Drug-Induced Esophageal Injury: A Look at Bisphosphonates and NSAIDs
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Esophageal injury has many etiologies and can be either iatrogenic or drug-induced. This article will discuss presentation, etiologies and preventive and management strategies for two of the most common drug classes associated with drug-induced esophageal injury, bisphosphonates and nonsteroidal anti-inflammatory drugs (NSAIDs). Other medications are also more prone to cause esophageal injury and those are listed in Table 1. Initially, the patient’s medication profile should be evaluated for any drugs that have the potential to cause esophageal injury, including all prescription and over-the-counter (OTC) medications.

Various types of patients may present with different signs and symptoms of esophageal injury. There are many types of esophageal injuries, including ulceration, perforations, strictures, and esophagitis and any of these may present with a feeling of something stuck in the patient’s throat. Patients may experience an abrupt onset of burning and retrosternal pain that may be aggravated by swallowing. The majority of presenting patients who are symptomatic have no history of any type of esophageal damage or any specific risk factors. Risk factors for esophageal injuries, including patient, drug/formulation, and administration factors are listed in Table 2. Certainly, patients with pre-existing esophageal or swallowing disorders will be more prone to esophageal injury. For example, gastroesophageal reflux disease (GERD) has a tendency to slow esophageal clearance time and decrease lower esophageal sphincter pressure. An administration risk factor is that in many cases, patients either did not take their medications with a sufficient amount of water or they took their medications while lying down. For formulation risk factors, gelatin capsules have a tendency to become lodged in the esophagus if taken with little or no water. Extended- or sustained-release formulations also have a tendency to be bulky and more prone to becoming lodged in the esophagus.

Bisphosphonates are receiving a great deal of attention with respect to their gastrointestinal side effect profile. In one study with alendronate, 1% of the patients experienced dysphagia and 1.5% experienced esophageal ulcers. In the Fracture Intervention Trial, discontinuation of therapy due to upper GI adverse effects were 3.2% with alendronate; 49-54% of these patients had a history of GI disorders and 54-89% used NSAIDs or aspirin at some point during the study. Alendronate may cause esophageal injury once in the stomach by being converted to the more noxious free acid form, which then becomes caustic to the esophagus when stomach contents are refluxed, leading to ulcers, esophagitis, and dysphagia. In most cases this
is a result of patients not taking their medication correctly.5 Patients are advised to stay upright for at least 30 minutes after taking alendronate and at least 60 minutes after taking ibandronate. These medications are contraindicated in patients who cannot follow the administration instructions and in those with coexisting esophageal disorders that prevent normal esophageal emptying.4,7 In those patients who find it difficult to follow the complex dosing instructions, especially the elderly, the once-weekly and now once-monthly bisphosphonates would decrease this burden.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known for causing gastric and duodenal ulcers and may also cause esophageal injury.3 One of the mechanisms by which this occurs is the fast dissolution rates of these agents which can expose the esophageal mucosa to the injurious medications before the esophagus can clear itself.1 All of the NSAIDs have the potential to cause esophageal damage, but the most common ones are naproxen, ibuprofen, aspirin, and indomethacin.8 It is important to notice that 3 out of the 4 of these NSAIDs are OTC medications, therefore it is imperative to counsel patients about the potential for these GI side effects and esophageal injury before they begin to take the medication. One specific population who seems to be more prone to esophageal injury with NSAIDs is the elderly, possibly due to the fact that many have arthritis and fractures and use NSAIDs more regularly.3 To reduce the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.9 Esophageal injuries that are caused by NSAIDs usually heal shortly after the cessation of the offending agent.1 A comparison of bisphosphonates and NSAIDs can be found in Table 1.1

There are several preventive measures to minimize the risk of drug-induced esophageal injury. A considerable amount of liquid taken after the drug is imperative in the minimization of esophageal damage. It is recommended that at least 100 mL of liquid be used as a post-dose chaser and that a lubricating sip of water prior to administration may also be helpful.1 For the bisphosphonates, six to eight ounces of plain water should be taken along with the medication.4,7 For medications taken at bedtime, patients should take the dose five to ten minutes prior to lying down to improve esophageal clearance.1 It is important for pharmacists and other health care professionals to counsel patients on a regular basis about the safe administration of their medications to minimize esophageal injury, especially for the bisphosphonates. Taking those medications appropriately (i.e. standing/sitting for 30-60 minutes after administration and drinking six to eight ounces of water with the medication) is the best way to minimize bisphosphonate-induced esophageal injury. Patients should also be encouraged to report any swallowing pain or difficulty to their physician or pharmacist. If patients are having problems taking their medications correctly, liquid formulations may be preferable since they reach the stomach faster; however, in some patients with dysphagias even liquids could reflux and cause injury. Recommendations for the prevention of esophageal damage are listed in Table 3.1

For management and treatment of esophageal injury, several factors must be considered. The type and severity of esophageal damage and the overall condition of the patient will dictate the best treatment. In the majority of esophageal injury cases, discontinuation of the causative agent will resolve the damage in days to weeks.2 Several different classes of medications have been used in the treatment of esophageal injury, including viscous lidocaine for pain control, and proton-pump inhibitors (PPI’s), H2-receptor blockers, antacids, sucralfate, and prednisone to speed healing.1,8 For the management and treatment of NSAID-induced esophageal injury, PPI’s and H2-receptor blockers are commonly given in conjunction with an NSAID. In severe cases of bisphosphonate-induced esophageal injury, discontinuation of the agent is crucial, along with the addition of acid-suppressive therapy or sucralfate, and/or local or systemic analgesia.8

In summary, esophageal injury can in fact be drug-induced. Healthcare professionals, especially doctors, pharmacists and nurses, can play an important role in helping to prevent, identify, minimize, and treat esophageal injury by simply recognizing the risk factors and knowing the medications that are commonly associated with esophageal injury. By educating patients and caregivers about the safe administration of their medications and monitoring their
tolerability, improving safety of drug use and minimizing the incidence of drug-induced esophageal injury can be accomplished.1

Table 1. Drug-Induced Esophageal Injury Summary of Other Medications2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Features</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Tetracyclines (tetracycline, doxycycline, and minocycline)</td>
<td>Esophageal mucosal damage characterized by ulcers and strictures</td>
<td>Capsules may lodge and quickly dissolve in esophagus; become acidic when dissolved in saliva leading to injury</td>
<td>Doxycycline capsules are most implicated</td>
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<td></td>
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<td>Risk factors are those with hiatal hernia</td>
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<tr>
<td>Potassium chloride</td>
<td>Esophageal mucosal damage characterized by strictures, localized edema, and/or nodule formation</td>
<td>Tablets lodging in esophagus produces a high concentration of potassium chloride in one area, resulting in mucosal damage</td>
<td>Extended-release and wax matrix tablets are most often implicated</td>
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<td>Risk factors are recumbent patients and those with left-atrial enlargement</td>
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<tr>
<td>Quinidine</td>
<td>Esophageal mucosal damage characterized by local edema, stricture formation, and/or nodule formation with thick exudates</td>
<td>Injurious when lodged in esophagus but mechanism not well defined but it is not pH-mediated</td>
<td>Quinidine liquid may be more safer than tablets</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Risk factors are older patients and those with cardiomegaly</td>
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<tr>
<td>Bisphosphonates</td>
<td>Esophageal mucosal damage characterized by ulcers, erosive esophagitis, odynophagia, dysphagia, hemorrhage, and stricture</td>
<td>Alendronate may be inherently caustic; once in the stomach, refluxed alendronate may damage the esophageal mucosa</td>
<td>In most cases of esophageal injury, patients did not follow administration instructions</td>
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<td>Risedronate film-coated tablets and alendronate wax-coated tablets may minimize esophageal damage</td>
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<tr>
<td>NSAIDs</td>
<td>Esophageal mucosal damage characterized by strictures</td>
<td>Fast dissolution rates expose the esophageal mucosa to the drug prior to swallowing</td>
<td>Since high use of NSAIDs in elderly, this population is at higher risk of esophageal injury</td>
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Table 2. Risk Factors for Esophageal Injury2

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Drug/Formulation Factors</th>
<th>Administration Factors</th>
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</table>
Elderly
Pre-existing esophageal or swallowing disorders (ex. dysphagia and reflux disease)

Gelatin capsules
Extended- or sustained-release
Large and bulky
Acidic and fast dissolution rates

Insufficient liquid bolus
Frequent dosing times/polypharmacy
Recumbent position
Concurrent alcohol use

Table 3. Recommendations for Prevention of Esophageal Damage

<table>
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<tr>
<th>Recommendation</th>
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<tr>
<td>Encourage intake of at least 100 mL of water after swallowing medication</td>
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<tr>
<td>Recommend a small intake of water prior to taking the medication</td>
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<tr>
<td>Recommend standing or sitting upright for at least five to ten minutes following drug administration (30-60 minutes if taking a bisphosphonate)</td>
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<tr>
<td>Discourage alcohol use</td>
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<tr>
<td>Select safest dosage forms when appropriate and available (ex: once-weekly bisphosphonate)</td>
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<tr>
<td>Suggest chewable, liquid, or crushable dosage forms in high-risk populations (ex: elderly)</td>
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<tr>
<td>Educate patients on signs and symptoms of esophageal injury</td>
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</table>

References available upon request.

Meet Some SSHP Members from “the Southern Piedmont”

Nan Freeman, Roswell, Georgia  Rick Pedrick, Seneca, S. Carolina
Jack Cole, Springville, Alabama  Pamila Cleaveland, La Grange, Georgia
John R. Sawyer, Anniston, Alabama  Brenda Skillman, Atlanta, Georgia
Richard Lowe, Atlanta, Georgia  Lisa McDonald, Birmingham, Alabama

Proverbs for People – Keys to Success

1. Don’t let unimportant things “bug” you
2. Develop your own flexibility
3. Keep a positive mental attitude
4. Be enthusiastic
5. Keep on trying, don’t give up
6. Don’t be afraid to start over
7. Think of something pleasant for the day ahead
8. Don’t reach for the impossible
MOMENTS IN BIRMINGHAM:
Photos of SSHP Annual Meeting 2005 Samford University

Above: SSHP members enjoy picnic at Birmingham Barons’ Baseball Game.

Above: SSHP members enjoy dinner at “The Club” on Red Mountain.

Above: SSHP members Fred Coleman and Charlotte Johnson network during a break.
Drug Information Update

Stavudine – The FDA recently announced the tentative approval of stavudine oral solution 1 mg/ml, the first generic version of the already approved Zerit. Under the President’s Emergency Plan for AIDS Relief program, this product is now available for consideration of purchase. However, due to existing patents and/or exclusivity rights, the marketing of this product will be prohibited in the U.S., even though the product meets all of the FDA’s standards for manufacturing quality, safety, and efficacy.

Nexavar – Nexavar (sorafenib tosylate) has been approved to treat advanced renal cell carcinoma, the most common type of cancer affecting the kidneys. In two trials with patients treated for advanced renal cell carcinoma, the Nexavar treated groups had more time between tumor progression and death. In the Nexavar group, median time to tumor progression or death was 167 days compared to 84 days in the non-treatment group. The most common side effects associated with Nexavar treatment include rash, diarrhea, increased blood pressure, and redness, pain, swelling or blisters on the palms of the hands or soles of the feet.

NeutroSpec – The FDA has suspended the sales and marketing of NeutroSpec (technetium fanolesomab) due to reports of life-threatening cardiopulmonary events following administration. NeutroSpec has been used for radionuclide imaging in patients with suspected appendicitis. Unapproved applications for which NeutroSpec has been used include osteomyelitis and other infections. The adverse events associated with its use usually have an onset of a few minutes after administration, and two deaths have been attributed to cardiopulmonary failure. Other adverse events reported include cardiac arrest, dyspnea, hypoxia, hypotension, and required resuscitation with fluids, vasopressors and oxygen.

Clarithromycin – A placebo controlled study in Denmark (CLARICOR study) has reported an increased mortality in patients with heart disease treated with clarithromycin. The difference in mortality became apparent after patients had been followed for one year or longer after the study drug had been administered. Previous trials of antibacterial drugs used in heart disease have failed to demonstrate a statistically significant impact on mortality. At this time however, the FDA is not recommending any changes to the use of clarithromycin.

HAPPY NEW YEAR FROM SSHP

SSHP sends best wishes to all members and friends for a very happy 2006 - the best to all with health, family/friends, and in professional and business activities. For easy access to lots of valuable information in the world of pharmacy, and great ce opportunities in 2006, explore www.seshp.org.
Drugs in the Literature


Meeting News from SSHP

SSHP Meeting Information 2006 - Great educational meetings for SSHP members are currently in the planning stages. The SSHP Annual Spring Meeting may be in North Carolina in April 2006, with the educational focus on acute care issues. This will probably be a joint educational meeting with the North Carolina Society of Health-System Pharmacists. Lots of time for networking and fun events will be included, so stay tune for more information on this meeting. The possibility of a joint meeting with the Georgia Society of Health-System Pharmacists is also being considered for later in 2006. These meetings offer great education, fun events, refreshment breaks, and great opportunities to network with other SSHP members as well as members of a different state society. Share practical ideas with your colleagues, and take some great knowledge on drug therapy issues plus some useful ideas for pharmacy programs and interventions back to your practice setting! Meet pharmacists that you can network with regularly on various pharmacy-related issues. Build your interstate colleague network by participating in SSHP activities. Stay tune to the SSHP website at [www.seshp.org](http://www.seshp.org) for updated meeting information. Also, you are encouraged to contribute any comments, questions, or interests you may have, any recent activities you have been involved with, or other topics of membership interest - just go to the “Guest Book” entry on the SSHP website. Let SSHP hear from you!