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SHANDS at the University of Florida

April 2004

Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 16, 2004. 3 drugs were added in the *Formulary* and no drugs were deleted. Therapeutic interchanges were approved for 3 products.

◆ ADDED

Docetaxel
(Taxotere® by Aventis)*

*Restricted to credentialed chemotherapy prescribers

Levobupivacaine
(Chirocaine® by CellTec)**+

**Restricted to use in regional blocks only
+Not currently available

Pentostatin
(Nipent® by SuperGen)*

◆ DELETED

None

◆ THERAPEUTIC INTERCHANGES

Albuterol (eg, Proventil®) MDI by **VHC** for **Albuterol Nebs**

Ipratropium (Atrovent®) MDI by **VHC** for **Ipratropium Nebs**

Albuterol + Ipratropium (Combivent®) MDI by **VHC** for **Albuterol + Ipratropium Nebs**

MDI = metered-dose inhaler

VHC = valved holding chamber (eg, AeroChamber®)

Nebs = solution for inhalation via a nebulizer

Docetaxel is a chemotherapeutic agent similar to paclitaxel, which has been listed in the *Formulary*.

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MEDICATION USE EVALUATION

Ongoing monitoring recommended for NovoSeven®

NovoSeven® is a recombinant version of the human clotting factor VIIa. Recombinant factor VIIa activates the conversion of factor X to Xa and IX to IXa. Factor Xa, in complex with other factors, converts prothrombin to thrombin. This leads to a hemostatic plug by converting fibrinogen to fibrin. Factor VIIa also activates factors IX and X on the surface of platelets to restore the formation of thrombin. This contributes thrombin to the fibrin network, even in the absence of an optimal initial platelet plug.

NovoSeven® monitoring will be ongoing. There is tremendous potential for misuse. The cost of a single day of therapy can be thousands of dollars and there are limited data to assess the cost benefit of this treatment.

NovoSeven® has a labeled indication for the treatment or the prevention of hemorrhage in patients with Hemophilia A or Hemophilia B who have inhibitors to Factor VIII or Factor IX. Because of its effects in the clotting cascade, it has been used off-label for a variety of bleeding conditions (eg, von Willebrand's disease, reversal of oral anticoagulant overdose, trauma, excessive surgical blood loss in patients unable to form clotting factors [eg, liver transplantation]).

NovoSeven® has been shown to be effective in the treatment of hemophilia in patients with elevated anti-human and anti-porcine inhibitor titers. The major safety concern is the risk of thrombosis.

Most data for the off-labeled use of NovoSeven® are case reports and case series. These uses are often difficult to study in randomized controlled trials. Data show that NovoSeven® effectively stops bleeding; however, this often does not prevent death in these patients.

Since NovoSeven® is extremely expensive, the off-label use of this drug has been monitored closely. Therefore, an audit of NovoSeven® use was done in adults and children at Shands at UF. 20 patients were evaluated in each arm of the audit. The data showed that NovoSeven® is used only for a small number of patients with hemophilia and inhibitors.

Most of the off-labeled use of NovoSeven® was for uncontrolled bleeding with coagulopathies despite multiple blood transfusions (ie, 95% adults and 29% pediatrics). These uses could be justified since 50% of the patients who had refractory bleeding responded (ie, stopped bleeding). However, there were inconsistencies in the dosages used.

In pediatric patients, nearly half of the NovoSeven® used was for patients with liver failure and coagulopathies. These patients were usually being prepared for liver transplantation. Once the patient has a new liver, their coagulopathies resolve. The use of

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INSIDE THIS ISSUE

Formulary update, *from page 1*
Docetaxel functions as an inhibitor of mitosis, resulting in cell death.

Docetaxel has FDA-labeled indications for the treatment of locally advanced or metastatic breast cancer after failure of previous chemotherapy or in combination with capecitabine (Xeloda®) in women previously treated with anthracyclines. Docetaxel also has a labeled indication for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC) after failure of prior treatment containing platinum agents and for the treatment of unresectable, advanced, or metastatic NSCLC in combination with cisplatin in chemotherapy-naïve patients.

The efficacy of docetaxel alone and in various combinations with other agents in treating these progressive diseases has been demonstrated in a number of randomized clinical trials. Docetaxel also has been used for the treatment of head, neck, ovarian, and prostate cancer as well as malignant melanoma.

A frequent toxicity seen with docetaxel therapy is neutropenia. Fluid retention is another potential serious adverse event. These effects are manageable with dose reduction and premedication with corticosteroids.

Docetaxel is contraindicated in patients whose AST and/or ALT are 1.5 times the upper limit of normal with a simultaneous alkaline phosphatase greater than 2.5 times the upper limit of normal. If a patient has a platelet count lower than 100,000 cells/mm3, therapy with docetaxel is also contraindicated. Precaution must be used if docetaxel is used concomitantly with other medications metabolized via the cytochrome P450 3A4 or 3A5 isoenzymes.

Like all cytotoxic chemotherapeutic drugs, docetaxel prescribing is limited to credentialed chemotherapy prescribers.

Levobupivacaine is the S-isomer of bupivacaine. It was developed after enantioselectivity was observed for the adverse effects of levobupivacaine. Levobupivacaine was originally reviewed for addition in the *Formulary* in June of 2000. It was not added in the *Formulary* at that time because published data did not support its improved safety or efficacy compared with bupivacaine. However, this was based on use as a local anesthetic and for epidural administration.

Levobupivacaine was re-reviewed for use in regional nerve blocks because safety is an issue. Accidental intravascular injection can occur. Large volumes (~30 mL) of anesthetics are injected at 1 time when local anesthetics are used for regional blocks.

The published information supporting the decreased toxicity observed with levobupivacaine consists of animal data and case reports. However, the likelihood of better evidence in this scenario is unlikely.

Levobupivacaine was added in the *Formulary* based on its theoretical advantages over bupivacaine. For example, levobupivacaine may be less likely to result in a cardiac arrest if an inadvertent intravascular injection occurs. The cost of treating a cardiac arrest would offset the increased pharmaceutical expenditures. Levobupivacaine is 6.5 times more expensive than bupivacaine.

Although levobupivacaine was added, it has been unavailable since November 2003. The manufacturer is currently looking for another distributor for the product. It will be available for use at the Florida Surgical Center and the Anesthesia Block Room when it becomes commercially available.

Pentostatin is a purine analog cytotoxic chemotherapeutic agent similar to fludarabine and cladribine. These agents have been shown to produce responses in a variety of incurable lymphoproliferative disorders. Among all the indolent lymphoproliferative diseases, chronic lymphocytic leukemia (CLL) accounts for 25% of all leukemias and is the most common form of lymphoid malignancy. It is currently considered an incurable disease. The goal of treatment is to alleviate symptoms and prevent life-threatening complications.

Conventional therapy with oral alkylating agents such as chlorambucil with or without corticosteroids produces partial responses in most patients, but rarely induces complete response. Since the late 1980s, newer purine analogs, such as fludarabine, have overtaken alkylating agents as first-line therapy for CLL due to their superior efficacy.

When patients are treated with combinations of fludarabine and alkylating agents, severe myelosuppression is the major dose-limiting toxicity. This leads to unacceptable toxicity, including prolonged pancytopenia with consequent infectious morbidity and mortality.

Of the purine analogs active in CLL, pentostatin appears to be the least myelosuppressive. It may offer an option in patients with lymphoproliferative disorders who have been heavily pre-treated with other purine analogs. Since myelosuppression is often the dose-limiting toxicity of alkylating agents, it is postulated that combination therapy with pentostatin, alkylating agents, and/or monoclonal antibodies is an approach to treatment of patients with CLL without prohibitive toxicity to normal tissues.

Pentostatin was added in the *Formulary* because of its lower incidence of myelosuppression compared with other purine analogs and its proven clinical activity against fludarabine-refractory CLL. Pentostatin is restricted to credentialed chemotherapy prescribers.

Albuterol metered-dose inhaler (MDI) administered by a **valved-holding chamber (VHC),** eg, AeroChamber®, will now routinely be interchanged for **albuterol nebulizations (nebs).** This interchange will also apply to **ipratropium MDI** by **VHC** for **ipratropium nebs** and the combination of **albuterol + ipratropium MDI** by **VHC** for **albuterol + ipratropium nebs**. Like all other therapeutic interchanges, this interchange will be noted in the chart as a "P&T-Authorized Interchange." In October 2003, the P&T Committee approved a policy that allowed therapeutic interchange of albuterol MDI by VHC for nebulized drug in ventilated patients in the SICU. This interchange now applies throughout the hospital.

There is strong evidence in both children and adults that inhaled drugs administered by MDI via a VHC are at least as good as nebulized drug. A study done more than 10 years ago in the Shands at UF Emergency Department showed that albuterol MDIs were as effective as nebulized albuterol for acute exacerbations of asthma in children and adults. A Cochrane systematic review clearly demonstrated the benefits of MDI over nebulized administration for the treatment of asthma. Also, studies have shown that MDIs are as effective as nebulized drug in COPD. Not only is the MDI route of administration as effective as nebulization, but also it is associated with fewer systemic adverse effects (eg, tachycardia).

This interchange will decrease the amount of time that a respiratory therapist takes to administer each dose. Other benefits of this interchange include improved patient training on how to use MDIs with VHCs. Respiratory therapists will educate patients (or their families) on how to use these devices. Also, patients will be able to take their VHC home with them for use in the outpatient setting. The administration of each MDI dose will be documented on the medication administration record (MAR), which is also an advantage.

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ANTI-INFECTIVE STEWARDSHIP

Vancomycin guidelines for use

Vancomycin-resistance is increasing, particularly in teaching hospitals. Vancomycin-resistant enterococcus (VRE) is the predominant vancomycin-resistant organism, although other resistant organisms have been reported (eg, vancomycin-resistant *Staphylococcus aureus*).

There is strong evidence linking the development of VRE to antibiotic exposure. Most patients receiving oral vancomycin for *Clostridium difficile* will become colonized with VRE. VRE development is associated with hospitalized patients who have been previously exposed to vancomycin. VRE spreads by self-contamination, patient-to-patient transmission via healthcare workers, and the colonization of environmental surfaces.

There has been a steady increase in vancomycin consumption over the last few years. Over 10% of the patients at Shands at UF receive vancomycin.

In order to limit the development of VRE, the Anti-Infective Stewardship Program will be targeting the overuse of vancomycin. The first step in this process is the development of guidelines for appropriate use. These guidelines will be used for educational purposes and for follow-up with vancomycin prescribers. The guidelines that were endorsed by the P&T Committee follow the Centers for Disease Control's recommendations. Before these guidelines are implemented, discussions will occur with the primary medical services affected by these changes to ensure all pertinent issues have been addressed.

Vancomycin use is considered appropriate for the following indications:

- Treatment of serious infections caused by beta-lactam resistant gram-positive organisms (eg, methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis*, ampicillin-resistant enterococcus).
- Treatment of infections caused by gram-positive organisms in patients who have serious allergies (eg, anaphylaxis, laryngeal edema, or urticaria) to beta-lactam antimicrobials.
- Treatment (ie, oral vancomycin) of patients who have failed metronidazole therapy for antibiotic-associated colitis.
- Empiric treatment of meningitis until gram-stain or culture results are available.
- Prophylaxis for major surgical procedures involving implantation of prosthetic materials in patients who have been hospitalized for greater than 48 hours.

Situations when vancomycin should not be used include the following:

- Treatment in response to a single blood culture for coagulase-negative staphylococcus, if other blood cultures taken during the same time frame are negative.
- Primary treatment of antibiotic-associated colitis.
- Empiric therapy for febrile neutropenia, unless initial evidence indicates that the patient has an infection caused by gram-positive organisms.
- Continued empiric therapy (ie, greater than 72 hours) for presumed infections in patients whose cultures are negative for beta-lactam resistant gram-positive organisms.
- For the eradication of MRSA colonization.
- For selective decontamination of the digestive tract.
- Use of vancomycin topical irrigation or application.
- Routine surgical prophylaxis in patients without life-threatening allergies to beta-lactam antimicrobials.

Following 48 to 72 hours of vancomycin therapy, a clinical pharmacist will evaluate each vancomycin order for compliance with the guidelines. The pharmacist will assist in streamlining therapy based on culture and sensitivity reports. Therapy not meeting guidelines should be stopped.

Prudent use of vancomycin along with appropriate infection control procedures should help stabilize vancomycin resistance.

Medication use eval, *from page 1*
NovoSeven® prevented excessive bleeding during transplantation surgeries.

The results of this audit suggest the use of NovoSeven® has not been excessive, but there is room for improvement. Use at Shands at UF is consistent with reports from other centers. However, many of the patients who received this drug did die. It is unclear how to determine the "success" of the use of NovoSeven®, when the ultimate outcome of the patient is often poor.

NovoSeven® monitoring will be ongoing. There is tremendous potential for misuse. The cost of a single day of therapy can be thousands of dollars and there are limited data to assess the cost benefit of this treatment.

Specific criteria for use (eg, indications, dose, and duration) will be developed for the various off-label uses of NovoSeven®. Also, the formation of a NovoSeven® review committee is being considered. This committee would be an expert panel of interested faculty who want to promote the responsible use of this resource. Off-label uses and dosages not meeting criteria would be reviewed.

Restricting the use of a drug like NovoSeven® is difficult to operationalize. Many patients receiving NovoSeven® for off-label indications (ie, uncontrolled bleeding) cannot tolerate the delay of an administrative approval procedure.

Formulary update, *from page 2*
The following dosage conversions will be used.

Nebulized Drug/Dose	MDI + VHC/Mouthpiece	MDI + VHC/Mask
Albuterol 2.5 mg	Albuterol 4 puffs	Albuterol 6 puffs
Ipratropium 0.5 mg	Ipratropium 4 puffs	Not recommended
Albuterol 2.5 mg + Ipratropium 0.5 mg	Combivent® 4 puffs	Not recommended

There will be exceptions when interchange will not occur. For example, patients must be able to perform a 10-second active breath hold and use the VHC. The interchange will be automatic, but prescribers can note in their original order to not interchange to MDIs.

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MEDICATION USE EVALUATION

Streamlining & empiric alternatives for fluoroquinolones

Fluoroquinolone antibiotics have been on the US market since 1987. The number of fluoroquinolones and the amount of use of this category of antibiotics has dramatically increased over the last decade. The popularity of these agents can be attributed to their broad spectrum of action, extensive penetration into infected tissue, and convenient dosage regimens.

Ciprofloxacin's popularity is attributed, in part, to its activity against gram-negative organisms, particularly *Pseudomonas aeruginosa*. The newer fluoroquinolones (eg, levofloxacin, gatifloxacin) are promoted for their extended gram-positive activity (eg, *Streptococcus pneumoniae*).

As with all antibiotics, extensive use (and misuse) has resulted in the development of resistant organisms. Therefore, the use of these agents must improve. Fluoroquinolones are expensive and there are opportunities to use alternative agents and/or streamline therapy to more specific antimicrobial agents.

Ciprofloxacin and gatifloxacin are the primary fluoroquinolones in the *Formulary*. Levofloxacin is restricted (ie, requires ID approval) and is rarely used. Increased use of these agents has led to the development of resistant bacteria at Shands at UF. This audit evaluated the current prescribing practices for ciprofloxacin and gatifloxacin and identified potential areas for improvement.

105 orders for ciprofloxacin and gatifloxacin were evaluated from February 1, 2004 to February 15, 2004. 79 orders (75%) were for ciprofloxacin and 26 (25%) were for gatifloxacin.

Most of the ciprofloxacin orders (81%) were for urinary tract infections (UTIs). Other infections treated with ciprofloxacin include intra-abdominal infections, pneumonias, and other miscellaneous infections. All gram-negative organisms isolated from the urine, except 1, were sensitive to ciprofloxacin. However, in most instances, the organisms were sensitive to other antibiotics (eg, cotrimoxazole, ampicillin, nitrofurantoin). This suggests streamlining or alternative empiric selection of antibiotics (eg, cotrimoxazole for uncomplicated UTIs) is possible.

Ciprofloxacin was occasionally used as part of combination therapy for suspected or documented multi-drug resistant organisms. This use is controversial. Empiric use of ciprofloxacin as part of a combination regimen in a severely ill patient may be warranted, but therapy should be tailored to a single agent once cultures and sensitivities are known.

Half of the gatifloxacin orders (50%) were for respiratory infections (ie, pneumonia, sinusitis, and COPD exacerbation). A few patients were treated for skin & soft tissue infections, intra-abdominal infections, and UTIs. There are also opportunities for streamlining gatifloxacin use.

This audit showed that fluoroquinolones are used extensively at Shands at UF, which is consistent with other institutions. There are opportunities to decrease use, especially with ciprofloxacin for UTIs. Based on the results of this audit, the Antibiotic Stewardship Program will first focus on education and then consider streamlining as workload permits.

Initial therapy for uncomplicated UTIs (ie, cystitis) should be cotrimoxazole for most patients without a sulfonamide allergy. A complicated UTI (eg, pyelonephritis, urological obstruction, presence of a Foley catheter) is a reasonable indication for ciprofloxacin; however, therapy should be streamlined within 48 to 72 hours based on culture and sensitivity reports.