Pathophysiology and Pharmacological Treatment of Gastroesophageal Reflux Disease

M. Storr   A. Meining   H.-D. Allescher

Department of Internal Medicine II, Technical University of Munich, Germany

Key Words

Gastroesophageal reflux disease · TLESR · Pathophysiology · Treatment

Abstract

Gastroesophageal reflux disease (GERD) is one of the most common diagnoses in a gastroenterologist's practice. Gastroesophageal reflux describes the retrograde movement of gastric contents through the lower esophageal sphincter (LES) to the esophagus. It is a common, normal phenomenon which may occur with or without accompanying symptoms. Symptoms associated with GERD include heartburn, acid regurgitation, noncardiac chest pain, dysphagia, globus pharyngitis, chronic cough, asthma, hoarseness, laryngitis, chronic sinusitis and dental erosions. The introduction of fiberoptic instruments and ambulatory devices for continuous monitoring of esophageal pH (24-hour pH monitoring) has led to great improvement in the ability to diagnose reflux disease and reflux-associated complications. The development of pathological reflux and GERD can be attributed to many factors. Pathophysiology of GERD includes incompetent LES because of a decreased LES pressure, transient lower esophageal sphincter relaxations (TLESRs) and deficient or delayed esophageal acid clearance. Uncomplicated GER may be treated by modification of life style and eating habits in an early stage of GERD. The various agents currently used for treatment of GERD include mucoprotective substances, antacids, H_2 blockers, prokinetics and proton pump inhibitors. Although these drugs are effective, they do not necessarily influence the underlying causes of the disease by improving the esophageal clearance, increasing the LESP or reducing the frequency of TLESRs. The following article gives an overview regarding current concepts of the pathophysiology and pharmacological treatment of GERD.

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Introduction

Gastroesophageal reflux disease (GERD) is one of the most common diagnoses in a gastroenterologist's practice. In industrialized countries between 10 and 20% of the population complain about heartburn, the most reliable symptom of GERD, at least once a week and 4–10% report daily onset [26, 37]. Further symptoms associated with GERD include acid regurgitation, noncardiac chest pain, dysphagia, globus pharyngitis, chronic cough, asthma, hoarseness, laryngitis, chronic sinusitis and dental erosions.

The introduction of fiberoptic instruments and ambulatory devices for continuous monitoring of esophageal pH (24-hour pH monitoring) has led to great improvement in the ability to diagnose reflux disease and reflux-associated complications (fig. 1). The endoscopic classification of GERD is shown in table 1. Endoscopic examination, the gold standard of the diagnostic procedures, permits both visualization and classification of esophagitis as well as diagnostic biopsy of the esophageal mu-
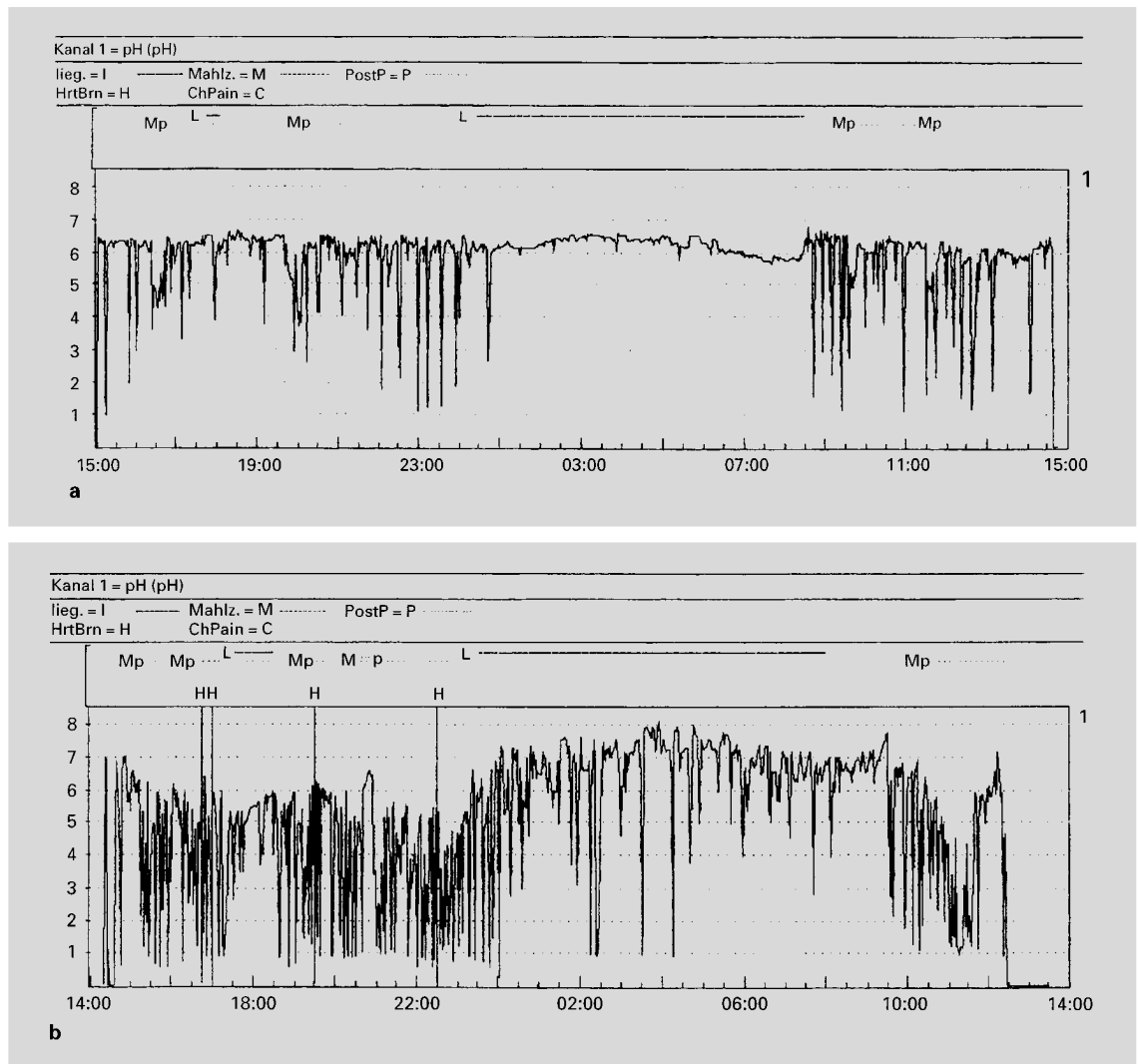
Dr. med. M. Storr
II. Medizinische Klinik und Poliklinik der Technischen Universität München
Ismaningerstrasse 22
D–81675 München (Germany)
Tel. +49 89 4140 2267, Fax +49 89 4140 4932, E-Mail martin.storr@lrz.tum.de

Fig. 1. Original records of 24-hour pH metry showing a normal (**a**) and pathological (**b**) record indicating pathological reflux during day- and nighttime.

cosa for the known complications of GERD: Barrett's esophagus and adenocarcinoma or other differential diagnoses such as squamous cell carcinoma. Since the examinations are somewhat uncomfortable for the patients and expensive, and since the proton pump inhibitors (PPI; e.g. omeprazole) exert profound acid inhibition and excellent symptom-relieving capacity, a short-term treatment with omeprazole as a diagnostic test for reflux disease appears efficient [36, 71]. In a prospective, randomized, double-blind multicenter study of 160 patients complaining of heartburn, 1 week of treatment with omeprazole (20 mg t.i.d.) proved to be a simple diagnostic test for GERD with a fairly high sensitivity of 75% but a poor specificity of 55% owing to the placebo effect.

In this study GERD was defined as reflux esophagitis Savary-Miller grades II–III by endoscopy or pH < 4 for more than 4% of the 24-hour pH monitoring [23]. It can be speculated that treatment of all stages of GERD seems necessary since the symptoms of heartburn and regurgitation alone are well known risk factors for the development of an adenocarcinoma of the esophagus or the gastric cardia [30].

Pathophysiological Background

Gastroesophageal reflux describes the retrograde movement of gastric contents through the lower esophageal

Table 1. Classification of reflux esophagitis according to Savary and Miller (1978; I–IV) and direct comparison to the Los Angeles classification (A–D)

	Savary and Miller	Los Angeles classification
Stage I/A	One or more longitudinal nonconfluent mucosal lesions with erythema, often covered with exudate above or extending from the gastroesophageal junction	Mucosal breaks confined to the mucosal fold, each no longer than 5 mm
Stage II/B	Confluent erosive and exudative mucosal lesions which do not cover the entire circumference of the esophagus	At least one mucosal break longer than 5 mm confined to the mucosal fold but not continuous between two folds
Stage III/C	Circumferential erosive and exudative mucosal lesions covering the whole esophageal mucous membrane	Mucosal breaks that are continuous between the tops of mucosal folds but not circumferential
Stage IV/D	Chronic mucosal lesions such as ulcerations with or without stricture formation	Extensive mucosal breaks engaging at least 75% of the esophageal circumference

Table 2. Pathophysiological mechanisms of GERD

Barrier function
  Lower esophageal sphincter (LES)
  Basal lower esophageal sphincter pressure (LESP)
  TLESRs
  Crural diaphragm
  Hiatal hernia
Acid clearance
  Peristaltic action of tubular esophagus
  Saliva production
Mucosal defense
  Preepithelial (mucus, bicarbonate)
  Epithelial (tight cell contacts, ion exchanger)
  Postepithelial (blood supply)
Gastric emptying
Abdominal pressure
Genetic predisposition?

Table 3. Normal values in 24-hour pH monitoring

	Normal values	
Fraction time with pH <4 in relation to		
Total measuring time, %	<4.5	(3.5–7)
Upright position, %	<8.4	(5.4–10.5)
Lying position, %	<3.4	(1.25–6.0)
Number of reflux episodes		
pH <4/24 h	<47	
Duration of reflux episodes		
Number of reflux episodes >5 min	<3.5	
Longest reflux episode, min	<20	

Figures in parentheses represent range.

sphincter (LES) to the esophagus (table 2). It is a common, normal phenomenon which may occur with or without accompanying symptoms. It may be divided into two categories, depending on whether it is a normal physiological reflux or pathological reflux which occurs in GERD. A pathological reflux is characterized as frequent reflux episodes of longer duration (>4% during 24 h), can occur during the day and/or night and may cause symptoms and inflammation/mucosal injury of the esophagus (table 3) [55].

The development of pathological reflux and GERD can be attributed to many factors. A minority of patients have an incompetent LES because of a decreased LES pressure (LESP), an increased intra-abdominal pressure (e.g. obesity, pregnancy) or a short LES (normal 2–5 cm). The normal LESP (10–25 mm Hg) varies with breathing, body position, body movements and also shows significant diurnal variations with the highest pressure during the night and the lowest during the day [55]. The LESP is influenced by a variety of drugs, food components and even hormones (table 2). Low LESP can be found among patients with severe reflux disease but many GERD patients have normal LESP. In these patients transient lower esophageal sphincter relaxations (TLESRs) can often be found as the underlying disorder causing pathological reflux (tables 4, 5). TLESR refers to episodes of LES relaxation that occur unrelated to swallowing, with the LESP decreasing to the gastric level for at least 10 s

Table 4. Criteria for TLESRs

Absence of pharyngeal swallow signal 4 s before to 2 s after the onset of LES relaxation (or a myohyoid electromyogram complex for 3 s before the onset of LES relaxation)
LES relaxation unaccompanied by primary esophageal peristalsis
LESP decrease ≥ 1 mm/s
Time from onset to complete relaxation ≤ 10 s
Nadir pressure ≤ 2 mm Hg
Pressure decreases to ≤ 2 mm Hg for more than 10 s

Table 5. Frequency of TLESR occurrence and association with acid reflux

	TLESR/h	TLESR associated with acid reflux, %
Normal subjects	2–6	40–50
GERD patients	3–8	60–70

(fig. 2). To date TLESRs are believed to be one of the main causes of pathological GER. Gastric distention due to postprandial fullness or intragastric air causing increased intragastric pressure is believed to be one of the main factors triggering TLESRs but the understanding of TLESRs is still incomplete. The physiological role of TLESRs seems to be venting the gastric lumen to allow the escape of excessive air, thus representing an abortive belch reflex [20, 39]. During the postprandial period TLESRs seem to be controlled by the cholecystokinin-A (CCK-A) receptor since during this period the CCK-A receptor antagonist loxiglumide abolishes the postprandial increase of the TLESR incidence in humans [72]. Within the reflex arc controlling the incidence of TLESRs nitric oxide (NO) seems to be an important mediator since inhibition of endogenous NO generation significantly reduces the increase of TLESR incidence following gastric distention in healthy volunteers [19]. Interestingly the TLESRs do not only involve the LES but also the crural diaphragm by a reflex arc including the phrenic nerve [40, 41]. This indicates that the TLESRs are a complex regulated phenomenon. Pharmacological options influencing TLESRs would be useful in GER treatment but randomized, placebo-controlled trials investigating how TLESRs can be modulated in GERD patients are still missing. Further research on TLESR physiology is of highest clinical interest. Research on dogs shows some evidence that the selective GABA$_B$ agonist baclofen inhibits TLESR occurrence probably via an ac-

tion on the central and peripheral GABA$_B$ receptor since GABA (which cannot cross blood-brain barrier) showed only a weak effect on TLESRs [32]. In patients with a hiatal hernia the LES is displaced proximally and there is evidence that LESP is decreased because of the loss of compensatory rise in LESP caused by diaphragmatic contractions during inspiration or rise of intra-abdominal pressure. Furthermore diaphragmatic contractions may impair esophageal clearance in patients with hiatal hernia (hiatal-esophageal reflux) and therefore promote GERD. Another risk factor for GERD is a deficient or delayed esophageal acid clearance due to (1) a decrease of salivation since the bicarbonate-rich saliva neutralizes the acid or (2) defects in esophageal motor activity which will impair the clearance function of esophageal motility. Esophageal clearance is dependent on voluntarily induced primary peristalsis (approximately 60 times per hour) and on secondary peristalsis which occurs in the absence of a pharyngeal swallow and which can be elicited by esophageal distention or acidification such as reflux [37, 57].

Secondary causes of GERD are reflux caused by gastric hypersecretion, gastric outlet obstruction such as due to ulceration and stricture, or delayed gastric emptying due to abnormalities such as gastric stasis, neuromuscular disorders, idiopathic gastroparesis, pyloric dysfunction, duodenal dysmotility or duodenogastroesophageal bile reflux [35]. Increased intragastric pressure causing GER can also be caused by obesity, pregnancy or failure of the normal receptive relaxation of the stomach due to neuropathy (e.g. diabetes) or vagotomy and concomitant increase of gastric pressure. In summary, multiple factors can contribute to the pathogenesis of GERD. Thus, despite excellent therapeutic options including the PPI a proper diagnosis should be established especially in patients resistant to common therapy to rule out secondary causes for GERD.

Treatment of GERD

Uncomplicated GER may be treated by modification of life style and eating habits in an early stage of GERD. These modifications include elevating the head of the bed, avoiding strong stimulators of acid secretion (e.g. coffee, alcohol), avoiding certain drugs (e.g. anticholinergics), specific foods (fats, chocolate) and smoking, all of which will reduce LESP. There are a wide range of substances which have been reported to affect the LESP and an overview is given in table 6 [58].
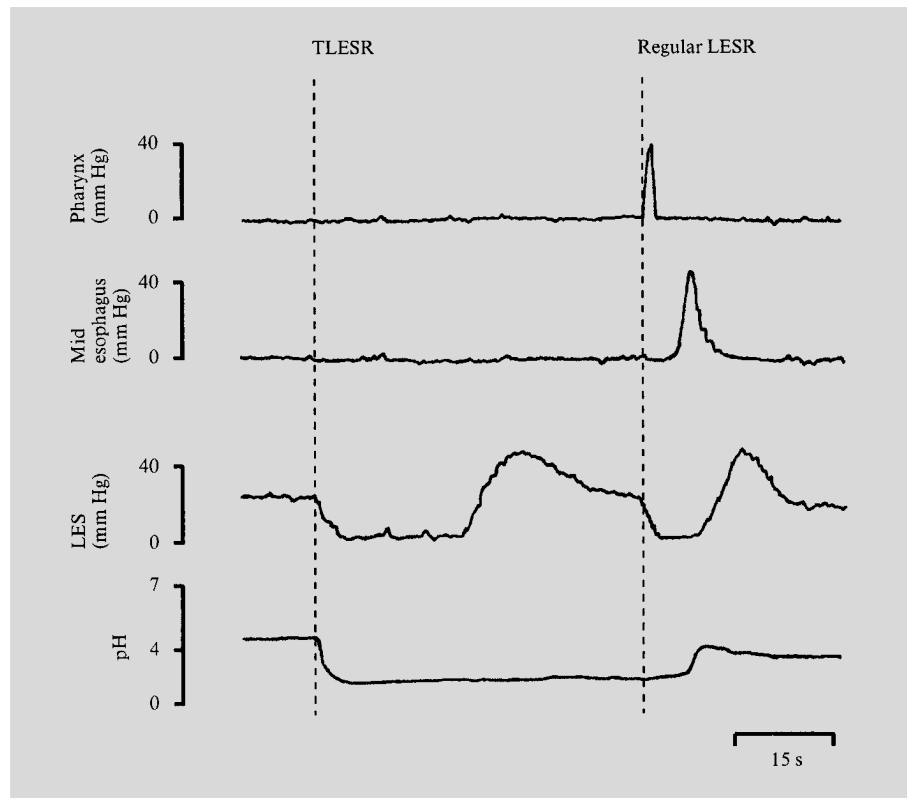
Fig. 2. Examples of a spontaneous TLESR associated with reflux and a regular LES relaxation (LESR) following a dry swallow indicated by pharyngeal contraction. The TLESR occurred in the absence of a swallow as manifested by the absence of a pharyngeal pressure wave.

Antacids

Antacids are probably the most widely used agents especially as over-the-counter drugs for the treatment of mild GER. Their beneficial effect is mainly due to the neutralization of acid and to some extent also to a mucoprotective effect but therapy with antacids is inferior to other therapeutic options.

Some antacids produce CO_2 which will increase gastric pressure and therefore might enhance the incidence of TLESR. The beneficial effect of these drugs is limited since they do not suppress acid production and therefore produce only temporary relief. These drugs can also cause side effects such as constipation or diarrhea due to their aluminum and magnesium content. Their therapeutic benefit lies primarily in the symptomatic control of sporadic reflux episodes and in reflux treatment during pregnancy.

Mucoprotective Agents

Mucoprotectives including sucralfate and algine acid are thought to provide a protective coating on esophageal mucosal lesions. In animal experiments sucralfate has been shown to be effective in preventing the development of acid-induced esophagitis [25]. Furthermore, the mucoprotective action of this drug was suggested to be beneficial in alkaline gastroesophageal reflux-induced esophagitis [13]. The value of mucoprotectives in GERD treatment is low and they can possibly be used in very mild GERD.

Proton Pump Inhibitors

PPI are so far the most potent agents for the treatment of reflux esophagitis. These drugs are effective in healing reflux esophagitis and relieving related symptoms. Several studies have demonstrated that omeprazole is superior to H_2 blockers or prokinetics in the treatment of reflux esophagitis [4, 14, 31].

Both H_2 blockers and PPI provide symptomatic relief in nonerosive GERD but H_2 blockers are often ineffective in healing erosive esophagitis [31]. In a randomized, prospective, placebo-controlled study of 221 patients with symptomatic nonulcerative esophagitis or with heartburn without esophagitis omeprazole (20 mg) was superior to

Table 6. Modification of the LESP

	Increases LESP	Decreases LESP	TLESR
Hormones	Motilin Histamine Pancreatic polypeptide	Cholecystokinin Secretin Progesterone Glucagon Neurotensin Gastrin	Cholecystokinin +
Neurotransmitter	Histamine Acetylcholine Bombesin Substance P Neurokinin A	VIP Dopamine CGRP NO	NO + GABA −
Drugs	Bethanechol Carbachol Metoclopramide Domperidone Cisapride Mosapride α-Adrenergics Erythromycin	Atropine N-Butylscopolamine Cimetropium bromide Theophylline Nitrate Dopamine Ca^{2+} antagonists Loperamide Molsidomine L-Arginine β-Adrenergics Benzodiazepines Botulinum toxin	Atropine − Morphine − Loxiglumide − (CCK-A antagonist) Anesthesia − NO antagonists − Baclofen −
Food components	Protein Red pepper	Alcohol Fat Chocolate Peppermint Acid	Fat + Cold stress − Gastric distention + Acid + Gas +

+ = Increases number of TLESR; − = decreases number of TLESR.

cimetidine (400 mg; q.i.d.) after 4 weeks of treatment for the relief of all grades of heartburn in GERD, whether or not the patient has unequivocal endoscopic esophagitis (66 vs. 31%) [4]. Comparable to the H₂ blockers, omeprazole is also superior to therapy with prokinetics in the treatment of symptoms in patients with GERD, regardless of the presence of erosive esophagitis. In a double-blind, randomized, multicenter study, resolution of heartburn was achieved in 65% of patients by omeprazole (20 mg) treatment, compared to 41% of patients by cisapride (10 mg; q.i.d.) [14]. There have been comparable results for symptomatic GERD by other authors as well and it has been further demonstrated that treatment of GERD with PPI provides the best cost efficacy compared to treatment with other drugs [12, 27, 51, 56].

For severe esophagitis even high doses of H₂ blockers do not appear to be as effective as PPI [50]. In a randomized, double-blinded study on patients with symptomatic, endoscopically confirmed erosive GERD, omeprazole (20 mg) was superior to cimetidine (400 mg; q.i.d.) in healing esophagitis after 8 weeks (71 vs. 35%) and was superior in inducing a regression to normal of pathological changes in history (67 vs. 48%) [5]. Based on efficacy, safety and cost-effectiveness, omeprazole should be the drug of choice for the treatment of patients with endoscopically confirmed erosive GERD [27, 28, 56].

Maintenance therapy after omeprazole (40 mg)-induced was investigated in a randomized prospective study on 175 patients with endoscopically confirmed reflux esophagitis. In this clinical trial omeprazole (20 mg) alone

or in combination with cisapride (30 mg; t.i.d.) was more effective than ranitidine (150 mg; t.i.d.) alone or cisapride alone, and the combination of omeprazole and cisapride was also more effective than ranitidine plus cisapride. After 12 months 89% of the patients in the omeprazole plus cisapride group were still in remission compared to 80% in the omeprazole group, 66% in the ranitidine plus cisapride group, 54% in the cisapride group and 49% in the ranitidine group [65]. Comparable results have been demonstrated by many other authors and therefore omeprazole or another PPI (lansoprazole, pantoprazole, rabeprazole) should be the drug of choice in the maintenance therapy after erosive GERD lesions have healed [6, 27, 28, 48, 50, 56].

Interesting results comparing proton pump inhibitor therapy in GERD patients with esophagitis to surgical treatment (antireflux surgery) in a randomized order were recently presented by the Nordic GORD Study Group [34]. Laparoscopic fundoplication is superior to therapy with omeprazole 20 mg but when the dosage of the PPI is increased the efficacy is the same [33].

PPIs are not only useful in patients with acid GER, they are also potent in reducing duodenogastroesophageal bile reflux most likely by reducing the intragastric volume. Omeprazole (20 mg; t.i.d.) was shown to be effective in reducing not only acid reflux but also bile reflux into the esophagus from 28.9 to 2.4% as demonstrated in a study of 12 patients with Barrett's esophagus [35]. Both, gastric acid and duodenal contents (bile) are thought to be responsible for mucosal damage in the esophagus.

H_2 Antagonists

H_2 receptor antagonists such as cimetidine, ranitidine and famotidine are widely used and accepted for the treatment of GERD and their effectiveness has been clearly documented in double-blind, placebo-controlled studies [42]. H_2 blockers effectively block gastric acid secretion and thus prevent acid reflux into the esophagus. Whether the H_2 blockers might also affect the esophageal motility directly or indirectly is still controversial [2]. Baldi et al. [3] reported an increase of LESP in patients with GERD treated with H_2 blockers and it has been shown that H_2 blockers cause an increase of gastrin which could be sufficient to increase the LESP [2, 28].

Prokinetics

Metoclopramide. Metoclopramide stimulates gastrointestinal motility by blockade of dopamine D_2 receptors as well as blockade of serotonin-3 (5-HT$_3$) receptors and possible action on the serotonin-4 (5-HT$_4$) receptors. Metoclopramide was shown to increase LESP, esophageal contraction amplitude and gastric emptying [1, 54]. Because of its effect on LESP and gastric emptying metoclopramide can be used in GERD. However, the long-term use of this drug is limited by its side effects on the central nervous system (extrapyramidal motor effects, hyperprolactinemia) due to the dopamine D_2 receptor blockade [1]. Because of its central antiemetic effect it can be used when GERD is associated with nausea or vomiting in combination with acid blocking drugs.

Domperidone. Domperidone stimulates gastrointestinal motility almost exclusively via blockade of peripheral dopamine D_2 receptors [8]. The effect of domperidone on esophageal motility is similar to the effect of metoclopramide but due to its chemical structure domperidone does not penetrate into the central nervous system and therefore lacks central side effects. Domperidone increases LESP, peristaltic amplitude and the propagation velocity. These effects can also be demonstrated in patients with GERD [67]. It has been proven that this drug has a positive effect in patients with reflux esophagitis, however, its effect is inferior to that of H_2 blockers or omeprazole [29].

Cisapride. Cisapride, a substituted piperadimyl benzamide, is a prokinetic agent which seems to increase the release of acetylcholine from enteric neurons and hence stimulates muscle action mainly via an action on the 5-HT$_4$ receptor. Cisapride promotes motor activity at all levels of the gastrointestinal tract [9], but in contrast to metoclopramide and domperidone has no antidopaminergic properties.

In a double-blind, crossover study cisapride (20 mg; p.o.) significantly increased LESP in normal healthy subjects [17, 66]. Corazziari et al. [11] demonstrated that intravenous cisapride enhanced esophageal peristalsis and that this effect of cisapride could be blocked by atropine. In contrast the stimulatory effect on the LESP was not completely abolished by atropine suggesting a muscarinic independent mechanism. Cisapride given intravenously (10 mg) is effective in increasing the esophageal body peristaltic amplitude in healthy volunteers demonstrated in a double-blind, crossover trial. However, this action on the tubular esophagus could not be demonstrated with oral cisapride (20 mg) [17].

Several prokinetics have been used in patients with GERD. Cisapride, the most recent drug, has been shown to increase esophageal transit and emptying, LESP and gastric emptying [17]. In patients with GERD, cisapride increases LESP [11, 52] and proved to be as effective as

ranitidine in symptomatic relief and in mucosal healing in patients with mild or moderate esophagitis [22] and there might even be an additive effect of cisapride when combined with an H_2 blocker [17].

In patients with reflux esophagitis a 30% reduction of esophageal acid exposure can be achieved by a conventional dose of 2×150 mg ranitidine. This can be improved to 60% by combination with cisapride (2×20 mg) probably by enhancing clearance of the tubular esophagus and reduction of gastric reflux by increasing LESP [21]. Cisapride in combination with H_2 blockers has been shown to increase the healing rate in patients with erosive esophagitis compared to a therapy with cisapride or H_2 blocker alone [15, 16]. Cisapride (10–20 mg) is superior to placebo in preventing a relapse of a previously healed reflux esophagitis [62, 65].

Within the group of prokinetics cisapride effects seem to be superior to the other prokinetic agents in GERD patients [68], but healing rates remain significantly lower than those for PPI therapy [52]. Cisapride in higher doses has recently been reported to induce prolongation of the QT interval and consequently cardiac arrhythmia and torsades de pointes tachycardia in critically ill patients [49]. The increased toxicity of cisapride was mainly observed when concomitant treatment with other drugs that interfere with cytochrome P450 3A4 (CYP3A4) are given such as erythromycin, diltiazem or azole antifungals [61]. Also grapefruit juice can interfere with this metabolic pathway and should at least theoretically be avoided. A prior electrocardiogram is recommended under appropriate circumstances and cisapride should not be given to patients with unstable heart disease liable to arrhythmias.

Mosapride. Mosapride citrate, a substituted benzamide, is a novel prokinetic agent enhancing upper but not lower gastrointestinal motility by stimulating 5-HT$_4$ receptors suggesting a 5-HT$_4$ receptor heterogeneity within the gastrointestinal tract [38, 70]. In a first clinical study mosapride showed a therapeutic effect on patients with GERD [69] and in a randomized, double-blind, placebo-controlled study in GERD patients mosapride (40 mg; q.i.d.) significantly reduced the acid reflux into the esophagus, proven by pH monitoring [53].

Other prokinetics like HTF 919, the substituted benzamides such as zacopride and renzapride and the benzimidazolon derivates BIMU1, BIMU2, LY353433 and RS23597-190 all act at the 5-HT$_4$ receptor with higher selectivity, longer duration of action and higher oral activity. These agents enhance prokinetic activity in animal experiments but clinical data have not been available to date [10].

Further Pharmacological Approaches

Motilin Receptor Agonists

The macrolide antibiotic erythromycin has recently been reported to exert profound prokinetic properties via an agonist action on the motilin receptor. Erythromycin (200 mg; i.v.), known to exert gastrokinetic action, significantly increases LESP, esophageal contraction amplitude, duration and propagation velocity in healthy volunteers [64]. Erythromycin (200/500 mg) given intravenously reduces postprandial GER in GERD patients by 50% [43, 47]. However, these results could not be verified when erythromycin (250/500 mg) was given orally [7]. Erythromycin also has improved esophageal transit in patients with diabetes and autonomic dysfunction [24, 63]. There are promising results with LY267108, an erythromycin analogue without antibiotic activity, which shows comparable effects in cat esophageal motility, but to date no data on LY267108 or other motilides on esophageal motility in humans have been published [18].

Opiates

In 8 healthy volunteers Penagini et al. [45, 46] demonstrated that morphine (100 µg/kg; i.v.) decreases the magnitude and duration of swallow-induced LES relaxation and increases the propagation velocity of propulsion without affecting the amplitude of primary peristalsis. Both effects were almost completely blocked by the fairly selective opioid µ-receptor antagonist naloxone, suggesting that the morphine effect is mediated via the opioid µ-receptor [59, 60]. In contrast, loperamide, a peripherally acting opiate, shows a relaxant effect on LESP in achalasia patients if given intravenously. This relaxant effect of loperamide could not be reversed by naloxone indicating an action other than on µ-opioid receptors [44]. Intraluminal infusion of loperamide at the level of the LES was ineffective suggesting that the drug must undergo intestinal absorption to elicit its effect on the LES. The loperamide study further suggests that the morphine effect is most likely an action via central opioid receptors [44]. In a study on 8 patients with GERD, morphine (100 µg/kg; i.v.) significantly reduced the number and duration of reflux episodes, an effect which is completely blocked by naloxone. The residual LESP was not affected but the number of TLESRs in this patient selection was reduced markedly [45]. However, due to their central and peripheral side effects these opioids are not applicable to GERD patients.

Conclusion

According to its high prevalence GERD is a common problem in daily practice. To date TLESRs (75%) and decreased LESP (20%), which can be diagnosed by manometry, are believed to be the major motility disorders underlying GERD. The main symptoms are heartburn and noncardiac chest pain. There are powerful medications for GERD treatment and endoscopic diagnosis should not be neglected since even minor symptoms could be the first signal for another differential diagnostic disease (e.g. carcinoma). As reflux of acid is regarded to be the major aggressive factor acting on the esophageal mucosa, therapy has concentrated on blockade or neutralization of gastric acid. However, there is some evidence that prokinetics can also be beneficial in the treatment and prophylaxis of GERD. The various agents currently used for treatment of GERD include mucoprotective substances, antacids, H_2 blockers and PPIs. Although these drugs are effective, they do not necessarily influence the underlying causes of the disease by improving the esophageal clearance, increasing the LESP or reducing the frequency of TLESRs. To date it seems to be reasonable to combine these drugs with a prokinetic drug to restore the defective motility patterns but prokinetics probably do not influence the incidence of TLESRs and therefore newer drugs are needed to specifically treat this motility disorder. In acute as well as long-term treatment of reflux esophagitis treatment with PPI shows the best results, compared to other drugs, and also has the best cost-efficacy, if the treatment of complications is taken into account. PPI should, therefore, be the preferred drug in the treatment of more severe forms of erosive GERD.

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