The Role of Baclofen in the Treatment of Gastroesophageal Reflux Disease

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Abstract

Objective. To describe the evidence for baclofen in the treatment of gastroesophageal reflux disease (GERD). **Data Sources.** A search of PubMed and Google Scholar was performed using the terms *baclofen*, *gastroesophageal reflux disease*, and *treatment*. **Study Selection and Data Extraction.** Publications were reviewed manually for relevance, and studies that addressed the use of baclofen in the treatment of adult symptomatic GERD patients were included. **Data Synthesis.** Nine studies were evaluated. Baclofen was shown to significantly reduce transient lower esophageal sphincter relaxations (TLESRs), postprandial acid reflux events, and median number of acid-related symptoms in 6 studies evaluating either a single dose of baclofen or short courses of 2 days or less. Three studies followed patients over a slightly longer period of time. These studies confirmed the results of the shorter trials by finding a decrease in supine duodenal reflux episodes, decreased periods when the pH was less than 4, and improvements in symptom scores in patients refractory to proton pump inhibitors. Side effects most frequently reported included drowsiness and dizziness. **Conclusions.** Baclofen can be considered for the treatment of refractory GERD following diagnostic evaluation. It has been shown to reduce TLESRs, reflux episodes, and reflux-related symptoms with minimal side effects in short-term trials. Future studies demonstrating the long-term efficacy and tolerability of baclofen in the treatment of GERD would help solidify its place in therapy.

Keywords

baclofen, gastroesophageal reflux disease, GERD, treatment

Background

Gastroesophageal reflux disease (GERD) is defined as symptoms or complications arising from the reflux of gastric contents into the esophagus, oral cavity, or lungs. It is one of the most common disorders affecting the gastrointestinal tract and affects nearly 20% of the US population.¹ According to the 2013 Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease, a presumptive diagnosis of GERD can be made based on symptoms of heartburn and regurgitation. When GERD is suspected, a trial of a proton pump inhibitor (PPI) is reasonable to confirm the diagnosis; however, a negative PPI trial does not rule out GERD. Upper endoscopy can be considered to rule out a GERD complication in the presence of alarm symptoms (eg, dysphagia). Ambulatory esophageal reflux monitoring with either a telemetry capsule or trans-nasal catheter is indicated in situations when the diagnosis of GERD is in question. It is the only test that determines the presence of abnormal esophageal acid exposure, reflux frequency, and association of symptoms with reflux episodes.¹

Untreated GERD can cause injury to the esophagus and can lead to more serious conditions, such as Barrett's esophagus and esophageal adenocarcinoma. The primary treatment for GERD is acid suppression with once daily dosing of a

PPI. No major differences in efficacy between the available PPIs have been shown in studies with regard to symptom relief.¹ Despite aggressive acid suppression with a PPI, up to 30% of GERD patients continue to experience symptoms of reflux.² This significant population of patients demonstrates the need for additional therapeutic options when PPI treatment alone is insufficient.

Patients who partially respond to once-daily PPI dosing may be increased to twice-daily administration. Additionally, an H₂-receptor antagonist (H₂RA) at night can be added to daily PPI therapy in patients with nighttime reflux. Prokinetic therapy with metoclopramide can also be added, but it has been associated with central nervous system side effects such as drowsiness, agitation, depression, and dystonic reactions. Patients who continue to be symptomatic

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and for whom ambulatory reflux monitoring confirms reflux as the cause of symptoms may consider other options including surgery or the transient lower esophageal sphincter relaxations (TLESR) inhibitor, baclofen. Reflux events can be confirmed when esophageal pH drops below 4.³ Esophageal manometry is used to measure lower esophageal sphincter (LES) pressure and to determine if TLESRs are occurring. When LES pressure declines more than 3 mm Hg to a level less than 2 mm Hg above the intragastric pressure, and this decline occurs for more than 5 seconds after a swallow, it is termed a TLESR.⁴ Additionally, LES relaxations that are associated with swallows but last longer than 10 seconds are also considered TLESRs.⁴

The pathophysiology behind persistent GERD symptoms despite appropriate acid suppression identifies a potential area for further pharmacologic intervention. Incompetence of the LES, impaired resistance of the esophageal mucosa, decreased esophageal clearance, and increased TLESRs all contribute to the symptoms of GERD.³ Among these mechanisms, increased TLESRs have been shown to be the main pathophysiological cause of reflux in patients suffering from GERD.³ Gamma-aminobutyric acid class B (GABA_B) receptors play an important role in TLESRs and are found in neurons in the motor nucleus of the vagal nerve and nucleus tract solitarius.³ Baclofen, a GABA_B agonist, may be used as an add-on therapy aimed at reducing the occurrence of TLESRs.

Baclofen is a skeletal muscle relaxant that works by inhibiting polysynaptic and monosynaptic afferent pathways at the level of the spinal cord. It is a derivative of GABA and stimulates GABA_B receptors, leading to decreased excitatory input into alpha-motor neurons. Baclofen is Food and Drug Administration approved for spasticity resulting from multiple sclerosis and other spinal cord injuries. Baclofen should be initiated cautiously in patients with epilepsy, as increased seizure frequency and EEG deterioration have been reported with baclofen use. Common side effects of oral baclofen therapy include nausea, hypotension, asthenia, dizziness, headache, somnolence, and fatigue.⁵

As a GABA_B agonist, baclofen may be a treatment option to reduce TLESRs and reflux events. An examination of the current evidence is needed to describe the clinical efficacy of baclofen given its therapeutic potential and the shortage of alternative treatment options in GERD. This review describes the evidence for baclofen in the treatment of GERD.

Data Sources

A search of PubMed (1966 through March 2015) and Google Scholar was performed using the terms *baclofen*, *gastroesophageal reflux disease*, and *treatment*. Publications were reviewed manually for relevance, and studies were

included if they evaluated and addressed the use of baclofen in the treatment of GERD in symptomatic adult patients.

Nine trials are included in the literature review. Six of the trials examined reflux events, reflux symptoms, and LES function after either single doses of baclofen or short courses of less than 2 days. Three trials were of longer duration and followed patients for a minimum of 14 days.

Literature Review

Zhang et al conducted a randomized, placebo-controlled crossover trial that looked at the effect of baclofen on TLESRs in patients with GERD. After stopping all acid suppressing and motility agents for at least 4 days, 20 patients received a single dose of either baclofen 40 mg or a placebo administered 1 hour before a meal. The patients were then crossed over to the other treatment at least 1 week later. This trial found that patients on baclofen experienced a significant reduction in TLESRs from a median of 15 to 9 for the 3-hour postprandial period ($P < .0002$). The trial also found that baclofen significantly reduced the rate of reflux episodes by 43% from 7 to 4 episodes for that same 3-hour period ($P < .02$). Significant side effect differences were not seen.⁶

Cange et al randomized 20 patients with established reflux disease to either baclofen 40 mg or placebo given as a single dose. All antisecretory and prokinetic drugs were stopped at least 1 week before study day. After a 4-week washout period, the patients were crossed over to the other treatment. The number of reflux episodes was decreased from 73 to 46 ($P < .0001$) over the 12-hour study period and the fraction of time with the pH < 4 was decreased by 19% ($P < .039$). Reports of belching were also significantly reduced in the baclofen-treated patients from 69 to 32 episodes ($P < .01$). The most common adverse effect was mild vertigo reported in 8 patients when taking baclofen and 1 patient when taking placebo.⁷

Van Herwaarden et al investigated a change in reflux symptoms in 37 patients receiving 2 days of baclofen 40 mg daily or placebo. They also monitored pH and esophageal manometry changes in a subset of 20 patients who completed an additional 2 days of baclofen or placebo therapy. All reflux medications were stopped at least a week before the study period. Patients were crossed over to the other treatment after a 3- to 10-day washout period. All measurements were performed 3 hours after a provocation test meal. Baclofen treatment significantly decreased reflux events from 12.4 to 8.3 ($P = .03$) and TLESRs from 22.8 to 15.1 ($P < .0001$) but did not affect overall LES pressure. Baclofen did not affect the number of patients complaining of moderate to severe heartburn when compared with placebo (44% vs 47%, $P = ns$). Two patients did not complete the study due to nausea but the study does not indicate if this was after baclofen or placebo administration.⁸

A randomized controlled trial by Vela et al looked at the effect of baclofen on both postprandial acid reflux events and non-acid reflux events. In a crossover design, 9 healthy volunteers and 9 with heartburn were treated with either baclofen 40 mg or placebo and then given a meal expected to precipitate reflux events. No baseline endoscopy was performed, and all acid controlling medications were stopped 1 week prior to starting the study. In the 9 heartburn patients, baclofen reduced the number of acid reflux events from 15 to 6 ($P = .004$) and non-acid reflux events from 4 to 2 ($P = .003$). The median number of acid-related symptoms was reduced from 9 to 1 ($P = .008$). In healthy patients, baclofen reduced the number of acid reflux events from 7 to 1 ($P = .02$) and non-acid reflux events from 2 to 0 ($P = .005$). Seven of the 18 patients experienced side effects, including mild dizziness, nausea, and vomiting when taking baclofen.⁹

Grossi et al conducted a 48-hour manometric study of 23 patients with endoscopically documented esophagitis who had been stopped on their antisecretory medications for at least 4 weeks. Fourteen patients received baclofen 10 mg 4 times daily for 24 hours, 7 patients received placebo, and 2 patients were excluded due to LES pressure of less than 10 mm Hg. Compared with baseline values, baclofen patients were found to have a decreased number of swallows from 1583 to 1254 ($P = .02$), an increased LES basal tone from 20.5 to 24.8 mm Hg ($P = .01$), and a decreased number of TLESRs from 57.5 to 41.5 ($P = .01$). There were no significant differences in any of these outcomes in the placebo patients when compared to their baselines. One patient receiving baclofen complained of a headache and one of mild dizziness but both completed the trial.⁴

A small randomized, placebo controlled, crossover trial by Orr et al looked at the effect of baclofen on nocturnal GERD symptoms and sleep quality. Participants had to have GERD complaints at least twice per week, and all acid suppressing agents were stopped 10 to 14 days before the trial began. Patients received either a single dose of baclofen 40 mg or placebo 90 minutes before bed. Baclofen reduced the number of reflux events after sleep onset by 56% ($P < .05$). Total sleep time and sleep efficiency were both increased during baclofen treatment.¹⁰

The first study that looked at baclofen for a longer period of time was conducted by Koek et al. In this unblinded trial in which baseline values served as the control, patients who had persistent heartburn or regurgitation despite at least 3 months of treatment with a twice-daily PPI were eligible. Sixteen patients agreed to participate in the 14-day trial. They were continued on omeprazole 20 mg twice daily and had baclofen 5 mg 3 times daily with meals added to their regimen. The baclofen dose was titrated up to 20 mg TID over the next 10 days. Results from this study showed a decrease in number of supine duodenal reflux episodes,

which are defined as an increase in esophageal bilirubin absorbance, from 23 during treatment with only omeprazole to 12 once baclofen was added ($P = .06$). The number of duodenal reflux episodes lasting greater than 5 minutes also decreased from 5 during treatment with omeprazole alone to 2 once baclofen was added ($P < .05$). The symptom severity score measured with a 14-symptom questionnaire decreased significantly with treatment from 10.3 to 5.8 ($P < .01$). Side effects occurred in 4 patients during the baclofen treatment and included mild nausea and drowsiness. No dose reductions were needed and no patients withdrew from the study.¹¹

Ciccaglione and Marzio conducted a trial that looked at both the effect of acute and chronic administration of baclofen on patients with GERD. All reflux and nonsteroidal anti-inflammatory medications were stopped at least 30 days before the study period. For the chronic phase of the study, 18 patients completed a 4-week symptom control treatment phase. Twelve patients were titrated to baclofen 10 mg QID, and 6 patients received placebo. After 4 weeks of therapy, the number of reflux episodes over a 24-hour period for the patients taking baclofen as compared to their baselines decreased significantly from 220 to 52 ($P < .003$), and the percentage of time with a pH < 4 also decreased significantly from 5.8% to 2.7% ($P < .02$). There was no difference from baseline after 4 weeks of therapy in the patients receiving placebo. Two patients on baclofen withdrew after 10 days, one due to low blood pressure and one due to sedation.¹²

Cossentino et al conducted the largest randomized placebo-controlled trial examining the effects and tolerability of baclofen in patients with GERD. Forty-three GERD patients were randomized to receive either baclofen or placebo for a 2-week period. The baclofen dose was titrated up to 20 mg 3 times a day before meals over a 6-day period. Esophageal manometry, 24-hour pH monitoring, and a symptom questionnaire were used to assess the treatment effect of baclofen. Patients were required to stop all previous GERD medications and were given 30 tablets of an antacid for breakthrough symptoms. Thirty-four subjects completed the trial. Seven of the 9 subjects who dropped out were in the baclofen group, and dizziness was the most common reason for discontinuation. Significant improvements in 24-hour pH score from 51 to 30 ($P = .02$), percent upright reflux from 14% to 9.2% ($P = .016$), percent total reflux from 11% to 6.6% ($P = .003$), number of reflux episodes from 142 to 113 ($P = .018$), and number of reflux episodes greater than 5 minutes from 5 to 4 ($P = .016$) were found to favor the baclofen-treated patients. Reflux symptoms including belching, regurgitation, and total symptom score were improved with baclofen; however, there was no significant difference in antacid use between groups. While drowsiness is a frequently reported side effect of baclofen, it was not reported in this trial.³

Discussion

Baclofen demonstrates promise as an additional agent in the armamentarium of GERD treatment. Six short-term randomized controlled trials indicate baclofen has the ability to reduce TLESRs, the rate of reflux episodes, and the number of reflux events, thereby potentially improving quality of life.^{4,6-10} Three slightly longer trials seem to support these findings.^{3,11,12}

When acid suppression is insufficient to control GERD symptoms, the different mechanism of action of baclofen in preventing reflux events makes it a promising adjunctive therapy. No serious adverse events have been reported in the trials reviewed here; however, the short duration of therapy may contribute to this outcome. Baclofen is associated with centrally acting side effects,³ with drowsiness and dizziness being the most reported in the studies reviewed. Tolerability did not seem to be an issue, but again, the short duration of the trials may be masking tolerability issues.

Among patients who find optimized PPI therapy insufficient to control their GERD symptoms, very few treatment options exist. The first is adding an H₂RA at bedtime to help control symptoms. Tachyphylaxis after several weeks of H₂RA therapy has been encountered, making it a suboptimal strategy.¹ Another option is adding a prokinetic agent such as metoclopramide to improve gastric emptying; however, this is associated with a myriad of central nervous system side effects. Surgery may be another management strategy but is generally not recommended in patients who do not respond to PPI therapy.¹ Although evidence is not strong to support routine use of baclofen in GERD, it does have a place in management of refractory GERD due to the limited treatment options. Since small trials have demonstrated some effectiveness, a trial of baclofen is a reasonable option when optimal PPI treatment is inadequate and no non-GERD etiology can explain residual symptoms. It is important to carefully monitor for side effects when baclofen is initiated and throughout treatment.

Summary

Baclofen can be considered for the treatment of refractory GERD following diagnostic evaluation. It has been shown to be efficacious in reducing TLESRs, reflux episodes, and reflux-related symptoms in small, short-term trials. Side effects such as drowsiness and dizziness should be monitored while on baclofen therapy. Despite the lack of long-term efficacy data, the limited treatment options available for GERD patients who respond insufficiently to PPI therapy make baclofen a reasonable choice. Future larger prospective studies of long-term tolerability and efficacy of baclofen would provide more insight into baclofen's role in GERD treatment.

Declaration of Conflicting Interests

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