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Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 20, 2002. 7 drugs were added in the *Formulary* and 3 drugs were deleted: 3 drugs were designated not available.

◆ ADDED

Brimonidine
(Alphagan-P® by Allergan)

Dorzolamide
(Trusopt® by Merck)

Insulin Aspart
(Novalog® by Novo Nordisk)

Latanoprost
(Xalatan® by Pharmacia)

Levobunolol
(Betagan® by Allergan)

Levonorgestrel
(Plan B® by Women's Capital Corporation)

Perflutren lipid microspheres
(Definity® by Bristol-Myers Squibb)

◆ DELETED

Caffeine + Ergotamine
(Cafergot® by Novartis)

Cromolyn Ophthalmic
(Crolom® by Bausch and Lomb)

Insulin Lispro
(Humalog® by Lilly)*

***Designated not available**

◆ NONFORMULARY, NOT AVAILABLE

Dorzolamide + Timolol
(Cosopt® by Merck)

Levalbuterol
(Xopenex® by Sepracor)

continued on next page

NONFORMULARY DRUG USE

New nonformulary system begins October 1st

Prescribers, nurses, pharmacists, and just about everybody else agree that nonformulary drugs can be a hassle. Paperwork, pages, telephone calls, and frustration are linked to nonformulary drugs.

Unfortunately, nonformulary drugs are here to stay. There are thousands of drugs on the market, and it is impractical for Shands at UF to have them all. Patients referred to Shands will be on drugs not listed in the *Formulary*. However, changes are being made to the current nonformulary system that will hopefully decrease some of the hassle associated with nonformulary drugs. The goal is to improve communication and decrease workload, but maintain the integrity of the formulary system.

Improved communication about nonformulary drugs is a major goal of the revision of the nonformulary system. When a nonformulary drug is prescribed, communication will now be done with stickers that become a permanent part of the chart. There will no longer be a nonformulary form. The form was initially designed as a means of collecting information, but it morphed into a communications tool—something it was not designed to do. The old nonformulary form was not a permanent part of the chart and there was a chance that it would be misplaced.

If a nonformulary drug is already available in the Pharmacy, it will be dispensed. There will be no paperwork for the prescriber. There will be an informational sticker placed in the chart notifying the prescriber that it may not be in stock the next time that it is ordered and explaining the method for requesting its addition in the *Formulary*.

If a nonformulary drug is not stocked, its "priority" will determine what happens next. High-priority drugs are medications that, if not given immediately, will result in a deleterious outcome for the patient (eg, pain management medication, antibiotic, intravenous hypotensive agents, medications necessary to maintain therapeutic blood levels, drugs used for coagulopathies, orphan drugs, investigational drugs). There will be an attempt to obtain these medications as soon as possible or to recommend an alternative that is listed in the *Formulary*. The prescriber and the patient's nurse will be contacted by telephone as soon as possible to resolve the situation.

Most nonformulary drugs will be "medium priority." This category is what nonformulary systems were really designed for. If an order is written for a medium priority nonformulary drug, a sticker will be placed in the chart with recommended alternatives. If there are no alternatives or the prescriber chooses not to take the recommendations, the prescriber must write a new order. The order should be titled "Nonformulary Justification." The nonformulary drug must be re-ordered and include the reason for use and why it is superior to the formulary alternative. Please state the expected duration of therapy. Expect that it will take 24 to 48 hours from the receipt of the Nonformulary Justification until the patient will receive the drug.

Low-priority drugs have little potential for harm if not administered, have questionable therapeutic benefit,

(continued on page 3)

INSIDE THIS ISSUE

Formulary update, *from page 1*

Brimonidine, **dorzolamide**, **latanoprost,** and **levobunolol** are all topical agents used in the treatment of glaucoma. All were considered for formulary addition based on non-formulary use.

Glaucoma is increased intraocular pressure that results from aqueous humor, which fills the chamber behind the cornea and in front of the lens. All glaucoma therapies either decrease production or increase outflow of aqueous humor.

There are many choices for the topical treatment of glaucoma; however, beta-blocking agents (eg, timolol) remain the drugs of choice and are still the most common initial therapy for most patients. Beta-blockers are very effective and are reasonably priced. The use of other agents should generally be reserved for patients who do not respond to a beta-blocker or who have concomitant medical conditions that make the use of beta-blockers illogical (eg, asthma).

Left untreated, glaucoma can result in damage to the optic nerve and loss of vision. A delay in the treatment of glaucoma could result in adverse patient outcomes.

Brimonidine is a selective alpha-agonist used in the treatment of glaucoma. Brimonidine decreases intraocular pressure by reducing aqueous humor production and increasing aqueous humor outflow. The labeling lists the dosage as 3 times a day (TID), but many clinicians have found that twice-daily dosing is equally effective.

About 25% of patients complain of dry mouth, eye redness, or stinging. Allergic reactions have occurred in about 10% of patients. Drowsiness occurs in approximately 10% of patients. Brimonidine has recently been reformulated to a lower strength (Alphagan® P vs Alphagan®), which may decrease the incidence of adverse reactions.

Dorzolamide is a specific topical inhibitor of carbonic anhydrase II, an isoenzyme of carbonic anhydrase in the eye that controls the production of aqueous humor. Dorzolamide 2% given 3 times a day for up to 1 year was shown to be as effective as timolol 0.5% twice a day and betaxolol 0.5% given twice a day in a double-blind, randomized comparison. A direct comparison between dorzolamide 2% and brinzolamide 1% (another topical carbonic anhydrase inhibitor) given twice daily found these 2 agents to have equivalent efficacy.

Dorzolamide is reported to cause ocular discomfort (eg, stinging, burning, blurred vision, itching, and tearing). Altered taste is a common adverse effect. Depression, anorexia, and dementia also have been reported with dorzolamide.

Cosopt® is a fixed combination of **dorzolamide and timolol.** This combination has been directly compared to the individual ingredients and there is no difference in efficacy. Therefore, Cosopt® has been designated non-formulary and not available and the individual ingredients should be substituted.

Latanoprost is an analog of prostaglandin F2-alpha. It is a selective agonist at the FP-subtype of prostaglandin receptors. Latanoprost increases the outflow of aqueous humor and reduces intraocular pressure.

There are several published studies and a meta-analysis that shows that latanoprost is at least as effective as topical timolol in the treatment of chronic glaucoma. Most of the published data comparing topical prostaglandins with another active ingredient is for latanoprost. The data for other prostaglandin analogs (ie, travoprost, unoprostone, and bimatoprost) are limited. There is 1 published trial that compares latanoprost and travoprost that found that these agents have similar efficacy.

Latanoprost, like all prostaglandin analogs, is generally well-tolerated. Mild conjunctival hyperemia, itching, burning, stinging, and dry eyes are reported. Iris pigmentation occurs with chronic use. Patients with multicolored eyes are most vulnerable. Latanoprost is also reported to increase eyelash growth and pigmentation.

Levobunolol is a nonselective topical beta-blocker that reduces the production of aqueous humor by inhibiting adrenergic processes within the ciliary body. Levobunolol has been shown to be equally effective as timolol; however, more adverse effects were reported in the levobunolol groups. Limited data suggest that levobunolol is more effective than betaxolol.

Levobunolol is associated with ocular discomfort (stinging, burning, and blepharoconjunctivitis). Rarely iridocyclitis and decreased corneal sensitivity have been noted. Systemic effects including headache, asthenia, and cardiovascular symptoms have been reported.

Insulin aspart and **insulin lispro** are rapid-acting insulin analogs that can be injected immediately before a meal. These short-acting agents have been associated with less postprandial and nocturnal hypoglycemia than regular insulin, but they have not been associated with better overall blood sugar control (ie, hemoglobin A1C) or better patient outcomes (ie, less retinopathy, nephropathy, neuropathy).

Insulin aspart is considered equivalent to insulin lispro on a unit-to-unit basis and it is considerably less expensive in both the inpatient and outpatient settings. Therefore, insulin lispro was deleted from the *Formulary* and insulin apart was added in the *Formulary.* Insulin lispro was designated nonformulary and not available. Prescribers of insulin lispro will be contacted for an order change to insulin aspart during their hospitalization.

Levonorgestrel is a synthetic progestin oral contraceptive. It is marketed in a special 2-dose package as an emergency contraceptive (ie, Plan B®). Emergency contraceptives are used in the inpatient setting for sexual assault victims.

Although Ovral® was the first agent used as an emergency contraceptive or "morning after pill," there are now commercially packaged emergency contraceptives.

Plan B® is 2 levonorgestrel 0.75-mg tablets: 1 tablet is given as soon as possible and the second tablet is given 12 hours later. The Plan B® package can be labeled and given to the patient upon discharge.

A literature review, including the ACOG Practice Bulletin:*Emergency Oral Contraception*, suggests that levonorgestrel is the preferred emergency contraceptive. The progestin-only method of emergency contraceptive produces less nausea and may be more effective than the combination oral contraceptive methods.

Perflutren lipid microspheres is the third diagnostic agent marketed to enhance echocardiography. Optison® (human albumin microspheres injectable suspension, octafluoropropane formulation), the second echocardiography contrast agent, was added in the *Formulary* August 1998.

Clinical trial data show that perflutren can improve suboptimal echocardiograms. There are no published studies that compare Definity® and Optison®. Definity® has a shorter duration of effect and repeat injections can be used.

The risk of adverse effects appears to be low with perflutren lipid microspheres. Concern about blood pressure changes and ECG changes were noted in the FDA's summary basis of approval, however.

Although Definity® is expensive, the improvement in diagnostic echocardiograms may be beneficial for some patients. The cost of Definity® will be offset by a decrease in inconclusive echocardiogram

results. Inconclusive echocardiograms could lead to other diagnostic procedures (nuclear studies) and increased associated costs. There is little cost difference between Definity® and Optison®.

Definity® was added in the *Formulary* for a 1-year evaluation. At that time, the criteria for the use of Definity® versus Optison® will be specified. The use of Definity® will be limited to diagnostic echocardiography.

Caffeine + ergotamine is an abortive treatment for migraine and cluster headaches. Although effective and relatively inexpensive, it has fallen out of favor compared with newer agents like the triptans. Cafergot® tablets and suppositories were deleted from the *Formulary* because of low use.

Cromolyn ophthalmic solution is a topical mast cell stabilizer that is used for allergic conjunctivitis. It is rarely used in the inpatient setting. Therefore, cromolyn ophthalmic was deleted from the *Formulary*.

Levalbuterol is the R-isomer of albuterol. It is used for the same indications as albuterol. This agent has recently been requested nonformulary and is a high-priority nonformulary drug. It is approximately 15-times more expensive than albuterol.

Levalbuterol is promoted as being a safer alternative to "racemic" albuterol. Claims include that the S-isomer works in opposition to R-albuterol, that the S-isomer is responsible for tolerance to albuterol, that the S-isomer increases airway hyperresponsiveness, that the S-isomer is responsible for the paradoxical bronchospasm seen with albuterol, and that the S-albuterol causes the systemic effects seen with albuterol. There are several well-done reviews that refute these possible issues and conclude that levalbuterol offers no advantage over albuterol. Therefore, the P&T Committee designated levalbuterol nonformulary and not available.

THERAPEUTIC DRUG MONITORING

Vancomycin dosing and monitoring in adults

Despite the lack of data supporting the practice, routine therapeutic monitoring of serum vancomycin concentrations continues to be done. The rationale for monitoring vancomycin concentrations (to improve efficacy and avoid toxicity) has been extrapolated from the aminoglycoside literature. However, the aminoglycosides and vancomycin do not exhibit the same pharmacodynamic properties.

Aminoglycoside bacterial killing of gram-negative bacteria is concentration-dependent and is more rapid and complete for gram-negative bacteria when peak concentrations of 10 times the MIC of the organism are achieved. This supports the rationale for using high-dose, "once-daily" aminoglycoside therapy and for monitoring peak concentrations when traditional aminoglycoside dosing is used.

Vancomycin, on the other hand, exhibits concentration-independent killing and bacterial killing is not enhanced in concentrations above 4 to 5 times the MIC of the organism.[1,2] In addition, unlike aminoglycosides which should be dosed on ideal or adjusted body weight, vancomycin should generally be dosed based on total body weight.[3]

The therapeutic range of vancomycin concentrations was initially established as peaks of 30 to 40 mcg/mL and troughs of 5 to 10 mcg/mL since the MIC of most susceptible organisms is well below 5 mcg/mL and toxicity occurred at concentrations above 30 to 40 mcg/mL. However, the risk of toxicity, such as nephrotoxicity and ototoxicity and its relation to vancomycin, has not been well established.

Ototoxicity has been reported in patients with serum concentrations in excess of 80 mcg/mL; however, some of these patients also received other agents that have been associated with ototoxicity (ie, erythromycin). Based on these reports of ototoxicity, vancomycin serum concentration monitoring became part of routine in clinical practice.

The nephrotoxicity of vancomycin has not been well-established since other confounding conditions (such as concomitant aminoglycoside use) were present in the majority of reported cases of nephrotoxicity.[4,5] Some of the toxicity of vancomycin has been attributed to impurities in earlier formulations of the drug. Due to the lack of established toxicity with vancomycin trough concentrations, many institutions, including Shands at UF, use a trough concentration range of 5 to 15 mcg/mL. It is unlikely that toxicity occurs with trough concentrations of up to 20 mcg/mL.

The most logical administration method for concentration-independent antibiotics is continuous infusion. However, this is often inconvenient and not necessary for antibiotics such as vancomycin that have longer half-lives and for which goal serum concentrations can usually be maintained with every 12-hour dosing in adults. Since achieving a target peak concentration at the site of the infection is not necessary and since serum peak and mean steady-state vancomycin concentrations can be predicted based on a single trough concentration, routine monitoring of peak concentrations is no longer recommended.[6]

(continued on next page)

Nonformulary drug use,
from page 1

or are expected to have no impact on the patient's clinical outcome if stopped. Prescribers will be strongly encouraged to change to a formulary alternative or stop these low-priority drugs. If a Nonformulary Justification is written for these drugs, they will be obtained within 96 hours.

Most orders for nonformulary drugs will be honored. There are nonformulary drugs that have been designated not available. These drugs do not have a "priority" and will not be obtained. Some nonformulary drugs will be automatically interchanged to a P&T-approved formulary alternative. If patients have their home medications, a specific order can be written for these medications that will allow them to take their own supply. The order must be specific, however, stating the drug, strength, and dosage. It must also specifying that the patient may use their own supply.

If you have any questions about the new nonformulary policy, please contact the decentralized pharmacy in your area.

A list of nonformulary priorities, nonformulary and not available drugs, and drugs that are therapeutically interchanged can be found on the Pharmacy website on the intranet at http://intranet.shands.org/pharm/menu.htm.

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Drug monitoring, *from page 3*

Many institutions use vancomycin-dosing nomograms to provide therapeutic mean steady-state vancomycin and trough concentrations without the need for routine serum concentration monitoring. The Anti-Infective Subcommittee evaluated published vancomycin nomograms and those used by other institutions. A simplified version of the Karam nomogram[7] was selected. Pocket cards with this nomogram are available from the decentralized pharmacies and at http://intranet.shands.org.pharm/vanconomogram.pdf.

This nomogram was prospectively evaluated in 240 patients. Clinical and microbiological outcomes were compared in patients who were dosed with the nomogram to those who were dosed and monitored by traditional pharmacokinetic equations (evaluated retrospectively) targeting a peak of 30 to 40 mcg/mL and a trough of 5 to 10 mcg/mL. The nomogram was developed using standard pharmacokinetic equations and published population pharmacokinetic parameters to provide a predicted trough concentration of 5 to 20 mcg/mL. Standard doses of 500 mg or 1000 mg were given at standard intervals of 8, 12, and 24 hours. The nomogram is based on actual body weight and the estimated creatinine clearance using the Cockcroft-Gault equation. A single trough serum concentration was drawn on day 5 of therapy and the regimen was adjusted as follows: > 20 mcg/mL, dose decreased by 50% for patients receiving 1 gram or the interval was increased (ie from 8 to 12 or 12 to 24) for patients receiving 500 mg; < 5 mcg/mL, interval decreased to next standard interval.[7]

The number of concentrations drawn per patient per day and the number of serum concentrations that resulted in a change in therapy were significantly fewer in patients whose doses were determined with the nomogram. There was no difference in clinical cure, improvement, failure, or microbiological cure between the 2 groups. There was no difference in the incidence of nephrotoxicity between the 2 groups. The incidence of nephrotoxicity in the patients who received vancomycin alone was 3.1% in the pharmacokinetic group and 8.6% in the nomogram group, but this was not statistically significant. Of the patients who had trough concentrations drawn (n=77), 94% had trough concentrations within the target range. Five patients had trough concentrations outside of the target ranging from 3.4 to 35.5 mcg/mL.[7]

Routine monitoring of vancomycin serum concentrations is not necessary. Despite this, vancomycin concentrations continue to be routinely ordered at Shands. Infectious Diseases physicians and clinical pharmacists no longer recommend vancomycin peak concentrations, except in extreme circumstances (ie, infections at sites that are more difficult to penetrate such as meningitis or endocarditis in patients who are not responding to therapy). Despite this recommendation, some clinicians continue to routinely order vancomycin peak and trough concentrations for all patients. The implementation of a simplified vancomycin dosing nomogram based on the patient's weight and estimated creatinine clearance may allow for substantial reductions in vancomycin serum concentration monitoring.

By Joanne J. Orrick, PharmD, BCPS

REFERENCES

1. Freeman CD, Quintilliani R, Nightingale C. Vancomycin therapeutic drug monitoring: is it necessary? Ann Pharmacother 1993;27:594-8.
2. Zimmerman AE, Katona BG, Plaisance KI. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. Pharmacotherapy 1995;15:85-91.
3. Penzak SR, Gubbins PO, Rodvold KA. Therapeutic drug monitoring of vancomycin in a morbidly obese patient. TDM 1998;20:261-265.
4. Cantu TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: Reappraisal of their clinical value. Clin Infect Dis 1995;25:228-34.
5. Farber BF, Moellering RC. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. Antimicrob Agents Chemother. 1983;23:138-41.
6. Andres, I, Lopez R, Leonor P, et al. Vancomycin monitoring: one or two serum levels? TDM 1997;19:614-9.
7. Karam CM, and McKinnon PS, Neuhauser MM, et al. Outcome Assessment of Minimizing Vancomycin Monitoring and Dosage Adjustments. Pharmacotherapy 1999;19:257-66.