

Medical Management of Gastroesophageal Reflux Disease and the Challenges: A Review

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a disorder in the digestive system of the body. GERD in the acute stage is controlled by changing lifestyle. Medicines like antacids, mucosal protective, and prokinetic agents reduce acute GERD by reducing acidity and increasing the motility of the stomach. Proton pump inhibitors (PPIs) are the primary choice of medication for treating GERD, but it is an ineffective number of gastric hypersecretory and other disorders. Ilaprazole, and tenatoprazole are currently under trial in humans and reported to have a longer duration of action. Histamine₂ receptors remove some of the PPIs side effects. Tegoprazan is a potent γ -amino butyric acid agonist to treat GERD but has central nervous system side effects, which could be removed as adjunct drugs. Raseglurant and mavogluran have a potential effect in treating GERD, but a major challenge is reducing hepatotoxicity. Dronabinol is the only approved medication for cannabinoid receptors with better efficacy in treating GERD. Challenges that arise during GERD are minimized by using a better combination of drugs. Mylanta, omeprazole, and sustained released baclofen, domperidone, omeprazole, esomeprazole, and rebamipide are more effective and have been used recently in combination for treating GERD patients. Combinations therapy is more effective than monotherapy and also decreases therapeutic challenges which arise by using monotherapy of these drugs in GERD patients.

Keywords: Adenocarcinoma, Barrett oesophagus, Combination therapy, Monotherapy.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is an abnormality in the physiology of the digestive system. The cause of abnormality may be dysfunction in the valve, dysphagia, regurgitation, and obesity. GERD symptoms start with a burning sensation in the stomach. If not controlled, severe symptoms like difficulty breathing, choking of the esophagus, structural esophagus, Barrett's esophagus, and finally, adenocarcinoma develop, leading to GERD patients' death.¹ For treating GERD, lower esophageal sphincter, peristalsis movement of the esophagus, central and peripheral coordination, which affect the digestive system, are crucial.

Along with primary health care, taking suitable medical treatment not only gives patients relief but also treats the disease completely.² Medical treatment starts by giving antacid in the acute stage, and if the symptom still persists, antacid-alginate are given. In the chronic stage of GERD, proton pump inhibitor (PPIs), histamine 2 receptor antagonists (H₂RAs), potassium competitive acid blockers (PCAB), and several other drugs are medicated at a low dose and then at high doses. If the severity of GERD still persists suitable combination of drugs is given. Prokinetic and mucosal protective agents reduce GERD by covering the esophagus inner mucosa by forming a strong

barrier to reduce the direct exposure to acids. Prokinetic agents increase the stomach's motility so that there is low acidity.^{3,4} Metabotropic glutamate receptor inhibitors, cannabinoid receptors (CB) agonist/antagonists, γ -Aminobutyric acid receptor agonist and several other receptor-specific drugs regulate the function of the esophagus digestive system and bring back the health of GERD patients to normal.^{5,6}

CHALLENGES IN REMOVING DIGESTIVE DISORDER

Challenges include maintaining proper digestion in GERD by removing digestive disorders. Digestive disorder comprises obesity, excess acid production inside the stomach, and controlling the proper function of enzyme. Oesophago-gastric junction is the area of the gastrointestinal tract where certain risk factors alter esophagus-gastric valve movement. Risk factors cause abnormal skeletal and smooth muscle function, peristaltic movement of the esophagus, diaphragmatic movement, central nervous stimulation of nerves and receptor underlying the gastrointestinal tract all give rise to reflux disease.⁷

Removing Digestive Disorder

Digestive disorder in GERD could be improved by giving the proper amount of meals. Its quality, quantity, and type of food

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given are very important. GERD patients should be given easily digestible food. Overfeeding is avoided so that the pressure of the stomach does not exceed the pressure of the valve, which controls reflux at an esophagus-gastric junction.⁸ Major challenges in removing digestive disorder are proper digestion of food with reducing all the risk factors that cause indigestion.

Removing Obesity in GERD patients

Obesity occurs due to various factors such as a change in the function of the enzyme, high fatty food accumulation, acidity, decrease in motility of the stomach, and several other factors. Providing low-cost diet sodas, soft drinks, fruit juices, and other healthier beverages could make an initiative to reduce GERD among the population. Major challenges in removing obesity disorder are evaluating obese patients and identifying risk factors for patients and then making a suitable medical treatment to overcome the disease.⁹ Obesity is removed by taking proper meals and avoiding a lifestyle that increase GERD.^{10,11} Table 1 narrates the food to be avoided depending on the severity of GERD patients.

DRUGS USED IN THE TREATMENT OF GERD

Antacids

Antacids give symptomatic relief in GERD and also reduce excess pH levels inside the stomach. Antacid alginate combination could be an alternative method for reducing acidity. The extra antacid dose should be avoided as this leads to metal toxicity. The major challenges in giving antacid-alginate combination are recommending suitable doses and preventing patients from taking drugs over the long term as it only provides symptomatic relief for GERD patients for a limited time. Overdosing may lead to neurotoxicity, cardiotoxicity, and death of patients.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) include pantoprazole, rebeprazole, omeprazole and esomoprazole. An increase in stomach acidity is due to an increase in the number of functional proton pumps inside the stomach. PPIs block the H⁺K⁺ATPase enzyme. Parietal cells contain H⁺K⁺ ATPase enzyme. PPIs act on parietal cells, which are responsible for excess acidity. Parietal cell activated by acetylcholine H⁺K⁺ATPase. H⁺K⁺ ATPase is phosphorylated by Mg²⁺ATP in exchange of proton. The next reaction is dephosphorylating of potassium and then reabsorption. This causes cytoplasmic exchange of potassium with hydrogen. The β subunit of the proton pump consists of up to six to seven N- linked glycosylation linked to H⁺K⁺ ATPase. In the α subunit, carboxylic end is located. Various transmembrane segments (TM) TM 4 TM5 TM6 TM 8 contain ion binding segment. Transportation of R-NH₃⁺ toward the carboxyl-terminal catalyzes export of proton to luminal face of a pump is inhibited.²⁵ PPIs decrease the acidity of the stomach, but if GERD severity persists, the dose should be increased. Two new PPIs, omeprazole and tenatoprazole, are currently under trial in humans and reported to have a long half-life with an increase in the duration of action than previously available drugs. The advantage of using these drugs over previous available PPIs is their pharmacological action is not affected by whether drugs are taken day or night, and their intrinsic limitations of action are beyond the previously available PPI drugs.²⁶ The major challenge is the development of PPIs refractoriness in approximately 40 to 55% of GERD patients taking PPIs. PPIs are effective drugs but prolong decrease the therapeutic effect of drugs and cause a nocturnal acid breakdown. PPIs therapy is ineffective in patients with gastric acid hypersecretory states like Zollinger-Ellison syndrome, duodenal-gastroesophageal (bile) reflux, impairment of

Table 1: Foods to be avoided in GERD patients

Severity	Fruits	Sweet desert	Fat/oil	Grain	Meats
Little reflux	Watermelon, Apple, papaya, grapes, pear.	Jelly beans, sherbet, Graham cracker, angel food cakes	No fat salad, cookies, mayo	White bread, plain cereal	Fish chicken, egg white, lean steak
Moderate reflux	Blueberry, peach, raspberry, mango	Ice cream, pudding, potato chips (baked),	Mustard oil, olive oil, soya sauce	Muffin, garlic bread	Ground bean, chicken, hot dogs
High reflux	Orange, lemon, citrus fruit	Potato chips, chocolate cakes, doughnut	Oil and Vinegar	Marconi, pasta, sauce	Chicken nugget, ground beef, Buffalo wing ¹²

Table 2: Drugs used in the treatment of GERD

Antacid	Calcium carbonate, Magnesium carbonate, Sodium hydroxide ¹³
Proton pump inhibitors	Pantoprazole, Rabeprazole, Lansoprazole, Omeprazole ¹⁴
Histamine 2 receptor antagonist	Cimetidine, Nizatidine, Famotidine ¹⁵
Potassium competitive acid blocker	Vonoprazan, Linaprazan, Soraprazan ¹⁶
Alginate	Alginic acid-polymethyl methacrylate, Algicon, Gaviscon, Pyrogastrone, Alginate and their other derivative ¹⁷
Receptor drugs	γ-Aminobutyric acid (GABA) receptor agonist, ¹⁸ Cannabinoid receptor (CB) Agonist/ AntagonistmGluR5 Antagonists
Prokinetic agents	Domperidone, Tegaserod, Itopride, Rikkunshito, Metoclopramide ¹⁹
Mucosal protective agent	Sucralfate, Misoprostol ²⁰
Combination of drugs used in GERD treatment	Antacids alginate formulation, ²¹ Domperidone and Omeprazole ²² , Omeprazole and sustained released Baclofen, ²³ Aluminum Hydroxide, Magnesium and Simethicone ²⁴

esophageal mucosal integrity, esophageal hypersensitivity, psychological comorbidity like depression, anxiety, life stress, concomitant functional bowel disorder. In this case, suitable alternative drug therapy should be available to overcome the side effects.²⁷

Histamine 2 Receptor Antagonist

Histamine receptors are present in parietal cells, which are responsible for acid production in the stomach. Histamine receptor antagonist (H2RAs) drugs like cimetidine and nizatidine famotidine decrease acid production. They treat GERD but also give symptomatic relief. It shows action over 60 hours, and its therapeutic action starts in four to six hours. Intermittent doses of H2 receptor drugs are given to GERD patients.²⁸ H2 blockers relieve heartburn, GERD, duodenal and gastric ulcers, upper gastrointestinal bleeding, gastric hypersecretory disease, and several others. Cimetidine is one of the effects given in GERD patients.²⁹ The major challenges are overcoming side effects like hepatotoxicity, neurotoxicity and cardiotoxicity, tachyphylaxis, and failure of H2RAs in treating severe esophagitis in GERD patients without affecting the efficacy and potency of drugs.³⁰ Lafutidine and lavoltidine are novel H2RAs in trail and reported to have high healing rate and treatment efficacy in GERD. Lafutidine was found to have 71% endoscopic healing rate in comparison to 61.4% and 9.7% in famotidine and placebo. Lavoltidine in the previous trail was found to be potent, but its trail was stopped due to the carcinogenic effect found in mice and rats. Presently there is no further information on these drugs in any trails.³¹

Potassium Competitive Acid Blocker

Vonoprazan, linaprazan, revapraan, soraprazan are the various potassium competitive acid blocker (PCAB) drugs that act on the H⁺K⁺ ATPase enzyme and inhibit its activity. It is as much effective as PPIs drugs. Vonoprazan, revaprazan (YH1885), soraprazan, and AZD0865 are more effective PCAB gives quick relief to GERD patients.³² A model based on four strategies was developed in Japan to determine cost-effective therapeutic efficacy by giving drugs in four ways (a) intermittent PPI using lansoprazole (LPZ), (b) intermittent P-CAB; (c) maintenance PPI using Lansoprazole; (d) maintenance PCAB. At the end of the study, intermittent PCAB is the most cost-effective drug compared to others.³³ PCAB therapeutic action does not affect whether a meal is taken or not. PCAB does not destruct easily and also does not require acidic pH, and remains stable over a long period of time. PCAB are used to inhibit acid, and this inhibition of acid secretion cannot be reversed. Recently one new PCAB that is available in the market are tegoprazan (CJ-12420) which is (S)-4-((5, 7-difluorochroman-4-yl)oxy)-N, N, 2-trimethyl-1H-benzo[d]imidazole-6-carboxamide, increase gastrointestinal motility and improve nocturnal acid breakdown (NAB).³⁴ Tegoprazan. *In vivo* model of dog is found to inhibit gastric acid secretion, distribute rapidly in tissue and reverse pentagastrin-induced gastric pH, increase gastrointestinal motility.^{35,36}

Prokinetic Agents

A different class of prokinetic agents are cholinergic agents, anti-dopaminergic agents, benzamides, macrolides, cholecystokinin antagonists, opiate μ /K agonist.³⁷ Prokinetic agents' function is to increase the stomach's motility and give strength to the lower esophageal sphincter. An increase in motility in the stomach decreases the duration of digestion of food in the stomach. If food residues in the stomach over a short period, then there is no need of extra acid production inside the stomach, and there is no increase in the severity of GERD. One of the classes of prokinetic agents is the cholinergic agonist. Cholinergic agonist shows pharmacological action by acting on M2 receptor. They increase peristaltic activity and increase muscle tone and tension in the esophagus. Peristaltic movement in the esophagus and lower esophageal sphincter function is maintained under control by taking bethanechol. Bethachol is not usually prescribed in GERD patients due to cholinergic side effects.³⁸ Another class of prokinetic agents is anti-dopaminergic, in which pharmacological action is mediated via central and peripheral receptors present in the chemoreceptor zone. Metchlorpropamide with benzamide shows an anti-peristaltic effect by decreasing the sensitivity of receptors to stimulating agents such as levodopa and apomorphine, thereby preventing inhibition of slow gastric emptying and expediting gastric emptying. Metcholpropamide has additional action against third type of serotonin receptors. The associated side effects are torticollis, trismus, opisthotonus, akathisia, dystonia, oculogyric, Parkinson symptoms, laryngospasm, and dystonia.³⁹ Macrolide has promotility effect in GERD patients. They decrease gastric content to aspirate and cause an injurious effect on patients. Reflux has been reported in most patients.⁴⁰ Macrolides are motilin receptor agonists. They act on the duodenum and increase motility and accelerate gastric emptying. Cardiovascular risk is always associated with a high dose of erythromycin. Cholecystokinin act as anti-GERD agent by increasing lower esophageal sphincter relaxation and pressure through stimulation of CCK receptor.⁴¹ Opioid receptors act as prokinetic agents and are present in the gut and brain. In the gut, opioids decrease gastrointestinal motility by μ receptors. Opioid such as loperamide has ant secretory activity by mesenteric and sub mucosa by serotonin, serotonin stimulate nor adrenaline secretion which has inhibitory activity on enterocyte secretion at alpha 2 adrenoreceptor.⁴² The major challenges in giving prokinetic agents to GERD patients is it's not given alone. It has limited efficacy and always requires acid-suppressive drugs to treat the disease.

Mucosal Protective Agent

Sucralfate, prostaglandin, and misoprostol are the various mucosal protective agents. Mucosal protective agents protect the esophageal mucosa by acidic exposure. They form a protective covering over the esophagus mucosa and prevent acid leakage. When orally taken, mucosal protective agents reach the stomach, interact with the positive end of the protein, and form a gel that acts as a barrier to the permeation of acids.⁴³

Prostaglandins perform their function by inhibiting acid secretion via EP3 and IP receptors.⁴⁴ Prostaglandin heals ulcer caused by acid through granulation tissue formation, increasing epithelial tissue growth factor and promoting angiogenesis. Prostaglandin also decreases the formation of inflammatory mediators, which cause mucosal injury in GERD patients.^{45,46} Fibroblast, a growth factor, is increased by using mucosal protective agents, which increase the prostaglandin level in the stomach that promote healing.^{47,48} Mucosal protective agents perform cytoprotective action by stabilizing renal clearance, bile acid, and pepsin. The therapeutic efficacy of mucosal protection is comparable to H2RAs in GERD. Mucosal protective agents with other drugs change the pharmacokinetic and pharmacodynamics properties. Changes in the acid level and decrease in the concentration of some enzymes in the stomach lead to a decrease or increase in action of other drugs.⁴⁹ Cimetidine action is increased when taken with mucosal protective agents. Mucosal protective agents should not be used with PPIs and H2RAs. Constipation with black stool is the side effect of mucosal protective agents.⁵⁰ The major challenges for GERD patients in giving mucosal protective agents are they only cover the esophagus mucosa; if GERD is not treated, then at certain stage, the acid level reaches to stage where these agents fail to protect the esophagus.

γ -Amino Butyric Acid (GABA) Receptor Agonist

In endocrine and enteric nerve, GABA receptors are present. Its pharmacological action is mediated via the GABA receptor. GABA-A and GABA-B both types of GABA receptors, in which GABA-A is present throughout the gastrointestinal tract. It regulates gastric emptying and gastric secretion. GABA receptors perform its action by mechano-sensitive gastric vagal afferents. Mechano-sensitive gastric vagal afferents coordinate with a synaptic neuron headed toward the brain stem. In the brain stem certain neurons are inhibited by GABA, which increases GERD, and this is considered to be the site of action of GABA-B receptor agonists.^{51,52} Baclofen is a non-adrenergic and non-cholinergic inhibitor that acts on GABA receptors and increases contraction. In GERD, baclofen reduce heartburn and regurgitation post prandial epigastric pain by acting on the intestine and inhibiting transient lower esophageal sphincter relaxation.⁵³ Baclofen has the ability to reach the brain and show side effects that can only be reduced by giving baclofen with suitable agents. Cholinergic neurons increase gastric tone. AZD9343 is R enantiomer of baclofen XP19986 with an improved pharmacological profile and with a reduction in drowsiness and paresthesia in GERD. GABA receptors modulate transient lower esophageal function.^{54,55} Lesogaberan, a GABA-B receptor agonist with better efficacy as a potential agent for add-on therapy for GERD patients.⁵⁶ In a trial, arbaclofen placarbil with PPIs is reported to serve as potential anti-GERD agents. Lesogaberan, and arbaclofen placarbil possess severe side effects if used unevenly its further investigation and formulation with a suitable combination of drugs may serve as novel agents to treat GERD. GABA receptor agonist's side effects in GERD are drowsiness,

accommodation disorders, nausea, vomiting, diarrhea, and dizziness.⁵⁷ The major challenges in treating GERD by giving GABA drugs are its proper evaluation and formulation into a suitable form to be used as add on therapy with the minimal central nervous system and abdominal side effects.

Cannabinoid Receptor (CB) Agonist/Antagonist

CB comes under the superfamily of Gi protein-coupled receptors. $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC) is the active component of. Cannabinoids in the gastrointestinal system are endo-cannabinoids that serve as gastro-protective agents and also regulate intestinal motility. Two types of endo-cannabinoids, anandamide (CB 1) and 2-arachidonylglycerol (CB 2), are present in myenteric, submucosal neurons, and epithelial cells.⁵⁹ CB 1 increase appetite and CB 2 receptor have an emetic role. CB1 receptor regulates total lower esophageal receptor by ganglion and vagal afferent.⁶⁰ It also decreases reflux events that perform a dose-dependent inhibition of total lower esophageal relaxations (TLESRs). It also decreases swallowing rate. Dronabinol is the only approved medication for CB receptors. CB receptor improves colonic transit and gastrointestinal motility.^{61,62} CB receptor completes its action within half to one hour. CB receptors metabolize by hydroxylation. Tachycardia occurs in most GERD patients, along with it asthenia, balance problems, confusion, dizziness, disorientation, drowsiness, nausea, somnolence, diarrhea, euphoria, dry mouth, fatigue, hallucination and vomiting are the side effects of taking CB drugs.^{63,64} The major challenges for treating GERD by CB receptor are its suitable modulation by proper activation and inactivation by controlling protein and enzyme involved in the treatment of GERD.⁶⁵

Metabotropic Glutamate Receptor Inhibitors (mGluRs)

mGluRs inhibitors are C (family 3) family of G-protein-coupled receptors. mGluRs are present in the brain cerebrum, post synaptic neurons, and other peripheral part of the body. It performs its action by vagal sensory neurons. mGluRs are classified into three groups; excitatory action of glutamate is mediated via mGluR1 and 5 in a group first. In the second group, there are mGluR2 and 3, and in 3rd group, mGluRs 4, 6, 7, and 8 are inhibitory.^{66,67} mGluR5 performs its action by non-competitive allosteric modulation. Glutamate functions on pre-and post-synaptic neurotransmission in the central nervous system. mGluR5 reduces the sensory signal produced by glutamate after binding to the receptor. mGluR5 decreases TLESRs by acting peripherally and vagal in GERD.^{68,69}

Raseglurant, another name of ADX10059 performs its action by allosteric modulation of mGluR5. In a recent double-blind study, ADX10059 reduce reflux disease by decreasing esophageal acid exposure time. In a placebo-controlled double-blind study of 103 GERD patients. GERD symptom was increased in patients responsive to PPIs after treatment of ADX10059. It is reported to cause heartburn regurgitation and sleep disturbance in GERD patients. Some adverse effects associated are dizziness, vertigo, and 27% reduction of TLESRs, while 51% reflux was found by a non-competitive antagonist of mGluRs.^{70,71} AZD2066, mavoglurant (AFQ056),

recently new drugs of MGLuRs found to have a potential effect in treating GERD.⁷² Mavoglurant in a randomized clinical trial in dogs reduces the number of transient lower esophageal sphincter relaxations and also reflux incidence. Mavoglurant could serve as an effective anti-GERD agent in patients refractive to PPIs.⁷³ Major challenges in giving MGLuRs in GERD are reducing hepatotoxicity and making the drugs more clinically beneficial.

COMBINATION THERAPY AN ALTERNATIVE AND EFFECTIVE METHOD FOR GERD PATIENTS

Monotherapy is effective in most patients, but its overuse gives certain limitations in several GERD patients. Limitation includes decrease in potency of drugs at low dose with delay in onset of action, an increase in a side effect, and a decrease in potency of drugs to give symptomatic relief in GERD. To overcome the limitation of Combination therapy is currently in use to develop new formulations that have higher potency, greater tolerance, and synergistic action to give fast relief to GERD patients.

Antacid and Alginate

Antacid and alginate combinations show additive effects in GERD. Antacid reduces acid, and alginate protects esophagus damage by forming a protective layer. In the United States gaviscon is a preparation of antacids alginate available for GERD patients in solid dosage and liquid dosage. These preparations contain a mixture of aluminum, magnesium hydroxide, and carbonates and are effective in most GERD patients.^{74,75}

In a double-blind, randomized clinical trial, a placebo-controlled study to assess the clinical efficacy and safety of alginate-antacid were selected in the formulation of (Gaviscon Double Action) chewable tablets. Patients in the age range of between 18 and 65 years old with uncomplicated symptoms of GERD were selected for these trials. Gaviscon DA tablet is made of three compounds: sodium alginate, sodium bicarbonate, and calcium carbonate in 250, 106.5, and 187.5 mg, respectively. Placebo tablets contain mannitol and xylitol. Gaviscon DA tablet is given four times a day for seven consecutive days at 30 minutes after meals are taken three times and one time before lying in bed in this trial. Evaluation of GERD patients is performed on a reflux disease questionnaire (RDQ) and the overall treatment evaluation (OTE).⁷⁶ RDQ contains a set of 12 questions for assessment of symptoms frequency and severity in GERD patients. OTE is another parameter for the assessment of response to GERD patients. At the end of this trial, it is reported that gaviscon DA significantly decreases overall GERD symptoms.^{77,78}

Esomeprazole and Rebamipide

Esomeprazole and Rebamipide combination are evaluated for the treatment of GERD patients in multicenter randomized clinical trials of 501 GERD patients. In monotherapy, esomeprazole in 40mg daily, whereas in combination therapy, esomeprazole (40 mg) with 300 mg rebamipide daily was

given over 4 weeks. GERD disorders like heartburn, acid regurgitation, and four upper gastrointestinal symptoms were evaluated at the end of the study. It is reported that esomeprazole in monotherapy is less effective in comparison to combination therapy of esomeprazole with Rebamipide.⁷⁹

Domperidone and Omeprazole

Domperidone and omeprazole combinations are evaluated for the treatment of GERD patients. In randomized controlled clinical trials of the phase 4 study, GERD patients were randomly given either group 1 (omeprazole 20 mg and domperidone 30 mg) or group 2 (omeprazole 20 mg) in an equal proportion. 2 capsules in the morning daily were given for 8 weeks. GERD patients were evaluated on a virtual analog score which ranged from zero lowest to a maximum of ten. Self-assessment of GERD patients were performed by GERD-Q questionnaire. Esophagogastroduodenoscopy was also formed and categorized patients on the Los Angeles grade scale. It is reported at the end of the study that a combination of domperidone and omeprazole treats GERD.^{80,81} domperidone and omeprazole reduce the acidity of the stomach by increasing gastrointestinal motility. It gave better relief over the long term when the domperidone and omeprazole combination was used in comparison to using omeprazole monotherapy in GERD. Domperidone and omeprazole is taken one hour before meals. Side effects associated with this combination are diarrhea, stomach pain, dryness in the mouth, headache, and flatulence.⁸²

Omeprazole and Sustained Released Baclofen

Omeprazole and sustained released baclofen combination are evaluated to determine therapeutic efficacy in GERD. In a double-blind placebo-controlled trial, GERD patients were given omeprazole, baclofen, and placebo, omeprazole baclofen combination. Omeprazole was given at a dose of 20 mg and baclofen tablet 10 mg twice daily or a placebo for two weeks. GERD assessments were performed by GERD questionnaire on patients.⁸³ It is reported at the end of the study that omeprazole and sustained released baclofen treat GERD effectively and reduce a symptom in patients. Omeprazole is PPI. Its act on the proton pump and reduce acid secretion. Sustained released baclofen lower esophageal sphincter pressure, and reduce transient esophageal relaxation in GERD.⁸⁴

Aluminum Hydroxide, Magnesium, and Simethicone

Mylanta (McNeil) contains aluminum hydroxide, calcium or magnesium carbonate, and simethicone is used to treat GERD patients. The combination of aluminum and magnesium in GERD reduce acidity, prolong the duration of action and reduce side effect of diarrhea and constipation.⁸⁵ Simethicone acts as an antifoaming agent to decrease bubble formation in the stomach by gas and make passage for food to move easily toward the intestine. Combinations of these drugs are available in the market easily and treat GERD effectively.⁸⁶

CONCLUSION

GERD is treated by changing lifestyle, which includes controlling diet, maintaining posture, and decreasing the

risk factors of GERD. Medical treatment by antacid, alginate combination, mucosal protective agents, prokinetic, and other drugs give symptomatic relief. PPIs are the primary choice of medication to treat GERD, but their long-term use makes it ineffective with increased side effects. H2RAs are also used to overcome PPIs refractoriness, but certain limitation still persists while taking these drugs. PCAB treats GERD, but it is effective if a dose is given in an intermittent manner. Receptor-specific drugs like lesogaberan and arbaclofen placarbil are GABA receptor drugs that could be used as novel drugs if suitable as an adjunct therapy to treat GERD. MGluRs inhibitors treat GERD by reducing the TLESR and give GERD patients relief, but hepatotoxicity occurs in most patients. Raseglurant, AZD2066, mavoglurant (AFQ056) are MGluRs drugs are under trial and reported to have improved efficacy. Monotherapy is less effective in GERD than combination therapy. Combination effective are Mylanta with omeprazole and sustained released baclofen, domperidone and omeprazole, esomeprazole and rebamipide. Gaviscon DA tablet is under trial and is effective in treating GERD. These combinations of drugs overcome challenges that are there in monotherapy, but some side effects still persist, which could be removed easily by proper medical management. Combination therapy is the best therapy to treat GERD. However, a more suitable combination of drugs is to be formulated that not only treats GERD but also reduces side effects that arise by using mono-therapeutically.

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