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DRUG-INDUCED ("PILL") ESOPHAGITIS: A REMINDER

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Acid reflux is by far the most common cause of esophagitis. Because of the frequency and familiarity most clinicians have with acid reflux injury, there is a tendency to attribute all esophagitis to reflux and consequently other causes often go undetected. The basis for good differential diagnosis of the non-reflux causes of esophagitis is best understood only if one takes a good history and has an understanding of the endoscopic features of acid reflux injury. Esophagitis due to acid reflux always involves the squamocolumnar junction (i.e. junction of esophageal mucosa with stomach or gastric mucosa) at some point in its circumference. Although so-called stepping stone erosions may be seen proximal to the main squamocolumnar junction, they will always be associated with other endoscopic signs of mucosal injury at the squamocolumnar junction. When one sees esophagitis proximal to a normal squamocolumnar junction, an immediate suspicion for other etiologies should arise. It is also important to remember that typical acid reflux injury may be altered or enhanced by related factors such as pill impaction and injury or the prior use of an indwelling nasogastric tube.

Although many drugs are recognized as causes of drug-induced esophagitis, this potentially lethal disorder is little known among primary care physicians and many specialists. Esophageal injury due to "pills" was first reported in 1970 by Pemberton. Several comprehensive reviews have been published. We have evaluated 23 patients with the various forms of drug-induced esophagitis with most having severe strictures requiring dilation.

The more commonly used drugs that have caused esophageal injury in the United States include potassium chloride tablets (especially the wax matrix form such as Slow-K), tetracycline, doxycycline, quinidine gluconate (Quinaglute), ferrous sulfate, ascorbic acid, and most recently alendronate (Fosamax).

The drug formulation appears to be an important

factor in the potential for delayed passage and mucosal injury. For instance, capsules of doxycycline have been shown to remain in the esophagus three times as frequently as tablets of the same compound. The size of the tablet or capsule seems important as well. Three of our last five cases of "pill" esophagitis have been severe esophageal strictures at the level of the aortic arch in patients taking quinidine gluconate. This tablet is 13 mm in diameter (about 1/2 inch).

Common factors in the genesis of drug-induced esophagitis are esophageal, the "physiologic" narrowing at the level of the aortic arch, obstruction by strictures and cancer, disordered esophageal motility, or any combination of these. In the absence of obstruction, the patient usually gives a history of taking the medicine while in a recumbent position or without sufficient liquid just before retiring at night. Drug-induced esophagitis may also be associated with esophageal motility abnormalities, such as esophageal spasm, and achalasia or with left atrial enlargement, which may cause compression and partial occlusion of the esophageal lumen. The most common contributory factors are ingestion of the drug without adequate fluid, recumbency immediately after ingestion, tablet or capsules of large size, and the chemical composition of the drug.

The pill-taking habits of the patient are a vital aspect of the history in suspected cases. Certain diseases and their related therapy suggest the diagnosis and site of injury. The patient with cardiomegaly (enlarged heart) and left atrial enlargement typically sustains esophageal injury from potassium chloride or quinidine at a level 30 to 35 cm from the incisor teeth, that is, at the level of esophageal compression by the enlarged left atrium. The person without intrinsic esophageal disease or cardiomegaly will more often develop pill esophagitis from transient impaction of drugs at the level of the aortic arch (22 to 24 cm) or proximally. After discontinuation of the drug, the acute mucosal injury heals within several weeks without other therapy. If prolonged deep injury has

DRUG-INDUCED (“PILL”) ESOPHAGITIS: A REMINDER (continued)

occurred, severe mural fibrosis with stricture are the end results. The teenager with acne or the traveler (often a physician or nurse) trying to prevent or treat traveler's diarrhea typically presents with odynophagia and a lesion in the upper esophagus caused by doxycycline. The patient with arthritis may develop esophagitis from aspirin, naproxen (Naprosyn), indomethacin, or other anti-inflammatory drugs. Another important point is that drug injury may aggravate, or render atypical, the lesions of acid reflux esophagitis.

Over 70 drugs have been reported to cause esophageal injury. The classic symptoms are odynophagia (pain with swallowing) (74%), continuous retrosternal pain (72%), dysphagia (20%), or combinations of these symptoms. Elderly patients may have dysphagia alone, and often drug-induced esophagitis and stenosis are never considered in the differential diagnosis. Several of our patients complained of severe dysphagia without odynophagia or chest pain and were considered to be suffering from occult malignancy by the referring physician because of their advanced ages and the location and radiographic appearance of the stenotic lesions. A proper history suggested the correct diagnosis in all. Three were taking quinidine gluconate and had strictures at the aortic arch level, the fourth was taking potassium chloride and quinine sulfate in tablet form, and the fifth potassium chloride (Slow-K). The latter had a stricture at 30 cm, the level of his enlarged left atrium that was compressing his esophagus. With continued ingestion of the offending drug, the esophageal injury may extend proximally from the original stenosis, thereby making diagnosis and therapy more

difficult and increasing the risk of severe injury. Potassium chloride injury has been the most lethal, with at least nine deaths resulting from either ulceration with bleeding, perforation, or mediastinal abscess and from the long-term effect of a severe esophageal stricture.

It has become apparent that certain drugs, for example, doxycycline, ferrous sulfate and aspirin, produce only acute mucosal injury that heals completely when the drug is stopped and does not lead to stricture formation. Others, such as quinine sulfate, quinidine gluconate, slow release potassium chloride and alendronate will cause severe esophageal stricture.

The latest drug added to the esophageal injury list is alendronate (Fosamax), a selective inhibitor of osteoclast-mediated bone resorption, that is used to treat osteoporosis in post-menopausal women and Paget disease of bone. Endoscopic findings include erosions or ulcerations and exudative inflammation with thickening of the esophageal wall and stricture.

Ordinarily, little thought is given to instructing patients in the proper way to swallow medications that are in solid form, either tablet or capsule. The delay in passage of tablets through the esophagus under the influence of recumbency and a small volume of fluid was amply demonstrated by Evans and Roberts. They found a delay in passage of an aspirin-sized barium tablet through the esophagus beyond 5 minutes in over 50% of subjects when in the recumbent position. The message is clear – avoid low fluid volume and recumbency when taking any form of medication.

ENDOSCOPIC THERAPY OF GASTROESOPHAGEAL REFLUX DISEASE (GERD): IS IT TIME FOR A MORATORIUM?

Milton C. Johnson, M.D.

SURGICAL ANTI-REFLUX PROCEDURE

The most commonly employed anti-reflux procedure is the Nissen fundoplication performed laparoscopically. Laparoscopic Nissen fundoplication (LNF) may result in effective healing of esophagitis; may control gastroesophageal reflux GER symptoms (especially, belching); and may produce remission of GERD-related symptoms and improve the quality of life in 90% of patients treated. The effectiveness of the fundoplication, however, diminishes over a 5 to 10 year period. Fifty percent of patients require medical anti-reflux therapy to control recurrent or persistent GER symptoms after surgical anti-reflux procedures. Some patients may report the development of new symptoms following fundoplication. These symptoms include: 1) dysphagia; 2) gas/bloat; 3) increase flatus; and 4) difficulty with belching or vomiting. The best candidate for surgical anti-reflux procedures demonstrates the following characteristics: 1) well-documented GERD with or without a hiatal hernia; 2) esophagitis

discovered at endoscopy; 3) abnormal 24-hour or 48-hour ambulatory pH monitoring; 4) normal esophageal motility study; and 5) evidence of at least partial symptom relief with proton pump inhibitor (PPI) therapy.

ENDOSCOPIC ANTI-REFLUX PROCEDURES

Endoscopic procedures have been developed as less invasive alternatives to surgical fundoplication to treat GERD. The endoscopic procedures include: 1) Stretta; 2) EndoCinch; 3) Enteryx; 4) Gatekeeper; and 5) NDO full-thickness plication. Overall, the endoscopic procedures control symptoms in nearly 80% of patients undergoing treatment. Endoscopic procedures reduce, but do not completely eliminate the need for medical anti-reflux therapy. The long-term effectiveness of endoscopic procedures, as a whole, is unknown due to their recent introduction and short-term use when compared to medical anti-reflux therapy (proton pump inhibitors or PPIs) or surgical anti-reflux therapy. In addition, the effectiveness

of any endoscopic procedure to control extra-esophageal symptoms (cough, hoarseness) or reduce the development of Barrett esophagus or esophageal cancer is unknown.

The Stretta (Curon Medical, Sunnyvale, CA) system consists of a radio-frequency generator and a delivery catheter comprised of a soft shaft, and a balloon-basket assembly with four electrodes positioned radially around the balloon. When the catheter is positioned and the needles are deployed into the inner circular muscle of the gastroesophageal junction, energy is delivered to each electrode to create a series of thermal lesions in the muscle. The region of the lower esophageal sphincter at the gastroesophageal junction (GEJ) is reinforced by this method. Complications have been reported.

EndoCinch (Bard Endoscopic Technologies, Billerica, MA) is an endoscopic suturing system with multiple components. The device is introduced through an over-tube. The device can pass single or multiple sutures at a time. The aim of the device is to alter the gastroesophageal junction (GEJ) by tightening the gastric cardia (upper stomach) along the lesser curvature of the stomach. The procedure accentuates the natural barrier opposing GER. Loose or lost sutures account for the chief reason for recurrent GER symptoms.

Enteryx (Boston Scientific, Natick, USA) is a biopolymer that is slowly injected along the muscle layer or the deep submucosal layer of the gastric cardia (upper stomach) during endoscopy. Polymerization (chemical reaction in which a compound is made into a polymer) of the implanted material occurs following injection. Fluoroscopy (a device transmitting x-rays) allows for visualization of the biopolymer as it is injected into the deep layers of the wall of the gastric cardia. A “bulking” effect results in the region of the GEJ after successful implantation; and, the natural, defensive barrier opposing GER is enhanced.

The Gatekeeper (Medtronic Inc., Tolochenaz, Switzerland) procedure involves implantation of expandable miniature hydrogel prostheses in the region of the GEJ during endoscopy. The implanted material is injected into the submucosal layer of the wall. The submucosal expansion of the prostheses inside the wall at the GEJ produces a “bulking” effect in the region. The result produces a better defensive barrier to oppose GER.

The NDO full-thickness plicator (NDO Surgical, Inc., Mansfield, MA) produces a full-thickness (transmural) plication using a pre-tied, suture-based implant. While looking backwards toward the gastric cardia (upper stomach) during endoscopy, the plicator is applied to the GEJ. The NDO system requires an over-tube to introduce it into the stomach and consists of three components. They include: 1) a plicator; 2) a tissue retracting helical catheter; and 3) a pre-tied suture insert.

The newest “endoscopic suturing device” is the ESD System (Wilson-Cook Medical, Inc., Winston-Salem, NC). The ESD system produces a full-thickness (transmural) plication in the region of the GEJ during endoscopy. The ESD system is introduced through an externally fixed working channel and does not require an over-tube to introduce it into the stomach. It consists of three components. They include: 1) an external working channel; 2) a flexible

Sew-Right device; and 3) a flexible Tie-knot device. Loose or lost sutures were frequently discovered during follow-up periods and they accounted for the chief reason for recurrent GER symptoms.

Medical anti-reflux therapy remains the single, most important intervention in the treatment of gastroesophageal reflux disease (GERD). Proton pump inhibitors are the best class of drugs to control the symptoms of gastroesophageal reflux (GER) and heal esophagitis. Many patients will consider alternative interventions to avoid daily administration of a PPI drug and/or to avoid the cost of daily PPI usage. Some patients and health care providers believe that surgical or endoscopic anti-reflux procedures will reduce their risk of developing GERD-related complications (erosions, ulcers, stricture, Barrett esophagus and esophageal cancer). Others accept the belief that surgical and endoscopic anti-reflux procedures better control GER symptoms of heartburn and regurgitation than does medical anti-reflux therapy. In fact, PPI daily administration controls GER symptoms and heals esophagitis in greater than 95%. Only 5% or less of all patients with GERD will require alternative anti-reflux procedures to control symptoms and heal esophagitis. There is no current endoscopic anti-reflux procedure that is proven to prevent the risk of GERD-related complications. In addition, there is limited study data to date, supporting the concept that either open or laparoscopic surgical procedures heal esophagitis or prevent complications of GERD. Endoscopic procedures to control GER should not yet be considered as the best alternative therapy until more data have been collected through further research, especially in light of a growing list of limitations and complications associated with the current group of endoscopic procedures as a whole.

An editorial by Walt Hogan (Medical College of Wisconsin) in the latest issue of the American Journal of Gastroenterology reviews the safety and efficacy issues of all of the current endoscopic procedures approved for use by the United States Food and Drug Administration in the new millennium. The following list of statements represents the current operational or market status of the various endoscopic procedures following a thorough re-assessment of their safety and efficacy since conception: 1) Enteryx has been withdrawn from clinical practice since September 23, 2005; 2) the ESD System and the Gatekeeper System have been withdrawn from clinical practice; 3) the EndoCinch sutures lack durability and compromise the overall effectiveness of this procedure and there are reports of major bleeding associated with the system; 4) the Stretta procedure, in a randomized controlled trial (Stretta compared to a “sham” or placebo group), has been shown not to significantly reduce esophageal acid exposure or reduce the requirements for acid-suppressant medications (PPIs); 5) the Stretta procedure has resulted in three patient-related deaths and perforation (rupture) of the GEJ. In view of the recent safety and efficacy issues of endoscopic procedures, one must ask whether or not it is time for the community of gastroenterologists and all who perform endoscopy to call for and initiate a moratorium on the use of endoscopic anti-reflux procedures for GERD in clinical practice for now.

THINGS TO REMEMBER

1. **OFFICE HOURS:** 8:00 a.m. 'til 5:00 p.m. Monday through Friday. Telephone hours: 8:00 a.m. 'til 5:00 p.m. Also, our emergency telephone number for after hours is (813) 974-2201

2. **BILLING:** Payment for services rendered is due at the time of your visit. Please be prepared to pay any co-payments due at the time of your visit to the Center. Patients who have problems with their physician or facility fee bills should contact Gayle Stephens, Financial Specialist, at the University of South Florida Medical Clinics at (813) 974-3575 between the hours of 9:00 a.m. and 4:00 p.m. Monday through Thursday.

For those patients who are from out-of-town, a new toll-free number has been added for you to call with billing questions. The number is 1-888-873-3627. This number is for calls originating in Florida and is only for billing questions and help with insurance authorizations.

3. **HAS YOUR INSURANCE COMPANY OR PRIMARY CARE PHYSICIAN CHANGED?** With an ever changing medical insurance market (shopping for the best contract, companies merging, others closing their doors, etc), you may have changed insurance company. If you changed your insurance company you may have a new primary care physician. Maybe you have moved and had to choose a new doctor closer to your home. Regardless of the circumstances we would very much appreciate your contacting our office to let us know, (813) 974-3374. This will not only insure we can obtain the necessary authorizations/pre-certifications and that your medical bills go to the right insurance company but it will help us make sure your medical records are forwarded to the right doctor. Thank you for helping us keep the records straight. Thank you for helping us keep the records straight.

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