

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Medical Therapies to Effect Transient LES Relaxation

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G&H Could you discuss why there is a need for medical therapy to effect transient lower esophageal sphincter relaxation?

DC Reflux is an extremely common problem—it occurs in approximately 40% of our population—and proton pump inhibitors have been shown to be effective at eliminating gastric acid in the majority of patients. Over the last few years, due to the effectiveness of controlling the acid component of reflux, we have become aware that up to half of these reflux patients continue to have symptoms (most commonly, regurgitation and chronic cough) and will reflux even though there is minimal acid left in the stomach, due to the relaxation (ie, opening) of the sphincter. This reflux is considered nonacid reflux or weakly acidic reflux (ie, reflux of a pH greater than 4). It is very important at this point to stress that acid is not the cause of all reflux nor the only component of reflux that causes symptoms. Therefore, proton pump inhibitors do not completely eliminate reflux in all patients, even though for many years gastroenterologists assumed this to be true. In actuality, acid is not the only factor determining reflux; transient relaxations are the reason why people reflux. Reflux continues no matter what the acidity level of the stomach. As there is a growing interest in finding a second line of therapy to treat these continuing refluxers, this area is developing as a popular avenue for pharmaceutical research. However, as of yet, this is an area that has not been well explored. There is no drug currently approved by the US Food and Drug Administration for the purpose of treating transient lower esophageal sphincter (LES) relaxations.

G&H What drugs are currently under development for this indication?

DC The drug baclofen, which has been on the market for a number of years, was approved for treatment of muscle spasticity and is normally used for cerebral palsy patients and patients with other neuromuscular diseases. Although not indicated for it, baclofen is also occasionally used in patients with reflux. This is a recent development; gastroenterologists never used it in the past. Presently, I would estimate that perhaps 1 in 20 gastroenterologists have used baclofen on occasion to treat reflux. Studies from the last 10 years have shown that baclofen given orally will inhibit transient LES relaxations, particularly in the postprandial period. Initial studies came from Australia, and there have been additional studies in Belgium and Italy as well as from our young investigators, Drs. Vela and Tutuian, here in the United States. These studies have all shown that baclofen inhibits transient LES relaxation and decreases the number of reflux episodes. Based upon these data, several small controlled studies have been performed with baclofen.

More recently, researchers have tried to develop a baclofen derivative called arbaclofen to inhibit reflux. This drug is the R-isomer of the baclofen molecule, and it is being produced by XenoPort, a biopharmaceutical company in California. A mechanistic study that the Medical University of South Carolina participated in showed that arbaclofen successfully decreases the number of reflux episodes and symptoms for a period of up to 12 hours with a single dose. This is a fairly encouraging initial study, which is currently in press for publication in the

American Journal of Gastroenterology. The researchers have subsequently performed a small clinical trial comparing baclofen to placebo in a group of approximately 150 patients who have “failed” proton pump inhibitor therapy. (Failure was defined as the presence of some symptoms despite proton pump inhibitor therapy.) In this clinical trial, positive results were obtained. Based upon these results, a third study is in the process of being organized. This derivative of baclofen is one of the frontrunners for submission to the US Food and Drug Administration.

The second drug currently being developed, by AstraZeneca, is AZD 3355, a baclofen-type drug that inhibits transient LES relaxations. This drug is believed to have more peripheral action (ie, it works more at the receptors in the stomach rather than just affecting the central nervous system). I have not been involved in any studies investigating this drug, but there has been a European multicenter study with encouraging results for its use as add-on therapy (not primary therapy) in patients who had less than a complete response to a proton pump inhibitor.

The third drug in development is being made by Addex Pharmaceuticals in Switzerland (ADX 10059). This drug is also thought to be primarily a peripherally active inhibitor of transient LES relaxations. There are two associated studies currently ongoing: a European study that recently showed positive results, and a US multicenter study that we are participating in that has just been closed to subject entry. The results of the latter study will be analyzed shortly.

G&H Could you explain more specifically the mechanism of action of these drugs?

DC In the past, physicians used to think that reflux occurred only with a chronically weak sphincter (a “failed valve” that could not maintain pressure). As we began to study reflux more, we recognized the fact that most people with reflux actually have a normal pressure in their LES. The problem was that the sphincter would frequently relax spontaneously, causing the pressure to drop and stay low for perhaps a minute or two, and then the sphincter would recover its pressure again. However, during the time when the sphincter was relaxing, gastric contents were able to reflux into the esophagus. These transient LES relaxations usually occur after a meal, when the stomach is full and there is a lot of material there. The filling or distending of the stomach triggers these transient sphincter relaxations, allowing reflux to occur. By and large, reflux is related to how much the stomach is filled: the bigger the meal, the more the reflux. What we are trying to do is inhibit reflux by preventing the sphincter from relaxing, particularly when there is food in the stomach. Thus, most of these therapies are aimed at the postprandial period. Standard baclofen has a duration of 3–4 hours. I am not familiar

with the specifics of the pharmacodynamics of the newer drugs currently in development, though I do know that the study currently in press for arbaclofen showed that a single morning dose was effective for up to 12 hours.

G&H Thus far, have there been any significant side effects or concerns with these emerging medical therapies?

DC These drugs can all potentially have a negative effect on the central nervous system. Certainly, standard baclofen is known to have these side effects, which include drowsiness and dizziness, and are dose-related. With a large enough dose, drowsiness can occur in all patients. That is why we try to start treatment at a low dose and titrate therapy up. Arbaclofen, with its improved delivery and absorption systems, can probably be given in smaller doses and still be effective. In the early studies so far, it appears that fewer central nervous system side effects are associated with this drug. The other two drugs, the AstraZeneca drug and the Addex drug, are primarily peripherally active and, at least in theory, should have less of a central nervous system effect. This appears to be the case, but it is still too early to tell; we need to see the publication of these studies and have additional clinical experience with these drugs before we can know for sure.

G&H Do you foresee these drugs becoming available to clinicians in the near future, or is official approval still far off?

DC Excluding standard baclofen, none of these drugs are available yet, but I think we are getting close. There is a good deal of interest in this area because of the continuing reflux problem. Each of these drugs has undergone a clinical study that has been completed or is close to being completed. Thus, I am hopeful that we might see a submission to the US Food and Drug Administration within the near future and at least one of these drugs may be released within the next year or two. I would certainly like to see this; it would be very helpful to have an option besides standard baclofen. Gastroenterologists use standard baclofen often these days but have to be very careful with its use and vigilant for side effects. I recently had a patient who was a perfect candidate for baclofen, but whose job precluded using the drug due to the high risk of drowsiness.

G&H Could these emerging drugs ultimately be used as frontline therapy, or will they likely remain as add-on therapy?

DC The way I view these drugs is based on how patients have presented to me: they have gastroesophageal reflux disease; they are put on proton pump inhibitor therapy;

they improve but are not asymptomatic; finally, they end up being referred to me for a consultation. If they have documented reflux, I would likely give them one of these drugs, as an add-on to their baseline proton pump inhibitor. It is possible that if these drugs are effective in stopping transient relaxations of the LES that they may be effective first-line therapies for some people. However, studies examining this possibility have not yet been conducted.

G&H As there are no drugs currently approved for transient LES relaxation, what alternative approaches are usually used in these patients?

DC Instead of just inhibiting the relaxations of the sphincter, gastroenterologists can perform a surgical procedure to stop the reflux. Fundoplication, which is usually performed laparoscopically, has been used for 20–30 years. Performed by an experienced surgeon, for the appropriate indication, fundoplication is a very effective procedure. We have reported a success rate of 94% at follow-up a year and a half later based upon data from our laboratory at the Medical University of South Carolina from a group of patients in whom we made the diagnosis of symptomatic nonacid reflux and whom we sent to surgery.

Another option is endoscopic repair at the LES to inhibit reflux. There have been many studies on this

approach, particularly within the last 10 years, trying to determine a method of performing fundoplication through endoscopy without actually operating on the patient. Several variations are still being attempted, but to date, no researcher has arrived at an approach that is effective and successful for the majority of the time. The thought process behind this approach has been that there must be a way to use an endoscope to place several sutures around the sphincter area and tighten it up to stop the reflux, but thus far, it has not been very successful.

Suggested Reading

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