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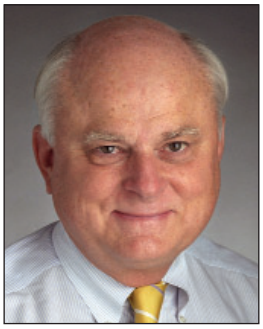
Pharmacological Management of Chronic Gastroparesis

John A. Bonino



Richard W. McCallum

The aim of this article is to provide the practicing gastroenterologist and trainee as well as internists and primary care physicians a broad based review of pharmacological therapy available for the medical management of patients with chronic gastroparesis. We emphasize aggressive combination treatments involving antiemetics, prokinetics, and analgesics and discuss guidelines for clinicians to achieve symptomatic control of this very challenging clinical entity. Advances in understanding the mechanisms associated with chronic nausea and vomiting, as well as gastric stasis, have set the stage for therapies which are better targeted to underlying pathophysiology as well as for more rational pharmacologic approaches.

INTRODUCTION

Gastroparesis continues to be a challenging area of gastroenterology that can be a source of frustration for patients and clinicians alike. Gastroparesis is a symptomatic, chronic disorder characterized by delayed gastric emptying in the absence of anatomic evidence of mechanical gastric outlet problems or intestinal obstruction. Causes of gastroparesis are numerous and run the spectrum from metabolic and endocrine disorders, collagen vascular disease, post-surgical and vagotomy settings, medication induced, to idiopathic in nature (1). Treatment of this complex disorder has centered around pharmacologic and dietary therapy for a number of years, and more recently the role of gastric neuro-stimulation for the more severe cases.

Symptoms attributed to this entity are quite variable but include: early satiety, postprandial fullness, nausea, vomiting, bloating, and abdominal discomfort (2). Though there is much discussion surrounding various methods for assessment of gastric motor function and dysfunction, most centers utilize scintigraphic techniques involving isotope labeled meals as an objective measurement of gastric emptying.

(continued on page 46)

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(continued from page 44)

Pharmacological therapy for gastroparesis has been based around utilization of several therapies that control either the symptoms of gastroparesis or address gastric emptying. while accompanying adjuvant medications may focus on achieving control of the underlying problem. (e.g., diabetes).

ANTIEMETICS

Commonly encountered antiemetic agents, that are frequently utilized, act both on peripheral and central neural structures that explain the cascade leading to nausea and vomiting.

Phenothiazines are dopamine receptor antagonists that act at the level of the chemoreceptor trigger zone in the medulla oblongata and include prochlorperazine and promethazine. These agents may be administered in a variety of ways including tablet, liquid suspension, suppository, or injection. Unfortunately, side effects in this class are relatively common and include sedation and as well as extrapyramidal effects (3). Parenteral prochlorperazine has undergone increased scrutiny recently by the FDA, cautioning its use due to several reports of associated tissue necrosis.

Antihistamines, acting on H_1 receptors, exhibit central antiemetic affects and include diphenhydramine, dimenhydrinate, and meclizine. These agents are best known for their efficacy in nausea secondary to motion sickness, through effects on H_1 receptors in the vestibular apparatus (3). Scopolamine, a nonselective muscarinic antagonist, blocks cholinergic signaling from the vestibular system to the CNS. It is available both as a transdermal patch and in an oral formulation (Scopace). The oral formulation may be particularly useful in individuals with skin reactions to the transdermal attachment and is dosed from 0.4 mg-0.8 mg up to four times a day as needed. The 1.5 mg transdermal patch is placed behind the ear, and replaced every three days. Scopolamine's anticholinergic affects may include drowsiness, fatigue, and blurred vision (3). The anticholinergic activity of this drug does not appear to worsen gastroparesis or significantly counteract the activity of prokinetic agents.

Serotonin (5-HT_3) receptor antagonists represent a newer generation of antiemetics including ondansetron, granisetron, and dolasetron. Their primary indication is prophylaxis of chemotherapy and radiation induced nausea and vomiting. In gastroparesis patients, given orally, these agents may be superior to some of the older antiemetics, but their significant cost may limit their use as chronically administered oral agents. There may be a defendable role for these agents when given as 4 mg doses for "back up" once per day or less. For now, their main role is intravenous use in inpatient or emergency department settings during prolonged vomiting episodes. These agents are believed to act primarily in the medulla oblongata to exert their antiemetic effect (4). Several studies now seem to demonstrate the efficacy of this class in the gastroparetic setting and also indicate that they do not further delay gastric emptying (5,6).

Tricyclic antidepressants may also exhibit antinausea effects that may be of use in the gastroparetic population (7,8). In a recently published retrospective study of diabetic patients with at least moderately severe chronic nausea and vomiting, tricyclic antidepressants provided moderately improved symptomatic nausea control in 86% and complete symptom resolution in 14% of a subset of patients with documented delayed gastric emptying (8). Dosages of tricyclic antidepressants (amitriptyline, nortriptyline, desipramine) in the study ranged from 10–75 mg/day. Our center utilizes both amitriptyline and nortriptyline with starting dosages between 10–20 mg administered at bedtime. This dose is titrated up over several weeks, in 10mg increments, to a nightly dosage of 50–100 mg. Anticholinergic and sedative side effects may limit the maximum dosage achieved.

Other drugs with antiemetic effects have also been adopted for the gastroparetic population. Among those, benzodiazepines and cannabinoid derivatives, have gained special attention. Lorazepam and diazepam, are two benzodiazepines frequently used for anticipatory nausea and vomiting before administration of chemotherapy. These agents can be of particular use in patients where anxiety plays a key role in their symptoms. Cannabinoid use in chemotherapy induced nausea and vomiting was the subject of a recent systemic review utilizing data from over thirty randomized trials with comparison to either antiemetics or placebo (9). This meta-analysis concluded that cannabinoids may be useful as mood enhancing adju-

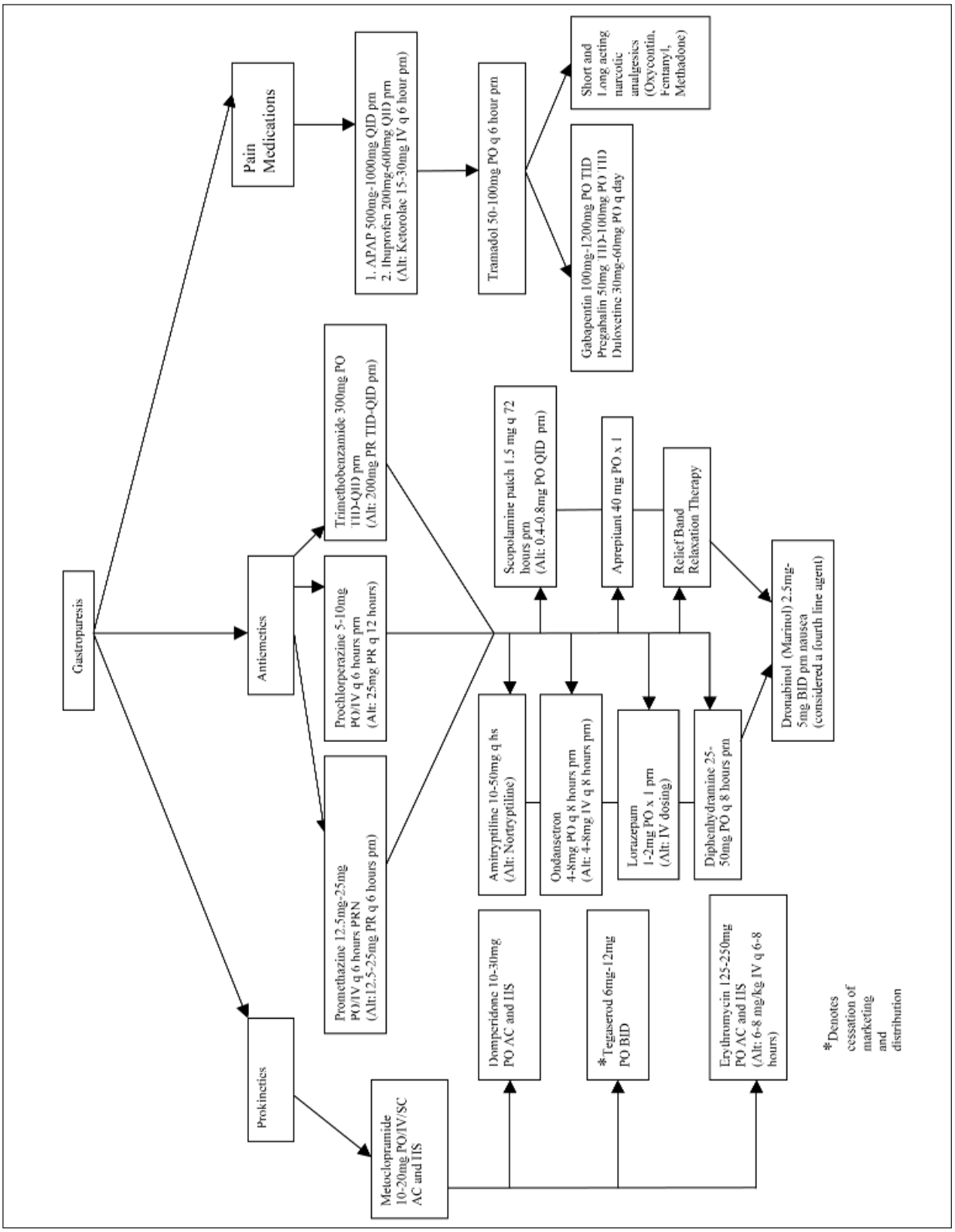

Table 1: A proposed pharmacological treatment algorithm for chronic gastroparesis emphasizing and maximizing the concept of combination therapy to quickly gain effective symptom control. The strategy is in-line with the "step-down" approach where once achieving amelioration of symptoms, a tapering schedule can then be slowly attempted.

vant for controlling chemotherapy related nausea. We assign a priority of "third line" therapy to dronabinol (Marinol) in the gastroparetic population at a dosage of 2.5 mg to 5 mg BID as an adjuvant to improve both nausea as well as help poor appetite and weight loss (Table 1). Careful patient selection and close monitoring for adverse reactions such as sedation, dizziness, and other psychotropic effects is required.

Apepritant (Emend), a substance P and neurokinin 1 receptor antagonist, has been gaining increasing acceptance in the oncologic community as an adjuvant to traditional antiemetics given for chemotherapy induced nausea and vomiting (10). Several studies now suggest its potential benefit in chemotherapy induced nausea and vomiting when used in conjunction with other antiemetics (11–14). Common side effects may include constipation, fatigue, nausea, and diarrhea. A common dosing regimen for nausea, while using highly emetogenic chemotherapy, is 125 mg on day one of chemotherapy followed by 80 mg/day for days two through four. Aprepitant's utility and appropriate dosing in gastroparetic patients is unknown. Our personal experience has been utilization of this drug in an adjuvant role to other antiemetics, largely due to cost and availability.

A novel technique of controlling nausea without any adverse events involves acupuncture at P6 acupuncture point, with a wrist band containing an electrode that stimulates the median nerve of the nondominant hand (Relief Band).

PROKINETICS

The main class of drugs frequently utilized in treatment of gastroparetics are those with prokinetic properties. Prokinetic medications promote antral contractility, correct gastric dysrhythmias, improve antroduodenal coordination, and in some cases accelerate small bowel and colon transit leading to better segmental and total gut transit as well as improving absorption and nutrition. Certain prokinetics such as domperidone and metoclopramide also demonstrate antiemetic qualities. In general, these medications are dosed approximately 30 minutes before meals to maximize clinical benefit. Nighttime doses are also administered to facilitate nocturnal gastric emptying of solids, and augment the fasting motor pattern particularly phase 3 of the migrating motor complex (the "intestinal housekeeper"). Response to these agents is often judged clinically rather than with scintigraphic studies which appear to correlate poorly with symptoms (15).

Metoclopramide has been utilized for over a quarter of a century to treat gastroparesis and carries an FDA indication for this use. The drug exhibits both prokinetic and antiemetic actions. It releases acetylcholine from intrinsic myenteric cholinergic neurons via both activation of 5-HT_4 receptors and inhibition of dopamine receptors. It also exhibits weak 5-HT_3 receptor antagonism (1). Its prokinetic properties are largely confined to the proximal gut where it increases esophageal, fundic, antral, and duodenal contractile amplitudes.

The efficacy of this drug is often limited by side effects observed in both short and long-term use as well as the potential development of tolerance. Extrapyramidal reactions, such as torticollis, akithesia, tremor, and insomnia are common. This can at times be reversed by use of oral or IV diphenhydramine. Up to half of patients may report somnolence while on metoclopramide (16). Parkinson-like symptoms, depression, and prolactin related events can occur in anywhere from 1%–15% (17,18). The most feared symptom is tardive dyskinesia and consists of involuntary movements of the face, tongue, or extremities. These effects may not be reversible on discontinuation of the medication. One study showed a relative risk for tardive dyskinesia of 1.67 (95% confidence interval, 0.93 to 2.97), and relative risk for drug-induced parkinsonism of 4.0 (95% confidence interval, 1.5 to 10.5) in those treated with metoclopramide compared to controls (19). In addition to stopping metoclopramide, benztropine (Cogentin) at doses of 1 to 2 mg orally daily can help reverse some of the Parkinsonian rigidity induced of this prokinetic agent.

Metoclopramide can also aggravate underlying depression, and caution must be used in this patient population. Other reported side effects include breast engorgement, lactation, and menstrual abnormalities which are likely due to increased prolactin secretion associated with the drug. Overall it is estimated that up to 40% of patients are not able to be maintained on this

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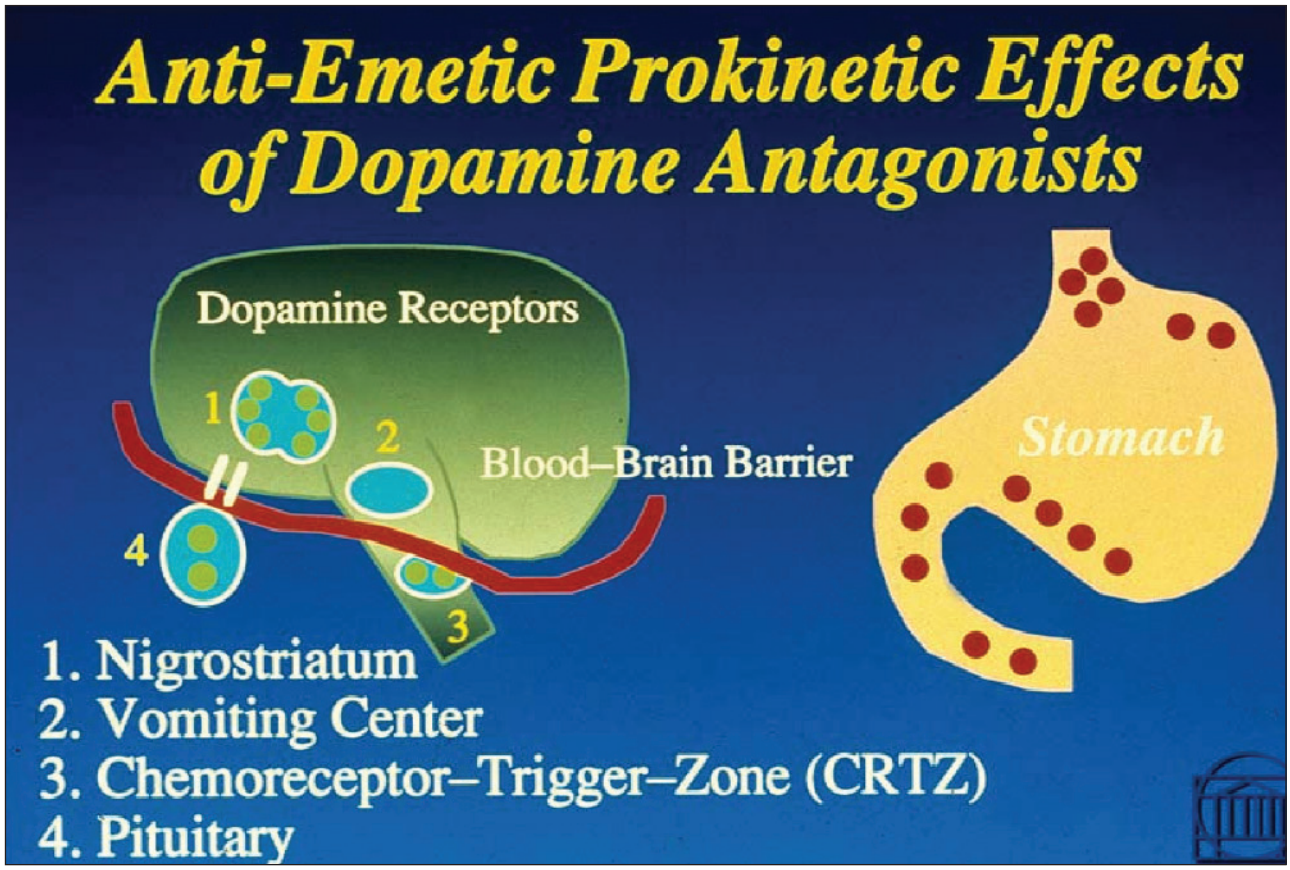

Figure 1: Depiction of the mechanisms of both antiemetic and prokinetic action of dopaminergic receptor antagonists and the distribution of dopamine receptors centrally and peripherally.

agent due to side effects. The medical-legal ramifications of metoclopramide are not to be taken lightly (20). Detailed documentation in the medical record of discussions regarding side effects of the drug with the patient and family are very important, not only at the initiation of treatment, but also during followup visits.

The usual starting dose of metoclopramide for adult patients is 10 mg, 30 minutes before meals and at bedtime. This dosage can be increased up to 20 mg three to four times daily (mealtime and bedtime) if response is suboptimal and there are no side effects. This drug may also be given as a liquid suspension. Its intravenous injection dosing interval can range from 10 mg every six hours, to every two hours as needed in those with more severe symptoms. In addition, subcutaneous dosing may be useful particularly at home, guaranteeing adequate absorption when vomiting is imminent or occurring. A subcutaneous dosage of 10 mg, given one to four times daily, as tolerated, can supplement oral dosing on an "as needed" basis (21). This guarantees absorption of the drug to a plasma level similar to intravenous use, and then can be slowly tapered (21).

Domperidone (Motilium) is a peripherally acting dopamine-2 receptor antagonist. The effects of domperidone on the upper gut are similar to those of metoclopramide (22). Domperidone, however, does not, or only minimally crosses the blood-brain barrier, and therefore appears to have a superior CNS side effect profile compared to metoclopramide (Figure 1) (16). Domperidone exhibits its antiemetic effects via action on the area postrema of the brainstem. Several randomized trials have shown a positive effect of domperidone in the symptomatic control of diabetic gastroparesis (24–27). Also, domperidone has provided symptom relief and improvement in quality of life in patients with

different etiologies of gastroparesis (23). Dosing of domperidone begins at 10mg before meals and at bedtime. This dose can be increased as needed up to 30 mg AC and q HS. A sufficient trial of the drug is required to assess activity of the drug, and this should be at least two months of therapy at the maximal dose of 120 mg/day. The most common side effects of domperidone, seen in <10% of patients, relate to induction of hyperprolactinemia and include breast enlargement, galactorrhea, and irregular menses. An intravenous form of the drug was removed from the market in the 1980s due to generation of cardiac arrhythmias. The oral formulation of the drug is currently only available through an IND (investigational new drug) application from the FDA for use in the United States, and access to purchasing the agent is through Canada, New Zealand and a compounding pharmacy in Texas. Further information on obtaining an IND for use of the drug can be found at http://www.fda.gov/cder/news/domperidone.htm. This type of protocol can be obtained by any physician. The FDA provides an IND and the protocol is passed by a local institutional review board. Our institution utilizes an informed consent document before initiating therapy and ECG evidence of a QT interval <470 milliseconds. This has allowed more extensive availability to our patients who carry information about domperidone with them which can be informative to the other physicians involved in their care.

Tegaserod, an aminoguinidine compound, is a partial 5-HT_4 receptor agonist that has been approved for treatment of constipation predominant IBS in women and for constipation in both men and women under age 65. 5-HT_4 receptor activation appears to further augment the peristaltic reflex in the intestinal tracts of both animals and humans (28). Prather and colleagues demonstrated that Tegaserod at doses of 2 mg BID, accelerated orocecal transit time in patients with constipation-predominant IBS (29). Utilizing scintigraphic methods of measurement, Degen and colleagues have demonstrated that tegaserod accelerated gastric emptying, small bowel transit, and colonic transit in both healthy male and female volunteers utilizing 6 mg BID compared to placebo (30). These prokinetic effects have been especially prominent in males (31). In several unpublished studies, and in abstracts from presentations, tegaserod was shown to accelerate solid-phase gastric emptying in patients with gastroparesis at doses higher than those used for constipation predominant IBS (32). Our recommendation is to increase tegaserod dosing slowly from 6 mg BID to TID and 12 mg BID or 6mg QID, keeping in mind that diarrhea may limit dosing.

Shortly before this publication, on March 30, 2007, Novartis Pharmaceuticals (in response to an FDA request) suspended its U.S. marketing and sales of tegaserod. A retrospective analysis of a pooled clinical trial database of over 18,600 patients showed a statistically significant difference in cardiovascular events in those taking tegaserod (0.11%) compared to placebo (0.01%). There was no specific dosing or time frame related to when the events occurred. One possible explanation is that tegaserod is also a partial 5-HT_1 receptor antagonist. Sumatriptan (Imitrex), also is a 5-HT_1 agonist, and its profile includes chest pain aggravating angina. Genetic polymorphism could favor 5-HT_1 dominance in a rare subset of patients receiving tegaserod. We are hopeful that as the profile of patients at increased risk for cardiovascular problems while on tegaserod is identified, utilization of this drug may recommence. Until that time, limited use through an IND may be considered and access may be obtained by calling the following telephone number, 1-888-NOW-NOVA, through Novartis Pharmaceuticals.

Macrolide antibiotics have also received much attention as adjuvant medications to domperidone and metoclopramide for their motilin receptor agonist properties. Though most effective when used intravenously, both intravenous and oral forms of erythromycin have been shown to improve gastric emptying, and produce significant improvement in symptoms of both idiopathic and diabetic gastroparetics. The intravenous dosage is 2–3 mg/kg every six to eight hours for post-operative and other ileus settings. The oral dosing ranges from 125 mg–250 mg three times daily before meals and should be given as a suspension to facilitate emptying and absorption in gastroparesis (33). Concerns about precipitation of potentially life-threatening arrhythmias has limited its use, particularly in the setting of agents such as fluconazole and itraconazole which inhibit the hepatic cytochrome coenzyme CYP 314 (34). Increasing interest surrounds newer generation macrolides such as

azithromycin. A recent paper, submitted in abstract form only, compared manometric data from 10 patients undergoing infusion with erythromycin 200 mg IV versus azithromycin 500 mg IV. The results suggested similar potent stimulation of antral activity between the two drugs with a longer duration of activity for azithromycin (35). Further development of novel non-antimicrobial motilin receptor agonists continues to evolve and one of these, mitemcinal, appears to be the most promising (36).

Cisapride was an agent utilized for gastroparetics in the past although its official FDA approval in 1989 was for nocturnal reflux symptoms. A 5-HT_4 agonist, this drug facilitated the release of acetylcholine from myenteric cholinergic nerves throughout the gut stimulating antral and duodenal contractions, and acceleration of gastric emptying (1). Unfortunately, post-marketing surveillance identified a number of cases of cardiac arrhythmias and sudden cardiac death thought related to the direct action of cisapride on cardiac potassium channels resulting in QT prolongation. The drug was withdrawn from the U.S. market in 2000, and now is only available through compassionate-use/limited access programs under strict patient monitoring through Janssen Pharmaceutica.

The compound ATI-7505 is derived from cisapride, but is devoid of cardiotoxicity and is not metabolized by the cytochrome P-450 system. It is currently being evaluated by Proctor and Gamble, and may offer a new alternative for gastroparetic patients in the future.

CHRONIC ABDOMINAL PAIN

We have found that chronic abdominal pain is a common and important aspect as well as a therapeutic challenge in many gastroparetic patients. One study suggested that abdominal pain may occur in up to 89% of patients with gastroparesis (37). The abdominal pain is usually in the upper abdomen and epigastric region. The pathogenesis of abdominal pain and discomfort in patients with gastroparesis is poorly defined. The degree of abdominal pain and severity of gastric empyting delay appear to be poorly correlated. Poor gastric accommodation, hypersensitivity to gastric distention, effects of retained gastric acid and bile, and autonomic neuropathy have all been suggested as potential mechanisms to explain the abdominal pain in gastroparesis (once gallbladder disease has been excluded).

Concerns over use of pain medications in gastroparetics has centered around difficulties with predictable intestinal absorption and the negative effects on worsening the impaired motility state. Our center initially utilizes acetaminophen and NSAIDs as first line therapies. Since endogenous prostaglandins may have a role in gastric dysrhythmia, we frequently utilize intravenous ketorolac to interrupt gastric dysrhythmias in inpatient diabetic gastroparetics with both nausea/vomiting and abdominal pain, while closely monitoring for renal toxicity (38). Pimentel and colleagues, in an abstract, have reported improvement in symptoms and EGG (electrogastrography) detected bradygastric rhythms by use of indomethacin (39).

Tricyclic antidepressants represent the oldest class of antidepressant medications in the pharmaceutical armamentarium. These medications have been demonstrated to be effective in relieving not only depression, but a variety of chronic pain syndromes as well, especially those in which neuropathic elements are prominent. In addition to reducing sensitivity and pain, these medications may be useful as they stimulate appetite and weight gain, as well as promote sleep. All of the tricyclics are at least moderately sedating, and are typically dosed in a single daily dose at or shortly before bedtime. Daytime dosing is not recommended because of their propensity for causing excessive daytime sedation. Patients initiating tricyclic antidepressant therapy should be well-educated about these possible side effects, as well as other common side effects. Of these other side effects, the most problematic is orthostatic hypotension. Patients should be cautioned against sudden changes in position (from lying or sitting to standing, in particular) due to the potential for falling. Of note, tricyclic antidepressants have the potential to produce palpitations and intracardiac conduction slowing. For this reason, if there is any question about the patient's cardiac status, obtaining an ECG prior to initiation of therapy is recommended, with serial follow-up studies as needed.

Among these medications, perhaps the best-known and most widely used is amitriptyline. Many

psychiatrists, however, prefer to use two other medications, nortriptyline and desipramine, due to their better side effect profile. Both nortriptyline and desipramine still produce the beneficial effects on appetite and sleep, but may be less prone to cause problematic side effects such as dry mouth, constipation, and orthostatic hypotension. Other tricyclic antidepressant medications have demonstrated their usefulness in treating pain and depression, but there is little reason to believe that a patient who fails to respond to one tricyclic will be likely to respond to another.

Dosing of amitriptyline, nortriptyline, and desipramine is similar, and all can be started at 10–25 mg dosed nightly. The lower end of this dosage range may be particularly useful for individuals who may be more susceptible to the side effects of these medications. Doses can be increased by another 10–25 mg every four to five days as tolerated. Once a dose of 75–100 mg per day is reached, it might be prudent to obtain plasma levels of these medications, as they have well-defined therapeutic plasma level ranges.

Selective serotonin reuptake inhibitors (SSRIs) represent a newer class of antidepressants and have gained great favor in the treatment of depression and other anxiety disorders. These medications are much better-tolerated, with respect to side effects, and usually offer the convenience of once-daily dosing. Unfortunately, there is very scant evidence to suggest that these medications are helpful in reducing pain and gastrointestinal sensitivity, beyond the effect on pain conferred by the reduction of depression. Therefore, these medications are not suggested as first- or even second-line options for the treatment of these syndromes. In addition, these medications have the unfortunate propensity to cause increased nausea, especially within the first week or so of initiating therapy. Notably, one SSRI, fluoxetine, may even reduce appetite and potentiate weight loss.

SSRIs do appear to be effective in reducing panic attack frequency in individuals with panic disorder. This property may be particularly helpful in the subset of gastroparetic patients where some symptoms may be related to anxiety states. Paroxetine (Paxil) has an FDA-approved indication for the treatment of panic disorder, social anxiety disorder, and pre-menstrual dysphoric disorder, in addition to major depression. Paroxetine, in contrast to most of the other SSRIs, also tends to cause weight gain. One of the SSRIs, mirtazepine (Remeron), is known to increase both appetite and sedation, unlike most of the other SSRIs. Due to this sedative property mirtazepine is the only SSRI that is routinely administered at bedtime. Most other SSRIs may be administered either in the morning or at bedtime, depending on patient preference.

Another increasing utilized class of antidepressants with possible utility in the gastroparetic population are the serotonin and norepinephrine reuptake inhibitors (SNRIs). Two of these agents, currently on the market, have been found to be useful in treating chronic pain, especially pain of a neuropathic origin, and thus may be useful second-line agents for patients with gastrointestinal sensitivity. Venlafaxine (Effexor) and duloxetine (Cymbalta) both increase the levels of serotonin and norephinephrine in the body due to their inhibition of reuptake by pre-synaptic cells.

Duloxetine is indicated by the FDA for the treatment of major depressive disorder, diabetic peripheral neuropathic pain, and generalized anxiety disorder. Venlafaxine is indicated for treating major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder. Very little work has been done with respect to their effectiveness in individuals with gastrointestinal disorders. These medications are generally well-tolerated by patients, as they have minimal side effects. One side effect, requiring special attention, is their tendency to increase hypertension.

In addition, two other agents with efficacy in neuropathic pain such as gabapentin (Neurontin) and pregabalin (Lyrica) deserve special attention in the gastroparetic population. They may have an adjuvant role, primarily in the diabetic setting. Pregabalin, is a structural derivative of the inhibitory neurotransmitter gammaaminobutyric acid (GABA) and is molecularly similar to gabapentin. The initial dose of pregabalin is 50 mg three times per day. The dose may be increased up to 300 mg/day depending on efficacy and tolerability. Dosing of pregabalin should be adjusted in patients with renal dysfunction. Common adverse reactions include dizziness, somnolence, and dry mouth. A non-narcotic pain medication, such as tramadol, should be tried as first line agents to avoid narcotics.

(continued on page 58)

(continued from page 56)

In gastroparetics who tolerate oral medications, and require better pain control, a trial of short acting narcotics such as oxycodone, morphine, or dilaudid (several times more potent than morphine) with the option of transitioning to longer acting oral narcotics (Oxycontin and MSContin) for a more stable delivery of narcotic analgesia. If the situation evolves into chronic therapy being required, we favor both transdermal and oral transmucosal fentanyl to ensure drug delivery in the patient with delayed gastric emptying and or frequent vomiting. Transdermal fentanyl appears to provide simple and adequate pain relief with reliable concentrations distributed to the blood. Patches vary in dosages and start as low as 12.5 mcg/hour, and are changed every 72 hours. Oral transmucosal fentanyl has also found a role in the form of Actique lozenges for breakthrough pain control. A transmucosal lozenge (Actiq) has a dosage of 400 mcg of fentanyl, equivalent to 4 mg of intravenous morphine.

We have also utilized methadone as a narcotic alternative for chronic pain, where a long acting agent is preferable. This drug may carry a better gastrointestinal side effect profile than traditional narcotic analgesics, including less associated nausea and vomiting and constipation. It is important that methadone is dosed every eight hours based on the half life of the drug and begin with a dose of 5 mg tid (40). However, as with all narcotic use, vigilance for constipation is necessary and prophylactic milk of magnesia and/or magnesium citrate can be an inexpensive and effective treatment.

Chronic narcotic dosing, particularly during intravenous use in the hospital, is a real challenge to gut motility. Narcan, given orally, can be helpful without interfering with central pain control and can be given concomitantly with the narcotic agent. Recently, a peripherally acting mu-opioid antagonist designed to block adverse side effects of opioids on the intestinal tract without interfering with beneficial analgesic effects was approved by the FDA. This agent, alvimopan (Entereg), at a dose of 6 mg/day was shown to be effective on post-operative ileus settings and data could be extrapolated to a chronic narcotic setting (41). Shortly before this manuscript was submitted for publication, alvimopan's manufacturers (GlaxoSmithKline and Adolor) withdrew the agent due to concerns over cardiovascular safety and concerns for potential tumor development observed during a recent phase three, double blind, placebo controlled trial of alvimopan designed to evaluate long term safety and tolerability. Serious cardiac adverse events were reported in 2.6% of patients undergoing treatment with alvimopan, compared to 1.12% of those receiving placebo. This difference was not statistically significant. We await further information about this situation. However, the concept of mu and kappa antagonists is an exciting area for addressing gut narcotic effects.

CONCLUSION

In summary in this review we have emphasized how an aggressive combination of pharmacological therapies, based on knowledge of their mechanisms of action, can offer an effective strategy of treatment for patients with gastroparesis. Antiemetics, prokinetics, and analgesics should be utilized in combination to quickly ameliorate the array of symptomatology we have described by adopting this "step-down" approach, while also emphasizing dietary modification. When medical therapy is not able to sustain symptom relief and quality of life the novel therapy of gastric electrical stimulation is the next proven option for treatment of this challenging patient population. ■

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