

HISTAMINE-2 RECEPTOR ANTAGONISTS

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Acid peptic disease is a spectrum of disorders of esophagus, stomach and duodenum where mucosal injury is caused by gastric acid and pepsin. Several agents like antacids, histamine-2 (H_2) receptor antagonists, cytoprotective agents and anticholinergics, etc. have been used to treat these disorders. Of these, H_2 receptor antagonists have been widely and successfully used for the treatment of acid peptic disease in adults. Only limited clinical and pharmacological data exist regarding their usage in the pediatric population(1). At present H_2 receptor antagonists available for clinical use include cimetidine, ranitidine, famotidine and nizatidine. Of these, safe and efficacious dosage regimen in children, using pharmacokinetic and phar-

macodynamic studies, have been established for cimetidine and ranitidine.

Mechanism of action

Acid secretion from gastric parietal cells is stimulated by agonistic substrate binding to three types of receptors on the cell surface. These are histamine (H_2), gastrin and muscarinic cholinergic receptors. Two types of histamine receptors have been identified in the intact gastric mucosa. One is associated with vasculature and is perhaps of H_1 type. The second one found on the parietal cell, is clearly of H_2 type. Of the three receptors, H_2 are the most dominant. H_2 receptor is coupled to adenylate cyclase and when activated results in elevation of parietal cell cyclic AMP which in turn stimulates the parietal cells to secrete acid(2). The H_2 receptor antagonists reduce gastric acid secretion elicited by histamine and other H_2 agonists by dose dependent competitive mechanism. They also inhibit acid secretion in response to gastrin and to a lesser extent to other muscarinic agonists and thereby significantly reduce the basal and nocturnal acid secretion and acid secretion stimulated by food, gastric distension and drugs(2,3). Although H_2 receptor antagonists produce competitive inhibition of H_2 receptors, each is structurally distinct, i.e., cimetidine has an imidazole ring just like histamine, ranitidine possesses a furan ring and the more recent H_2 blockers famotidine and nizatidine have a thiazole ring. The relative potency of each H_2 receptor antagonist differs. Ranitidine has been shown to be 3-11, nizatidine 4 and famotidine 20-27 times more potent than cimetidine(4).

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Pharmacology

H₂ receptor antagonists are well absorbed orally and peak blood levels are obtained within 1-2 hours after ingestion. The bioavailability after an oral dose is maximum with nizatidine (90%) whereas, with all other H₂ blockers it is only about 50% (3). This is because all these agents with the exception of nizatidine undergo extensive metabolism during post absorption passage through liver (first pass effect). Cimetidine in a dose of 20-30 mg/kg/day administered in six divided intravenous bolus doses produces a steady state of plasma concentration of 1.3 to 2.9 µg/ml (5). A serum concentration of 40-50 ng/ml of ranitidine produces acid suppression by 90%. To achieve this concentration, an oral dose of 1.25-1.90 mg/kg every 12 hours or an intravenous bolus dose ranging from 0.13-0.8 mg/kg is required (6). The maximum acid suppression occurs between 1.5-3 hours and the effect lasts for 5-6 hours. About 50% of oral dose of cimetidine is excreted unchanged in urine and the other half is excreted in the metabolized

form (chiefly sulfoxide). Hence, in patients with renal insufficiency it becomes necessary to reduce the dosage of the drug to half. In contrast, 50% of ranitidine is eliminated by hepatic metabolism, therefore, in states of impaired liver functions like cirrhosis, fulminant hepatic failure, etc., the half life of ranitidine increases and correspondingly a reduction in the dosage becomes mandatory (7). Plasma half life of cimetidine, ranitidine and famotidine varies from 2-3 hours whereas the same for nizatidine is 1.3 hours. Cimetidine is available in the form of tablets (200 mg, 300 mg, 400 mg and 800 mg) and also as injections (200 mg per 2 ml) under various brand names. Ranitidine is marketed in tablet form (150 mg and 300 mg) and as parenteral preparation (50 mg per 2 ml). The dosages of H₂ receptor antagonists are given in the Table.

Drug interactions

Cimetidine inhibits cytochrome P-450 mixed function oxidase (MFO) system. This results in reduction in hepatic clear-

TABLE I—Dosages* of H₂ Receptor Antagonists

	Drug	Route of administration	Dosage
Neonates	Cimetidine	IV	8 mg/kg/24 h q 12 hrly
	Ranitidine	IV	0.2 mg/kg/h
Children	Cimetidine	Oral	20-40 mg/kg/day q 4-6 h
		IV	20-30 mg/kg/day q 4-6 h
	Ranitidine	Oral	2.5-3.8 mg/kg/24 h q 12 h
		IV	0.13-0.8 mg/kg bolus 6-8 h
	Famotidine#	IV	0.4 mg/kg/dose q 8 h

*Ref. 5, 6, 11, 14 # See the text.

ance leading to increased serum concentrations of many drugs like warfarin, theophylline, phenytoin, benzodiazepines, lidocaine and propranolol(3,8). In some cases increased blood levels of these agents may result in clinically evident toxicity such as bleeding from warfarin, arrhythmias and convulsions from theophylline, nystagmus, ataxia and confusion from phenytoin, *etc.* The true incidence of these interactions has not been established. The potency of ranitidine, famotidine and nizatidine to inhibit P-450 MFO system is only one-tenth of that of cimetidine. Hence the drug interactions are rare with these newer H₂ blockers(3). Therefore, it is preferable to use H₂ blockers other than cimetidine when these are to be prescribed in conjunction with one of the interacting drugs mentioned above.

Therapeutic uses

Acid peptic disease in children is a well described entity. The conditions described under this category are duodenal ulcer, gastric ulcer, esophagitis, gastritis, duodenitis or combined lesions. Most of these disorders in older children share a common symptom of pain abdomen requiring endoscopic evaluation. Sixty seven children with pain abdomen were evaluated by us endoscopically. We found gastritis in 38.8%, esophagitis in 20.8%, duodenitis and duodenal ulcers in 7.6% each, gastric ulcers in 5.9% and combined lesions in 19.3%. Literature reveals that duodenal and gastric ulcers in children may be primary or secondary. In contrast to adults, primary gastric and duodenal ulcers are usually found in older children of more than 10 years of age(9). Primary duodenal ulcers usually heal with 6 weeks of therapy with H₂ receptor antagonists. However, recurrence of ulcers occurs in over one-third

of patients(10). These recurrences can be suppressed by maintenance therapy in selected cases with single night time dose of H₂ blockers.

Severe systemic illnesses like septicemia, burns, pneumonia and possibly corticosteroid administration cause secondary duodenal ulcers. Most of the secondary ulcers occur in neonates, infants and children below 10 years of age and usually present with complications like gastrointestinal bleeding and perforation(9). H₂ receptor antagonists have a definite role to play in the prophylaxis and treatment of secondary ulcers. Both cimetidine and ranitidine have also been used to treat life threatening gastrointestinal hemorrhage in neonates(11). Gastric ulcers, though seen rarely in children, are treated in a similar manner. Acute or chronic gastritis, duodenitis either alone or in combination with ulcer disease have been treated successfully with H₂ receptor antagonists. Recent studies both in adults and children have confirmed an association between colonization with *Helicobacter pylori* (*H. pylori*) and chronic antral gastritis. There is a strong association between *H. pylori* associated chronic antral gastritis and chronic duodenal ulcer. For effective treatment of these lesions both healing of the lesions as well as eradication of *H. pylori* are required. To achieve this H₂ antagonists are being currently used as an adjunct in combination with one or more of the antimicrobials like metronidazole, tinidazole, amoxycillin and colloidal bismuth subcitrate, *etc.*(12).

In children H₂ blockers are also useful in the management of esophagitis caused by gastroesophageal reflux(13). Though these drugs do not affect the underlying cause of reflux, healing of esophagitis with these agents relieve the symptoms and may

correct inflammation associated dysfunction of the lower esophageal sphincter. These drugs have been used as preanaesthetic medication prior to emergency surgery to reduce aspiration of gastric acid contents(3) and also recently in the treatment of urticaria and anaphylaxis not responding to H₁ blockers alone(3). Other indications include rarer disorders of hypersecretory states associated with Zollinger-Ellison Syndrome, systemic mastocytosis and basophilic leukemia.

Recently, famotidine given intravenously has been found to be safe and useful in suppressing gastric acidity in children in an intensive care setting(14). A dose of 0.4 mg/kg/dose was effective in most of the patients while rest responded to a dose of 0.8 mg/kg. In contrast to adults where 12 hourly dosage is recommended, this uncontrolled study recommended 8 hourly dosing schedule to keep the gastric pH above 4.

Adverse effects

The incidence of side effects with cimetidine is about 5%. Most common side effects are headache, dizziness, myalgia, nausea, skin rashes and itching(8). Antian-drogenic side effects like gynecomastia are observed in 0.2% of cases receiving long term high dose therapy. Rarely cimetidine usage may produce reversible bone marrow suppression, hepatitis and anaphylaxis. Adverse effects with ranitidine therapy are rare and these may be in the form of hyperprolactinemia, diarrhea, pancytopenia, hepatocellular dysfunction, rash and arthralgias. Similar, adverse effects have been noted following famotidine usage in adults. Besides, this drug may also produce orbital edema, tinnitus and taste disorders(3,7). Rapid intravenous infusion of H₂ blockers may cause bradycardia and histamine release(3).

Thus, H₂ receptor antagonists are useful therapeutic agents for the management of acid peptic disease and related disorders in children. Ranitidine, at present, is the agent of choice. This is due to its safety, easy dosage schedule, minimal drug interactions and rarity of adverse effects in comparison to cimetidine. However, in patients with hepatic insufficiency, dosage modification may be required. Only limited pharmacological data is available regarding the usage of famotidine in children and it indicates that variability of response to intravenous famotidine and the rapid development of tolerance in majority of patients appear to limit its use. In addition, famotidine cannot be recommended for routine use in children till prospective controlled trials are carried out and its safety and efficacy is established.

In recent years, another potent anti-secretory drug has become available for treatment of acid peptic disease and related hypersecretory states. Omeprazole is a substituted benzimidazole, that inhibits the enzyme H⁺-K⁺ ATPase in a noncompetitive, selective manner in the parietal cell secretory membrane, producing a long lasting suppression of gastric acid secretion. In adults, omeprazole has been well tolerated without significant adverse effects or laboratory abnormalities apart from mild hypergastrinemia. It is being widely used in the treatment of Zollinger-Ellison syndrome, severe reflux esophagitis and duodenal ulcers refractory to treatment with H₂ receptor antagonists. Controlled prospective trials proving the safety of omeprazole in the pediatric population are, however, lacking at the present moment. In occasional reports, omeprazole has been used to treat severe peptic ulcer disease in children refractory to H₂ receptor antagonists and it did not produce any adverse

reactions during a 3-year follow-up period(15). Until appropriate controlled trials establish the safety of omeprazole in the pediatric population, it should be used only after failure of treatment with conventional H₂ receptor antagonists.

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