional heartburn (normal esophageal pH) received oral ranitidine 150 mg bid or placebo for 7 consecutive days (double-blind, randomized, crossover study) and underwent mechanical (Barostat balloon distention) and chemical (Bernstein acid infusion) stimulation on study day 1 (90 min post-dose) and study day 7. After a single dose of ranitidine 150 mg, time to pain with esophageal acid

infusion was increased by 29% ( $P < 0.05$ ) and heartburn pain was decreased by 20% (VAS score,  $P < 0.06$ ) and 23% (Likert score,  $P < 0.02$ ) compared with placebo. After 1 wk of ranitidine dosing, subjects still exhibited decreased sensitivity to esophageal acid exposure. In contrast, mechanical (balloon distention) sensory parameters were not altered by ranitidine<sup>[36]</sup>. These data show that an H<sub>2</sub>RA can significantly decrease esophageal sensitivity to acid exposure, potentially providing symptom relief without significantly decreasing esophageal acid exposure.

Taken together, these data support that patients with frequent heartburn may be better managed by daily use of an OTC PPI, rather than repeated doses of H<sub>2</sub>RAs. Two well-controlled clinical studies showed that an OTC dose of omeprazole was superior to OTC doses of ranitidine for the management of frequent heartburn<sup>[28,37]</sup>. In a randomized controlled trial in 144 patients with endoscopically verified erosive esophagitis, Sandmark *et al.*<sup>[37]</sup> found that symptoms had resolved in 51% of patients treated with omeprazole 20 mg daily by the end of the first week of treatment compared with 27% of patients treated with ranitidine 150 mg twice daily ( $P = 0.009$ ). Similar results were found in a larger controlled study in 677 patients with heartburn and either no or mild erosive esophagitis<sup>[28]</sup>. Patients were randomized to one of three treatment regimens, and omeprazole was found to be superior to ranitidine, with 55%, 40%, and 26% of patients symptom-free who were treated with omeprazole 20 mg, omeprazole 10 mg, or ranitidine 150 mg, respectively ( $P < 0.001$ )<sup>[28]</sup>.

## CONCLUSION

While a single dose of an H<sub>2</sub>RA can be effective for controlling gastric acid and preventing or relieving isolated heartburn episodes, repeat dosing for more frequent heartburn may lead to the rapid development and sustained effects of tachyphylaxis. Even if symptom relief is achieved with multiple doses of an H<sub>2</sub>RA, it may be due to desensitization of the esophagus to acid, potentially providing symptom relief without significantly decreasing esophageal acid exposure. Other OTC strategies, such as a PPI, may be needed to optimize management of frequent heartburn.

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