



# H<sub>2</sub> Blockers – Indications, Effectiveness and Long-term Use

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The H<sub>2</sub> blockers (also called H<sub>2</sub> antagonists) were the first effective drugs for peptic ulcer. In the 1980s, they were the backbone of treatment for ulcers and gastroesophageal reflux disease (GERD). Now, antibiotics cure non-NSAID ulcers, and proton pump inhibitors (PPIs) are better for GERD. Therefore, H<sub>2</sub> antagonists face an uncertain future as prescription drugs. Nonetheless, they are comparatively cheap, effective, and very safe for heartburn relief. Lower dose preparations are available over-the-counter.

## History and rationale

Histamine stimulates the parietal cells in the stomach lining to produce hydrochloric acid. Histamine also affects the H<sub>1</sub> receptors on the nasal mucosa, bronchi, and skin that participate in allergic reactions such as hay fever and hives. These can be treated by antihistamines such as diphenhydramine (e.g., Benadryl, Siladryl) that block the H<sub>1</sub> receptor. The British pharmacologist, Sir James Black noted that antihistamines block systemic histamine (H<sub>1</sub>) effects, but not stomach acid stimulation. He reasoned there must be a second histamine (H<sub>2</sub>) receptor in the stomach lining. He synthesised and tested histamine-like molecules searching for those that only inhibited acid secretion. The first commercially available H<sub>2</sub> receptor antagonist, cimetidine was a great success helping Black to earn the 1988 Nobel Prize in Medicine. For the first time, doctors could heal peptic ulcers with a drug.

## The histamine H<sub>2</sub> antagonists

There are four H<sub>2</sub> antagonists available by prescription (Table 1). They are equally effective in their available doses and compete for the same receptor, so switching to another when one fails is likely to be futile. Increasing the dose may help.

## Action

The H<sub>2</sub> antagonists compete with histamine for H<sub>2</sub> receptors on the stomach's parietal cells and thereby depress the production of hydrochloric acid. They are rapidly absorbed reaching peak blood levels in 1 to 3 hours. Acid-suppression lasts several hours thereafter and permits peptic ulcers to heal over a few weeks. It also counteracts the corrosive effects of acid refluxing into the esophagus (gullet) that causes heartburn and sometimes bleeding or swallowing difficulties.

## Unwanted actions

H<sub>2</sub> antagonists have been so widely used that many side effects are attributed to them, although not necessarily caused by them. Unexpected effects required cessation in only 1.5% of patients receiving the drugs in clinical trials, compared to 1.2% for the placebo. The H<sub>2</sub> blocking drugs are very safe – even an accidental overdose of cimetidine was without consequence. They are so safe that authorities permit their sale without prescription. Nevertheless, unwanted side effects sometimes occur. For a complete list of the rarely reported side effects refer to ([www.nlm.nih.gov/medlineplus/druginfo/uspdi/202283.html](http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202283.html))

H<sub>2</sub> antagonists cross the blood-brain barrier and interact with histamine H<sub>2</sub> receptors in the brain. Uncommon central nervous system side effects include headache, dizziness, anxiety, drowsiness (somnolence), and depression. Cimetidine is reported to cause confusion in the elderly. Cardiac side effects are most common in the old and the ill, where drug interactions are more likely. Unwanted effects include hypertension, hypotension, and irregular or slow heartbeat. Famotidine may weaken heart muscle contraction in patients with heart disease. These effects are unlikely in a healthy young person. If used in large doses or for long periods, cimetidine may have feminizing effects in men that cause breast development (gynecomastia), impotence, loss of sex drive, and elevation of the pituitary hormone prolactin. While disconcerting, these effects are rare and thankfully reversed when the drug is stopped. The other H<sub>2</sub> blockers are less feminizing.

## Drug interactions

Alcohol is partly metabolized in the stomach through an enzyme called alcohol dehydrogenase (ADH). Except for famotidine, the H<sub>2</sub> antagonists seem to inhibit gastric ADH resulting in higher than expected blood alcohol levels. However, some studies cast doubt on this ADH effect. Until more data are available, if you drink, do not drive, especially while taking an H<sub>2</sub> antagonist. Proton pump inhibitors, or PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole) require an acid medium to convert to their active metabolite, so H<sub>2</sub> antagonists should not be taken with them. Cimetidine inhibits a liver enzyme called cytochrome P450 that facilitates drug metabolism. If given with certain other drugs, cimetidine may

delay their destruction and raise their blood levels. When the blood level is critical [as with theophylline (bronchodilator), warfarin (anticoagulant), or phenytoin (antiepileptic)], cimetidine should be avoided lest toxicity occur. Cardiac drugs such as quinidine, lidocaine, nifedipine, verapamil, procainamide, and propranolol are subject to similar dangers. Patients taking tricyclic antidepressants such as imipramine, amitriptyline, or doxepin should reduce the dose by half during cimetidine treatment to avoid toxic effects. Some of the benzodiazepine drugs (diazepam, midazolam, chlordiazepoxide) are 30% less metabolized when taken with cimetidine. This may be enough to confuse the elderly or depress breathing if there is marginal respiratory function. Other H<sub>2</sub> blockers have less cytochrome P450 effects. By reducing the absorption of ketoconazole, H<sub>2</sub> blockers can impair the effectiveness of this anti fungal agent.

Safety has not been proven in pregnant women and the drugs appear in breast milk. In kidney failure blood levels of the H<sub>2</sub> antagonists themselves may rise, so the dose should be reduced accordingly. If kidney excretion is impaired, famotidine blood levels rise and the drug can pass through the blood/brain barrier causing mental disturbances. The overriding messages are to avoid polytherapy (the use of more than one drug), and never use the H<sub>2</sub> antagonists without a firm indication. If you must take other medication, discuss H<sub>2</sub> blocker use with a pharmacist or doctor. It makes sense to avoid cimetidine if you are elderly or taking other drugs. Despite these caveats, it appears that H<sub>2</sub> blockers are safe even over long periods.

### Use

Uses for H<sub>2</sub> blockers are fewer than just a decade ago. A short course of PPIs and antibiotics has supplanted H<sub>2</sub> receptor antagonists for the treatment of gastric or duodenal ulcer. In patients at risk, long-term maintenance with these drugs prevents gastric erosions and duodenal ulcers that are caused by non-steroidal anti-inflammatory drugs (NSAIDs), but their ability to prevent gastric ulcers is less certain.

H<sub>2</sub> antagonists are effective in most cases of heartburn that do not respond to anti-reflux and life-style measures (See *Gastroesophageal Reflux Disease*. IFFGD Fact Sheet No. 502). However, severe heartburn, especially if complicated by inflammation of the esophagus (esophagitis) with bleeding or stricture, requires a proton pump inhibitor. H<sub>2</sub> antagonists are misused if taken for dyspepsia, irritable bowel syndrome, or other abdominal pains that are unaffected by the presence of gastric acid. Failure of an H<sub>2</sub> blocker to relieve heartburn in a few days, bleeding, or swallowing difficulties should be promptly reported to a physician. Sometimes H<sub>2</sub> blockers are used with standard antihistamines for the treatment of hives. For most other uncommon uses such as pancreatitis and the Zollinger-Ellison syndrome they have been supplanted by PPIs.

### Dose and administration

H<sub>2</sub> antagonist dosages appear in Table 1. A single bedtime dose achieves almost as good results as divided doses. The H<sub>2</sub> antagonist should be given separately from antacids. Over-the-counter preparations containing half of the lowest prescription dose are sold in small amounts for short-term use. In addition to the four patented drugs named in Table 1, there are many generic versions. These come in a variety of formulations; capsules, pills, chewable, liquid, effervescent, or combined with antacids. Like the prescription formulations, they are usually taken twice daily. Users should always read the label, and any questions addressed to a pharmacist or doctor.

### Summary

Histamine H<sub>2</sub> antagonists inhibit the action of histamine on gastric H<sub>2</sub> receptors thereby decreasing gastric acidity. They were considered a breakthrough in the treatment of peptic ulcer disease a quarter century ago. Now that antibiotics cure non-NSAID ulcers, and PPIs control severe esophagitis, there is much less need for them. Nevertheless, they are safe and inexpensive. Lower-dose, over-the-counter preparations are useful for moderate and occasional heartburn. Data do not support their use in abdominal pains due to other causes. Some doctors recommend a short trial for non-ulcer dyspepsia, despite lack of proof that they are effective.

### Reference List

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DRUG	TRADE NAME*	US Prescription Dose+	Cautions
CIMETIDINE	Tagamet	200mg four times daily 400mg twice daily 800mg at bedtime	alters drug metabolism, gynecomastia, impotence, confusion in elderly
ranitidine	Zantac	150mg twice daily 300mg at bedtime	less effect on drug metabolism
nizatidine	Axid	150mg twice daily	use with caution in

		300at bedtime	decreased kidney or liver function
famotidine	Pepcid	20mg twice daily 40mg at bedtime	use with caution in heart or kidney failure

\*There are also generic forms, but in their labels all must use the chemical names shown in the left hand column.

+These doses differ in Canada and other countries.

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