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Using Proton Pump Inhibitors in Children

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Proton pump inhibitors (PPIs) offer a distinctly different mechanism for reducing gastric acidity than H_2 blockers or anticholinergics. These agents, omeprazole and lansoprazole, have been found to be successful in the treatment of gastric and duodenal ulcers, including those related to *Helicobacter pylori* infection, gastroesophageal reflux disease (GERD), and chronic hypersecretory conditions such as Zollinger-Ellison syndrome.[1-4]

Mechanism of Action

Omeprazole and lansoprazole act by inhibiting parietal cell H^+/K^+ ATPase, the "proton pump." The PPIs are both prodrugs, which once released from their granular coating, are converted in an acidic environment to the active sulfenamide form. The active drug then forms a covalent bond to cysteine residues of actively secreting proton pumps. As a result of this irreversible bond, the inhibition of gastric acid production is nearly complete and lasts until new pumps are synthesized. Because the PPIs act at the final point of gastric acid production, they are effective regardless of the source of stimulus: histamine, gastrin, or acetylcholine.[1-3]

Indications

The PPIs are currently approved by the Food and Drug Administration for the treatment of gastric and duodenal ulcers, GERD, and hypersecretory conditions in adults.[4]

Use in Children

Despite their indication for adults and the lack of pediatric dosage formulations, PPIs have gained wide-spread use in the treatment of gastric acid disorders in children.[2,5-21] Several groups have examined the efficacy of omeprazole in the treatment of GERD in infants and children.[6-15] In 1993, Gunasekarn and Hassall[6] reported their experience using omeprazole to treat 15 children (ages 10 months to 17 years) with grade 3 or 4 GERD. Therapy was initiated with doses of 10 or 20 mg per day. Patients remained on therapy from 5 to 26 months (average 12 months). Dosages were titrated based on the results of 24-hour intraesophageal pH studies and symptomatic improvement. The effective dose ranged from 0.7 to 3.3 mg/kg/day, with a mean of 2 mg/kg/day. At the 4-6 month follow-up, all patients had healing of erosions and experienced improvement in clinical symptoms.

That same year, Cucchiara et al[7] conducted a randomized, controlled trial in 32 children (aged 6 months to 13 years) comparing omeprazole to ranitidine for refractory esophagitis. Patients received either omeprazole 40 mg/1.73m^2 given once daily or ranitidine 10 mg/kg given twice daily for 8 weeks. Symptomatic improvement occurred in 83% of children given omeprazole and 69% of children given ranitidine. Esophageal healing, as determined by endoscopy, was noted in 75% of the children in the omeprazole group and 62% of the children receiving ranitidine. None of the differences were statistically significant. The authors concluded that omeprazole was as effective as ranitidine in treating GERD in children.

A number of subsequent studies have added support for the role of omeprazole in infants and children with GERD.[9-15] Many of these studies have included children with neurologic impairment who have difficulties with swallowing and severe reflux disease. In these patients, long-term use of omeprazole appears to offer a useful alternative to antireflux surgery.

Although peptic ulcer disease is much less common in children than GERD, there have been reports of using PPIs to heal ulcers and to eradicate *H. pylori*.[16-20] Kato and colleagues[17] studied 22 children (aged 8 to 16 years) with gastric and duodenal ulcers who were given omeprazole as part of a multidrug regimen to eradicate *H. pylori*. Patients received either a dual drug regimen of omeprazole 0.6 mg/kg with amoxicillin 30 mg/kg given twice daily for 2

weeks or a three drug regimen including the first two agents plus clarithromycin 15 mg/kg twice daily. In children with active ulcers, omeprazole was continued for an additional 4 weeks. Comparisons of endoscopic biopsy results from the time of initiation to completion revealed healing of all ulcers. *H. pylori* was eradicated in 70% of the children on the dual regimen and 92% on the triple regimen.

In the past year, several other groups have replicated the success demonstrated in Kato's study using triple drug regimens for a one-week period.[18-20] Researchers from both Sweden and Israel have found a one-week course of omeprazole, clarithromycin, and metronidazole to be 85-90% effective in eradicating *H. pylori* in children.[18-19] Kato's group has also published their results demonstrating the efficacy of lansoprazole as an alternative to omeprazole.[20]

PPIs have been used in children to treat Barrett's esophagus, hyperpepsinogenemia type I with antral G cell hyperfunction (pseudo Zollinger-Ellison syndrome), and complications resulting from gastrocystoplasty. These agents have also been used to reduce gastric residual volume and increase pH prior to surgery, and to improve fat absorption in children with cystic fibrosis.[2,5,21]

Pharmacokinetics and Pharmacodynamics

Both omeprazole and lansoprazole are degraded in an acidic medium. If given alone, the active drug would be degraded in the stomach before reaching the site of activity. As a result, both drugs are produced as capsules which contain enteric-coated granules.[2] Absorption of the drug is rapid once the granules enter the small intestine. Absolute bioavailability of lansoprazole is 80%. The bioavailability of omeprazole is only 30 to 40% with initial doses, but increases with continued administration. Both drugs are more than 95% protein bound.[4]

Both drugs are metabolized by hepatic cytochrome P450 enzymes. Omeprazole is metabolized by CYP2C19, while lansoprazole is metabolized by CYP3A4/5 and CYP2C19 enzymes. Both drugs form inactive metabolites. Approximately 77% of an omeprazole dose is eliminated unchanged in the urine, compared to 33% of a lansoprazole dose. The elimination half-life of omeprazole ranges from 0.5 to 3.5 hours in adults. Lansoprazole has an average half-life of 1.7 hours in adults.[4] There are no pharmacokinetic studies of these agents in children published at this time, but unpublished data suggest a more rapid clearance of omeprazole in children compared to adults.[2]

Half-life is not correlated to duration of action. Duration of gastric acid suppression is better estimated by the length of time that the drugs bind to the parietal H^+/K^+ ATPase enzyme. For both agents, the duration of action in adults is greater than 24 hours, allowing once daily dosing in most patients.[2,4]

Elimination half-life is increased for both drugs in patients with hepatic dysfunction. There is a greater effect on lansoprazole, with area under the curve values increasing by 500% in some patients. It is recommended that the dose of lansoprazole be reduced in patients with significant hepatic disease. No dosage adjustments are necessary for either agent in patients with renal impairment.[4]

Drug Interactions

PPIs have the potential for a number of drug interactions. Because of their effect on gastric acidity, PPIs can reduce the bioavailability of drugs that require a low pH for absorption, such as ampicillin, cyanocobalamin, digoxin, iron, or ketoconazole. Sucralfate decreases the absorption of omeprazole and lansoprazole; administration of these agents should be separated by at least 30 minutes.[4]

The metabolism of omeprazole and lansoprazole by cytochrome P450 enzymes is another potential source of drug interactions. Omeprazole is involved with more drug interactions because of its greater activity at CYP2C19. It inhibits the metabolism of clarithromycin, benzodiazepines, phenytoin, and warfarin. The clinical significance of these reactions is highly variable among patients. Lansoprazole inhibits the metabolism of theophylline. Patients receiving any of these combinations should be closely monitored for signs of drug accumulation.

The drug interaction between omeprazole and clarithromycin is unique. Each drug inhibits the metabolism of the other, resulting in increased serum concentrations of both agents. The result of this interaction may actually be beneficial to the patient during short-term therapy. The success of multidrug regimens to eradicate *H. pylori* may be due to the higher concentrations of the drugs achieved when given together.[3,4]

Adverse Effects

In general, PPIs are well tolerated. The most frequently reported adverse effects during clinical trials in adults and children were diarrhea (3-4% of patients), abdominal pain (1-4%), nausea (1-2%), headache (1-9%), dizziness (1-2%), and rash (1%).[4] The incidence of these adverse effects has not been significantly different between omeprazole and lansoprazole in trials conducted to date.[22]

Omeprazole has been associated with rare cases of pancreatitis, agranulocytosis, and toxic epidermal necrolysis. Some of these cases have been fatal.[4] There have also been reports of interstitial nephritis and optic neuritis with PPI use.[1] All of these severe reactions appear to be idiosyncratic, with no relation to dose.

Laboratory values may be affected by PPI use. Both omeprazole and lansoprazole have been associated with transient elevations in liver function studies. A decrease in hemoglobin and hematocrit levels has also been reported, but appears to occur more frequently in patients treated with lansoprazole.[22]

Concerns for the development of carcinoid changes in gastric cells with long-term PPI use have not been substantiated. It should be noted, however, that hypergastrinemia, histiologic changes in gastric cells (hyperplasia, pseudohypertrophy, and fundic gland cysts), and gastric polyps have all been described in children, as well as adults, receiving PPIs.[2]

Dosing Recommendations

Both omeprazole and lansoprazole are produced as delayed release solid oral dosage forms. Omeprazole is available in 10 and 20 mg capsules (Prilosec®; Astra). For the treatment of GERD or duodenal ulcers, the recommended dose for adults is 20 mg daily. For gastric ulcers, the dose should be increased to 40 mg daily. For eradication of *H. pylori*, the regimen for adults is 20 mg omeprazole with 500 mg clarithromycin and 1 gram amoxicillin twice daily for 10 days. [4]

In case reports and clinical trials, children older than 3 years of age have typically been treated with adult doses. Most papers report the use of 20 mg in children less than 10 years or 30 kg and 40 mg in older, larger children. Some studies have titrated by patient weight, with regimens ranging from 0.2 to 3.5 mg/kg/day. It has been suggested by dose-ranging studies that an optimal starting dose is 0.7 mg/kg/day.[2,6]

Lansoprazole is available in 15 and 30 mg capsules (Prevacid®; TAP Pharm.) In adults, the starting dose for duodenal ulcers is 15 mg once daily; for gastric ulcers or erosive esophagitis, the dose is 30 mg once daily. For duodenal ulcers associated with *H. pylori*, the regimen for adults is 30 mg lansoprazole plus 500 mg clarithromycin and 1 gram amoxicillin twice daily for 2 weeks. [4]

There are limited data in children using lansoprazole. In the study by Kato and coworkers, a lansoprazole dose of 0.75 mg/kg was given twice daily for 1 week as part of a triple drug therapy for eradicating *H. pylori*.

Omeprazole and lansoprazole are formulated in capsules containing enteric-coated granules. The gelatin capsule dissolves in the stomach, releasing the granules. The polymer coating of the granules has been designed to dissolve only at a pH greater than 6, so dissolution occurs in the duodenum. In patients unable to swallow the capsules or in those for whom less than a full capsule is needed, the capsules may be opened and the granules mixed with a slightly acidic substance, such as applesauce, yogurt, or apple, orange, or cranberry juice. The use of an acidic substance preserves the enteric coating of the granules, allowing them to remain intact until they reach the small intestine.[2,5]

Administering the granules provides a similar bioavailability to intact capsules. The primary drawback of this method is the temptation for the patient to chew on the granules. Biting down on the granules not only releases a very bitter taste, but also destroys the protective coating which prevents the contents from being exposed to gastric acid. In addition, patients receiving PPIs through feeding tubes may find the drug-juice slurry clogs the tube.

Several authors have attempted to avoid this issue by administering sodium bicarbonate along with the drug to buffer the stomach. In theory, this method protects the drug from being activated in the stomach, and allows it to pass into the duodenum for absorption.[2] Phillips and colleagues have described a method for preparing an omeprazole suspension using sodium bicarbonate and flavored with root beer for children.[23] Quercia and coworkers have also published their method for creating an extemporaneous omeprazole liquid.[24] These formulations are useful alternatives for children who have not been able to swallow the granules

with juice. Newer formulations that utilize micropellets of drug that more readily mix with liquids is under investigation.

Summary

PPIs are highly effective therapies for ulcers, GERD, or hypersecretory diseases. They provide a high level of gastric acid inhibition with relatively few adverse effects. The primary limitation of this therapeutic class is the lack of a titratable dosage formulation for children.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/26/99:

1. Celecoxib (Celebrex®) was added to the formulary as a second line agent for the treatment of arthritis. Celecoxib is the first agent to be marketed from the new class of selective cyclooxygenase type 2 (COX-2) inhibitors. These agents are designed to provide more specific anti-inflammatory effects with less adverse effects on gastric mucosa. Celecoxib is restricted to the Rheumatology service.
2. An extended-release formulation of niacin (Niaspan®) was also added to the formulary.
3. Tretinoin Microsphere Gel (Retin-A Micro®) was added to the formulary for the treatment of severe acne and other dermatologic conditions.
4. The following nonsteroidal anti-inflammatory agents were removed from the formulary: diflunisal, ketoprofen, and piroxicam.

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