Formulary Update

Doxylamine succinate/pyridoxine (Diclegis®)

Doxylamine succinate/pyridoxine HCl (Diclegis®) is the only FDA approved medication for treatment of **nausea and vomiting of pregnancy** in women who do not respond to conservative management. It is Pregnancy Category A and **the dose is 2 tablets daily** at night on an empty stomach. Dosage can be up to 4 tablets/day in divided doses if symptoms do not resolve. The most common adverse effect is somnolence, therefore, it is recommended to use caution with other CNS depressants, and is contraindicated with MAOIs.

Eculizumab (Soliris®)

Eculizumab is the only medication that is FDA approved for **hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH).** Alternatives to management include plasma exchange/infusion, blood transfusion, high dose steroids, or bone marrow transplantation. Eculizumab is a **humanized monoclonal antibody** shown to be highly effective in reducing intravascular hemolysis in patients with aHUS and PNH. Eculizumab is **restricted to Luckow Infusion only.**

Poractant alfa (Curosurf®)

Poractant alfa is a porcine-derived **surfactant** indicated for intratracheal administration for rescue treatment of **respiratory distress syndrome (RDS) in premature infants**. The current formulary alternative is calfactant (Infasurf®). Poractant alfa is an option for smaller babies, weighing 1500 grams or less, as **the volume administered per dose is 50 to 60% of the dosing volume of calfactant**. Poractant alfa, and all surfactants, should only be ordered and administered by clinicians with training and experience in managing RDS in premature babies.

Ocrelizumab (Ocrevus®)

Ocrelizumab is **recombinant humanized, glycosylated IgG1 monoclonal antibody** indicated to treat **adult patients with relapsing or primary progressive forms of multiple sclerosis**. Ocrelizumab has a high affinity for CD20 expressing B-cells, leading to cell-mediated phagocytosis, cell-mediated cytotoxicity and induction of apoptosis. Ocrelizumab is **restricted to Luckow Pavilion**.

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Pharmacy Focus

In this issue:

No Verbal Orders for Chemotherapy

By David Turberville, PharmD

Luckow Oncology Clinical Pharmacy Specialist

The American Society of Health-System Pharmacist (ASHP) has published guidelines to define the **best practices for the safe ordering and use of chemotherapy and biotherapy agents.** ASHP currently defines chemotherapy and biotherapy agents as any medication that is listed in section 10:00 of the American Hospital Formulary Service (AHFS) pharmacologic-therapeutic classification system and has at least one FDA-labeled indication to prevent or treat cancer, even if not listed in AHFS 10:00 or is an investigational medication being used to prevent or treat cancer.

ASHP guidelines specifically address verbal orders for chemotherapy medications. According to the best practices, "except for discontinuing treatment, medication-use **systems should not permit healthcare providers to use or accept verbal orders to commence or modify a chemotherapy medication**. Verbal communication for chemotherapy orders, whether face-to-face or over the telephone, circumvents an essential checkpoint in the order-verification process, whether they are communicated directly to persons who prepare the medications or received and reported by one or more intermediaries."

In support of the goal of patient safety, and upon approval from Oncology P&T, TVH P&T, and the Medical Board, **the Pharmacy Department shall not accept any verbal orders to modify existing chemotherapy regimens, doses, routes, frequency or duration**. Verbal orders to hold or discontinue existing chemotherapy and verbal order for supportive care (i.e. anti-emetics, hydration) are exempt from this policy.

References:
Goldspiel B, Hoffman JM, Griffith NL, et al. ASHP guidelines on preventing medication errors with chemotherapy and biotherapy. Am J HealthSyst Pharm. 2015; 72:e6–35.
TVH Department of Pharmacy Policy and Procedure Manual. Division 7 (sterile products), Chapter 4 (chemotherapy), Subject 12 (definition of chemotherapy/verbal orders for chemotherapy.

Drug Info Corner

By: Majd Abedrabbo, FDU PharmD Candidate 2018
Sasha Falbaum, PharmD

Question: ***How much grapefruit juice is recommended to be given with each statin?***

Response:

Statins are a class of medications that have an effect on lipids by lowering LDL, VLDL, and TG and increasing HDL. They inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that converts HMG-CoA to mevalonate, a rate-limiting step in the biosynthesis of cholesterol.[1] **There are a total of seven HMG-CoA reductase inhibitors**: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin , rosuvastatin, and simvastatin.

Although these statins are in the same class, **they are metabolized differently, which leads to drug/drug and drug/food interactions**. A family of enzymes known as CYP450 are responsible for catalyzing oxidative processes and have the ability to reduce and terminate the effect of other drugs.[2] **Atorvastatin, lovastatin, and simvastatin are metabolized by CYP3A4**; therefore strong CYP3A4 inhibitors should be avoided.[1,3,4] **Pravastatin undergoes extensive first-pass metabolism in the liver** and **rosuvastatin is metabolized by CYP2C9 and CYP2C19**.[7,8]

When reviewing drug/food interactions, **one interaction of note is with statins and grapefruit juice**. It is usually recommended that a patient on statin therapy is to completely avoid grapefruit juice, but that is not the case for all statin therapy. Grapefruit juice is a strong CYP3A4 inhibitor, therefore, **based on statin metabolism, we can determine if grapefruit juice should be completely *avoided* versus *limited* to a specific amount.** According to Lilja et al, 200 mL of grapefruit juice daily increases simvastatin AUC by 3.6-fold and the Cmax is increased by 3.9-fold; which can lead to a higher incidence of myopathy.[9] The effect of grapefruit juice on simvastatin pharmacokinetics changes considerably during the first 24 hours after ingestion.[9] Package inserts recommend avoiding large quantities of grapefruit juice (>1 quart daily) in simvastatin and lovastatin.[1] While on atorvastatin therapy, grapefruit juice inhibits CYP3A4 and can increase plasma concentrations of atorvastatin when consuming more than 1.2 liters per day.[3] Ando et al concluded that grapefruit juice significantly increases the AUC of atorvastatin by 83% and pitavastatin AUC was increased by only 13%.[10] The anticipated increased concentrations of atorvastatin were well established, while there was a minimal effect on pitavastatin pharmacokinetics.

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Drug Info Corner

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Clinical studies recommend that consumption of grapefruit juice be avoided during atorvastatin, lovastatin, or simvastatin therapy. If intake of grapefruit juice were essential to the patient, limit the quantity to 240 mL per day in order to avoid amounts that will cause statin toxicity based on the package insert. Potential drug therapy alternatives while drinking grapefruit juice are pravastatin, fluvastatin, rosuvastatin, or pitavastatin, though further studies are needed to know the exact limitations of grapefruit juice while taking these medications.

HMG-CoA Reductase Inhibitor	Metabolism	Grapefruit Juice Recommendation
simvastatin (Zocor®)	CYP3A4	Studies: Not recommended Package insert: < 1 quart* daily
atorvastatin (Lipitor®)	CYP3A4	Studies: Not recommended Package insert: < 1.2 liters* daily
lovastatin (Mevacor®)	CYP3A4	Studies: Not recommended Package insert: < 1 quart* daily
fluvastatin (Lescol®)	Primarily CYP2C9 (75%), CYP2C8 (5%), and CYP3A4 (20%)	Possible alternative; further studies needed
pitavastatin (Livalo®)	Primarily UGT1A3 and UGT2B7; slightly by CYP2C9 and CYP2C8	Possible alternative; further studies needed
pravastatin (Pravachol®)	1st pass metabolism	Possible alternative; further studies needed
rosuvastatin (Crestor®)	CYP2C9 and CYP2C19	Possible alternative; further studies needed
*defined as large quantity of grapefruit juice consumption according to respective package insert		

References:

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2. Bailey D, Dresser G. Interactions between grapefruit juice and cardiovascular drugs. American Journal Of Cardiovascular Drugs: Drugs, Devices, And Other Interventions [serial online]. 2004;4(5):281-297. Available from: MEDLINE with Full Text, Ipswich, MA. Accessed July 12, 2017.
3. Atorvastatin [package insert]. New York, NY: Pfizer; 2012.
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5. Fluvastatin [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; 2012.
6. Pitavastatin [package insert]. Cincinnati, OH: Kowa Pharmaceuticals; 2009.
7. Pravastatin [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 1991.
8. Rosuvastatin [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2010.
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10. Ando H, Tsuruoka S, Fujimura A, et al. Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. British Journal Of Clinical Pharmacology [serial online]. November 2005;60(5):494-497. Available from: MEDLINE with Full Text, Ipswich, MA. Accessed July 12, 2017.

Meet the new Pharmacy Residents

The Valley Hospital Pharmacy Residency Program is nationally accredited by the American Society of Health-System Pharmacists. Upon graduation from schools of pharmacy, pharmacists may choose to further their education through a one-year long post-doctoral residency. This additional training exposes new practitioners to the different aspects of the practice of pharmacy, offers the opportunity to manage special patient populations, and allows application of knowledge and skills in participating as an interprofessional team member.

Mark Levy, PharmD

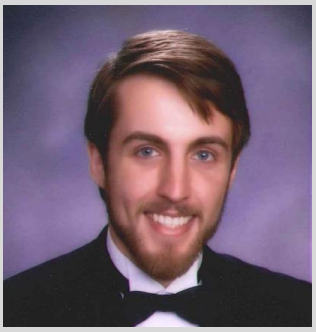
PGY-1 Pharmacy Practice Resident

Dr. Mark Levy graduated from the University of Connecticut with a Bachelor degree in Nutritional Sciences, and then went on to pursue a Doctor of Pharmacy at the University of Buffalo in New York. Mark gained interest in the field while working in Florida Hospital during his Ph.D. program in molecular pharmacology. His areas of interest include critical care, infectious diseases, and informatics/management. His outside hobbies consist of playing poker, traveling, and working out. Upon completion of the residency program, Mark plans to obtain a clinical pharmacy specialist position.

Michael Gabriele, PharmD

PGY-1 Community Pharmacy Resident

Dr. Michael J. Gabriele is the pharmacist for The Valley Hospital's new PGY-1 Community Residency position. After growing up nearby in Clifton, NJ, Michael completed a Doctor of Pharmacy in May 2017 at Rutgers University in New Brunswick, NJ. He is excited to be working closely with the pharmacists in our new outpatient pharmacy to enhance the transitions of care that our patients experience as they are treated and discharged from our institution. Aside from his interest in the developing field of transitions of care, Michael enjoys spending his times indoors playing video games with his friends or outdoors at the beach, gardening, hiking, or camping.



Brianne Traub, PharmD

PGY-1 Pharmacy Practice Resident

Dr. Brianne Traub is from Wayne, NJ, and earned a Doctor of Pharmacy from Philadelphia College of Pharmacy. Brianne is excited to continue to expand the roles of pharamcists and improve patient care. Her clinical interests include ambulatory care and anticoagulation, and is eager to see where her interests lie after the upcoming year. Aside from pharamcy, Brianne likes playing basketball as she played in college as well as coaching a girls basketball team in her spare time. Brianne also likes to stay active by running and playing soccer.

Serotonin Syndrome

By: Andro Youssef, FDU PharmD Candidate 2018
Sasha Falbaum, PharmD

Serotonin syndrome (SS) is due to by the increased serotonergic activity in the peripheral and central postsynaptic 5HT-1A and 5HT-2A receptors.[1] It is not an idiopathic disease, but an adverse drug reaction caused by a drug-drug interaction, self-poisoning, or a therapeutic drug use. The mechanism by which it may occur is when there is an increase in serotonin to toxic levels at the postsynaptic cleft. This results in the inhibition of serotonin uptake, decreased serotonin metabolism, increased serotonin synthesis, increased serotonin release, activation of serotonergic receptors, or inhibition of CYP450 microsomal oxidases.[1]

Common medications associated with SS include:

- Antidepressants: SSRIs, SNRIs, TCAs, MAOIs, bupropion, mirtazapine, trazodone, nefazodone
- Antiemetics : ondansetron, granisetron
- dextromethorphan
- linezolid
- methylene blue
- metoclopramide
- Some opioids: methadone, tramadol, tapentadol, oxycodone, fentanyl, meperidine
- phentermine
- St. John's wort
- triptans

SS is not very common, however the number of cases has been increasing rapidly in the past three decades because of an increased use in serotonergic medications. Given that clinicians do not see patients with SS regularly, it is often overlooked.[3] In 2002, the Toxic Exposure Surveillance System identified 26,733 occurrences of selective serotonin-reuptake inhibitor (SSRI) exposure, leading to major toxic effects in 7,349 patients and resulting in 93 deaths.[2] According to post-marketing surveillance studies, there was an incidence of 0.4 cases per 1,000 patient-months for those who were taking nefazodone.[2] SS occurs in approximately 14-16% of persons who overdose on SSRIs.[2]

SS is diagnosed clinically; the patient has to be using a serotonergic medication or SS inducing medications along with an abnormal history and/or physical symptoms. The ***symptoms*** are commonly referred to as a triad: ***mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities***.[2] SS is divided into three levels based on the ***severity:*** mild, moderate, or severe.

There is ***no guideline for the treatment of SS***; however, ***managing the symptoms*** is very important to prevent further deterioration or mortality, and treatment is dependent on the severity of symptoms. The first step is to stop the offending agent(s),[1,3] and hydration if hypovolemia is present. Agitation and muscle rigidity may be treated with benzodiazepines. Cooling blankets are recommended for hyperthermia. In severe cases, the use of a 5HT-antagonist, cyproheptadine, is recommended to prevent fatal progression.[3]

Symptoms appear within 24 hours and can resolve within 24 hours treatment.[1] Although SS is uncommon, recognition of risks and symptoms is important because severe SS is life threatening. Accurate patient history, thorough medication list, and physical exam are critical . Since offending agents may be available over the counter, pateint education is important as well.

References:
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3.Frank C. Recognition and treatment of serotonin syndrome. *Le Médecin de famille canadien 2008* ; 54.