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SHANDS at the University of Florida

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# Drugs & Therapy BULLETIN

## FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met October 16, 2001. 2 drugs were added in the *Formulary*. 2 drugs were restricted. No dosage forms were deleted. 1 drug was designated not available.

**◆ ADDED**

**Alemtuzumab (Campath® 1H by Berlex)**

**Tamsulosin (Flomax® by Boehringer Ingelheim)**

**◆ RESTRICTED**

**Neostigmine (Prostigmin® by ICN)**

**Nifedipine Immediate-release (Procardia® by Pfizer)**

**◆ DELETED**

**None**

**◆ NONFORMULARY, NOT AVAILABLE**

**Terazosin (Hytrin® by Abbott)**

**Alemtuzumab** is a humanized monoclonal antibody that binds to lymphocytes at the CD52 receptor and stimulates antibody-mediated cell lysis. It is used in patients with refractory B-cell chronic lymphocytic leukemia (CLL).

There are data (although limited) that suggest that alemtuzumab produces a response in patients with CLL who have failed standard therapy (ie, chlorambucil or other alkylating agents and a purine analog like fludarabine). There are, however, more data currently available for alemtuzumab in refractory CLL than with other monoclonal antibodies to lymphocytes (eg, rituximab).

*(continued on next page)*

DRUG INFORMATION FORUM

## Alternatives to nifedipine for hypertensive urgencies

Hypertensive urgencies are those situations in which it is desirable to reduce blood pressure within a few hours.[1] These episodes have been defined as diastolic blood pressures greater than 120 to 140 mm Hg without evidence of progressive target organ damage. Hypertensive urgencies are not hypertensive emergencies, which should always be managed with parenteral antihypertensive agents to prevent end organ damage. Elevated blood pressure alone in the absence of symptoms or new organ damage rarely requires emergency therapy.

**Because serious adverse events have been associated with the use of immediate-release nifedipine in adults with hypertensive urgencies, alternate therapies should be used.**

Bite-and-chew, sublingual, and oral immediate-release nifedipine have been traditionally used to manage hypertensive urgencies. However, a moratorium on the use of immediate-release nifedipine for hypertensive urgencies has existed for roughly the last 5 years.[2]

Many institutions have removed immediate-release nifedipine from their formularies. Shands at UF kept immediate-release in the *Formulary* for use in pregnant women as a tocolytic[3] and in children experiencing hypertensive urgencies[4] (*see Formulary Update*). Because serious adverse events (including deaths) have been associated with the use of immediate-release nifedipine in adults with hypertensive urgencies, alternate therapies should be used.

Drug therapy may not even be needed. Allowing patients to rest in a supine position in a quiet, dark room can lower blood pressure.[5] If the patient's blood pressure does not decrease after 15 to 30 minutes, drug therapy is needed.

The JNC VI recommends oral therapy with drugs that have relatively fast onsets of action to manage hypertensive urgencies. Loop diuretics, beta-blockers, ACE-inhibitors, or alpha-2-antagonists are listed as alternatives to calcium channel blockers.

The stated goal of therapy for hypertensive urgencies is to reduce arterial blood pressure by no more than 25% (within minutes to 2 hours), then towards 160/100 mm Hg within 2 to 6 hours. Excessive falls in pressure should be avoided to prevent renal, cerebral, or coronary ischemia.

There are surprisingly few published recommendations for drugs and dosages for the management of hypertensive urgencies in standard references. *The Washington Manual* recommends clonidine loading and explicitly recommends against the use of nifedipine.[6]

Oral clonidine loading begins with a 0.1- to 0.2-mg oral loading dose. This dose is followed by 0.1 mg orally every hour to a total of 0.5 to 0.7 mg or until the target blood pressure is reached. The onset of effect should occur within 1 to 2 hours and the peak effect should occur in 2 to 4 hours. The duration of effect is greater than 6 hours.

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## INSIDE THIS ISSUE

***Formulary update,*** *from page 1*

Alemtuzumab is given intravenously (IV) over a 2-hour period 3-times a week for up to 12 weeks. Serious infusion-related reactions can occur. Rigors, fever, and nausea are common. Hypotension, rash, fatigue, urticaria, dyspnea, pruritus, headache, and diarrhea are also reported. It is important that patients be carefully monitored during their infusion. Gradual escalation of the dose is required when therapy is begun or any time that therapy is restarted after a period greater than or equal to 7 days. Pre-medication with diphenhydramine 50 mg and acetaminophen 650 mg administered 30 minutes before the infusion may decrease the incidence of infusion-related reactions. Other pre-medications (eg, antiemetics, meperidine, and corticosteroids) are also sometimes used.

Alemtuzumab is immunosuppressive and can result in serious infectious complications. Bacterial, viral, fungal, and protozoan infections have been reported in patients receiving alemtuzumab therapy. Prophylaxis for *Pneumocystis carinii* pneumonia (PCP) and herpes virus infections has been shown to decrease, but not eliminate, the occurrence of these infections.

Serious and, in rare instances, fatal pancytopenia or marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia have occurred in patients receiving alemtuzumab therapy. Single doses of greater than 30 mg of alemtuzumab or cumulative doses greater than 90 mg per week are not recommended because these doses are associated with a higher incidence of pancytopenia.

Reimbursement is an important issue with this agent. It is very expensive. Assuming approximately $1200 per dose, the typical 12-week course of therapy will cost approximately $50,000. At the time the P&T Committee evaluated alemtuzumab, there was no Medicare billing code for this product in the Cancer Center.

Ironically, private oncologists in the community setting would have received reimbursement by Medicare for this drug. Patients were referred back to their private oncologist whenever possible. However, there were rare patients who could not be referred back to their community oncologist and who had treatment-resistant CLL and who were candidates for alemtuzumab.

Alemtuzumab was added in the *Formulary* after a code became available for Medicare billing in the outpatient setting. Alemtuzumab should be used only for patients with CLL who have failed an alkylating agent and a purine analog.

**Tamsulosin** and **terazosin** are commonly prescribed nonformulary drugs. Both are alpha-blockers that are usually used to treat elderly males with benign prostatic hypertrophy (BPH) who are admitted to the hospital for other reasons. There are many studies that show that alpha-blockers are effective in the management of BPH.

Tamsulosin was chosen to represent this class because it is the most selective of the alpha-1a-receptor blockers. Alpha-1a-receptors are primarily located in the prostate. Tamsulosin is associated with less hypotension compared with other drugs in this class (eg, terazosin). Beginning therapy in the hospital is irrational, since these drugs do not act quickly. A response usually takes 2 weeks. Treatment of BPH should be started in the outpatient setting. Tamsulosin was selected for hospitalized patients requiring continuation of a medication for symptomatic BPH.

Tamsulosin is commonly used in the community. Nearly twice as many nonformulary doses of tamsulosin have been dispensed compared with nonformulary doses of terazosin. Therefore, there will be fewer switches needed with tamsulosin as the formulary representative for this class of drugs compared with terazosin.

This decision does not suggest that tamsulosin is the preferred agent for outpatient therapy. Tamulosin is roughly twice the cost of terazosin in the community. Terazosin was designated nonformulary and not available to decrease the number of drugs that are needed in inventory.

Automatic interchange of tamsulosin for terazosin was not approved. However, most patients can be safely switched from any dose of terazosin to 0.4 mg per day of tamsulosin. The low propensity of tamsulosin to cause hypotension makes this switch practical.

A complete list of drugs that are nonformulary and not available is posted on the Shands intranet at http://intranet.shands.org/pharm/nonformulary_&_not_available.htm.

Parenteral **neostigmine** dosages greater than 1 mg (or dosages greater than 0.02 mg/kg in pediatric patients) will not be permitted on general wards or intermediate care units (IMCs). Parenteral neostigmine administration in these doses requires continuous physician oversight along with electrocardiographic and automated blood pressure monitoring. This level of monitoring currently exists only in an ICU setting or in the OR.

Recently published data have promoted the use of large doses of neostigmine for acute colonic pseudo-obstruction (*NEJM* 1999;341:137-41). Although possibly effective, the adverse effects of neostigmine are not fully appreciated. Serious complications of intravenous neostigmine include sinus bradycardia, bronchospasm, and increased bronchial secretions. The clinical trials with this agent have required the presence of a physician for 30 minutes after the administration of injectable neostigmine for colonic pseudo-obstruction to monitor for serious adverse events.

**If neostigmine is used in large doses to treat colonic pseudo-obstruction in an ICU setting, the patient should be monitored for at least 75 minutes and until vital signs have returned to baseline and are stable.**

If neostigmine is used in large doses to treat colonic pseudo-obstruction in an ICU setting, the patient should be monitored for at least 75 minutes and until vital signs have returned to baseline and are stable. It is recommended that vital signs be monitored every 5 minutes during the first 30 minutes and every 15 minutes for the next 45 minutes (ie, 75 minutes total).

**Immediate-release nifedipine** is an oral liquid-filled capsule form of a dihydropyridine calcium channel blocker. Because of its vasodilatory properties, nifedipine has been used to treat hypertension and angina. The immediate-release dosage form of nifedipine is rarely used today because it has to be given 3 times a day. Drugs given 3 times a day often have compliance problems. Also, the short duration of effect of the immediate-release dosage form results in fluctuation in blood pressure effects, especially in the morning. Extended-release nifedipine has replaced the immediate-release product for chronic use.

*(continued on next page)*

***Formulary update,*** *from page 2*

The immediate-release dosage form of nifedipine has been used to treat hypertensive urgencies. It was often prescribed by the bite-and-chew or sublingual "routes." Although popular, the rapid reduction in blood pressure from immediate-release nifedipine has occasionally led to severe complications and has even been associated with patient deaths. The most recent guidelines for the treatment of hypertension (ie, JNC VI) state that, "the inability to control the rate and degree of fall in blood pressure makes [the use of immediate-release nifedipine] unacceptable." These concerns have stimulated many institutions to remove immediate-release nifedipine from their formularies.

A medication evaluation of a convenience sample of 30 patients who received immediate-release nifedipine was done at Shands at UF from December 2000 to May 2001. This audit showed that immediate-release nifedipine was still being used for some adult patients with hypertensive urgencies, despite concerns about potential adverse effects. Based on these results, the P&T Committee has prohibited the use of immediate-release nifedipine in adult patients for hypertensive urgencies.

Immediate-release nifedipine was not removed from the *Formulary* because 2 reasonable uses were identified in the medication use evaluation. Approximately 30% of the use of immediate-release nifedipine was in the OB-GYN areas as a tocolytic. There are data to support the use of immediate-release nifedipine for tocolysis; however, it is still important to monitor these patients' blood pressure responses.

Immediate-release nifedipine was commonly used in pediatric patients for hypertensive urgencies. The safety concerns about immediate-release nifedipine in adults do not appear to be applicable to pediatric patients who have more resilient cardiovascular systems. A recent study published in the July issue of the *Journal of Pediatrics* showed that immediate-release nifedipine was effective, and no cardiovascular or neurologic adverse effects were noted—despite blood pressure reductions greater than 25% in a substantial number of the patients studied. These data justified the continued prudent use of nifedipine immediate-release in patients less than 18 years of age.

**POLICIES AND PROCEDURES**

# Restricting the promotion of restricted drugs

There are rules that drug manufacturers' sales representatives must follow to continue to be able to visit the hospital and promote their products. For example, "drug reps" cannot promote nonformulary drugs to housestaff, be in patient care areas, or leave promotional items (eg, pens, pads) in hospital areas—including all geographic boundaries of Shands at UF (eg, hallways, conference rooms).

The Pharmacy and Therapeutic Committee has approved a new restriction on the promotion of drugs for drug reps. Over the last several years, there has been an increasing number of restricted drugs. These drugs may be restricted by indication, location, or most commonly by medical service. These drugs are restricted because they have a limited, but important need. They may be particularly difficult to use and/or very expensive.

If these agents were nonformulary, they could not be promoted. However, by being in the *Formulary,* yet restricted, the promotion of these agents was not limited.

This policy has been changed. Now drug reps cannot promote restricted drugs in the hospital setting. Indiscriminate promotion of restricted drugs was not rational and was inconsistent with the logic that caused the P&T Committee to designate the drugs as restricted.

The Department of Pharmacy Services is responsible for enforcing the Guidelines for Drug Manufacturers' Sales Representatives. The Director of Pharmacy Services enforces infractions of this policy in a step-wise manner per infraction. This could lead to a suspension from the hospital for 3 to 6 months. The policy states that, at the Director's discretion, further disciplinary action could be taken following any infraction. If you notice this policy being violated, it is your responsibility to notify the Director of Pharmacy (265-0404).

***Drug information forum,*** *from page 1*

A reduction of 20 mm Hg or more is recommended by the Washington Manual. Blood pressure should be monitored every 15 minutes during the 1st hour, every hour during the 2nd hour, then every hour. A diuretic may be added after at least 6 hours. Sedation is an expected adverse effect associated with oral clonidine loading.

There are also published recommendations for the use of oral captopril in the management of hypertensive urgencies.[6] Captopril 6.25 to 25 mg (often given sublingually) is given as a "loading dose." If there is no response at 1 to 2 hours, another 6.25- to 25-mg dose of captopril may be given. The onset of captopril is expected to be rapid (ie, approximately 5 to 30 minutes). Whether the sublingual route makes a difference in the onset of action has not been adequately studied. The maximum response should be in 30 minutes to an hour and the duration of effect approximately 6 hours.

Oral labetalol has also been used in the treatment of hypertensive urgencies.[7] A dosage of 200 to 400 mg initially followed by a repeat dose in 4 hours has been recommended. Of the options discussed, oral labetalol has the slowest onset (as much as 2 hours) and peak effect (3 to 4 hours). The duration of effect is also approximately 6 hours.

Thus, there are several available alternatives to immediate-release nifedipine to treat hypertensive urgencies. The selection among clonidine, captopril, and labetalol should be based on patient-specific factors that require that these drugs be avoided. Clonidine should be avoided in patients with bradycardia, sick-sinus syndrome, cardiac conduction defects, and severe cerebrovascular disease. Captopril should be avoided in patients with bilateral renal artery stenosis. Labetalol should be avoided in patients with asthma, bradycardia, and 2nd- or 3rd-degree AV heart block.

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