# Pediatric Pharmacotherapy

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## Use of Famotidine in Infants and Children

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The histamine type-2 receptor antagonists ($H_2$RAs) have made a significant impact on the prevention and management of gastroesophageal reflux and ulcers. This class includes cimetidine, ranitidine, famotidine, and nizatidine. Cimetidine, the first $H_2$RA available, has been largely replaced by the newer agents in the class due to its adverse effect profile and the potential to cause significant drug interactions. The other $H_2$RAs are considered equivalent.[1-3] The University of Virginia Pharmacy and Therapeutics Committee has recently approved a therapeutic interchange program for this class, with famotidine as the agent of choice.

Mechanism of Action

The $H_2$RAs are reversible, competitive antagonists at histamine type-2 receptors, primarily on the parietal cells within the gastrointestinal mucosa. This class is highly specific, with little activity at $H_1$ or anticholineric receptors. As a result of $H_2$ receptor antagonism, these agents inhibit gastric acid secretion, both in terms of volume produced and hydrogen ion content.

Indications

Famotidine is currently approved by the Food and Drug Administration for both treatment and maintenance therapy of duodenal ulcers, in addition to the treatment of gastric ulcers, pathological hypersecretory conditions, and gastroesophageal reflux disease (GERD) in adults. These indications apply only to the prescription dosage formulations. Famotidine is also available without a prescription for the symptomatic relief of acid indigestion in adults.[2] As with all the $H_2$RAs, famotidine is not approved for use in children.[1,2]

Use in Infants and Children

Despite the lack of FDA approval, the $H_2$RAs have been widely used in the pediatric population. There are nearly a dozen publications describing famotidine use in infants and children. The majority of these studies have focused on the use of famotidine in the prevention of stress erosions.[4-7]

In 1991, Treem and colleagues[5] studied 18 critically ill children, ages 2 months to 5 years, receiving famotidine to prevent gastrointestinal bleeding. Continuous intragastric pH monitoring was used to establish an effective dose of intravenous famotidine in these patients. The majority of patients (13/18) achieved an intragastric pH $\geq$ 4.0 for a period of at least 6 hours with a dose of 0.4 mg/kg. Most patients remained within the desired pH range for approximately 9 hours after a famotidine dose.

Unfortunately, few studies are available to document the efficacy of long-term famotidine therapy. Behrens and coworkers[6] compared 36 children (ages 10 days to 19 years) who received no stress erosion prophylaxis after cardiac surgery to a later group of 43 children (ages 35 days to 9 years) who were given either pirenzepine (an antimuscarinic agent) or famotidine, both at 1 mg/kg/day until enterally fed. In this study, the incidence of ulceration decreased from 25% in the untreated group to 2% in patients receiving prophylaxis.

Famotidine has also been shown to be effective in the treatment of reflux esophagitis and gastroduodenal ulcers in children.[8,9] In these studies, dosages of 0.5 to 1 mg/kg were administered every 8 or 12 hours.

Nagita and colleagues[9] demonstrated the efficacy of famotidine in a group of 14 boys, ages 6 to 15 years, with gastric or duodenal ulcers. Patients received doses of 0.5 mg/kg twice daily, either orally or intravenously for a period of 8 weeks. All patients were healed at the end of the treatment period. No adverse effects were observed with this regimen. It should be noted that the patients responded to therapy despite the inability to maintain pH levels > 5.0 for the entire dosing interval.

Pharmacokinetics/Pharmacodynamics

After intravenous administration, famotidine achieves maximum acid inhibition (increasing the pH to $\geq$ 5) within 30 minutes. Oral dosing produces an onset of acid suppression within 1 hour; the maximum effect occurs within 1 to 3 hours. Oral bioavailability in adult and pediatric patients is approximately 50%.

In adults, standard intravenous or oral doses maintain acid suppression for 10 to 12 hours.[1,2,9] Pediatric patients, however, appear to have a shorter duration of acid control with standard dosing.[3] As seen in the studies by Kraus[4], Treem[5], James[7], and Nagita[9], the duration of effective acid suppression from famotidine in children appears to be approximately 5 to 9 hours.

This pharmacodynamic response may, in part, be explained by pharmacokinetic differences in children. Volume of distribution has varied from 1.4 to 2.4 L/kg in the studies conducted to date. Elimination half-life has been more consistent, with average values ranging from 2.2 to 3.3 hours. Clearance values have ranged from 0.3-0.48 L/hr/kg. These values reflect a slightly faster elimination of famotidine in children than adults. These differences are small, however, and may not be clinically significant.

Drug Interactions

Unlike cimetidine, famotidine does not bind to cytochrome P450 enzymes and is not associated with significant drug interactions. This is a considerable advantage when selecting an $H_2RA$ for children requiring complex chronic medication regimens.

There is a potential for reduced absorption of medications requiring an acidic gastrointestinal environment, such as ketoconazole, after famotidine use. The clinical significance of this drug interaction has not been determined.

Adverse Effects

Famotidine has a relatively mild adverse effect profile. It does not have the antiandrogenic or CNS effects associated with cimetidine. In clinical trials of adults receiving famotidine, the most frequently reported adverse effects were headache (in 4.7% of patients), dizziness (1.3%), and either diarrhea (1.7%) or constipation (1.2%). These values are similar to those reported for ranitidine.[2,10]

Infrequent reactions that have been reported following famotidine use include thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), leukopenia, agranulocytosis, rash and pruritis, anorexia and dry mouth, paresthesias, dry skin, flushing, tinnitus, changes in taste perception, palpitations, conjunctival injection and orbital edema, and fever. A single report of a tonic-clonic seizure occurring after famotidine administration has been reported, although causality was not clearly established.[2,10]

There is little experience with overdoses of famotidine. Doses of up to 640 mg/day have been given to adults with hypersecretory disorders without adverse effects.[2,10,11]

Dosing Recommendations

As seen in the variety of dosages used in clinical trials, the dosing recommendations for famotidine in the pediatric population are not well established. Several different dosing strategies have been used, including both twice and three times daily dosing. Based on the available pharmacokinetic/dynamic studies and pH probe data collected by the members of the Pediatric Gastroenterology Division of the Department of Pediatrics, the recommended famotidine dosing regimen at the Children's Medical Center at the University of Virginia is 0.4 mg/kg given PO or IV every 8 hours.

Th adult dosage is recommended for children 12 years of age or older. Parenteral famotidine is typically given in a dose of 20 mg every 12 hours. Oral dosing differs according to the disease state. For the treatment of ulcers, 40 mg PO should be given once daily at bedtime. For GERD, the dosage is 20 to 40 mg PO twice daily.[2] To convert patients from ranitidine to famotidine, divde the ranitidine dose by 7.5.

Following initiation of therapy, the dosage may be titrated based on patient response. Although not well studied in children, the occurrence of tachyphylaxis to famotidine has been described in adults. This should be considered in any child who fails to respond to increasing dosages.

In patients with severe renal dysfunction (i.e. creatinine clearance < 10 ml/min), there is a potential for famotidine accumulation. Although no dose-related toxicities have been identified in these patients, it is recommended that the dosing interval be prolonged.[2]

Intravenous famotidine may be administered by IV push at a rate ≤ 10 mg/minute. It may be added to parenteral nutrition solutions and is compatible when administered at the Y-site with a number of medications (Table).[2,12] Oral famotidine may be administered with or without food.[2]

*Table. Examples of intravenous medications compatible with famotidine*

aminophylline
ampicillin
cefazolin
cefotaxime
ceftazidime
dexamethasone
dobutamine
dopamine
epinephrine
fat emulsion
fluconazole
furosemide
gentamicin
heparin
midazolam
morphine
ondansetron
potassium chloride
phytonadione
sodium bicarbonate

Summary

Famotidine, like the other $H_2$RAs, is useful for both prophylaxis and treatment of reflux and ulcers in children. It offers the advantages of having relatively few adverse effects and no significant drug interactions. The ideal dosing regimen is still debated, with most investigators choosing either an every 8 or every 12 hour dosing interval. Additional clinical trials, particularly in infants and young children, are needed to better establish the safety and efficacy of current dosing strategies.

**References**


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## Pharmacology Literature Review

Analgesic Dosing in Children

The authors of this article present an interesting view: that dosing based solely on body weight may not be appropriate for many analgesics. They suggest that simply "scaling down" adult doses may result in inappropriately high dosages of opioids and that dosing should accommodate more specific age-related pharmacokinetic changes. Differences in hepatic metabolic rates and protein binding are among the arguments used to support this hypothesis. Anderson BJ, McKee AD, Holford NHG. Size, myths and the clinical pharmacokinetics of analgesia in p(a)ediatric patients. **Clin Pharmacokinet 1997;33:313-27.**

Buprenorphine Withdrawal

A case of withdrawal occurring in a neonate exposed in utero to buprenorphine (Buprenex®) is presented. The patient's mother was given buprenorphine 4 mg/day in order to taper off heroin. The infant was born at term without apparent complications. At 48 hours of age, the patient developed signs of agitation, insomnia, tremor, yawning, and a fever. The authors present serum buprenorphine and norbuprenorphine concentration data for mother and patient, as well as drug concentrations in the patient's urine and meconium, and the mother's

breastmilk. Marquet P, Chevrel, Lavignasse P, et al. Buprenorphine withdrawal syndrome in a newborn. **Clin Pharmacol Ther 1997;62:569-71.**

Prevention and Treatment of RSV

This extensive review covers the studies conducted to date in both prevention and treatment of respiratory syncytial virus (RSV) infections. The authors address the use of ribavirin and RSVIG in infants as well as their possible role in patients who have undergone bone marrow transplantation. Investigational agents, such as monoclonal RSVIG and RSV vaccines, are also discussed. Ottolini MG, Hemming VG. **Drugs 1997;54:867-84.**

Tacrolimus Review

Tacrolimus (FK506) has been in use in the United States for several years. This agent was developed as an alternative to cyclosporine, with the goal of reducing adverse effects. While tacrolimus is well tolerated by most patients, it can produce significant adverse reactions, such as diabetes mellitus, neurotoxicity, and nephrotoxicity. This review provides a complete discussion of the clinical trials published with tacrolimus. Following an introductory section on mechanism of action and adverse effects, the clinical studies are categorized by organ type. Spencer CM, Goa KL, Gillis JC. Tacrolimus: An update of its pharmacology and clinical efficacy in the management of organ transplantation. **Drugs 1997;54:925-75.**

Zinc and the Common Cold

The use of zinc lozenges to minimize symptoms of the common cold has received considerable attention in the lay press. This article attempts to bring together the research conducted to date, focusing on both the benefit and potential adverse effects of zinc therapy. The authors conclude that zinc gluconate lozenges containing at least 7.5 mg of elemental zinc appear to reduce both the duration and severity of cold symptoms with minimal risk of adverse effects. Data on other zinc preparations as well as studies of the efficacy of prophylactic administration are lacking. Garland ML, Hagmeyer KO. The role of zinc lozenges in treatment of the common cold. **Ann Pharmacother 1998;32:63-9.**

## Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/23/98:

1. Diazepam rectal gel in a ready-to-administer kit, (Diastat®), was added to the formulary. This product is designed for emergency treatment of seizures outside the hospital setting. Prescriptions for this agent are restricted to outpatients or patients seen in the emergency department. Diazepam rectal gel is available in 2.5, 5, 10, 15, and 20 mg strengths. The kit contains two doses, in plastic applicators, and lubricating jelly. For children 2 to 5 years of age, the recommended rectal diazepam dose is 0.5 mg/kg. For children 6 to 11 years, a dose of 0.3 mg/kg may be used. In older children, a dose of 0.2 mg/kg may be given, up to 20 mg.

2. Tiagabine (Gabitril®) was approved for use in the treatment of partial seizures. It is restricted to use by Neurology and Pediatric Neurology. The initial dosage recommended for children $\geq$ 12 years of age is 4 mg taken once daily. Doses may be titrated upwards, based on clinical response, at weekly intervals.

3. Danaparoid (Orgaran®), a low molecular weight heparinoid, was approved for use in those patients requiring anticoagulation who are known to have heparin-induced thrombocytopenia (HIT). The usual adult dosage is 750 anti-$X_a$ units (0.6 ml) SC twice daily. For readers interested in HIT, the February issue of Annals of Pharmacotherapy features a series of 5 cases with a review of the literature (**Ann Pharmacother 1998;32:55-9**).

4. Ropinirole (Requip®), a dopamine receptor agonist, was approved for the treatment of Parkinson's disease.

5. The annual and quarterly results of the Adverse Drug Reaction Reporting Program were presented. For more information, please contact Dr. Michelle McCarthy at 924-8034.

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