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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 20, 2001. 3 drugs or dosage forms were added in the *Formulary* and 2 drugs or dosage forms were deleted.

◆ ADDED

factor 9 concentrate, human-derived (Mononine® by Aventis-Behring)

quetiapine (Seroquel® by Astra Zeneca)

tramadol (Ultram® by Ortho McNeil)

◆ DELETED

disulfiram (Antabuse® by Odyssey)

factor 9 concentrate, human-derived (AlphaNine® SD by Alpha)

Mononine® and **AlphaNine® SD** are human-derived factor 9 concentrate products. A 1999 review of these products concluded that there is no difference between these products and that the least expensive product should be listed in the *Formulary*. In 1999, AlphaNine® SD was listed because it was less expensive. AlphaNine® SD was deleted and Mononine® added in the *Formulary*, because Mononine® was less expensive.

Both products undergo multiple viral depletion and inactivation steps in their production processes; therefore, safety is not a selection criterion. Both products have undetectable levels of other clotting factors (eg, 2, 7, and 10), which are found in less pure clotting complex concentrates.

Quetiapine is an atypical antipsychotic drug similar to olanzapine and clozapine (which is not in the *Formulary*). It is used for the treat-

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ADVERSE DRUG REACTION PREVENTION

Taking medication can be a pain in the...esophagus

A patient is prescribed doxycycline twice a day for a skin infection. The 1st dose is taken with a small sip of water, then the patient lies down to go to sleep. 3 hours later he awakens with severe chest pain. The patient, fearing that he is having a heart attack, goes to the Emergency Department. After a cardiac cause of the chest pain has been ruled out, an esophageal ulcer is diagnosed by endoscopy. Dietary modification and a proton pump inhibitor are prescribed and the symptoms gradually improved over a 2-week period. The doxycycline prescription vial had a warning label in 6-point type that stated that it should be taken with a full glass of water, but the patient did not appreciate the importance of this warning.

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Medications cause esophagitis and esophageal ulcers by a local irritant effect. With slow esophageal transit, irritation and ulceration may occur. The patient can experience severe pain that he or she may not associate with the medication.

Medication-induced esophagitis can be a painful experience that can be very worrying to patients. Most of the time, if the causative agent is immediately stopped and the patient's symptoms treated, medication-induced esophagitis does not cause serious long-term effects.[1] However, if the causative medication is not stopped, esophageal stricture may occur. In very rare instances, death has been associated with very irritating agents.

Over 70 medications have been reported to be associated with medication-induced esophagitis.[2] Doxycycline- and tetracycline-associated esophagitis are well described in the literature. Although *relatively* frequent, doxycycline-induced esophagitis is usually a self-limited occurrence.[3] Clindamycin and other antibiotics have also been associated with medication-induced esophagitis. Other medications associated with medication-induced esophagitis include oral potassium supplements (especially the sustained-release products), quinidine, nonsteroidal anti-inflammatory agents (NSAIDs) like ibuprofen and aspirin, alendronate, iron products, and ascorbic acid. Potassium chloride, quinidine and alendronate have been associated with the most serious cases. Death has been associated with potassium chloride-induced esophagitis.

Medications cause esophagitis and esophageal ulcers by a local irritant effect. With slow esophageal transit, irritation and ulceration may occur. The patient can experience severe pain that he or she may not associate with the medication.

This potential adverse effect is generally under-appreciated. The good news is that it can almost always be avoided, if patients take their medications correctly. Patients should always be in the upright position and take their medications with at least 8

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INSIDE THIS ISSUE

Formulary, *from page 1*

ment of the manifestations of psychotic disorders including schizophrenia. Like clozapine, olanzapine, and risperidone, quetiapine has a greater affinity for blocking serotonin receptors than dopamine receptors. Quetiapine also antagonizes histamine H1 and adrenergic alpha1 and alpha2 receptors. Somnolence, dizziness, constipation, postural hypotension, and dry mouth do occur in some patients. It is not associated with extrapyramidal symptoms. Quetiapine use is associated with moderate weight gain.

The initial dosage of quetiapine is 25 mg twice a day. The dosage is increased in increments of 25 to 50 mg twice to 3-times a day on the 2nd and 3rd days. The target dosage range is 300 to 400 mg per day given in divided doses BID or TID, which should be reached by the 4th day of therapy. Dosage adjustments do not need to be made for renal dysfunction. Although quetiapine is extensively metabolized by the liver, no dosage adjustments are recommended for hepatic impairment.

Although there are no studies directly comparing quetiapine with risperidone, olanzapine, or clozapine, it is expected that it will be used as an alternative to these agents. Like these drugs, quetiapine is more effective in treating negative symptoms of schizophrenia compared with haloperidol. Olanzapine, risperidone, and quetiapine cost about the same (ie, $200 to $400 per month), depending on the dosage used.

Tramadol is an oral, centrally-acting analgesic. It has a low affinity for opiate receptors and blocks reuptake of norepinephrine and serotonin. It has a labeled indication for moderate to severe pain and is often prescribed because it is not a controlled substance.

Tramadol is not recommended for acute pain. In has a slow onset of action (eg, 1 hour) and it takes several hours to reach its peak effects. Using tramadol on an "as-needed" (ie, prn) basis is irrational. Because of its mechanism of action and slow onset, tramadol use is most rational as an alternative to opiate-containing products for chronic pain.

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Information from addiction experts suggests that tramadol is abused by health care professionals and others who have a history of abusing other drugs. Although not legally a controlled substance, tramadol will be handled as if it is a controlled substance.

Tramadol is not more effective than opiate-containing products like acetaminophen with codeine or acetaminophen with oxycodone. Several studies have shown that tramadol is less effective than these combination analgesics.

Since tramadol is not a controlled substance, it is often prescribed instead of opiate-containing products. Information from addiction experts suggests that tramadol is abused by health care professionals and others who have a history of abusing other drugs. The main reason that tramadol was added in the *Formulary* was to implement tighter controls on its use. Although not legally a controlled substance, tramadol will be handled as if it is a controlled substance. Each dose dispensed from the Suremed® cabinet is electonically recorded to ensure accurate inventory control. All other inventory will be stored in the controlled-substances vault. Tramadol is not recommended in patients with a substance abuse problem. It has been shown to reinitiate physical dependence in patients who have been physically dependent on opiates.

Tramadol use is associated with several common adverse effects. Tramadol can cause nausea, dizziness, constipation, sedation, and headache. It may increase the sedative effect of alcohol and hypnotics. Seizures have been reported in patients receiving tramadol. Patients with a history of seizures and those concomitantly taking an antidepressant, an MAO inhibitor, or an antipsychotic drug may be at increased risk.

Disulfiram has been used as a deterrent in patients with a history of ethanol abuse. It is used in motivated patients who are receiving concomitant psychotherapy. Disulfiram, by producing an unpleasant reaction when alcohol is ingested, promotes abstinence until self-motivation can be established.

Disulfiram interferes with alcohol metabolism and results in the accumulation of acetaldehyde. High levels of acetaldehyde causes patients to experience a throbbing headache, dyspnea, throbbing in the neck, nausea, vomiting, diaphoresis, thirst, palpitations, hypotension, and other unpleasant symptoms.

There has been minimal use of disulfiram over the last 3 years and none in the last 6 months. It was deleted form the *Formulary* because there should be limited use for disulfiram in the inpatient setting. If there is a rare need for disulfiram, it can be requested through the nonformulary process.

ADRP, *from page 1*

ounces of water. It is important that they do not immediately lie down after taking a high-risk medication. If food does not interact with the absorption of the medication (like it would with alendronate), taking a small amount of food after taking the medication can help with esophageal transit.

If medication-induced esophagitis occurs, the medication should be immediately stopped. Patients are generally managed like patients with gastroesophageal reflux (GERD). In addition to dietary restrictions and elevation of the patient's head when they lie down, proton-pump inhibitors and sucralfate have been used to decrease esophageal pain. Most symptoms resolve within 2 weeks; however, treatment may be needed for as long as 4 to 6 weeks.

The patient presented at the beginning of this article was at high risk for medication-induced esophagitis. Doxycycline is a medication known to cause problems.[3] The patient took the capsule with a small sip of water, which dramatically slowed esophageal transit. Gelatin capsules are particularly a problem, because they become

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MEDICATIONS THAT CAN CAUSE ESOPHAGITIS

- Potassium Chloride
- Alendronate
- Porfimer
- Quinidine
- NSAIDs (eg, ibuprofen)
- Doxycycline
- Clindamycin
- Iron products (eg, ferrous sulfate)
- Ascorbic acid
- Pancrelipase
- Oral corticosteroids
- Zidovudine

COST MANAGEMENT

Improving antiemetic use

Nausea and vomiting are common complaints of hospitalized patients. Because patient comfort is imperative, patients must receive appropriate therapy. However, appropriate therapy does not have to mean more expensive. Often, less expensive agents are equally effective. Appropriate also does not mean larger dosages. Larger dosages may not improve efficacy and may increase adverse effects like sedation.

Inappropriate use can consume valuable resources that can better be used elsewhere. Last year Shands at UF spent $400,000 on ondansetron alone. Much of the use of ondansetron could have been switched to less expensive, yet equally effective agents. Also, changing the route of administration could decrease patient costs.

The table below lists the comparative costs of common antiemetics listed in the *Formulary*. Although ondansetron is the preferred agent listed in the *Formulary* for chemotherapy-induced nausea and vomiting (N&V), it should be used only at the 8-mg-BID dose in combination with dexamethasone for moderate-to-highly emetogenic chemotherapy. For those patients in whom corticosteroids cannot or should not be used, higher doses of ondansetron *may* be needed. For less emetogenic chemotherapy, a single dose of ondansetron 8 mg (with or without dexamethasone) is often effective. Often, ondansetron is not necessary. Delayed N&V after chemotherapy can be managed with alternative agents. The American Society of Clinical Oncology recommends the combination of metoclopramide and dexamethasone for delayed N&V after chemotherapy.

There are other reasonable choices for post-operative N&V, instead of ondansetron. Ondansetron is 5-times more expensive than droperidol. Droperidol (Inapsine®) has been shown to be as effective as ondansetron for post-operative N&V, even when used at low doses (eg, 0.625, 1.25, and 2.5 mg).[1] Although droperidol can cause sedation, at low dosages this is not severe. Administering antiemetics for post-operative N&V 15 to 30 minutes prior to the end of surgery appears to be more effective than with induction of anesthesia, particularly for long procedures.

Promethazine (Phenergan®) and prochlorperazine (Compazine®)are also reasonable choices for many patients who experience post-operative N&V. Although there has been a nationwide shortage of prochlorperazine injection, supplies are expected soon. These agents are effective, low-cost, and available in multiple dosage forms (injection, tablets, and suppositories).

Promethazine and prochlorperazine can cause sedation in some patients. Prochlorperazine has been shown to work quickly and may cause less sedation.[2] Rarely, these agents can cause dystonic reactions. Although these reactions can be frightening, they are rarely serious and can be easily managed with agents such as diphenhydramine.

Much of the antiemetic use at Shands at UF is for N&V associated with causes other than chemotherapy or surgery. These *other* causes of N&V are varied and are usually treated conservatively. Most often, the appropriate therapy is the removal of the offending agent or treatment of the condition causing N&V.

Medications are common causes of N&V. Morphine and other opiates stimulate the chemoreceptor trigger zone (CTZ). Digoxin, especially with high serum concentrations, can stimulate the CTZ. Medications that cause N&V by other mechanisms include nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, and gastrointestinal medications including sulfasalazine.

Gastrointestinal and systemic infections can cause N&V. These infections may be bacterial, viral, or parasitic. Treatment of the bacterial or parasitic infection is important.

Emotional responses to unpleasant stimuli (eg, smells, tastes) or psychogenic stress may cause N&V. Antiemetics with sedative effects may be preferable in these situations. Benzodiazepines (eg, lorazepam) may also be beneficial. Although benzodiazepines do not have antiemetic effects, they do sedate the patient and have amnesic effects.

Metabolic causes of nausea include uremia, diabetic ketoacidosis, hypercalcemia, hypoxemia, and hyperthyroidism. They can cause nausea by stimulating the CTZ. Management of the cause of nausea is more important than managing the symptoms.

For all of the *other* causes of N&V, patients should be kept comfortable by 1st treating the underlying cause of the N&V and then treating symptomatically with antiemetic agents. Antiemetics should be ordered on a 1-time basis. Patients should be reassessed frequently and not given antiemetics on an *as needed* (ie, prn) basis.

Patients that experience N&V due to *other* causes should be treated with agents such as promethazine and prochlorperazine as 1st-line agents. These drugs have proven efficacy for uncomplicated N&V. They are ideal choices based on their various dosage forms and relative low cost.

Droperidol can be used for uncomplicated N&V as a 2nd-line agent. It is effective in low doses (ie, 0.625 mg, 1.25 mg, or 2.5 mg). Coupled with its low-cost and relatively few side effects, droperidol is an often overlooked alternative to prochlorperazine and promethazine.

Ondansetron can be used as an alternative to other agents for uncomplicated N&V. However, it should **not** be used as a 1st-line agent. It should only be used if side effects have prevented the use of other agents or if other agents have proven to be ineffective. Ondansetron is only indicated for chemotherapy-induced and postoperative N&V. Due to its high cost, it should be reserved for these indications or when N&V is refractory to other agents.

By Katie Smith, PharmD

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COST COMPARISON OF *FORMULARY* ANTIEMETICS

Promethazine (Phenergan®)	25 mg tablet	$0.33
	25 mg suppository	$2.88
	25 mg injection	$1.78
Prochlorperazine (Compazine®)	5 mg tablet	$0.31
	10 mg injection	$0.57
	5 mg suppository	$2.04
Droperidol (Inapsine®)	5 mg injection	$3.51
Ondansetron (Zofran®)	4 mg injection	$16.03
	4 mg tablet	$11.09
	8 mg tablet	$18.47

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ADRP, *from page 2*
sticky with a small amount of water. Immediately lying down dramatically increases the chances of a problem.

Even though over 70 medications have been associated with medication-induced esophagitis, this list is relatively short considering the large number of medications (see the table on page 2). Knowing the high-risk medications can be helpful; however, routinely having patients take their tablets and capsules with a full glass of water is the best practice. Telling patients to read the auxiliary labels on prescription bottles is also helpful. Patients with esophageal compression or constriction should avoid high-risk medications.

Properties of medications that have been associated with medication-induced esophagitis include the chemical nature of the medication (ie, a local irritant), its solubility, and the contact time with the mucosa. Contact time is associated with the shape of the tablet or capsule. Small, oval, heavier tablets are easier to swallow. Coated tablets may be better.

Patients that are chronically bedridden are particularly at risk. Thus, hospitalized patients are a concern. It is difficult for hospitalized patients to sit up, take each medication with a full glass of water, and avoid immediately lying back down. This is the reason that alendronate (Fosamax®) use is not allowed while patients are hospitalized unless they meet very rigid criteria. Stopping a patient's alendronate for several days will not have a clinical impact on a patient's osteoporosis, yet an esophageal ulcer could lead to significant complications and prolonged hospitalization.

Properties of medications that have been associated with medication-induced esophagitis include the chemical nature of the medication (ie, a local irritant), its solubility, and the contact time with the mucosa.

Alendronate is taken with 6 to 8 ounces of water. A patient **must not** lie back down for at least 30 minutes **and** until after they have had their first meal to decrease the risk of the tablet lodging in the esophagus and causing an ulcer. Patients should not chew or suck on the tablet. Patients should never take an alendronate tablet at bedtime. If a patient develops symptoms of esophageal irritation, it should be stopped.

If requested through the nonformulary process, alendronate will not be acquired and dispensed. Patients will also not be allowed to use their own supply of alendronate from home. An order discontinuing alendronate "per P&T-approved policy" will be written in the patient's chart. If patients are hospitalized for more than 14 days and they can follow the recommended administration guidelines, an exception to this policy can be made.

Appropriate patient education is important in preventing medication-induced esophagitis. When patients are bedridden, it is important that the health care professional administering the medication understands the importance of proper medication administration.

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