

Drug Therapy Topics: Newsletter Changes

Elizabeth Rudy, D.V.M., R.Ph.

Welcome to the spring issue of *Drug Therapy Topics*! We would like to announce some changes in the focus and format of the newsletter. Starting with this issue, Drug Therapy Topics will be published on a quarterly basis. Because the newsletter serves as a major source of communication between the Pharmacy and Therapeutics (P&T) Committee, the Department of Pharmacy, and the medical staff, future issues will feature a more comprehensive review of P&T Committee actions. Our goal is to provide our readers with timely coverage of important medication-related issues brought to the P&T Committee. Topics that will receive expanded coverage include approved formulary drug additions and deletions, medication-use evaluations, drug class reviews, and important changes in institution policies and procedures.

Our expanded P&T Committee coverage now includes online access to full-text drug monographs, drug use evaluations, and drug class reviews. This detailed information can be accessed (UW NetID required) by visiting the UWMC/HMC Drug Information Center website at <http://uw.pnrx.org/> and then clicking on the "Pharmacy and Therapeutics Committee" link in the home page header, or by clicking on the "Recent P&T Actions" link under the UW Formulary tab on the home page. Additionally, all back issues of Drug Therapy Topics and The D-Zone will continue to be archived at <http://uw.pnrx.org/therapyTopics.asp>.

Each issue of *Drug Therapy Topics* will still contain a feature article. Articles will cover both timely pharmacotherapy-related topics and institution-specific subject matter such as new medical center cost-saving initiatives and/or programs. We welcome and encourage feedback from our readers, including suggestions for article ideas and comments on the content of each newsletter issue. Please send comments and suggestions to erudy@u.washington.edu.

How Much "D" Do We Need?

Jason Yeh, Pharm. D.

Vitamin D is an important nutrient that has sparked interest in the healthcare community because of its potential benefits. Vitamin D is essential for maintaining calcium and phosphorus homeostasis and may prevent bone loss, improve muscle strength, and reduce the risk of fractures in the elderly.¹⁻⁵ In addition, recent studies have suggested potential roles for vitamin D in preventing cancer, cardiovascular disease, diabetes, and several other diseases.^{1,2,6-8}

Structurally a steroid hormone, vitamin D is obtained from exposure to sunlight, diet, and supplementation. Ultraviolet (UV) radiation penetrates the skin and converts 7-dehydrocholesterol to previtamin D₃, which is rapidly converted to vitamin D.^{1,2} Although vitamin D can be formed in skin by UV light, prolonged exposure may increase the risk for skin cancer.² Because the optimal amount of sunlight exposure is unclear, the risk for skin cancer must be weighed against the benefits of stimulating vitamin D production. Foods, such as bread, milk, yogurt, and orange juice, are often fortified with vitamin D.^{2,9} However, experts observe that eating vitamin D rich foods alone does not provide sufficient vitamin D supplementation in adults.^{1,2,9}

Skin production of vitamin D declines with age. Studies suggest that over 50% of elderly individuals still living in the community are vitamin D deficient.¹⁰⁻¹² In addition, people living in higher latitudes may have minimal exposure to sunlight and are more prone to vitamin D deficiency.^{1,2,13}

continued

TABLE 1: Causes of Vitamin D Deficiency^{1,7}

• Elderly	• Rickets
• Skin grafts for burns	• Hyperthyroidism
• Above 35° northern latitude	• Primary hyperparathyroidism
• Cystic fibrosis	• Cancer-induced osteomalacia
• Celiac/Crohn's disease	• Granulomatous disorders (sarcoidosis, TB, lymphoma)
• Pregnancy/Lactation	• Medications (anticonvulsants, glucocorticoids, antiretrovirals, immunosuppressants)
• Liver failure	
• Nephrotic syndrome	
• Chronic kidney disease	

TABLE 2: Recommended Vitamin D Supplementation^{1,13,17}

Vitamin D deficiency (25-OHD < 20ng/mL)	Ergocalciferol 50,000 IU PO every wk X 8 wks, repeat if 25-OHD < 20ng/mL
Vitamin D insufficiency (25-OHD = 20–30ng/mL)	Cholecalciferol 1000 IU PO daily
Maintenance Dosage	Ergocalciferol 50,000 IU PO every 2 weeks -OR- Cholecalciferol 1000 IU PO daily

Even people who receive adequate sunlight exposure during the summer may not have enough vitamin D during the winter months. Table 1 lists patient populations that may have insufficient intake of vitamin D.

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (25-OHD).^{1,2} Monitoring levels of 25-OHD is the standard for assessing a patient's vitamin D status. Although there is no consensus on the optimal level of 25-OHD, vitamin D insufficiency in adults is often defined as a 25-OHD concentration of 20–30ng/mL, whereas vitamin D deficiency is defined as a 25-OHD level < 20ng/mL.^{1,13} Routine monitoring of 25-OHD levels is not necessary in all individuals, but it is reasonable to obtain levels in patients evaluated for osteoporosis, patients with malabsorption issues, and patients that are home-bound or institutionalized.^{1,14}

The two most common forms of vitamin D supplementation are ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). Vitamin D₂ is found in plants and comes from UV irradiation of ergosterol. Vitamin D₃ is made by UV irradiation of 7-dehydrocholesterol found in the skin. Cod liver oil and oily fish, such as salmon, mackerel, and sardines are also natural sources of vitamin D₃.^{1,2}

Recommended dosing for vitamin D supplementation applies to both ergocalciferol and cholecalciferol because both forms undergo metabolism in the liver to form 25-OHD.

On the basis of the limited evidence available, cholecalciferol is generally regarded as more potent than ergocalciferol.^{1,15,16} However, a recent study suggests that ergocalciferol may be as effective as cholecalciferol in maintaining 25-OHD levels and improving bone health.¹⁷ Treatment decisions will often be based on patient compliance and supplement availability. Cholecalciferol is taken daily and is available over-the-counter. Ergocalciferol requires less frequent dosing but is only available through prescription.

The recommendations from the Institute of Medicine for adequate daily intake of vitamin D include 200 International Units (IU) for children and adults < 50 years of age, 400 IU for adults 50–70 years of age, and 600 IU for adults > 70 years of age.¹⁸ However, many experts agree that the current guidelines for daily vitamin D intake are insufficient and do not reflect clinical studies conducted over the past decade.^{1,9,13,19} Studies suggest that only 50% of adults would reach the optimal level of 25-OHD (36–40ng/mL) with daily supplementation of 700–1000 IU vitamin D.^{9,20,21} Thus, the recommended daily vitamin D intake may be at least 1000 IU.

The optimal dose and dosing interval for vitamin D supplementation is not clearly defined due to varying age, race, latitude, season, and lifestyle factors. Generally, every 100 IU of vitamin D will increase the 25-OHD level by about 1ng/mL.^{7,14} Levels of 25-OHD should be checked two months after initiating supplementation.^{1,14,22} Recommendations for vitamin D supplementation in adults are listed in Table 2.

Vitamin D toxicity is extremely rare, but has been associated with ergocalciferol doses > 50,000 IU per day and 25-OHD levels > 150ng/mL. Signs of toxicity include hypercalcemia and hyperphosphatemia, which increase the risk of renal calculi formation.¹ Doses of cholecalciferol up to 2000 IU per day have been traditionally recognized as safe, with new evidence demonstrating safety at up to 10,000 IU per day.^{7,23} Experts agree that the tolerable upper intake level of vitamin D should be updated to reflect these findings.^{23,24}

Vitamin D insufficiency is common in many adults and often goes undetected. Patients and providers should be aware of the high prevalence of vitamin D insufficiency and deficiency, particularly among elderly patients and patients with osteoporosis. Given the possible benefits and low cost of therapy, most adults should consider vitamin D supplementation with cholecalciferol 1000 IU per day. Individuals at high risk for vitamin D deficiency may require higher doses and should have 25-OHD levels monitored to ensure that supplementation is adequate.

ANGIOTENSIN CONVERTING ENZYME INHIBITOR-INDUCED ANGIOEDEMA: TAKING A SECOND LOOK

Elizabeth Rudy, D.V.M., R.Ph.

In 1998, the hospitalization rate in the United States for angioedema was 3.3 in 100,000.¹ By 2005, this rate had risen to 4.0 in 100,000. Twenty-four percent of these hospitalizations were coded for an adverse effect due to antihypertensive or cardiovascular agents. In their 2008 article, Lin and Shah theorized that one possible contributing factor for this rise in hospitalizations for angioedema was the increasingly prevalent use of angiotensin converting enzyme (ACE) inhibitors.¹ Although still considered a rare adverse drug reaction, the reported incidence of ACE inhibitor-associated angioedema without urticaria is estimated to range from 0.1% to 0.7% when calculated from post-marketing surveillance or epidemiological studies, to as much as 2.8% to 6% when prospectively ascertained in clinical trials.² It is estimated that approximately 20% of cases of ACE inhibitor-induced angioedema will result in symptoms that may be considered severe and life-threatening.³

ACE inhibitor-induced angioedema is characterized by sudden onset edematous swellings of the skin, mucous membranes, and/or subcutaneous tissues.^{4,5} Most often, angioedema presents as swelling of the tongue or lips, but also can produce edema of the nose, throat, glottis, and face.⁵ If the respiratory tract is affected, serious, potentially fatal adverse events such as airway obstruction and respiratory distress can occur.⁵ Although it is very rare, angioedema of the intestine (visceral angioedema) has also been reported.⁶ Nearly 60% of cases of ACE inhibitor-associated angioedema occur within the first week of therapy; however, the interval between drug initiation and the onset of angioedema may range from a few hours to several years.^{7,8}

The mechanism behind ACE inhibitor-induced angioedema appears to involve an increase in serum levels of the peptide bradykinin.⁵ Increased levels of bradykinin have been demonstrated in plasma during an acute episode of angioedema.⁷ Angiotensin converting enzyme (ACE) acts to degrade bradykinin.⁵ Pharmacologic inhibition of ACE (by an ACE inhibitor) results in increased plasma levels of bradykinin.⁷ Elevated plasma bradykinin levels result in increased vasodilation and vascular permeability.⁵

Because ACE inhibitor-induced angioedema is a potentially life-threatening adverse reaction, prompt recognition and treatment of the condition is extremely important. Discontinuation of the suspected causative drug is the first step. When airway obstruction occurs, treatment with epinephrine, diphenhydramine, and methylprednisolone is often initiated.^{7,9} If acute airway obstruction occurs, resulting in potentially fatal respiratory compromise, then intubation or a tracheotomy may be necessary.^{7,8}

The prescribing practitioner can take several precautionary measures to prevent and/or reduce the chance that a patient will experience ACE inhibitor-induced angioedema. Of primary importance is getting a detailed patient history before a medication is prescribed. The patient should be questioned as to whether they have experienced angioedema in the past and whether the symptoms were associated with a specific medication. Answers to these questions can help identify patients with hereditary or acquired angioedema who may be particularly susceptible to drug-induced angioedema. Any patient with a new prescription for an ACE inhibitor should be educated about the symptoms of this adverse reaction.

ANGIOTENSIN II RECEPTOR BLOCKERS: SAFE FOR PATIENTS WITH A HISTORY OF ACE INHIBITOR-INDUCED ANGIOEDEMA?

The rate of angioedema cross-sensitivity in patients with a prior history of ACE inhibitor-associated angioedema when treated with an angiotensin II receptor blocker (ARB) is estimated to be about 8%.¹⁰ Because this percentage is so low, the use of an ARB in patients with a history of ACE inhibitor-induced angioedema is not an absolute contraindication.¹⁰ However, because of the potentially life-threatening nature of this adverse effect, any change in therapy should be initiated with extreme caution.¹¹ For patients with a history of ACE inhibitor-induced angioedema who have medical conditions such as diabetes, congestive heart failure, or post-myocardial infarction, where ARB therapy has been shown to improve outcomes, then a switch may be warranted.^{11,12} However, for patients with uncomplicated hypertension, use of an ARB is not recommended because other, potentially safer antihypertensive treatment options are available.¹¹ Additionally, if a patient has experienced severe airway obstruction due to ACE inhibitor therapy, then switching them to an ARB, regardless of the condition being treated, would not be recommended.¹¹ Finally, patients with a history of ACE inhibitor-induced angioedema switched to an ARB need to be educated about the benefits of ARB treatment versus the risks of angioedema and be instructed to watch for potential adverse effects.

P&T COMMITTEE BRIEF SUMMARY September 16, 2008 through March 17, 2009

FORMULARY ADDITIONS

Bortezomib (Velcade®) 3.5mg vial Added 09/16/08	
Chemotherapeutic agent for the treatment of multiple myeloma and relapsed or refractory mantle cell lymphoma.	
DOSE	Per oncology
CLASS	Proteasome inhibitor
ADVERSE EFFECTS	Asthenia, peripheral neuropathy, blood dyscrasias, anorexia, parasthesia, hypotension, rash, nasopharyngitis, diarrhea, nausea, vomiting, constipation
INTERACTIONS	CYP 3A4, 2C9, or 1A2 inhibitors or inducers
PRECAUTIONS	Use caution in patients with neuropathy, dehydration, heart disease, hepatic impairment, a history of syncope, or those taking antihypertensives.
MONITOR	Per oncology

Fluocinolone acetonide intravitreal implant (Retisert®) Added 10/21/08	
Treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. Only for patients failing less invasive and/or expensive options.	
DOSE	The implant contains 1 tablet of 0.59mg of fluocinolone acetonide
CLASS	Corticosteroid
ADVERSE EFFECTS	Increased intraocular pressure, lens opacification, pain, conjunctival hyperemia/hemorrhage, blurred vision, reduced visual acuity
INTERACTIONS	None
PRECAUTIONS	Insertion of fluocinolone acetonide intravitreal implant must be performed by an ophthalmologist in the operating room under sterile conditions and providers must obtain prior authorization.
MONITOR	Per ophthalmology

Regadenoson (Lexiscan®) 0.4mg pre-filled syringe Added 10/21/08	
Pharmacological stress agent used for radionucleotide perfusion imaging in patients unable to undergo adequate exercise stress. Adenosine A2A receptor selectivity may theoretically make it safer than adenosine in patients with COPD or asthma.	
DOSE	0.4mg IV push followed by saline flush and radiopharmaceutical
CLASS	Adenosine A2A receptor agonist (adenosine activates all 4 distinct subtypes of the adenosine receptor family)
ADVERSE EFFECTS	Dyspnea, headache, flushing, chest discomfort, angina, ST segment depression
INTERACTIONS	Caffeine, theophylline, aminophylline, dipyridamole
PRECAUTIONS	Use caution in patients with known history of asthma, COPD, atrioventricular block, or hypotension.
MONITOR	ECG, ABG

Calcium citrate 315mg (elemental Ca) + Cholecalciferol 200 IU tablets Added 11/18/08	
Supplementation of calcium and vitamin D.	
DOSE	Generally 2 tablets PO daily (630mg elemental calcium + 400 IU vitamin D) adjusted per patient need
CLASS	Vitamin supplement
ADVERSE EFFECTS	Hypercalcemia, nausea, abdominal pain, constipation
INTERACTIONS	Quinolone antibiotics
PRECAUTIONS	Use caution in patients with renal impairment, history of kidney stones, hypoparathyroidism, or those taking additional vitamin supplements.
MONITOR	Calcium, phosphate, 25-hydroxyvitamin D

Methylnaltrexone (Relistor®) 12mg/0.6mL vial Added 01/20/09	
Treatment of opioid-induced constipation in patients with advanced illness unresponsive to laxative therapy. Use restricted to patients receiving chronic opioid therapy who have opioid-induced constipation that has been refractory to an adequate trial of stool softeners or laxatives.	
DOSE	Based on patient weight
CLASS	Peripherally acting mu-opioid receptor antagonist
ADVERSE EFFECTS	Dizziness, abdominal pain, flatulence, nausea, diarrhea
INTERACTIONS	No known interactions at this time
PRECAUTIONS	Severe or persistent diarrhea may occur. Use beyond 4 months has not been studied.
MONITOR	BUN, Creatinine, Glucose, Serum chloride, Serum potassium, Serum sodium

Romiplostim (Nplate®) 250mcg, 500mcg vials Added 01/20/09	
Third line agent for the treatment of chronic immune thrombocytopenia purpura in patients who have insufficient response to corticosteroids, IVIG, and/or splenectomy. Prescribing restricted to hematologists enrolled in the Nplate NEXUS distribution program.	
DOSE	1mg/kg based on actual body weight administered SQ once weekly adjusted to achieve platelet count $\geq 50 \times 10^9/L$, up to 10mcg/kg
CLASS	Thrombopoietin (TPO) receptor agonist
ADVERSE EFFECTS	Headache, arthralgia, dizziness, insomnia, myalgias, dyspepsia, parasthesia
INTERACTIONS	No formal drug interaction studies have been performed
PRECAUTIONS	May increase risk for bone marrow reticulium formation or progression. May increase risk for hematologic malignancy. Rebound thrombocytopenia may occur upon discontinuation. Risk of thromboembolism may increase with treatment.
MONITOR	CBC with differential

FORMULARY ADDITIONS continued

Tinidazole (Tindamax®) 250mg, 500mg tablets Added 01/20/09	
First line therapy for giardiasis and amebiasis, and second line behind metronidazole for trichomoniasis and <i>H. pylori</i> sequential therapy.	
DOSE	Trichomoniasis/Giardiasis: 2gm single oral dose with food Amebiasis: 2gm/d x 3-5 days with food <i>H. pylori</i>: 500mg BID x 5 days as part of sequential therapy
CLASS	Antiprotozoal nitromidazole
ADVERSE EFFECTS	Metallic taste, nausea, vomiting, anorexia, possible disulfiram reaction
INTERACTIONS (THEORETICAL)	Warfarin, lithium, phenytoin, cyclosporine, tacrolimus, fluorouracil, cholestyramine
PRECAUTIONS	Use caution in patients with hepatic impairment, candidiasis, alcohol use, or history of blood dyscrasias.
MONITOR	CBC, LFT's

Gadoxetate (Eovist®) 10mL vial Added 02/17/09	
For intravenous use in T1-weighted magnetic resonance imaging [MRI] of the liver to detect and characterize lesions in adults with known or suspected focal liver disease.	
DOSE	0.1mL/kg body weight [0.025mmol/kg body weight]
CLASS	Gadolinium-based contrast agent
ADVERSE EFFECTS	Flushing, feeling hot, nausea, headache, injection site reactions, dysgeusia, parosmia
INTERACTIONS	Anionic drugs primarily excreted in bile may reduce hepatic contrast enhancement and biliary excretion of gadoxetate sodium
PRECAUTIONS	Nephrogenic systemic fibrosis has occurred in patients with GFR < 30. Hypersensitivity reactions have occurred. May interfere with iron studies.
MONITOR	Per radiology

Insulin lispro pen (Humalog KwikPen®) 3mL Added 03/17/09	
Disposable insulin pen used for the administration of insulin lispro products. Use restricted to ambulatory patients/patients self-administering insulin while hospitalized.	
DOSE	Variable
CLASS	Rapid acting insulin
ADVERSE EFFECTS	Hypoglycemia
INTERACTIONS	None
PRECAUTIONS	Patients should be properly trained in the use of the pen to avoid hypo- or hyperglycemia.
MONITOR	Serum glucose

ANGIOTENSIN CONVERTING ENZYME INHIBITOR-INDUCED ANGIOEDEMA: TAKING A SECOND LOOK

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TABLE 1: Other Drugs Reported to Cause Angioedema without Urticaria

Amiodarone	Estrogen
Angiotensin II receptor blockers	Fibrinolytic agents
Antibiotics (rarely without urticaria)	Metoprolol
Calcium channel blockers	Nonsteroidal anti-inflammatory drugs
Contrast media (rarely without urticaria)	Paroxetine
	Risperidone

However to promote good patient compliance and provide adherence incentive, such counsel should be balanced with a reminder about the important role that these agents play in decreasing morbidity and mortality. Additionally, if a patient has experienced ACE inhibitor-induced angioedema in the past, then a change in therapy to a different ACE inhibitor is **not** recommended since this reaction is considered a class effect.⁷ Finally, patients receiving concurrent therapy with multiple medications that may cause angioedema (see Table 1) should be monitored closely by the prescribing practitioner.

References available on request

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- *Drug Therapy Topics*: Newsletter Changes, p1
- How Much “D” Do We Need?, p1-2
- Angiotensin Converting Enzyme Inhibitor-Induced Angioedema: Taking a Second Look, p3, p5
- P&T Committee Brief Summary, p4-5, back cover



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P&T COMMITTEE BRIEF SUMMARY September 16, 2008 through March 17, 2009 continued from inside

FORMULARY DELETIONS

Papain-Urea (Accuzyme [®] , Ziox [®] , Panafil [®])	Deleted due to FDA removal of these products from the market for safety concerns	Removed 11/18/08
Calcium glubionate	Removed due to lack of usage	Removed 11/18/08
Aripiprazole injectable (Aripiprazole [®])	Removed due to lack of usage	Removed 11/18/08
Aliskren (Tekturna [®])	Removed due to lack of usage	Removed 11/18/08

OTHER ACTIONS

09/16/08	Natalizumab (Tysabri [®])	EXPAND the restricted prescribing to include Dr. Scott Lee for refractory Crohn's disease, and Dr. Annette Wundes for MS.
03/17/09	Rifaximin (Xifaxan [®])	MODIFICATION to guidelines for appropriate use (see following details).

MODIFICATIONS TO THE GUIDELINES FOR APPROPRIATE RIFAXIMIN USE

A medication-use evaluation of rifaximin (indicated for the treatment of hepatic encephalopathy) recently conducted at UWMC showed that the drug had been prescribed appropriately in 77% of cases over a three-month period, with the majority of use due to continuation of outpatient therapy. In cases in which the drug was used inappropriately, six patients did not receive an adequate three-day trial of lactulose, and four patients received rifaximin for unapproved indications. Rifaximin has been shown to be non-inferior to lactulose in reducing altered mental status and has a reduced incidence of GI side effects. **Rifaximin is significantly more expensive than lactulose, and therefore needs to be reserved as second line therapy.** The cost for one day of therapy with rifaximin for hepatic encephalopathy (400mg every 8 hours) is \$25.92, which is significantly more than treatment with lactulose (20gm every 8 hours) at \$1.44. The P&T Committee recently approved recommendations to modify guidelines for the appropriate use of rifaximin. Guidelines for appropriate rifaximin use at UW Medicine are as follows:

HEPATIC ENCEPHALOPATHY

Indication: Contraindication to or treatment failure with lactulose 20-30gm PO TID-QID titrated to 3-4 bowel movements per day for 3 days.
Dose: Rifaximin 400mg PO TID