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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 19, 2002. 6 drugs were added in the *Formulary*. 3 drugs were deleted. 3 drugs were designated not available.

◆ ADDED

Bivalirudin*
(Angiomax® by The Medicines Company)

Cidofovir*
(Vistide® by Gilead Sciences)

Nitrofurantoin macrocrystals
(Macrobid® by Proctor & Gamble)

Ofloxacin otic
(Floxin® Otic by Daiichi Pharmaceuticals Corp.)

Tenofovir
(Viread® by Gilead Sciences)

Voriconazole*†
(Vfend® by Pfizer)

***Restricted**
†Investigational: will be added when commercially available

◆ DELETED

Indocyanine green injection

Nitrofurantoin macrocrystals‡
(eg, Macrodantin®)

Sodium tetradecyl sulfate
(Sotredecol®)

‡Not available and interchanged to Macrobid®

◆ NONFORMULARY, NOT AVAILABLE

Hydromorphone PCA cartridges (except 0.2 mg/mL)

Morphine PCA cartridges (except 1 mg/mL)

(Article begins on page 2)

THERAPEUTIC DRUG MONITORING

Ordering and interpreting drug levels—What you can do to improve the results

In August of 1999, there were changes made in the drug level ordering system. These changes included implementing a new laboratory computer system and removing pharmacists from the process of scheduling drug levels. Since that time, there have been many frustrations with the system due to the complexity of the ordering process, unusable results, and the need to stick patients on multiple occasions to get clinically useful results.

An evaluation of the therapeutic drug level monitoring (TDM) process was conducted between November 2000 and January 2001. Drug levels ordered for vancomycin and aminoglycosides on the non-ICU floors were analyzed for appropriateness of ordering by clinicians, scheduling by the unit clerk or nurse, drawing by phlebotomy or nursing, and reporting of times in the Hospital Information System (HIS). A total of 86 drug level orders were evaluated.

The clinician ordering of the drug level was deemed incorrect or inappropriate for 35% of the drug levels. Inappropriateness was due to 27% vague orders (ie, "vanco level"), 37% clinically inappropriate orders (ie, vancomycin peaks or gentamicin peak and trough for once-daily dosing), and 37% unnecessary orders (ie, multiple vancomycin troughs).

The unit clerk or nurse scheduling of the drug levels was deemed inappropriate for 23% of the drug levels. This inappropriateness was due to 54% ordered as routine phlebotomy draws rather than timed phlebotomy draws, 41% ordered too early, 20% ordered for the wrong dose, 5% missed order, and 5% ordered without a physician order.

The majority of the levels, 71%, were drawn by nursing while 28% were drawn by phlebotomy/respiratory (respiratory assumes drug level draws between the hours of 9:00 am and 8:00 pm). The drawing of the levels was inappropriate for 43% of the levels. The inappropriateness of drawing was due to 54% drawn too late, 41% drawn too early, 3% drawn with the wrong dose, and 3% drawn through the line with residual drug remaining.

The prior dose, date, and time information in HIS was also evaluated for 59 of the drug levels. Almost half of the levels, 46%, had incorrect prior dose, date, and time information in HIS.

Each step in the TDM process is important to yield accurate and clinically useful drug levels. Drug levels that are drawn at incorrect times or that have incorrect times reported in HIS may cause clinicians to improperly change a patient's medication regimen.

A TDM Continuous Quality Improvement team has been meeting for over a year to evaluate the TDM process and provide recommendations for improvements. Each person involved in the TDM process needs to do his or her part to ensure accurate and clinically useful drug levels that will ultimately improve patient care and patient satisfaction. The table on page 4 provides recommendations for clinicians to improve the TDM process through appropriateness of drug level orders and proper interpretation of results. (Recommendations for improving the drug level scheduling and drawing are being addressed through other forums.)

(continued on page 4)

Bivalirudin is the 4th agent on the US market that has been used for therapeutic anticoagulation in patients with heparin-induced thrombocytopenia-thrombosis (HITT). Argatroban, danaparoid, and lepirudin also have been used for prophylaxis and/or treatment of thromboembolism in patients with HITT. These agents are currently listed in the *Formulary*.

Bivalirudin, which is also known as hirulog, is a synthetic bivalent analog of hirudin. Its anticoagulant effect is the result of direct thrombin inhibition, which is reversible and transient. The onset of anticoagulant effect is immediate following direct IV injection of bivalirudin. Bivalirudin therapy prolongs several coagulation assays, including the activated clotting time (ACT). Coagulation times return to normal approximately 1 to 2 hours after an infusion of bivalirudin is stopped.

The FDA-labeled indication for bivalirudin is for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). There are no published clinical trials that evaluate the use of bivalirudin as an anticoagulant in patients undergoing CABG or off-pump cardiopulmonary bypass. A review of the Cochrane database, PubMed, and Current Contents revealed no case reports of the use of bivalirudin for cardiopulmonary bypass. There are published reports for danaparoid, lepirudin, and argatroban.

There are data published that show that bivalirudin is at least as effective as heparin for anticoagulation in PTCA. It appears to cause less bleeding than heparin in PTCA. However, this was based on a post-hoc analysis and further research is needed.

Angiomax® is supplied as 250-mg vial of a lyophilized powder. This vial is 1st diluted with sterile water (5 mL) and then further diluted with D5W or NS to yield a final concentration of 5 mg/mL. The labeled dosage of bivalirudin [for use in PTCA] is a 1 mg/kg IV bolus followed by a 4-hour IV infusion at 2.5 mg/kg/hr. After the 4-hour infusion, an infusion of 0.2 mg/kg/hr can be continued for up to 20 hours. It was always used with aspirin in PTCA. Patients with decreased renal function will need to be monitored and the dosage decreased as needed.

When used for therapeutic anticoagulation in patients with HITT who are undergoing CABG, patients will be given a 0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/hr. The dosage will be adjusted to a target ACT of 300 to 350 seconds.

Bivalirudin is less expensive than most of the other options that have been used to anticoagulate patients with HITT who undergo CABG. A comparable course of heparin would cost less than $10; therefore, bivalirudin should be reserved for patients who cannot tolerate heparin. Based on the dosage used in the labeling for PTCA, bivalirudin costs approximately $325 to $650 for a day (ie, 1 to 2 vials). Since the dosage used in cardiopulmonary bypass will be based on ACTs, it is difficult to estimate the daily cost.

Bivalirudin was listed in the *Formulary*, but it will be restricted to patients who have been reviewed by the Hematology Service. This is important to document the diagnosis of HITT and to recommend dosing and monitoring of bivalirudin.

◆

Systemic cidofovir is extremely nephrotoxic. The black box warning in the product labeling states that cases of acute renal failure resulting in dialysis and/or contributing to death have occurred with as few as 1 or 2 doses of cidofovir.

Cidofovir is an antiviral agent with activity against cytomegalovirus (CMV) and other herpes viruses. Cidofovir is an acyclic phosphonate nucleotide analog similar to acyclovir and ganciclovir. Cidofovir contains a phosphate moiety that is highly stable to serum estrase cleavage. Therefore, cidofovir is not dependent upon intracellular activation for its antiviral activity.

Cidofovir suppresses cytomegalovirus (CMV) replication by the selective inhibition of viral DNA synthesis. Cidofovir has a labeled indication for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Off-labeled indications of cidofovir include the treatment of adenovirus, papilloma virus infections, CMV infections in transplant patients, and the treatment for smallpox in the event of exposure to biological warfare.

Cidofovir has been used non-formulary to treat laryngeal papilloma. Laryngeal papilloma is a rare viral disease characterized by multiple benign growths in the middle and lower respiratory tract. There are case reports of the successful use of cidofovir by intralesional injection to treat laryngeal papilloma.

Adenovirus is a severe infection that occurs in bone marrow transplant recipients. Currently there are no medications with a labeled indication for the treatment of adenovirus infections. There are some case series that show that cidofovir may be helpful in patients with this severe infection. Although cidofovir is indicated only for cytomegalovirus (CMV) infections in HIV patients, its use may include treatment of adenovirus infections.

Systemic cidofovir is extremely nephrotoxic. The black box warning in the product labeling states that cases of acute renal failure resulting in dialysis and/or contributing to death have occurred with as few as 1 or 2 doses of cidofovir. Administration of cidofovir requires a specific administration technique that includes administration with probenecid and sufficient hydration. Therefore, safety is an important issue and supports the need to restrict this agent.

Cidofovir was added in the *Formulary* for systemic use in the treatment of adenovirus infections and resistant CMV infection and by intralesional injection for the treatment of laryngeal papillomas. The systemic use of cidofovir will be restricted to patients who have been approved by the Infectious Diseases Service or by Dr. Wingard in the Bone Marrow Transplant Unit.

Macrobid® is a twice-a-day dosage form of the urinary tract anti-infective nitrofurantoin. Nitrofurantoin is a synthetic, nitrofuran-derivative antibacterial agent. Nitrofurantoin is commercially available as capsules containing macrocrystals (**Macrodantin®**) and as Macrobid®, which is a dual-release capsule that contains 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate. Since Macrobid® is dosed twice daily, as compared with Macrodantin®, which is dosed 4 times daily, many clinicians prefer the twice-daily product.

Nitrofurantoin is used to treat urinary tract infections. It should not be used to treat systemic infections, since therapeutic plasma concentrations are not achieved.

Macrobid® was listed in the *Formulary* for the treatment of urinary tract infections due to susceptible organisms and Macrodantin® capsules were deleted from the *Formulary* and deemed non-formulary and not

available. Macrobid® will be automatically interchanged for Macrodantin® based on the following.

Order	Substitution
Macrodantin® 50 mg qid	Macrobid® 100 mg bid
Macrodantin® 100 mg qid	Macrobid® 100 mg bid
Macrodantin® 100 mg bid	Macrobid® 100 mg bid
Macrodantin® 50 mg qd	Macrobid® 100 mg qd
Macrodantin® 100 mg qd	Macrobid® 100 mg qd

These interchanges will be noted in the Orders section of the chart as P&T-Authorized changes.

Ofloxacin otic is the only otic dosage form of a fluoroquinolone. Before ofloxacin otic became available, some prescribers used ciprofloxacin ophthalmic in the ear, but patients complained of stinging with this product. Further, there is concern of medication errors when an ophthalmic product is administered in the ear.

Ofloxacin, like other fluoroquinolones, inhibits bacterial DNA topoisomerase in susceptible organisms. Ofloxacin is active against most gram-negative aerobic bacteria. It is also active against many gram-positive aerobic bacteria. It is less active versus gram-positive compared with gram-negative organisms.

Ofloxacin otic solution is used for the treatment of bacterial otitis externa, chronic suppurative otitis media (CSOM) with perforated tympanic membranes, and acute otitis media with tympanostomy tubes by susceptible organisms. It is usually well-tolerated; however, local reactions at the site of instillation and earache may occur in 3% or less of patients. Taste perversion following instillation of ofloxacin otic solution has been reported in 7% of patients with non-intact tympanic membranes. Pruritus has occurred in up to 4% of patients receiving ofloxacin otic solution

Prior to administration, ofloxacin otic solution should be warmed by holding the bottle in the hand for 1 to 2 minutes, since the instillation of a cold solution into the ear canal can cause dizziness. The usual dosage is 5 to 10 drops in each ear twice a day.

Ofloxacin otic is an alternative to Cortisporin® otic, which is already listed in the *Formulary*. Ofloxacin may be preferred in patients with perforated tympanic membranes and tympanostomy tubes due to the potential for otoxicity of the neomycin in Cortisporin®.

Tenofovir disoproxil fumarate is a nucleotide reverse transcriptase inhibitor. It is a prodrug of tenofovir, which is an analogue of adenosine monophosphate. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir diphosphate, which competitively inhibits the reverse transcriptase enzyme in the human immunodeficiency virus. Tenofovir is indicated for the treatment of HIV infection in combination with other antiretroviral agents in adults.

Tenofovir undergoes mainly renal elimination and is contraindicated in patients with a creatinine clearance (CrCl) < 60 mL/min. Unlike the protease inhibitors and non-nucleoside reverse transcriptase inhibitors, tenofovir does not interact with drugs that are metabolized by the cytochrome P450 system.

Since tenofovir has been studied only as part of salvage regimens in patients who have failed other therapies, the latest *Guidelines on the Use of Antiretroviral Agents by the Department of Health and Human Services* did not make a recommendation on the use of tenofovir as part of initial antiretroviral regimens.

Tenofovir was added in the *Formulary* because it is used in regimens for patients who have failed other therapies. Due to differences in resistance patterns, patients admitted to the hospital can continue their outpatient antiretroviral regimens.

Voriconazole is an investigational agent that was reviewed proactively because of the potential for misuse once the FDA approves it. It is currently still an investigational drug; however, it is anticipated that it could be marketed within the next few months.

Voriconazole is a second generation synthetic derivative of fluconazole. It is classified as a triazole antifungal. Voriconazole joins the class of azole antifungals along with fluconazole, itraconazole, and ketoconazole. Voriconazole has a broader spectrum of activity against Aspergillus species. It also causes more significant drug interactions, including significant interactions with transplant medications. Although voriconazole is not yet on the market, clinical trials of voriconazole document its use in invasive Aspergillus infections and as empiric antifungal treatment in febrile neutropenic patients.

The adverse effect profile for voriconazole includes the unique adverse effect of reversible blindness. Patients describe this reaction as a bright flashing light. Patients should be warned of this potential effect, since it is estimated that it occurs in roughly 25% of all patients who receive it. Thus far, this is a temporary effect and is not permanent. However, it has only been studied in approximately 1000 patients and the true adverse effect profile has not been determined.

The treatment of documented aspergillosis appears to be the most clearly defined use of voriconazole. Uses in nontransplant patients and for other fungal diseases (eg, candida) are not well-defined at this time. Voriconazole was added in the *Formulary* for a 6-month evaluation period, beginning when it is marketed. It will be restricted to patients who have been approved by the Infectious Diseases Services or Dr. Wingard in the Bone Marrow Transplant Unit.

Indocyanine green injection has been used as a diagnostic agent to determine cardiac output, liver blood flow, and in ophthalmologic angiography. None has been used at Shands at UF in the last 2 years. It was deleted from the *Formulary* based on this lack of use.

Sodium tetradecyl sulfate is no longer available. Therefore, it will be deleted from the *Formulary*. Sodium tetradecyl sulfate (Sotredecol®) was a parenteral sclerosing agent used for esophageal varices, hemorrhoids, and varicose veins of the legs. Sodium morrhuate is the sclerosing agent that remains listed in the *Formulary*.

The concentrations of **hydromorphone PCA cartridges** and **morphine PCA cartridges** were standardized. Having multiple concentrations of morphine and hydromorphone PCA cartridges can lead to medication errors and, possibly, adverse patient outcomes. Rather than produce nonstandard concentrations, increasing the basal rate of opioid is preferred.

Therefore, 1 standard morphine PCA cartridge (1 mg/mL) and 1 standard hydromorphone PCA cartridge (0.2 mg/mL) are listed in the *Formulary*. All other concentrations are designated nonformulary and not available.

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TIPS FOR CLINICIANS TO IMPROVE TDM

Recommendation	Comments
Do not order drug levels more than 24 hours in advance of the desired level	■ Medication administration times may change ■ Patient's status may change (ie, nursing line draw versus phlebotomy venipuncture)
Avoid vague drug level orders	■ Instead of ordering "vancomycin level," order "vancomycin trough"
Avoid incomplete drug level orders	■ Instead of ordering "vancomycin trough," order "vancomycin trough prior to 10 am dose" ■ Instead of ordering "vancomycin random," order "vancomycin random at 6 am"
Avoid clinically inappropriate drug levels	■ Vancomycin peak levels not routinely indicated (except for documented meningitis) ■ Aminoglycoside peak and trough levels are not appropriate for "once-daily" dosing – order an 8- to 10-hour post-dose random level instead
Avoid unnecessary drug levels	■ Avoid unnecessarily repeating drug levels ■ Avoid obtaining daily vancomycin random levels for patients in renal failure ■ Avoid routinely obtaining daily drug levels if the patient is on a stable dosing regimen
Interpret results carefully	■ Always double check the medication administration record (MAR) prior to changing a patient's regimen ■ Consult a pharmacist for assistance in interpreting results – many times the results can be extrapolated and the patient may not require another needlestick

By Joanne J. Orrick, PharmD, BCPS and Erin Totleben, PharmD