Pharmacological Reflux Therapies

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Principles of Pharmacological Therapies

The management of GERD was revolutionized by the introduction of histamine type 2 receptor antagonists (H2RA) in the 1970s and even more so with the introduction of proton pump inhibitors (PPI) in the 1980s, [1, 2]. The pharmacotherapy for GERD has expanded as our understanding of the mechanisms leading to GERD has advanced from the role of acid to include TLESRs (transient lower esophageal sphincter relaxations) [3, 4] and recognition that nonacid reflux can cause symptoms in some patients. The goals for pharmacotherapy for GERD are to control symptoms, promote gastric and esophageal tissue healing, improve health-related quality of life, prevent complications, and minimize the adverse effects.

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Acid Suppressants

Histamine Type 2 Receptor Antagonists (H2RA)

H2RAs are competitive, reversible inhibitors of the histamine type 2 receptor (H2R) in the gastric parietal cells. They have several advantages over antacids, including longer duration of action (4–8 h), greater efficacy, and prophylactic use.

The most common drugs in this class include cimetidine, ranitidine, famotidine, and nizatidine. Multiple randomized controlled trials (RCTs) in adults with cimetidine, ranitidine, and famotidine show that they are superior to placebo in improving symptoms and healing the esophageal mucosa [5]. Studies have shown that the efficacy of H2R agonist (A)s in achieving mucosal healing is much greater in mild esophagitis than in severe esophagitis [6]. Randomized controlled trials of infants and children with erosive esophagitis showed significant improvement in clinical and histopathology scores in the cimetidine as compared to the placebo-treated group. Similar results have been seen for nizatidine as well [7]. H2RAs have relatively short duration of action, a disadvantage when compared with PPIs as well as the development of tolerance, and incomplete inhibition of acid secretion [8].

Proton Pump Inhibitors (PPI)

PPIs are the most potent antisecretory agents, which irreversibly bind to the hydrogen-potassium

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ATPase pump in parietal cells, thereby blocking off the final common pathway in gastric acid secretion. PPIs maintain a higher pH for a longer length of time and inhibit all stages of acid secretion including meal-induced gastric acid secretion which results in improved efficacy.

Studies in adults demonstrate faster and better healing of erosive esophagitis with PPIs than with H2RA [9]. The drugs in this class include omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole. Omeprazole and esomeprazole are approved for use in pediatric patients in Europe and the United States. Lansoprazole is approved for pediatric patient use only in the United States. None of the PPIs are approved for use in infants to date.

Prokinetics

Prokinetic agents enhance gastrointestinal motility, resulting in better esophageal clearance and faster emptying of the stomach contents. They can also effect transient lower esophageal sphincter relaxation (TLESR) [10]. They tend to improve symptoms of regurgitation and vomiting. These drugs work through a variety of different mechanisms. The prokinetic agents include cisapride, metoclopramide, erythromycin, domperidone, bethanechol, and baclofen. Many have significant side effects and there is scarcity of data on their benefit in children [11]. Therefore, they are used in carefully screened patients where their potential benefit outweighs risks.

Adjuvant Therapies

Adjuvant therapies in the treatment of GERD include antacids and surface agents. These tend to provide immediate relief but are recommended for short-term use only.

Antacids

Antacids provide quick but short-lasting symptom relief from GERD. Their effect lasts 1–2 h. Most antacids have magnesium with either aluminum hydroxide or calcium carbonate. They neutralize gastric acid and protect the esophageal mucosa from exposure to acid in the refluxate. In treating esophagitis, pediatric studies have demonstrated that high-dose antacids can be as effective as H2RAs over a 12-week period [12]. However, they are not recommended for chronic because of concern of toxicity especially with aluminum-containing compounds. They are usually used in older children for symptomatic relief.

Surface Agents

Surface-active agents like sodium alginate and sucralfate form a protective coating over the mucosal lining of the stomach, thereby providing a barrier from gastric acid and pepsin. Sucralfate was shown to be as effective as cimetidine in the treatment of peptic esophagitis [13]. Concern for aluminum toxicity from these agents prohibits its chronic use in pediatrics.

Bismuth Compounds

Bismuth compounds include bismuth subsalicylate (BSS) and colloidal bismuth subcitrate (CBS). Bismuth is converted to insoluble complexes by gastric acid and preferentially deposited over ulcer beds where they combine with exposed protein moieties to form a glycoprotein-bismuth complex, providing a barrier from acid and pepsin. They are particularly useful in the treatment of *Helicobacter pylori*-induced disease as they inhibit urease and phospholipase enzymes produced by the bacteria, which help them survive in the acidic environment of the stomach. They are also useful adjuncts in the eradication of resistant *H. pylori* infection in an adults and children [14]. Higher doses and long-term use are associated with significant risks including neurotoxicity, nephrotoxicity, gingivostomatitis, colitis, and osteoarthropathy [15]. The salicylate moiety of BSS does get absorbed by the body and has the potential for causing Reye's syndrome and significant bleeding in patients with coagulopathy or gastrointestinal ulcers.

Combination Therapy

Often, a combination of various pharmacologic agents is used, such as a combination of H2RA and PPI or an acid suppressant and a prokinetic.

In very severe cases of GERD, a combination of pharmacotherapy with acid suppressants and motility agents along with surgical management could be employed.

Combination therapy involves utilization of pharmacologic agents with the same desired effect- such as a combination of acid suppressants. For example, in patients with nocturnal acid breakthrough (NAB) on PPI therapy, the addition of H2RA has shown to be of significant benefit [16]. In an adult study, 64 % of individuals on twice daily doses of a PPI had NAB. The addition of a nighttime dose of an H2RA to the PPI regimen decreased the acid exposure as measured by impedance and pH probe in all but 17 %.

Combination therapy with an acid suppressant and prokinetic may be beneficial in certain groups of patients. These include patients with nonerosive reflux disease who continue to be symptomatic [17]. Patients with certain underlying diseases that predispose to more severe GERD or exacerbation of other systemic diseases like chronic asthma and cystic fibrosis have benefited from combination therapy. In a pediatric study involving children with nonatopic asthma, the group of children receiving a combination of esomeprazole and metoclopramide had much better control of asthma, as good as the control group of children who had undergone fundoplication, while a second group that received only ranitidine alone had significantly more exacerbations [18].

Combination therapy can also be useful in neurologically impaired patients to improve quality of life and decrease the risk of aspiration if they continue having obvious regurgitation and vomiting [19]. Combination therapy also has a role in GERD made worse by abnormal esophageal motility secondary to repaired tracheoesophageal fistula and gastroparesis.

Step-Up vs. Step-Down Therapy

The initial diagnosis of GERD, in children and adults alike, is often based on clinical symptoms. Treatment is initiated to observe a response to therapy and adjustments are made as needed. The dilemma of optimizing treatment and avoiding aggressive therapy when it is not justified or an ineffective approach in patients with severe symptoms or warning signs often dictate the treatment applied. Cost-effectiveness will also influence the treatment [20].

Step-up therapy is usually preferred for mild GERD. It includes lifestyle changes and use of less potent acid suppressants. H2RA are typically employed instead of PPI. Therapy can be escalated by increasing the dose of the medicine or switching to more potent agents as indicated by clinical progression or further evaluation. It could also result in employing combination therapy with acid suppressors and prokinetics. The benefits of this approach are initial low cost of therapy, avoiding unnecessary medication, and decreased side effects from medication.

Step-down approach usually implies the use of potent medications like PPIs in adequate doses and then decreasing the dose or switching to an H2RA as the condition improves. It is employed in endoscopically proven severe GERD or if there are red flags indicating the presence of severe disease. The advantages to this approach are institution of very effective therapy in patients warranting aggressive treatment. It might even be more cost-effective by avoiding potential need for surgery in patients with complications of severe disease.

Common Pharmacologic Agents

Histamine Type 2 Receptor Antagonists

H2RAs reduce gastric acidity by inhibiting the histamine type 2 receptors in the gastric parietal cells. They tend to have a moderate effect on symptoms and healing in patients with esophagitis and are not very effective for severe erosive esophagitis. Their effect appears to be dose related. The knowledge that histamine resulted in gastric acid secretion led to the discovery of cimetidine, the first H2RA introduced in the late 1970s. Other agents subsequently introduced were ranitidine, famotidine, and nizatidine.

Pharmacology

Cimetidine is a 2-cyano- 1-methyl-3-(2-[(5-methyl- 1*H*-imidazol- 4-yl) methylthio] ethyl) guanidine. Replacement of the imidazole ring of cimetidine with furan ring resulted in the development of ranitidine and replacement of the imidazole ring with a 2-guanidinothiazole ring resulted in famotidine. These substitutions resulted in much better tolerability, longer-lasting action, and increased activity. Nizatidine was formed by the substitution of the furan ring of famotidine with a thiazole ring. In general, the latter three are much more potent than cimetidine.

Cimetidine and ranitidine show peak plasma concentration within 90 min of oral administration [21, 22]. They start reducing gastric acidity within 30 min of ingestion. H2RA reduce acid secretion stimulated principally by histamine and to a small extent that by gastrin and cholinomimetic agents through two mechanisms. First, histamine released from enterochromaffin-like (ECL) cells by gastrin or vagal stimulation is blocked from binding to the parietal cell H2-receptor. Secondly, in the presence of H2-receptor blockade, gastrin or acetylcholine has a diminished effect on acid secretion by direct stimulation. H2RAs are particularly effective at inhibiting nocturnal acid secretion, which depends largely on histamine. They have a modest impact on meal-stimulated acid secretion which is stimulated by gastrin and acetylcholine, as well as histamine. The H2RAs suppress acid secretion in a linear, dose-dependent manner [23, 24]. The volume of gastric secretion and the concentration of pepsin are also reduced.

Cimetidine, ranitidine, and famotidine have high first-pass metabolism reducing their bioavailability to about 50 %. Nizatidine undergoes very little first-pass metabolism and has a higher bioavailability [25]. Meals do not affect the bioavailability of H2RAs, but concurrent administration of antacids reduces their bioavailability by 10–20 %. Their effect lasts for about six hours. The response can be prolonged by administering more frequent or higher dose. Intravenously administered H2RAs have a 100 % bioavailability, and therefore, the dose has to be adjusted depending on the route. H2RAs can be effectively administered mixed in parenteral nutrition solutions [26]. H2RA cross the blood-brain barrier and are also secreted in breast milk [27].

H2RAs are cleared by a combination of hepatic and renal mechanisms. Cimetidine is principally metabolized in the liver and then excreted by the kidneys. Famotidine, ranitidine, and nizatidine rely on glomerular filtration and renal tubular secretion for their excretion. Therefore, the dose of all H2RA has to be decreased in renal failure and in premature neonates. The dose does not need to be adjusted in liver disease [1].

Toxicity

H2RA are generally considered to be very safe [28]. However, there are side effects that can mainly be categorized as idiosyncratic reactions, those due to drug-induced hypergastrinemia, and drug-induced hypochlorhydria.

Commonly reported side effects include headache, constipation, nausea, and skin rash. Cimetidine has the highest side effect profile of all the drugs in this class. H2RAs can be associated with different CNS side effects like confusion and mental depression. Cimetidine can especially cause these symptoms in patients with liver failure or renal impairment. In young children and infants, H2RAs can cause symptoms of irritability, headbanging, headache, or sleepiness. Unless the clinician is vigilant, these adverse reactions can be misconstrued as a manifestation of reflux and might result in even a higher dose being prescribed [29]. H2RAs can cause idiosyncratic and immune-mediated reactions like myelosuppression, hemolytic anemia, interstitial nephritis, and fever [30–33]. Cimetidine binds to androgen receptors and results in gynecomastia and other antiandrogen effects in adults [34]. These are generally not seen with other H2RAs.

Prolonged acid suppression has been associated with hypergastrinemia in animal studies [35]. Increased gastrin results in proliferation of enterochromaffin cells, which have been associated with carcinoid tumors [36]. However, its clinical significance in humans has not been demonstrated. Acid in the stomach serves as one of the primary lines of defense against ingested microbes. Prolonged acid suppression has been

associated with increased rates of community-acquired pneumonia in adults and children [37], gastroenteritis in children including *Clostridium difficile* [38, 39], candidemia, and necrotizing enterocolitis in preterm infants [40]. Decreased acid secretion has also been tied to vitamin B12 deficiency in adults [41].

Drug Interactions

Cimetidine binds to the cytochrome P450 enzyme in the liver which is responsible for metabolizing several other drugs. Therefore it may decrease metabolism of a wide number of drugs that rely on this pathway. These include cisapride, anticonvulsants, and benzodiazepines. Ranitidine does not bind avidly to the microsomal cytochrome P450 system and therefore does not interact with medications processed through this pathway. Famotidine and nizatidine do not bind to cytochrome P450 [42].

H2RAs can decrease the absorption of antifungals, cephalosporins, and certain iron compounds that rely on the gastric acidity for conversion to the ferrous form. Acid suppression can also decrease the effect of mesalamine preparations that are pH dependent by causing their premature release.

Drug Resistance

Prolonged use of H2RAs orally or parenterally has been shown to lead to tolerance of their antisecretory effect. A study analyzing intravenous ranitidine in children found loss of the antisecretory effect after 6 weeks of therapy [43]. Tachyphylaxis has been demonstrated in healthy adults with cimetidine, ranitidine, famotidine, and nizatidine [44]. Another study in adults demonstrated rapid development of tolerance over 1–2 weeks. With H2RA given in a single evening dose, tolerance was only evident during the night, whereas tolerance occurred throughout the day and night with the three- and four-times-a-day regimens [45].

Proton Pump Inhibitors

Proton pump inhibitors are very strong acid suppressants and are used in a wide variety of acid peptic disease [46]. They irreversibly inhibit the proton pump, thus blocking the effect of any stimulation for the life of the pump. There are six main PPI drugs: omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole.

Pharmacology

Omeprazole, lansoprazole, and pantoprazole contain as their core structure, 2-pyridyl methylsulfinyl benzimidazole.

These PPIs differ in their substitution patterns. They are basic compounds with a pKa of around 4.0 (except rabeprazole, with a pKa of 5), becoming activated when the pH of the medium is below their pKa [47]. The rate of conversion to the active form is inversely proportional to the pKa; rabeprazole is the PPI with the highest rate of conversion, followed by omeprazole, lansoprazole, and pantoprazole [48].

After oral administration, the PPIs are absorbed as prodrugs in the small bowel and enter the gastric parietal cells, from where they reach the extracellular canaliculi. At this site, due to the acid medium, they are transformed into the active form, which selectively and irreversibly binds the proton pumps.

Proton pumps (K^+-H^+ ATPase) situated in the parietal cell triggered by a cascade in response to three main stimuli, namely, histamine, acetylcholine, and gastrin. The pumps transport the H^+ ion against the steepest concentration gradient in the body, of 3,000,000:1. Chloride is diffused into the canaliculi of the parietal cell, to join with the H^+ ion to produce hydrochloric acid. The pump is a member of the ion transporting, P-type ATPase family or the ion-motive-phosphorylating ATPase family [49]. This family extends from bacteria to mammals. The classification depends on finding that ion-transport is coupled to a cycle of phosphorylation and dephosphorylation of the enzyme. It is made of two subunits: a larger catalytic alpha subunit responsible for the transport and catalytic functions and a smaller 300 amino acid beta subunit responsible for structural and membrane-targeting functions. The pumps have a relatively large cytoplasmic domain, a membrane domain, and a small extracytoplasmic

domain. The latter two domains are relevant to the mechanism and design of acid pump inhibitors.

The drugs designed to inhibit the pump, bind to it covalently. Thus, the pump has to be synthesized de novo to reestablish acid secretion, though some loss of compound may also occur. The pump half-life has been shown to be about 72 h [50]. The formation of disulfide bridges between the PPI and cysteine residues of the alpha subunit of the ATPase produces inhibition of acid secretion for up to 36 h [51]. The proton pumps are in an inactive state in cytoplasm. After stimulation, such as a meal, the pump is translocated to the membrane of the canaliculus, where it is activated. To inhibit this, omeprazole must reach a sufficient plasma concentration.

The pump turnover however is a dynamic process that varies by the canalicular: tubular ratio of the parietal cell [49]. In a generally stimulated state of the parietal cell, most of the pump population is present in the secretory canaliculus, while in the resting state, the pump is in the cytoplasmic tubules and not associated with the canaliculus. Since the major degradative pathway for the pump, inhibition of acid secretion, which generates decreased canalicular area, leads to decreased pump turnover as occurs with acid blocking agents such as ranitidine. Thus pump inhibitors that change the distribution between tubules and canaliculi change the half-life of the pump.

The duration of suppression of acid secretion does not depend on the peak concentration reached but on the area under the plasma concentration-time curve of the drug. The increase in the dose or the decrease in the dosage interval produces a nonlinear increase in the area under the curve (AUC) of omeprazole. This fact is due to the slower clearance and the effect of the hepatic metabolism [51].

Summary of Pharmacokinetics

These drugs are absorbed rapidly from the gastrointestinal tract. The time needed to reach the peak plasma concentration varies for the different kinds of PPIs.

In the case of immediate release formulations, the T-max was as short as 10 min and from 30 to 300 min for delayed release formulations. The T-max is longest for rabeprazole and shortest for immediate release omeprazole. After absorption, it is rapidly eliminated from the plasma, and in most cases, all the active drug is metabolized in 3–4 h.

The effect of reducing the acidity as measured by the effective time pH remains above 4 is not affected by the plasma drug concentration [52]. It appears to be related to the AUC. Thus in most cases, the drug is rapidly eliminated from the system, but the effect lasts 3–4 days.

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