Role of prokinetic agents in the treatment of gastroesophageal reflux disease

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M BOIVIN. Role of prokinetic agents in the treatment of gastroesophageal reflux disease. Can J Gastroenterol 1993;7(5):414-416. Most of the factors contributing to the development of reflux esophagitis (eg, transient lower esophageal sphincter relaxations, low basal pressure of the lower esophageal sphincter, impaired esophageal clearance and delayed gastric emptying) are related to upper gastrointestinal dysmotility. Prokinetic agents are able to counterbalance these motor derangements and are therefore useful in the medical treatment of gastroesophageal reflux disease.

Key Words: *Cholinergic agonist, Dopamine antagonists, Gastroesophageal reflux, Lower esophageal sphincter (LES), Prokinetic agents*

Le rôle des agents procinétiques dans le traitement du reflux gastro-œsophagien

RÉSUMÉ: Des anomalies de motricité, comme par exemple, une relaxation innappropriée du sphincter œsophagien inférieur, une hypotonie du sphincter œsophagien inférieur, des anomalies de contractions de l'œsophage et un retard de vidange gastrique, sont tous des facteurs pouvant contribuer au reflux gastro-oesophagien et par conséquent à l'œsophagite. L'utilisation d'agents procinétiques qui en corrigeant ces anomalies motrices s'avère donc un traitement efficace et global du reflux gastro-œsophagien.

THE CURRENT LITERATURE INDICATES that most of the factors which contribute to the development of reflux esophagitis depend on motility disorders of the esophagus or stomach. However, some studies suggest that impairment of esophageal mucosal defence and increased aggressiveness of gastric juice may be contributory factors in some patients. The motor defects that lead to reflux disease cause both abnormally frequent gastroesophageal reflux episodes and slow clearance of the refluxed material from the esophagus back into the stomach. This defective functioning causes excessive exposure of the distal esophagus to refluxate.

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Reflux episodes occur as a consequence of an incompetent lower esophageal sphincter (LES) which may manifest as intermittent inappropriate relaxations or, in more severe forms of the disease, as chronically low basal pressure. It appears that abnormally frequent transient LES relaxations, which are clearly distinguished from relaxations induced by normal swallowing, are the most important mechanism of gastroesophageal reflux. However, this hypothesis needs to be investigated further by monitoring esophageal motility and pH in ambulatory patients with reflux disease. In addition, it must be recalled that impaired esophageal clearance resulting in prolonged esophageal acid exposure contributes to the development of esophagitis. Delayed gastric emptying can also contribute to the development of reflux disease. This functional disorder allows the pathological retrograde flow of gastric contents into the distal esophagus. One logical approach to therapy would be to enhance the functioning of the LES sphincter and the propulsive function of the body of the esophagus. The use of prokinetic agents, which increase LES tone, enhance esophageal peristaltic contractions and stimulate gastric emptying, is appealing in the management of gastroesophageal reflux disease (GERD) because it addresses the chronic underlying factors that contribute to the condition.

Prokinetic agents (Table 1) influ-

ence gastrointestinal (GI) motility through one or more of the following pathways: directly or indirectly by promoting cholinergic tone; by antagonizing inhibitory neurotransmitters (eg, serotonin, dopamine).

CHOLINERGIC AGONIST

Bethanechol was the first prokinetic agent to be used to treat patients with GERD. Bethanechol is a cholinergic agonist which acts almost entirely at the muscarinic receptors, with little if any effect on nicotinic receptors. The agent increases LES pressure and esophageal clearance, but has little effect on gastric emptying (1). It also stimulates the secretion of saliva which may contribute to improved symptoms by the buffering action of saliva on gastric refluxate. Studies with the use of bethanechol in GERD have produced conflicting results (2-4), with clinical trials showing improvement in symptoms and in endoscopic esophagitis in the range of 40 to 50%. The dose of bethanechol used for the treatment of GERD (25 mg qid) is often not well tolerated because of side effects. The side effects, which develop as a result of enhanced parasympathetic tone, include abdominal cramps, diarrhea, salivation, flushing, bradycardia and blurred vision. They occur in 10 to 30% of patients thus limiting the use of bethanechol in the treatment of GERD.

DOPAMINE ANTAGONISTS

Metoclopramide mainly stimulates GI motility through dopamine receptor blockage and facilitation of acetylcholine release from post ganglionic cholinergic nerve terminals. The usefulness of metoclopramide in treating reflux is suggested by its effects on LES pressure (5), by increasing the amplitude of esophageal contraction and by improving gastric emptying (6,7). Controlled studies showed that metoclopramide improved symptoms (heartburn and regurgitation) and the need for antacid use in patients with GERD (8,9). Also a study comparing the efficacy of either metoclopramide (10 mg tid) or ranitidine (150 mg bid) showed that both drugs were effective in producing symptomatic and endoscopic improvement (10). Clinical trials with metoclopramide showed improvement of symptoms and esophagitis in a range of 40 to 60%. However, side effects were reported to occur in 10 to 20% of patients. The most troublesome side effects, particularly those related to the central nervous system (CNS) (agitation, somnolence and extrapyramidal symptoms), have limited its use (6).

Domperidone is a benzimidazole derivative that specifically antagonizes the inhibitory effects of dopamine on the upper intestinal tract. It is distinguished from other prokinetic agents in that it has no cholinergic activity. Unlike metoclopramide, domperidone has limited ability to cross the blood-brain barrier and therefore causes fewer CNS side effects. Side effects such as increased prolactin levels and gynecomastia are observed occasionally. Most studies with domperidone suggest that its effect in patients with reflux esophagitis may be due to improved gastric emptying (11) rather than improved esophageal motility and LES pressure (12-14). Some clinical trials showed that domperidone is equivalent to ranitidine in producing symptomatic and endoscopic improvement (15,16). However, other studies showed that domperidone produced limited improvement of symptoms (frequency of heartburn and incidence of reflux episodes) (11,17,18). At present, there are few reported studies showing clear beneficial effects of domperidone in patients with GERD using the standard dose of 10 mg tid or qid. However, increasing the dose of domperidone to 20 mg qid may be more effective in the treatment of patients with GERD.

SUBSTITUTED BENZAMIDES

Cisapride promotes GI motility and increases antroduodenal coordination by releasing acetylcholine from enteric neurons. Pharmacological studies have clearly shown that cisapride increases low LES pressure to normal values (19), improves the contractile activity of the esophagus (20-22) and increases gastric emptying rates (23).

Clinical studies on the use of cisapride in the treatment of GERD have shown that the agent improves symptoms and promotes esophageal healing (24-27). Rates of cure, measured objectively by endoscopy, were obtained in 63 to 85% of patients in clinical trials. Similar results in symptomatic improvement were obtained as well.

TABLE 1
Prokinetic agents

Cholinergic agonist
Bethanechol
Antidopaminergics
Metoclopramide
Domperidone
Substituted benzamides
Cisapride

Other studies showed that cisapride is at least as effective as either ranitidine or metoclopramide in the treatment of GERD (28,29). In an American-Canadian multicentre study (30), cisapride improved symptom scores, particularly in patients with low LES pressure suffering from moderate to severe heartburn.

The dose used in clinical studies with cisapride is 10 mg qid, which can, in some cases, impair patient compliance. Geldof et al (31) compared two dose regimens of cisapride (10 mg qid and 20 mg bid) with ranitidine (150 mg bid) in a double-blind controlled trial. All treatments proved equally effective in improving the endoscopically confirmed healing of esophagitis. These results suggest that administration of the medication twice a day may be as effective as four times a day.

In clinical trials, a transient increase in stool frequency was the only side effect reported more frequently than in patients receiving placebo. Given its excellent safety profile, cisapride could have a promising role in long term maintenance therapy for reflux, possibly in a twice-a-day or bedtime dose regimen (32).

CONCLUSION

GERD can be regarded as a motility disorder. Although blocking acid is an effective treatment for reflux, it does not overcome the underlying pathologic factor of GERD. By their effect on motor disturbances, prokinetic agents have an important role in the treatment of GERD. There is clear evidence that

these agents improve both subjective symptoms due to gastroesophageal reflux as well as the endoscopic and histological evidence of mucosal inflammation. These benefits are mediated through the effects of prokinetic agents on LES, esophageal motility and gastric emptying. Clinical studies with metoclopramide demonstrated its efficacy in the treatment of GERD but troublesome side effects have limited its use. Limited trials with domperidone have shown some evidence of efficacy in GERD, but its overall usefulness in controlling reflux symptoms and healing esophagitis is not well established. In contrast, clinical studies have shown that cisapride markedly improves symptoms and promotes esophageal healing in patients with GERD. This suggests that cisapride is the treatment of choice when considering a prokinetic agent in the treatment of patients with GERD.

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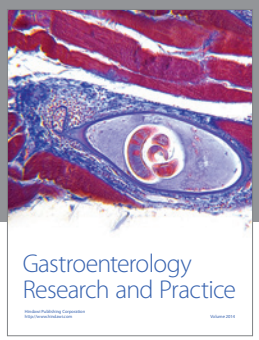

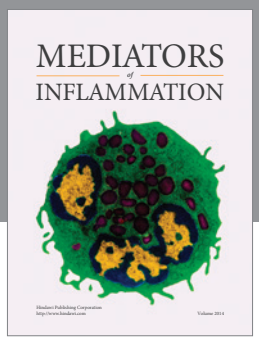

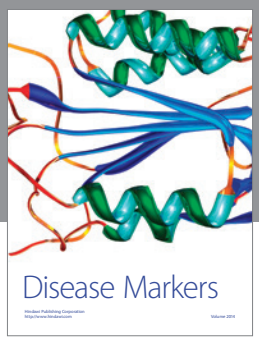

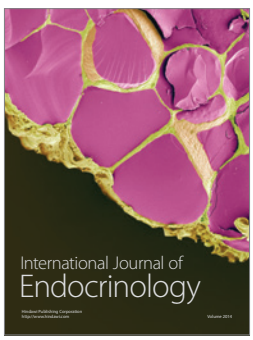

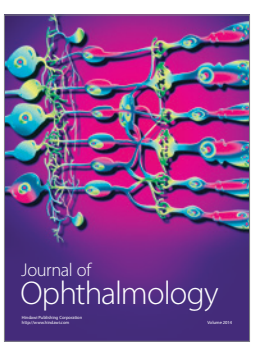

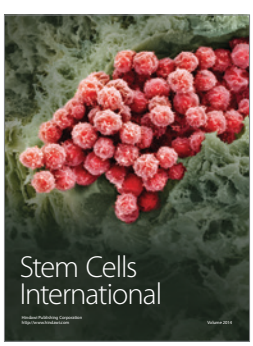

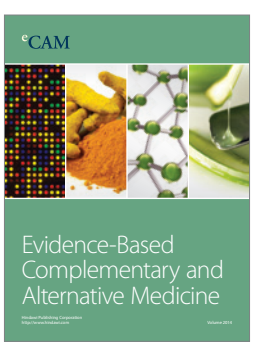

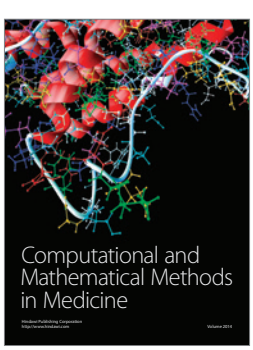

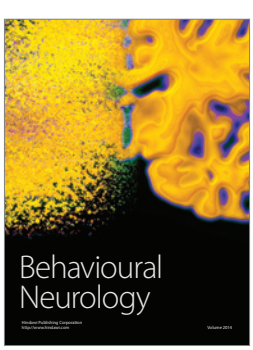

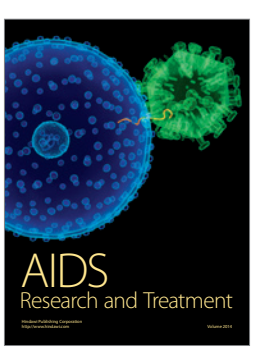

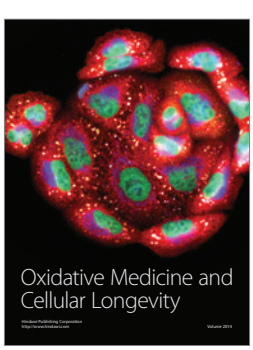

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