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FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 21, 2006. 4 products were added in the *Formulary* and 2 were deleted. 3 products were designated nonformulary and not available.

◆ ADDED

Erlotinib
(Tarceva® by Genentech)*

Irinotecan
(Camptosar® by Pfizer)*+

Pemetrexed
(Alimta® by Eli Lilly)*+

Venlafaxine Immediate-release
(Effexor® by Wyeth)

**Restricted to Oncology prescribers*
+Requires Pharmacy Administration approval for inpatient use

◆ DELETED

Enflurane (Ethrane® by Baxter)**

Insulin Zinc Suspension, Human
(Novolin® L by Novo Nordisk)**

***Nonformulary and Not Available*

◆ NONFORMULARY AND NOT AVAILABLE

Insulin Zinc Suspension
(various)

Several chemotherapy agents have not been listed in the *Formulary* because they are used primarily for the outpatient treatment of cancers. However, there are situations occasionally when these agents need to be administered in the inpatient setting. Usually this occurs when patients are admitted for another medical problem at the time when their scheduled outpatient therapy is due. There are also rare instances when patients require special monitoring during their treatment.

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MEDICATION ERROR PREVENTION

Problems for pediatric patients: What are we doing to prevent medication errors?

Medication errors have received quite a bit of attention and are a concern for all healthcare providers. Reports such as *To Err Is Human,* published by the Institute of Medicine, have brought attention to the importance of recognizing and preventing the medication errors that are occurring in hospitals today. These errors are especially concerning in the pediatric population due to their increased vulnerability to medication errors.

There are several reasons children are at increased risk for medication errors. These reasons include age-related changes in pharmacokinetic parameters (eg, volume of distribution and clearance); lack of appropriate dosage forms and concentrations; need for precise measurement of doses; and, lack of evidence regarding the appropriate doses, efficacy, and safety of medications in pediatric patients.[1]

A recent study assessing medication errors and adverse drug events in pediatric inpatients reported a similar incidence in pediatric and adult patients. However, this study also reported that *potential* adverse drug events occurred 3 times more often in pediatric patients when compared to adults.[2] The study was conducted in 1120 pediatric patients admitted to 2 academic medical centers over 6 weeks. Of the 616 medication errors found in the study, dosing errors were the most common (28%). The majority of medication errors (74%) occurred at the physician ordering stage. The strategies judged to be the most successful at preventing medication errors were computerized physician order entry (CPOE) and a ward-based clinical pharmacist.

Many strategies for the prevention of medication errors have been proposed.[2,3] These include technological advances, such as medication and patient barcoding, dose-checking software, and CPOE. These interventions may be effective in reducing error rates but are costly and require time to implement.

There are simpler means of avoiding medication errors that can be immediately incorporated into practice. These include avoiding the use of banned abbreviations, writing medication orders in a legible format, avoiding the use of terminal zeros following a decimal point, and utilizing a leading zero in front of a decimal point.

Another easy way to avoid medication errors, especially in pediatric patients, is to include the patient's weight on every order sheet. This allows other health care professionals, such as pharmacy and nursing staff, to double check doses using an accurate patient weight.

Calculation errors have been reported as 1 of the top 10 causes of medication errors in pediatric patients. The majority of medications used in pediatrics are dosed based on weight or body surface area, which necessitates calculations to provide the appropriate dose. An example of how a calculation error could occur is illustrated by the dosing of intravenous clindamycin. The typical dosing for this medication in pediatric patients is 40 mg/kg/day divided every 6 to 8 hours. In a 10 kg patient this equals 100 mg IV every 6 hours. A common mistake is to forget to divide the total daily dose by the number of

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INSIDE THIS ISSUE

Formulary update, *from page 1*

When these rarely-used chemotherapy agents are needed for inpatient use, they have to be specially obtained. Agents not listed in the *Formulary* are not stocked. Because this can result in delays in treatment, there has been an effort to review these agents and list them in the *Formulary.* Drugs are listed in the *Formulary* when there is a justification for their use, they can be stocked, and they need to be readily available.

This month, 3 chemotherapeutic agents were added in the *Formulary* (ie, erlotinib, irinotecan, and pemetrexed). Like all cytotoxic chemotherapy, credentialed chemotherapy prescribers must prescribe these agents using the Chemotherapy Order Form.

There will also be pharmacy administrative approval of the parenteral agents (ie, irinotecan and pemetrexed) to prevent shifting patients who could be treated as outpatients to the inpatient setting.

In some cases, administering these agents as inpatients is less expensive to patients (eg, less co-pays). However, inpatient reimbursements do not adequately cover expenses. Bed demand is too high for outpatient treatments to be shifted to the inpatient setting.

Erlotinib is an oral epidermal growth factor receptor tyrosine kinase inhibitor. Epidural growth factor is over-expressed on the cell surface of cancer cells. Although the mechanism of action is not known, erlotinib is thought to inhibit tumor growth and angiogenesis.

Erlotinib has a labeled indication as monotherapy for the treatment of patients with locally advanced non-small cell lung cancer (NSCLC) after failure of at least 1 prior chemotherapy regimen. This indication is based on its survival benefit demonstrated in a phase III randomized, placebo-controlled clinical study.

Erlotinib also has a labeled indication for use in combination with gemcitabine for locally advanced, unresectable pancreatic cancer. Evidence to support this indication comes from a multi-center, double-blinded, placebo-controlled, randomized phase III trial. Erlotinib showed a slight, but statistically significant, survival benefit in patients with locally advanced, unresectable metastatic pancreatic cancer.

Erlotinib has also been used off-label in combination with bevacizumab for metastatic renal cell carcinoma.

Erlotinib is generally well-tolerated, with rash and diarrhea being the most common adverse effects. The oral route of administration is an advantage for this agent. A 30-day supply of erlotinib costs around $1400 to $1600.

Irinotecan is a cytotoxic chemotherapy agent that belongs to a class of topoisomerase I inhibitors. It has a labeled indications for first-line therapy for treatment of colorectal cancer along with 5-fluorouracil (5-FU) and leucovorin (LV) and for single agent treatment of metastatic colorectal cancer that has recurred or progressed after 5-FU-based therapy.

As a first-line therapy for treatment of metastatic colorectal cancer, multiple phase III trials have shown significant improvements in overall response rates and median overall survival when irinotecan is used in combination with 5-FU/LV therapy and targeted therapy (bevacizumab) as compared to 5-FU/LV alone.

As a second-line therapy, both irinotecan monotherapy and in combination with a 5-FU-based regimen or with cetuximab have shown survival benefits over either 5-FU/LV therapy or supportive care in patients with metastatic colorectal cancer. A recent large phase III trial also has shown that the efficacy of irinotecan-based therapy is comparable with an oxaliplatin-containing regimen in colorectal cancer patients who failed the first-line therapy.

In adjuvant settings, the addition of irinotecan to standard 5-FU/LV chemotherapy, when compared to 5-FU/LV alone, has not been shown to offer benefit in patients with early stage colorectal cancer.

The most common adverse effects of irinotecan therapy are diarrhea and myelosuppression, which are dose-limiting. Diarrhea can occur early in treatment, within 24 hours of chemotherapy, or it can be delayed 24 hours after chemotherapy. Severe myelosuppression can occur with irinotecan combined with 5-FU/LV. Death from sepsis has been associated with severe neutropenia. Dosage adjustments are recommended based on the degree of diarrhea or neutropenia.

Some patients with a homozygous UGT1A1*28 allele have an increased risk for neutropenia. Irinotecan is metabolized by CYP3A4; therefore, it has many potential drug interactions, especially with agents that either induce or inhibit CYP3A4.

Pemetrexed is a folate antagonist antineoplastic. It inhibits thymidylate synthase, dihydrofolate reductase, and glycinamde ribonucleotide formyltransferase. These enzymes are folate-dependent and are involved in the de novo biosynthesis of thymidine and purine nucleotides. The result is a disruption of cellular replication.

Pemetrexed has a labeled indication for malignant pleural mesothelioma in patients ineligible for surgery. It also has a labeled indication for advanced metastatic non-small cell lung cancer (NSCLC) following prior chemotherapy.

Malignant pleural mesothelioma is a rare form of cancer associated with exposure to asbestos. NSCLC is more common as it is associated with cigarette smoking. Although surgery is used for both, chemotherapy is used when surgery is not possible or as an adjunct after surgery.

Clinical trials for malignant pleural mesothelioma show that patients who are not good candidates for surgical resection responded to pemetrexed plus cisplatin. This is impressive for a cancer that has been previously unresponsive to therapy.

Clinical trial data for NSCLC are not as clear with pemetrexed. In a comparative trial with docetaxel as a second-line therapy, pemetrexed ***For-***

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Medication error prev., *from page 1*

doses per day. This could result in an overdose of 400 mg IV every 6 hours.

In addition to including the patient's weight on all orders, another strategy to prevent calculation errors is to order medications in a dosage unit per weight per interval format (ie, mg/kg/dose or mg/kg/day). The Institute for Safe Medication Practices and the Pediatric Pharmacy Advocacy Group have published guidelines for the prevention of medication errors in pediatric patients.[1] Dosing medications in a weight-based format is a recommendation listed in these guidelines.

The Clinical Practice Committee (CPC) has decided to make the process of writing pediatric medication orders an Academic Quality Support Agreement (AQSA) indicator. All orders for pediatric patients, including medication orders, should contain the patient's current weight or the dosing weight to be used for that patient on the order sheet. Also, all medications that are dosed per weight should be written with the patient-specific dose followed by the weight-based dose. Medications given by continuous infusion should be written as dose per weight per time interval. The ease with which this process can be implemented and the impact it can have on patient safety make it a natural quality indicator.

By Sherl Drawdy, PharmD

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mulary update, *from page 2*
showed a similar response rate and was better-tolerated. These data were used by the 2005 National Comprehensive Cancer Network to recommend pemetrexed alone as a second-line treatment in patients who have experienced disease progression of NSCLC.

Myelosuppression is the major dose-limiting toxicity; however, it is usually mild when supplemental folic acid and cyanocobalamin are given. Rash was reported in up to 50% of patients in phase I and II trials. When dexamethasone is given, the incidence of rash drops to 12%.

Each 500-mg vial of pemetrexed costs $1945. The typical dose will require 2 vials; thus, each treatment will cost approximately $4000.

Venlafaxine immediate-release tablets were added in the *Formulary* because the extended-release capsules are problematic when patients' medications need to be given down a feeding tube. The contents of the extended-release capsule can clog the tubes.

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor. It is used for the treatment of depression, anxiety, panic disorder, social phobias, pain, and other off-labeled uses (eg, symptoms of menopause). The extended-release venlafaxine capsules may be better tolerated by some patients and require less frequent daily dosing (ie, once-daily versus 2-3 times daily) than the immediate-release tablets.

Enflurane is an inhaled anesthetic gas. It is unavailable from the manufacturer and was deleted from the *Formulary*. This agent is now considered obsolete.

Lente insulin and **human lente insulin** were discontinued by their manufacturers in 2005 because of lack of use. Supplies of lente insulin have now been depleted. There are no other manufacturers of human lente insulins. Therefore, Novolin-L was deleted from the *Formulary*. All forms of lente insulin are now not available.

Patients who have been receiving a lente insulin product will need to be converted to an intermediate-acting insulin product like NPH insulin (isophane insulin) or a long-acting insulin analog (eg, insulin glargine). Patients will need to be monitored closely to determine appropriate dosage conversions.

PRESCRIBING

Stressing appropriate stress ulcer prophylaxis

Stress ulceration is the most common cause of gastrointestinal bleeding in the intensive care unit and is associated with increased mortality. Therefore, stress ulcer prophylaxis with antisecretory medications is critical in high-risk patients. The best evidence exists for the use of histamine-2-receptor antagonists (H2RAs), but proton pump inhibitors (PPIs) are also used because they reliably increase gastric pH.

Prophylactic use of PPIs is often inappropriately expanded to include non-critically-ill patients without any obvious risk factors for stress ulceration. This "just-in-case" approach is attributed to the misconception that acid-suppressive therapy is benign.

Proton pump inhibitors have been associated with increased risks of pneumonia and *Clostridium difficile (C diff)* infections. To make matters worse, intravenous formulations of pantoprazole are currently in short supply. In order to ensure that patients who are at the highest risk of developing stress ulcers are able to receive proper therapy and provide intravenous PPIs for selected patients, we are working hard to promote appropriate use.

Major risk factors associated with the development of stress ulcers include mechanical ventilation for greater than 48 hours, renal failure, and coagulopathy.[1] Some additional risk factors include shock, sepsis, hepatic failure, multiple trauma, burns greater than 35% of total body surface area, organ transplant recipients, prolonged extracorporeal circulation, prolonged aortic cross-clamp time, head or spinal trauma, and prior history of peptic ulcer disease, or upper gastrointestinal (GI) bleeding. Many patients, however, are receiving PPIs without these risk factors.

A study that assessed the appropriate use of acid-suppression therapy in 834 patients of an internal medicine department determined that therapy was only indicated in 50.1% of patients. Most inappropriate acid-suppression therapy was for prophylaxis in low risk patients (64.8%). The authors noted that 38.5% of patients receiving PPIs were discharged on inappropriate treatment. In addition to not having risk factors associated with the critically ill, some common reasons for inappropriate acid-suppression therapy use were chronic liver diseases, biliopancreatic diseases, chronic gastritis, steroid use, warfarin use, and occasional nonsteroidal anti-inflammatory (NSAID) use.[2]

Recent studies have shown that acid-suppressive therapy can increase the risk of infections. Increased gastric pH may promote the growth of bacteria within the stomach, thereby increasing the risk of infection particularly with gram-negative bacilli from the duodenum. Aspiration and/or reflux of gastric contents via an endotracheal tube can increase the risk of developing pneumonia.

A study in 103 critically ill patients that determined risk factors for nosocomial pneumonia found sucralfate associated with a 65.2% increased risk of nosocomial pneumonia compared to 32.5% in the control group. Similarly, H2RAs were associated with a 95.6% increase in risk of development of nosocomial pneumonia compared to 73.7% risk associated with the control group.[3]

In a study that included 258 intubated, critically ill patients treated with antacid, ranitidine, or sucralfate, patients receiving acid-suppressive therapy had a higher rate of pneumonia 4 or more days after intubation than those receiving sucralfate (sucralfate 5%,antacids 16%, ranitidine 21%).[4]

The true effect of acid-suppression therapy on the development of nosocomial pneumonia has not been defined; however, there is reason for concern. Caution should be exerted with acid-suppressive therapy in patients at risk for nosocomial pneumonia.

Is inappropriate use of acid-suppression therapy contributing to the increasing incidence of *C diff* infections? Acid-suppression therapy increases gastric pH and decreases the natural acidic defense mechanism of the stomach responsible for the prevention of colonization of natural bacteria within the gastrointestinal tract. Thus, there is a proposed mechanism for the association between acid-suppression therapy and increased risk of developing enteric infections, especially with more virulent *C diff* strains surfacing.

One study observed the incidence of *C diff* in 1672 patients treated with a PPI or H2RA. The incidence of *C diff* infections increased from 1 per 100,000 cases in 1994 to 22 per 100,000 cases in 2004. There was an increased incidence of *C diff* infections associated with PPI and H2RA use. Therefore, the authors concluded that acid-suppressive therapy increases the risk of *C diff* colitis, with PPIs being associated with greater risk than H2RAs.[5]

In addition to the increased risk of infection associated with PPIs, the national shortage of intravenous PPIs makes matters worse. It is important for healthcare workers to work together to assure that patients who need an

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POLICIES AND PROCEDURES

New standard dosage times

The coordination of the Pharmacy Department's computer system and the electronically generated medication administration record (MAR) allows for widespread standardization of medication administration times. These times can be chosen for safety, convenience, or to minimize adverse effects. The following standardized dosage times were recently approved.

Filgrastim (G-CSF) will be given at 2000 (8 PM) daily. This allows time for laboratory results to come back, and for prescribers to discontinue therapy when it is no longer needed.

Efavirinz [Sustiva®] will be given at 2200. Efavirinz should be given at bedtime because it is associated with a high incidence of somnolence, dizziness, and other CNS adverse effects. Bedtime administration improves patient tolerance of this anti-retroviral agent.

Cyclosporine and tacrolimus will be given at 0800 & 2000 (ie, twice a day at 8 AM and 8 PM). Transplant patients are instructed to take their medications at the same time every day in the outpatient setting. This recommendation is for continuity of care in the inpatient setting and to emphasize consistency to patients. This also allows for therapeutic drug monitoring (ie, troughs) to be done at the same time each day.

Of course, medication orders that specify a time of administration will take precedence over these standardized times. If you have suggestions for additional standardized dosage administration times, please send them to hatton@ufl.edu.

Prescribing, *from page 3*
intravenous PPI (eg, active gastrointestinal bleed) receive therapy. Patients who have risk factors for developing stress ulcers should be prescribed an oral or parenteral H2RA.

However, one must keep in mind that even oral formulations of acid-suppressive therapy are not benign. Community-acquired pneumonia has been associated with acid-suppressive therapy.[6] Therefore, appropriate assessment of risk factors must be done before the addition of a PPI in order to decrease the risk of infections. When patients are no longer at risk for stress ulcers, acid-suppressive therapy should be stopped.

By Mona Patel, PharmD

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