

## MEDICAL PRACTICE

*New Drugs***H<sub>2</sub> receptor antagonists—cimetidine and ranitidine**

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Few drugs have so rapidly gained an established place in modern medicine as the histamine H<sub>2</sub> receptor antagonists. As a result of the inventiveness of James Black and his colleagues, the theoretical concept of a second class of histamine receptors became a therapeutic reality. The failure of classic antihistamine drugs (more appropriately H<sub>1</sub> receptor antagonists) to block the actions of histamine, particularly on gastric acid secretion but also on isolated heart and uterine muscle, may now be explained by the existence of both H<sub>1</sub> and H<sub>2</sub> receptors which can be blocked by their respective specific H<sub>1</sub> or H<sub>2</sub> antagonists (table).

*Classification of histamine receptors*

Location	Effect of stimulation	Antagonists
H <sub>1</sub> receptors: Blood vessels	Vasodilatation; increased capillary permeability	Diphenhydramine, promethazine, etc also have anticholinergic and sedative effects. Newer agents such as terfenadine are more specific
Smooth muscle, bronchi Skin	Contraction Triple response, itch	
H <sub>2</sub> receptors: Stomach Heart, blood vessels, uterus	Gastric acid secretion Function not established in man	Cimetidine Ranitidine

Fortunately, the H<sub>2</sub> antagonists inhibited not only the stimulatory effects of histamine on gastric acid secretion but also the actions of all other gastric stimulants. As a result these drugs have been used to treat disorders in which gastric juice is

thought to be aetiologically implicated, and they have proved effective in managing peptic ulceration. The dramatic symptomatic relief afforded to patients with ulcers has led to the use of H<sub>2</sub> receptor antagonists not only in diseases in which their therapeutic efficacy has been proved but also for all sorts of non-specific alimentary complaints. Although the incidence of adverse reactions to H<sub>2</sub> antagonists in current use is low, such indiscriminate misuse results not only in needless expense but is also potentially dangerous because proper investigation and treatment may be delayed.

The two H<sub>2</sub> antagonists in current general use are cimetidine and ranitidine. Cimetidine is a derivative of the histamine molecule in which the imidazole ring has been retained but the side chain has been modified. In ranitidine the nucleus has been altered to a furan ring and in addition the side chain is also different from that of histamine. A brief outline of the pharmacological properties of these two drugs provides the basis for their use in individual patients.

**Cimetidine**

After ingestion cimetidine is rapidly and almost completely absorbed, with a bioavailability approximating to 70% of the availability of an intravenous dose. Peak drug concentrations occur 30 to 90 minutes after ingestion in fasting subjects but are delayed by about an hour when taken with food. Although a sulphoxide metabolite is produced in the liver, most of the drug is excreted unchanged by the kidneys, so that cimetidine accumulates in patients with renal insufficiency and in the elderly. Renal tubular secretion of cimetidine is likely because its renal clearance exceeds glomerular filtration rate. Competition with renal secretion of creatinine may explain the transient rise in serum creatinine concentration that often occurs during the first few weeks of treatment with cimetidine.

Cimetidine crosses the placenta into the fetal circulation. Similarly, penetration of the blood brain barrier is presumed to occur, since cimetidine has been detected in both cerebrospinal

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fluid and brain tissue. The possibility of an interaction with cerebral  $H_2$  receptors may account for the mental confusion, drowsiness, and disorientation that sometimes occurs in patients with renal or combined renal and hepatic failure and in the elderly.

The elimination half life of cimetidine is about two hours. The duration of action may be prolonged by increasing the dose of the drug, which produces suppression of gastric secretion for up to eight hours.

Cimetidine is given by mouth or by injection. Intravenous use is usually restricted to emergencies, such as patients undergoing intensive care or treatment of upper gastrointestinal haemorrhage. Since hypotension may follow rapid intravenous administration, the drug should be given by slow injection lasting five to 10 minutes or, better still, in an intravenous infusion of either saline or dextrose. Cimetidine may also be given intramuscularly. The usual dose for healing for duodenal and gastric ulcers is 1 g/day in divided doses of 200 mg after meals and 400 mg before sleep. Recently 400 mg twice daily has also been recommended and in the United States four tablets of 300 mg are used. For prevention of ulcer relapse, 400 mg at night is the most widely used regimen. The duration of maintenance treatment is not yet known, but ulcer relapses have occurred after as long as five years of maintenance treatment with cimetidine, so that even longer term continuous treatment is necessary to control the periodic activity of ulcer disease.

Two actions of cimetidine that appear to be unrelated to  $H_2$  antagonism are its effects on the endocrine system and on hepatic drug metabolism. After intravenous injection of cimetidine concentrations of circulating prolactin increase. *In vitro*, cimetidine competes for androgen binding sites and although antiandrogenic effects have been reported in man, these are clinically usually unimportant. Gynaecomastia has been seen, particularly with high doses of cimetidine and is reversible on withdrawal of the drug. More important clinically, cimetidine binds to cytochrome P450 in hepatic microsomes and so reduces the clearance of the many drugs (including warfarin, diazepam, chlorthalidone, phenytoin, and propranolol) that are eliminated by oxidative metabolism. The metabolism of drugs that are primarily conjugated (benzodiazepines—lorazepam and oxazepam) does not seem to be altered. Interference with elimination, and consequent accentuation of pharmacological effects, is of particular importance for drugs such as warfarin and phenytoin that have a low therapeutic index. Cimetidine also seems to reduce liver blood flow and thereby decreases the systemic clearance of drugs that are highly extracted by the liver, such as lignocaine and propranolol.

### Ranitidine

Ranitidine is well absorbed after ingestion with a bioavailability of about 50%, suggesting appreciable presystemic elimination in addition to renal elimination. Peak plasma concentrations occur about two hours after ingestion. Few metabolites are formed and the elimination half life is about two hours. After intravenous administration 70% of the drug is excreted unchanged by the kidneys undergoing renal tubular secretion, in addition to filtration, although interference with creatinine excretion has not been reported. While concentrations of circulating ranitidine may be higher in older than in younger patients, and especially in patients with renal insufficiency, effects on the central nervous system have not been reported even though small amounts of the drug appear in the cerebrospinal fluid.

The plasma concentration of ranitidine that produces 50% inhibition of gastric acid secretion (0.1  $\mu\text{g/ml}$ ) is about one fifth that of cimetidine. This concentration is usually exceeded or maintained for at least six hours after ingestion of 150 mg, so that 150 mg ranitidine twice daily is generally sufficient to control gastric secretion.

It seems that ranitidine does not inhibit drug metabolism or

interfere with androgenic function. As with cimetidine, a transient rise in circulating transaminase concentrations, headaches, and rashes may occasionally develop. Prolonged use of either drug has not been associated with serious adverse effects.

### Uses of $H_2$ receptor antagonists

A definite clinical diagnosis must be made before starting treatment with  $H_2$  receptor antagonists. These drugs should not be used to treat non-specific abdominal complaints.

#### DUODENAL ULCERATION

If cimetidine (1 g/day) or ranitidine (150 mg twice daily) are used to treat an active ulcer relief of pain is usually apparent within a week and often within 48 hours. The ulcer is endoscopically healed in about 80% of patients after treatment for four to six weeks. If the ulcer persists treatment should be continued for a further four weeks, by which time most ulcers will have healed. The subsequent management depends largely on the natural history of the condition. Patients without a serious history of ulcer disease often remain ulcer free for many months or years after treatment. In patients who have a history of relapses maintenance treatment is indicated. Cimetidine 400 mg or ranitidine 150 mg at night reduce the number of relapses in a year from 70-80% to about 20%. Maintenance treatment, however, has to be continued for many years (we do not yet know how long) because most patients relapse if treatment is stopped. If relapse occurs during maintenance treatment the ulcer can usually be rehealed within four to six weeks as previously, and maintenance treatment may then be continued.

Failure to relieve pain must arouse suspicion that the ulcer is not the cause of the patient's symptoms and that some other disease such as oesophagitis or a disorder of the biliary tract or pancreas is responsible. On the other hand, it may mean that the patient is not taking the prescribed tablets, or that a larger—for instance, double the normal—dose of the  $H_2$  antagonist is required, since some patients appear to be "resistant" to the drug. This is particularly so when the ulcer disease is the principal clinical manifestation of a gastrinoma (Zollinger-Ellison syndrome). These patients may become resistant to cimetidine (and perhaps also to ranitidine) during the course of the disease. Switching from cimetidine to ranitidine has helped some patients with resistant gastric hypersecretion.

#### GASTRIC ULCERATION

Having excluded the possibility of malignancy, the same dosage schedule as for duodenal ulcers may be used to heal gastric ulcers. A six week course of treatment heals 75% of patients. As with duodenal ulcer, maintenance treatment is also usually necessary because recurrences are common. In general, the results of treating ulcers of the body of the stomach are excellent, although prepyloric ulcers may be more resistant to treatment. Endoscopic confirmation of healing is always necessary, since  $H_2$  antagonists may symptomatically improve and partially heal malignant ulcers.

#### GASTRO-OESOPHAGEAL REFLUX

Cimetidine has no direct effect on the lower oesophageal sphincter, while ranitidine has been reported to increase sphincter tone in some patients. Both drugs produce symptomatic relief, but endoscopic and histological improvement is less certain. Patients whose symptoms are not controlled by cimetidine may benefit from a change to ranitidine and vice versa.

## TREATMENT AND PREVENTION OF UPPER ALIMENTARY HAEMORRHAGE AND OTHER USES

Although widely used in treating acute gastrointestinal haemorrhage, H<sub>2</sub> receptor antagonists seem to be of use only in cases of bleeding from acute erosions and perhaps gastric ulcers. Obviously, drugs are not likely to stop bleeding from eroded arteries and surgical treatment is necessary if haemorrhage persists or recurs. H<sub>2</sub> antagonists are also often given to seriously ill patients and preoperatively to reduce the risk of "stress ulceration." Their role in these conditions is still controversial.

The drugs have also been used during labour in childbirth to minimise the risk of aspiration of gastric contents into the lungs when emergency anaesthesia is given.

Maldigestion in patients with pancreatic insufficiency (including cystic fibrosis) is often aggravated by gastric acid and pepsin destroying the residually secreted pancreatic enzymes and the enzymes of pancreatic extract given as replacement treatment. Cimetidine or ranitidine, taken in normal dosage 30 minutes before meals, improves digestion in these patients.

## CHOICE OF TREATMENT

Cimetidine and ranitidine are both safe drugs with, fortunately, remarkably little in the way of unwanted effects. In the general treatment of ulcer disease cimetidine and ranitidine seem equally effective. Cimetidine is cheaper but patient acceptability (or compliance) is better with two tablets a day of ranitidine than the five tablets of cimetidine that are usually prescribed, although it has been reported recently that cimetidine is also effective when given as 400 mg twice daily. Ranitidine is preferable for individuals with ulcers who also need treatment with other drugs that may interact with cimetidine—for instance, anti-coagulants, antiepileptics, and some beta-blockers. Ranitidine seems to be preferable for treating the ulcer disease associated with renal insufficiency, and perhaps also in the elderly, since drug induced mental confusion has not been reported during treatment with ranitidine. Nevertheless, caution should be exercised when treating such patients.

In managing patients with ulcer disease a choice must also be made between maintenance treatment with H<sub>2</sub> receptor antagonists or surgical treatment of the ulcer. Relapse of the ulcer occurs more often after maintenance treatment than after surgical treatment, but these relapses (such as the ones after surgery) may be rapidly healed by increasing the dosage of the drugs. On the other hand, long term treatment with cimetidine and ranitidine (for six and two years respectively) is not associated with serious side effects, while all surgical treatment is followed by symptomatic sequelae, which may be severe and are often irreversible, in about 10% of patients. Moreover, for surgery there is a small mortality rate even in expert hands and particularly when repeated surgery—that is, for recurrence of the ulcer—is required.

It has been suggested that long term use of gastric inhibitory drugs may predispose to gastric cancer. Reduction in gastric acidity is considered to result in bacterial colonisation of the stomach with nitrate reducing bacteria, which produce nitrite from dietary nitrate; the nitrite in turn reacts chemically with amines in food to produce nitroso compounds, some of which are mutagenic to bacteria and resemble compounds that produce gastric cancer when given to animals. Not one of these steps has been proved satisfactorily in man. Indeed, it is worth emphasising that while the connection between medical treatment and gastric cancer remains a hypothesis, the connection between some ulcer operations and gastric cancer is established, since 0.5-20% of patients who have undergone gastrectomy develop cancer of the gastric stump. No clinical connection between vagotomy and gastric cancer has yet been shown, although under experimental conditions vagotomy may predispose to gastric carcinogenesis. We conclude that because the complications after gastric surgery for ulcer disease are so

common, and in some cases both severe and irreversible, the treatment of uncomplicated ulcer disease by operation is now usually unwarranted. Long term treatment with H<sub>2</sub> receptor antagonists is the treatment of choice.

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*When, and with what, would you treat a woman with primary thrombocythaemia, and what is the prognosis?*

The first essential is to establish that it is primary thrombocythaemia and not thrombocytosis or thrombocythaemia associated with chronic myeloid leukaemia or primary polycythaemia. Platelet morphology, platelet function tests, the leucocyte alkaline phosphatase activity, the presence of a Philadelphia chromosome, and the presence or absence of splenomegaly will usually help to establish the diagnosis. If not, longer observation may be necessary. The immediate treatment depends on the presentation. If this is due to acute post-traumatic or haemorrhagic effects requiring urgent treatment a rapid control of bleeding can often be obtained by oral prednisolone 15 mg thrice daily. When the patient suffers from chronic spontaneous or post-traumatic bruising or bleeding the platelet count should be reduced by chemotherapy. The most commonly used and effective drug is busulphan in an initial dose of 2 mg thrice daily. In the patient who suffers predominantly from microvascular occlusive lesions—for instance, gangrene of the tips of the toes—the platelets must again be reduced by chemotherapy, but if the occlusive lesion is serious then dipyridamole 50 mg thrice daily may help the acute phase, but it must be used cautiously. The asymptomatic patient incidentally discovered should also be treated as they are at risk of severe post-traumatic bleeding. In all cases chemotherapy may produce only a slow reduction in the platelet count but it is necessary to persist, possibly with reduced doses if the white count falls, until the platelet count is around  $300 \times 10^9/l$ . The platelet count should then be maintained at about  $300-500 \times 10^9/l$  by intermittent treatment with the minimal quantities of these potentially mutagenic drugs. There is no obvious difference between treatment in men and women except for the unlikely event of an association of thrombocythaemia and pregnancy, when the possibility of deferring treatment until the end of pregnancy would depend on the severity of symptoms. The prognosis is good as proliferation is slow, and adequately treated patients may expect to survive normally for 15 years and more unless the condition transforms into myelofibrosis.—G WETHERLY-MEIN, professor of haematology, London.