

PJ PRACTICE CHECKLIST

H₂ ANTAGONISTS AND DYSPESIA

Three of the H₂ antagonists — cimetidine, famotidine and ranitidine — are now available for over-the-counter sale following reclassification from prescription only to pharmacy medicines. The drugs are marketed for short-term treatment of dyspepsia. This card outlines points to remember when counterprescribing the products and explains how the drugs work and the difference between them

PRACTICE POINTS

- OTC H₂-antagonists are effective for the short-term relief of dyspepsia
- There is still a case for using neutralising antacids, which are both effective and cheap for symptomatic relief
- H₂-antagonists should not be used for longer than two weeks on an OTC basis
- Avoiding offending foods is the most effective means of preventing meal-related dyspepsia
- Smoking exacerbates symptoms
- H₂-antagonists do not protect against the gastrointestinal effects of excessive alcohol consumption
- If one H₂-antagonist does not provide relief, it is unlikely that another will
- If cimetidine is recommended, it is essential that potentially serious drug interactions are excluded (see BNF for complete list)

WHO TO REFER

- Patients under 12 years of age
- Patients who are pregnant or breast-feeding
- Patients presenting with dyspepsia for the first time, especially if middle aged or older
- Patients with known renal and hepatic problems
- Patients with recent marked weight loss
- Patients who look decidedly unwell
- Patients who have difficulty in swallowing
- Patients receiving prescribed medication for upper gastrointestinal disease
- Patients being treated for other disease by the doctor
- Patients reporting marked changes in the nature or intensity of dyspeptic symptoms
- Patients reporting symptoms of gastrointestinal bleeding (dark, tarry stools)
- Patients receiving non-steroidal anti-inflammatory agents



WHAT IS DYSPEPSIA? Dyspepsia, or non-ulcer dyspepsia, has been defined as "upper abdominal or epigastric pain, discomfort, heartburn, nausea, vomiting or other symptoms considered to be referable to the upper gastrointestinal tract and lasting for more than four weeks, unrelated to exercise and for which no focal lesion or systemic disease can be found responsible". In relation to the current discussion this definition will be used except that vomiting is omitted and the duration is restricted to an upper limit of two weeks rather than a lower limit of four weeks so as to accommodate the requirement that OTC therapy should not exceed two weeks. In common usage dyspepsia is often used interchangeably with the terms indigestion and hyperacidity.

THERAPY: Symptomatic relief of the symptoms of dyspepsia is usually attempted with medications which reduce gastric acidity. This can be achieved by one of three main approaches: (i) neutralising antacids (eg, bicarbonates and hydroxides), (ii) histamine H₂-antagonists (eg, famotidine, cimetidine and ranitidine) and (iii) inhibitors of H⁺K⁺-ATPase, the enzyme system known as the proton pump because of its role in secreting H⁺ by the parietal cell (eg, omeprazole). Until the current deregulation of cimetidine, famotidine and ranitidine, only the neutralising antacids were available without a prescription in the UK.

H₂-ANTAGONISTS: Three endogenous agonists act on specific receptors on the parietal cell of the stomach to stimulate acid

secretion: acetylcholine, histamine and gastrin. Activation of the histamine H₂ receptor raises the level of both intracellular cyclic AMP and a protein kinase. The latter activates the proton pump and hence increases acid secretion. Of the three agonists, histamine is thought to be the most important - hence the effectiveness of the H₂-antagonists. These compounds occupy the H₂-receptors but do not trigger the sequence of events leading to acid secretion. To date, three H₂-antagonists (cimetidine, famotidine and ranitidine) are available on an OTC basis.

PHARMACOKINETICS: The elimination half-life of cimetidine is of the order of two hours. Ranitidine has a half-life of about two and a half hours while famotidine's half-life is approximately three hours. For all three compounds, inhibition of acid secretion is more prolonged than suggested by their half-lives. Accumulation does not seem to be a problem with repeated dosing and food does not affect bioavailability. The principal route of excretion of the H₂-antagonists is the kidney and the drugs are metabolised by the liver.

OTC INDICATIONS: current data sheet indications for prescription only H₂ antagonists are for a variety of conditions which respond to a decrease in acid output. Prominent among these are duodenal ulceration, benign gastric ulcer and gastro-oesophageal reflux disease. However, surveys of use patterns suggest that much of the prescribing of the drugs is for symptomatic relief of less specific gastrointestinal symptoms, notably dyspepsia, whether spontaneously occurring or meal-related. OTC use of H₂ antagonists is restricted to those "softer", indications variously described by terms such as heartburn, hyperacidity and, of

course, dyspepsia, with the emphasis being placed on short-term treatment.

DOSE RECOMMENDATIONS AND COMPARATIVE EFFICACY: The OTC dose for famotidine (10mg) is lower than the prescription doses which start at 20mg. The maximum daily OTC dose is 20mg. For cimetidine, a maximum dose of 200mg is approved for OTC use, with a maximum daily dose of 800mg. For ranitidine, the standard OTC product strength is 75mg and the maximum daily dose is 300mg. Clinical studies suggest that for relieving symptoms associated with provocative foods, the dose of H₂-antagonist should be taken one hour before food. Famotidine is longer acting than cimetidine, hence the difference in dosing schedule. For acute episodes, a single dose of cimetidine may well be adequate but, as with ranitidine, the results of clinical trials for the OTC indications have yet to be published.

COMBINATION PRODUCT: Cimetidine is now available as a liquid formulation containing sodium alginate. The formulation is specifically promoted for control of reflux oesophagitis on the strength of the alginate content. The liquid formulation may provide more rapid relief of symptoms than the tablet formulation. All the precautions relating to cimetidine, of course, hold.

DRUG INTERACTIONS: Cimetidine, but not ranitidine or famotidine, binds to cytochrome P450, thereby making interactions with drugs metabolised by this enzyme system possible. Particular care is required with such drugs when they also have a narrow therapeutic index (eg, phenytoin, cyclosporin, theophylline, oral anticoagulants and lignocaine). Benzodiazepines, propranolol and procainamide are among many other drugs

which may interact with cimetidine but such interactions appear to be of little clinical significance. Antacids do not appear to affect either the pharmacokinetics or the pharmacodynamics of the H₂-antagonists.

ADVERSE DRUG EFFECTS: Adverse effects are relatively rare with all three agents and appear qualitatively similar for all three compounds except that cimetidine affects gonadal function to some extent and cases of gynecomastia have been reported more frequently with this drug than with the other two agents. Decrease in sperm count is possible with cimetidine but only after prolonged treatment. OTC use as licensed is unlikely to cause any such problems. Headache, dizziness, diarrhoea and skin rashes are among adverse effects which have been reported to be associated with the H₂ antagonist compounds. However, extensive post-marketing surveillance has not established incidence rates of any side effects which could cause concern. Given the change in target population, vigilance is required and any suspected case of adverse effect reported to the patient's doctor.

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