

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met September 21, 2004. 3 products were added in the *Formulary* and nothing was deleted. 2 combination drugs and 2 dosage forms were designated nonformulary and not available.

◆ ADDED

Cyanocobalamin Tablets
(generic)

Risperidone Long-Acting Injection (Risperdal® Consta® by Janssen)*

Sodium Hyaluronate (Healon® & Healon-5® by Pharmacia and Viscoat® by Alcon)**

*Restricted to Shands at Vista (continues to be a medium-priority nonformulary drug at Shands at UF)

**Devices, not drugs, but stocked in the OR satellite because they come in a syringe and must be refrigerated.

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

Amlodipine + Atorvastatin
(Caduet® by Pfizer)***

Cyanocobalamin Extended-Release (various)

Cyanocobalamin Nasal Gel
(Nascobal® by Questor)

Ezetimibe + Simvastatin
(Vytorin® by Merck and Schering Plough)***

***Combination product automatically interchanged to individual ingredients

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ADVERSE DRUG REACTION PROGRAM

Minimizing “allergic” reactions to contrast media

Clinicians often wonder what risk factors they should consider when trying to manage patients who may have a reaction to radiopaque contrast media. Patients with a seafood allergy are often a concern since past literature states that cross-sensitivity may exist. A question also exists regarding why patients are sensitive to contrast media. Is it the iodine component or is it the osmolality of the product? Also, what can be done to prevent these reactions?

The term “allergy” is typically used to describe an adverse immune response, mediated by the IgE antibody, to a protein. In an allergic reaction, the target protein binds to the previously formed IgE antibodies, which are bound to IgE receptors on mast cells and basophils. The binding of IgE results in histamine release causing clinical symptoms or anaphylaxis.¹ Many researchers believe the mechanism of contrast reactions is not likely to be a “true allergy” and is more likely due to activation of complement or other mediators of the nonspecific immune system.² Therefore, “sensitivity” is a more appropriate term since it refers to a non-IgE-mediated adverse event.

Some clinicians believe that contrast media reactions are due to iodine. Iodine is a trace mineral required for the synthesis of thyroid hormones. Approximately 155 to 550 mcg of iodine are consumed daily from dietary sources like fish, iodized salt, and iodates used as bread preservatives.² To date, there have been no reports of allergy to iodized salt, which emphasizes how unlikely it is to be allergic to iodine. There have, however, been reports of patients with skin sensitivity to iodine-containing products. A common iodine-containing scrub used during surgical preps is povidone-iodine (Betadine®). In a study performed by Seguchi and

colleagues, 10 cases of contact dermatitis due to povidone-iodine preps were examined with patch tests. The investigators found that only 1 patient was sensitive to the iodine component, whereas 4 were sensitive to the povidone-iodine and 5 more were sensitive to other components of Betadine®.³

The American Academy of Allergy, Asthma, and Immunology states that allergic contact dermatitis from iodine-containing antibacterial preparations or reactions to contrast media should not be considered evidence of IgE-antibody-mediated iodine allergy. Many researchers agree that sensitivity to contrast media is not likely due to iodine, but is instead related to the high osmolality of contrast media. High-osmolality agents are more likely to cause adverse reactions than low osmolality preparations. The incidence of mild adverse reactions is 15% in patients receiving intravenous high-osmolality contrast media and up to 3% in patients receiving low-osmolality contrast media. Severe reactions are less frequent with an incidence of 0.22% with high-osmolality agents compared to 0.04% in patients receiving low-osmolality agents.⁴

Often before procedures involving contrast media, patients are asked about seafood allergies. Although seafood may contain iodine, IgE antibody mediated seafood allergy has never been attributed to iodine, but instead to specific proteins in fish and shellfish.¹ In 1975, Shehadi and colleagues

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Formulary update, from page 1

Cyanocobalamin oral tablets were added in the *Formulary* for use in the treatment of pernicious anemia and in combination with folate and thiamine for hyperhomocysteinemia. Intramuscular cyanocobalamin injection remains in the *Formulary*, but **extended-release cyanocobalamin** oral dosage forms and **cyanocobalamin nasal gel** were designated non-formulary and not available. Extended-release cyanocobalamin is considered irrational therapy and the nasal gel is not needed with the IM and oral options listed in the *Formulary*.

Cyanocobalamin tablets were evaluated because of frequent nonformulary use. Oral cyanocobalamin was not listed in the *Formulary* because of concerns about oral bioavailability when used to treat megaloblastic anemia.

Cyanocobalamin is the most widely used synthetic form of vitamin B₁₂. It is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis.

Vitamin B₁₂ is normally ingested from animal sources, including meats, eggs, and dairy products. The RDA is 2.4 mcg of vitamin B₁₂ daily. A typical Western diet provides 5 to 30 mcg/day. After ingestion, B₁₂ is bound by intrinsic factor, which is produced by gastric parietal cells. Bound vitamin B₁₂ is absorbed in the terminal ileum. Thus, normal absorption of dietary B₁₂ requires gastric intrinsic factor and an intact terminal ileum.

Total body stores of vitamin B₁₂ are 2 to 5 mg. Thus, B₁₂ deficiency takes years to develop and rarely occurs from dietary insufficiency except in strict vegans. Pernicious anemia usually occurs in the elderly and is due to atrophy of the gastric mucosa and intrinsic factor deficiency. Other causes of B₁₂ deficiency include gastric and ileal surgeries, ileal absorption problems such as Crohn's disease, sprue, and tapeworm infection.

B₁₂ replacement regimens vary, but the most common method is 1000 mcg of intramuscular cyanocobalamin daily for 1 week, then weekly for 1 month, then every 1 to 3 months for life. Hematocrit should return to normal in 2 months. 6 months or more may be needed for neurologic improvement, and up to 80% of patients will have at least partial resolution of neurologic manifestations.

An alternative to parenteral B₁₂ is high-dose oral therapy. This may be a reasonable option because of ease of administration compared with intramuscular injections.

Patients with pernicious anemia can absorb 1% to 2% of oral B₁₂

without the addition of intrinsic factor by simple diffusion, so treatment with daily oral B₁₂ 1000 to 2000 mcg can be considered in adherent patients. Data show that oral therapy works more slowly than parenteral regimens, but within 3 months there is no difference in effectiveness.

Systematic reviews have shown a strong correlation between elevated levels of homocysteine (hyperhomocysteinemia) and the risk of atherothrombotic vascular disease. Serum homocysteine levels can be lowered with regimens including folic acid, thiamine, and cyanocobalamin.

Although daily use of oral folate, thiamine, and cyanocobalamin will lower plasma homocysteine concentrations, it is still unclear whether this results in the prevention of coronary artery disease. A study has shown that supplementation with folic acid (1 mg), thiamine (10 mg), and oral cyanocobalamin (400 mcg) daily for 6 months lowered the rate of coronary restenosis after angioplasty in a randomized, blinded, placebo-controlled trial. Although the risk reductions for death and MI were not statistically significant, the reduction in restenosis was encouraging. Unfortunately, these results have not been replicated.

Risperidone long-acting injection is the first depot form of an atypical antipsychotic drug. It was evaluated because it is expensive (\$400 per dose) and has been used at Shands at Vista. It is rarely used at Shands at UF. Risperdal® Consta® has a labeled indication for the treatment of schizophrenia.

The efficacy of risperidone is well established with more effect on negative symptoms and fewer movement adverse effects compared with traditional antipsychotics. These benefits must be balanced by greater cost and weight gain, which may be associated with the development of diabetes.

The long-acting formulation of risperidone injection is an aqueous suspension of microspheres. Each microsphere is a small bead with a matrix of risperidone and a carbohydrate-based biodegradable copolymer, which is gradually hydrolyzed at the injection site releasing risperidone. Initially after an injection, very little risperidone is released. The release of risperidone begins 3 weeks after the first injection. This is why oral therapy with risperidone (or another antipsychotic) must be continued for 3 weeks after beginning Risperdal® Consta®.

The recommended dosage for Risperdal® Consta® is 25 mg IM every 2 weeks. Patients not responding to this dosage may respond to higher dosages (ie, 37.5 mg every 2 weeks or 50 mg every 2 weeks). Upward dosage

adjustment should not be made more frequently than every 4 weeks and the clinical effects of an increased dosage should not be expected for at least 3 weeks.

There is a published study that shows that Risperdal® Consta® is more effective than placebo. Data have been presented as an abstract that shows that Risperdal® Consta® is as effective as oral risperidone. It has not been compared with other depot antipsychotics.

The advantage of depot antipsychotics is the assurance of compliance. There are pharmacoeconomic evaluations done in other countries that suggest increased drug cost is offset by decreased use of healthcare resources with Risperdal® Consta®.

Continuing therapy for a patient who has been hospitalized is a reasonable criterion for Risperdal® Consta® use at Shands at UF. There are no good guidelines for replacing Risperdal® Consta® with oral therapy.

The adverse effects associated with Risperdal® Consta® are the same as those expected with oral risperidone, except pain at the injection site may also occur.

Sodium hyaluronate devices are used as a surgical aid in anterior segment ophthalmologic surgeries. It is designed to allow manipulation of eye tissue while minimizing the risk of damage to the corneal epithelium or other eye tissues.

Sodium hyaluronate has no pharmacological activity. It is a device and not a drug. It was evaluated by the P&T Committee only because it looks like a drug, not based on its action. Sodium hyaluronate comes in a syringe and must be stored in the refrigerator. Thus, it will be stored in the Operating Room Pharmacy.

These devices were not evaluated using an evidence-based approach. The available data for comparing devices are limited. It is not the intention of the P&T Committee to routinely evaluate devices; however, the appearance of sodium hyaluronate syringes and the need to refrigerate the product led to the pragmatic decision to make this device available from Pharmacy.

2 recently approved combination products (**amlodipine + atorvastatin** and **ezetimibe + simvastatin**) were designated nonformulary and not available. The individual ingredients of each agent will be automatically substituted for each of these products. The interchange policy was reviewed and pharmacists will be able to automatically dispense the individual ingredients of combination products
(continued on next page)

Adverse drug reaction, from page 1 conducted a study involving 112,000 patients to determine possible risk factors for contrast media sensitivity. They found that the overall incidence of adverse reactions in patients with a history of multiple allergies was almost double that of the general population (10.2% vs. 5.65%). The risk factors were certain food allergies (seafood and shellfish, eggs, milk, and chocolate), asthma, hayfever, and penicillin.⁵ Several articles have discounted allergy to seafood as a risk factor for receiving contrast media since no evidence exists supporting the relationship between the iodine in seafood and these reactions.

Patients at highest risk of contrast media reaction are those with a history of sensitivity to contrast media. The risk of having an adverse reaction doubles in patients with a history of asthma when compared to that of the general population, even if the asthma is controlled. Patients with multiple food or medication allergies and those with multiple medical problems are also more likely to develop complications from contrast media.⁶

Precaution should be taken to minimize reactions to contrast material in high-risk patients. Prophylactic premedication has been shown to decrease the risk of adverse effect, although it does not eliminate it. The American College of Radiology recommends 3 alternative prophylactic regimens.⁷

1. Oral corticosteroid + antihistamine: prednisone 50 mg orally at 13, 7, and 1 hour before the procedure plus diphenhydramine 50 mg intramuscularly or by mouth 1 hour before contrast administration.

2. Oral corticosteroid alone: methylprednisolone 30 mg orally 12 and 2 hours before procedure.
3. Intravenous corticosteroid + antihistamine (reserved for patients unable to take oral medications): hydrocortisone 200 mg intravenously at 13, 7 and 1 hour before the procedure plus diphenhydramine 50 mg intramuscularly 1 hour before contrast administration.

Patients should be treated with corticosteroids at least 6 hours before the procedure since pretreatment with intravenous corticosteroids immediately before the procedure is not effective. Low-osmolality contrast media also decreases the risk of an adverse reaction, especially in patients with a prior reaction. A further decrease in adverse reactions is achieved with the combination of low-osmolality contrast media and steroid prophylaxis.⁷

Based on the information presented, there is no correlation between seafood allergy and sensitivity to contrast

media. The iodine component of the contrast media does not appear to be the contributing factor; instead the osmolality of the contrast media is the most likely cause of adverse events. In order to prevent contrast media reactions in high-risk patients, corticosteroids and low-osmolality contrast media should be used.

by Shannon Holland, PharmD

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AVOID THESE ABBREVIATIONS...AND AVOID PROBLEMS

The following inappropriate abbreviations CANNOT be used. Please use an appropriate abbreviation to write a valid order.

<u>Inappropriate Abbreviation</u>	<u>Appropriate Abbreviation</u>
U.....	Spell "Units" instead
IU.....	Spell "International Units" or "Units" instead
μ (Greek mu symbol).....	Use "mcg" for micrograms
Doses less than 1 unit.....	Use leading zero (eg, 0.1 mg)
Doses greater than 1 unit.....	Do not use trailing zero (ie, 1 mg, not 1.0 mg)
QD or OD.....	Spell "daily" instead
< or >.....	Spell "less than" or "greater than"
MSO4.....	Spell "Morphine"
MgSO4.....	Spell "Magnesium sulfate"
CC.....	Use "mL" instead

Formulary update, from page 2 without contacting the prescriber for a new order. The pharmacist will note the interchange in the Orders and Progress Notes sections of the chart.

Combination products are becoming more popular. In the outpatient setting they offer several advantages. By combining therapies into 1 dosage form, patients' pill burdens are decreased. This will hopefully lead to increased compliance.

Also, patients who have third-party prescription benefits usually only pay 1 co-pay for 2 products. This reduces patients' out-of-pocket expenses.

Drug manufacturers like combination products because they help extend their patent protection. By marketing these products at a cost that is usually lower than the cost of the individual ingredients, they are able to drive market share to

the combination product. When 1 of the ingredients of the combination product becomes available generically, the price of the individual ingredients should then be considerably less than the combination product.

In the inpatient setting, adding additional dosage forms is a problem. The automatic dispensing cabinets (SureMed[®]) used to store a large number of oral solid dosage forms have limited capacity. If all strengths of Vytorin[®] and Caduet[®] were listed in the *Formulary*, it would add 12 additional products that we already stock as individual ingredients. The added expense of storage space can be prohibitive. Even though many combination products are less expensive than the individual ingredients, storage is a more important issue.

Vytorin[®] is a fixed-combination of 2 cholesterol-lowering medications that work by different mechanisms. Ezetimibe (Zetia[®]) is a cholesterol absorp-

tion inhibitor. Simvastatin (Zocor[®]) is a hydroxymethylglutaryl CoA (HMG-CoA) reductase inhibitor that decreases the production of cholesterol by competing with HMG-CoA for HMG-CoA reductase (a hepatic microsomal enzyme) and reducing the quantity of the cholesterol precursor, mevalonic acid. In a study comparing Vytorin[®] with atorvastatin (Lipitor[®]), Vytorin[®] was shown to have at least equal efficacy to atorvastatin in terms of percentage reduction in LDL.

Caduet[®] is a combination of a dihydropyridine calcium channel blocker (amlodipine) for hypertension and a HMG-CoA reductase inhibitor (atorvastatin) for hyperlipidemia. It is being marketed to the "30 million Americans who have both high cholesterol and high blood pressure."

Upon discharge, patients should restarted on Vytorin[®] or Caduet[®] and the individual ingredients stopped.

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POLICIES AND PROCEDURES

Therapeutic interchange — Update

A drug is ordered, but a different drug is dispensed and administered. The drug that is dispensed is not a generic equivalent of the ordered drug, but it is a "therapeutically equivalent" product. A single drug product is selected and listed in the *Formulary* for a therapeutic class. The drugs are not the same, but they are so similar that there is no clinically significant difference among the drugs in a class. All non-selected drugs are changed to the formulary class representative. The non-selected drugs are nonformulary and are not available—with a few exceptions.

This is therapeutic interchange. Therapeutic interchange is the substitution of various therapeutically equivalent drug products by pharmacists under arrangements of the authorized prescribers who have agreed on the conditions for the change.

Therapeutic interchange is reviewed and approved for the medical staff by the Pharmacy and Therapeutics Committee, which is a medical staff committee. Representatives from various medical specialties participate in the P&T Committee. If a drug class is used by a specific medical specialty and a

representative from that medical specialty is not on the P&T Committee, the department head is contacted to solicit input on that particular interchange.

Therapeutic interchange has been practiced for over 20 years at Shands at UF. Feedback from both attendings and housestaff consistently support the concept of interchanging to a product that is currently available, rather than constantly paging to have a new order written. Some institutions only list 1 agent in the class and constantly contact the prescriber to change the order to the formulary agent.

Since the medical staff are not contacted to write a new order, there has to be mechanism to notify the medical staff and nursing when an interchange occurs. When a drug is prescribed that is interchanged, documentation of the interchange is placed in the chart. This documentation is placed in both the Physician Orders section of the chart and the Progress Notes section.

There can be exceptions made to the interchange policy. If the patient has a rational reason not to receive the interchanged drug (ie, allergic to a dye in the interchanged product), the

change can be over-ruled. Experience has shown that these situations are very rare.

A continually updated version of the drugs that are therapeutically interchanged can be found on the intranet at <http://intranet.shands.org/pharm/therapeu.htm>. When a new product is added to the list, prescribers are notified that beginning the next month an interchange will occur. This gives prescribers an opportunity to change their habits. Most prescribers use the preferred agents. Interchanges are relatively infrequent — once the housestaff and other prescribers know the drug that is listed as the "class representative."

A similar process is used for other interchanges. As summarized in the *Formulary Update* article in this issue of the *Bulletin*, combination products will also be interchanged when the ingredients are listed in the *Formulary* and the exact amount of each ingredient is available. For example, an order for Vytorin® 10/10 will be changed to Ezetimibe 10 mg [Zetia®] and Simvastatin [Zocor®] 10 mg. The same documentation as for the therapeutic interchanges will occur.