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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met September 18, 2001. 6 drugs or dosage forms were added in the *Formulary*. 1 drug was deleted. 1 drug was restricted. 2 dosage forms were deleted.

◆ ADDED

Amino Acids (ProSol® 20% by Baxter)

Eptifibatide (Integrilin® by COR Therapeutics)

Fentanyl Transmucosal (Actiq® by Abbott)*

Infliximab (Remicade® by Centocor)*

Nesiritide (Natrecor® by Scios)

Sodium Benzoate, NF (extemporaneous)

***Restricted**

◆ RESTRICTED

Tirofiban (Aggrastat® by Merck)

◆ DELETED

Amino Acids (Travasol® 10% by Baxter)

Indomethacin Suppositories (Indocin® by Merck)

Amino acids are used to compound total parenteral nutrition (TPN) solutions. The primary amino acid solution used at Shands at UF has been changed from Travasol® 10% to ProSol® 20%. The motivation behind this change was to provide a more concentrated source of amino acids, which would allow additional protein supplementation. The amount of protein delivered by

(continued on next page)

NEWS

OxyContin®: Issues and updates

OxyContin® is a controlled-release form of the oral opiate agonist oxycodone that is given to patients to provide moderate-to-severe pain relief for up to 12 hours. It has potential for abuse and may lead to serious psychological or physical dependence; therefore, under the Controlled Substance Act, it is classified as a Schedule II controlled medication. The Drug Enforcement Administration (DEA) requires a complete and accurate record of inventories and transactions dealing with controlled or scheduled substances. According to Federal law, Schedule II medications may not be refilled, and patients must present a new prescription upon each visit. The DEA has detected an increase in OxyContin® diversion events over the last 10 years.

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OxyContin® has become a major substance of illegal misuse, abuse, and diversion.

Due to the opioid nature of OxyContin®, it has become a major substance of illegal misuse, abuse, and diversion. When OxyContin® is crushed, it can be snorted or dissolved in water and injected.[1] This allows for the rapid release and absorption of oxycodone, leading to a euphoric or analgesic effect that is comparable to the effects felt with the use of heroin. It has been given the slang term "hillbilly heroin" because early reports of abuse came from rural areas of Appalachia. The negative publicity that OxyContin® has been receiving has prompted awareness from health care professionals and government officials.

The abuse of oxycodone can cause respiratory depression and in some cases, death. Autopsies performed in recent years have shown the presence of oxycodone in an increasing number of bodies. In 1999, Philadelphia reported 17 bodies had been exposed to oxycodone. In 2000, the number of oxycodone-exposed bodies increased to 41.[2] The DEA reports that deaths related to oxycodone misuse in 20 metropolitan areas have increased by 400% since 1996.[3]

The US Food and Drug Administration (FDA) and the manufacturer of OxyContin®, Purdue Pharma LP, have teamed up to try and reduce the incidence of diversions, deaths, and abuse associated with the misuse of OxyContin®. Many ideas have been proposed, but only a few have been accepted and implemented. Specific changes to the labeling were made by the manufacturer to help improve prescription practices and increase the physicians' awareness of OxyContin®'s potential for abuse, diversion, and misuse. A "black-box" warning was placed in the labeling to help practitioners realize the strict indication for moderate to severe chronic pain or disorders or conditions that warrant its appropriate use as a Schedule II narcotic. This warning is the strongest warning that the FDA can issue for an approved drug. These changes were disseminated to physicians, pharmacists, and other health care professionals via a "Dear Healthcare Professional" letter

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INSIDE THIS ISSUE

Formulary update, *from page 1*
TPN solutions can be increased without additional fluid administration.

ProSol® is a mixture of essential and nonessential amino acids. It has a labeled indication as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance in patients where the alimentary tract cannot or should not be used; in patients where the gastrointestinal absorption of protein is impaired; or, in patients who have metabolic requirements for protein that are substantially increased (eg, burn patients).

Eptifibatide is a platelet glycoprotein (GP) IIb/IIIa inhibitor that decreases platelet aggregation and the complications that follow acute coronary syndromes (ACS), especially during percutaneous coronary interventions (PCI). Abciximab and tirofiban have been the GPIIb/IIIa inhibitors listed in the *Formulary*.

Following discontinuation of an eptifibatide or tirofiban infusion, platelet aggregation is reduced more than 50% of baseline within 4 hours and usually returns to normal within 8 hours. Abciximab remains platelet-bound for many days, has a higher affinity for the GP IIb/IIIa receptors than the other 2 agents, and has additional activity on the vitronectin receptor.

The recently published ESPRIT trial showed that eptifibatide decreases the combined endpoint of death-myocardial infarction-revascularization compared with placebo in patients at low-risk before PCI. This study included patients that had stent placements. When tirofiban was compared with abciximab (ReoPro®) in a similar population in the TARGET trial, abciximab was shown to be superior to tirofiban at 30 days.

Although there are no head-to-head comparisons between eptifibatide and tirofiban, eptifibatide is approximately 40% less expensive than tirofiban. The published data still suggest better outcomes in abciximab-treated patients for high risk patients undergoing PCI. Eptifibatide and tirofiban appear to have similar results in low-risk patients undergoing PCI. The effect of parenteral GP IIb/IIIa in patients with ACS who do not require PCI is less impressive with small improvements over placebo.

Tirofiban was kept in the *Formulary,* but restricted to use in patients who are transferred to Shands at UF and who are already receiving tirofiban. The appropriate method for switching among the GP IIb/IIIa inhibitors is not well-established.

In order to assure that GP IIb/IIIa inhibitors are used appropriately and that these patients are appropriately evaluated for PCI before starting therapy, a Cardiology Consult is required to prescribe these agents. Approval by Cardiology must be documented in the orders for all GP IIb/IIIa inhibitors (unless written by Cardiology). Orders for tirofiban must state that it is continuation of therapy from an outside hospital.

Transmucosal fentanyl lozenges on a stick (also known as fentanyl "lollipops") have a short duration of action and are titrated by removing the lozenge from the patient's mouth. This specialized dosage form of the opioid fentanyl was added in the *Formulary* for pain management in procedures (eg, debridement) needed by burn patients who do not have IV access.

Oral pain medications have variable onsets of action and longer durations of effect than are needed for most procedures in burn patients. A double-blind crossover study has been published comparing the efficacy of transmucosal fentanyl to oral hydromorphone in 14 pediatric inpatients without IV access who were undergoing daily burn wound care. The duration of wound care ranged from 10 to 50 minutes. The results of this small study showed that transmucosal fentanyl was as effective as oral hydromorphone.

Safety is a concern with the use of transmucosal fentanyl in this setting. Transmucosal fentanyl's package insert is very conservative. Therefore, transmucosal fentanyl was restricted to use in only burn patients. Further, a monitoring policy was approved to avoid the risk of respiratory depression.

Patients receiving transmucosal fentanyl will have oxygen saturation monitoring initiated at the time of medication administration. Oxygen saturation monitoring will continue for 60 minutes. At that time, patients will be reassessed. If the patient does not meet discharge criteria, the patient will be re-evaluated by a physician or nurse practitioner for further monitoring needs.

Discharge criteria include: the patient is easily awakened by normal or softly spoken verbal commands; the patient is oriented when awake (as appropriate for age); all vital signs are stable; there is no significant risk of losing the protective reflexes; the patient is able to maintain pre-procedure mobility with minimal assistance as appropriate for the procedure; and, the patient has minimal nausea and/or dizziness. Outpatients will not be allowed to drive home after receiving transmucosal fentanyl.

Infliximab is a monoclonal antibody to tumor necrosis factor with a labeled indication for the treatment of moderately to severely active Crohn's disease for the reduction of the signs and symptoms in patients who have an inadequate response to conventional therapy. Published clinical trial data show that single infusions of infliximab are associated with a clinical response in most therapy-resistant patients with Crohn's disease, but a clinical remission occurs in only approximately 1 in 3 patients. The response rate appears slow in these studies and peaks in about 2 weeks. For this reason (and poor reimbursement), infliximab was designated nonformulary and not available in March 1999. There are limited data that suggest that infliximab may act more rapidly than 2 weeks in some patients and is a viable alternative to hyperalimentation in a small subset of patients.

A typical adult dose of infliximab for Crohn's disease costs approximately $1800. When insurance carriers are contacted, they may state that they "cover" infliximab in the inpatient setting; however, it is rare that reimbursements actually increase incrementally to cover the increased cost of infliximab. Reimbursement for infliximab in the outpatient setting is good; therefore, it should be a rare exception when infliximab is given in the inpatient setting. Infliximab was added in the *Formulary,* but it is restricted to patients approved by the Gastroenterology Service. Although infliximab also has a labeled indication for rheumatoid arthritis, use for this indication in the inpatient setting was not approved.

Nesiritide is a recombinant B-type natriuretic peptide that mimics the body's endogenous hormone, which augments cardiac function and causes natriuresis. It was recently approved for acute decompensated congestive heart failure. Nesiritide is the 1st new drug used for acute decompensated heart failure in many years. Therefore, it was evaluated proactively by the P&T Committee because it could represent an advantage over existing therapies.

Nesiritide is an arterial and venous vasodilator that lowers pulmonary capillary wedge pressure (PCWP) in a dose-dependent manner. It does not induce reflex tachycardia. In early trials, it did cause significant hypotension; however, dosage adjustments have decreased this risk.

In a recently published trial, nesiritide showed significant effects on PCWP, global clinical status, and symptoms of acute heart failure compared with standard therapy

(continued on next page)

Formulary update, *from page 2*
(ie, nitroglycerin and dobutamine or milrinone). Data are pending from the Prospective Randomized Outcomes Study of Acute Decompensated Congestive Heart Failure Initially in Outpatients with Natrecor (PROACTION) trial.

Nesiritide was added in the *Formulary;* however, it use was restricted to the Cardiology Service. A day's supply of nesiritide costs approximately $400. The appropriate duration of therapy and monitoring will be established with more published information and experience.

Sodium Benzoate is listed as a chemical in the official monograph of the National Formulary (NF). Sodium benzoate is listed as NF, rather than USP, because it does not have any recognized therapeutic indication. Sodium benzoate is a preservative in foods (eg, soft drinks) and drugs.

A combination of sodium benzoate and sodium phenylacetate was listed in the *Formulary* for inborn metabolic errors in the urea cycle. When Ucephan® was removed from the market, Buphenyl® (sodium phenylacetate) replaced it in the *Formulary*. Sodium phenylacetate is an acceptable alternative for most inborn metabolic errors.

Rarely, however, patients are admitted with nonketotic hyperglycinemia. This rare inborn error of metabolism results in large amounts of glycine in body fluids. Most of these patients have severe brain damage and seizures. Sodium benzoate has been used to reduce the CSF concentrations of glycine, which may decrease the incidence of seizures. Therefore, a 100 mg/mL extemporaneously prepared solution of sodium benzoate will be listed in the *Formulary*.

Indomethacin suppositories have been discontinued by the manufacturer because of low sales. Historically, indomethacin suppositories were used for the treatment of various types of moderate to severe pain and inflammatory conditions when the oral route could not be used. There is no alternative manufacturer. Therefore, indomethacin suppositories will no longer be listed in the *Formulary.*

DRUG INFORMATION FORUM

What is the treatment for anthrax?

In the last 3 years, the Drug Information Service has received approximately 10 questions about the treatment and prevention of anthrax. Until recently, these questions were all about the anthrax vaccine. For example, military personel wanted to know the potential adverse effects or possible interactions of the vaccine. Unfortunately, now we are getting questions from health care professionals about the treatment of anthrax because of their concerns about bioterrorism.

Anthrax is an acute infectious disease caused by *Bacillus anthracis,* which is an aerobic, gram-positive, spore-forming, Bacillus species. Humans can become infected by contact, ingestion, or inhalation of *B. anthracis* from infected animals, contaminated animal products, or by breathing weapon-dispersed anthrax spores.

Cutaneous, gastrointestinal, and respiratory infections can occur after anthrax exposure. Cutaneous infections are usually curable, but they can have the potential to reach the systemic circulation and become fatal. In the United States, 224 cases of cutaneous anthrax were reported between 1944 and 1994.[1] Inhalational anthrax is fatal even with aggressive antimicrobial therapy. However, no cases of inhalational anthrax have been reported in the US since 1978.

Recommendations on antibiotic and vaccine use for anthrax infections due to a biological anthrax attack are based on animal studies, current antibiotic resistant patterns, and the possible requirement in treating large numbers of casualties. There are no clinical studies of the treatment of inhalational anthrax in humans. The current recommendations were reached by a consensus of a Working Group on Civilian Biodefense.[1,2]

Postexposure prophylaxis for asymptomatic patients with suspected exposure to anthrax spores includes an inactivated, cell-free anthrax vaccine in conjunction with an antibiotic such as ciprofloxacin 500 mg PO q12h (preferred initially), doxycycline 100 mg PO q12h, or amoxicillin 500 mg PO q8h for proven susceptible strains. Early therapeutic interventions are absolutely necessary.

Antibiotics with concomitant administration of 3 doses of anthrax vaccine should be taken for 30 to 45 days. If the anthrax vaccine is not available, prophylaxis with antibiotics is recommended to be taken for 60 days. The Working Group for Civilian Biodefense recommends oral fluoroquinolones (primarily ciprofloxacin, but ofloxacin 400 mg PO q12h or levofloxacin 500 mg PO q24h can be substituted) as the drugs of choice for initial therapy for adults, children, and pregnant women for postexposure prophylaxis. If fluoroquinolones are not available or are contraindicated, doxycycline can be used. Antibiotics can be changed after antibiotic susceptibility of anthrax is confirmed.

Postexposure vaccination consists of 3 injections: upon anthrax exposure, and at 2 and 4 weeks after exposure. Full protection as determined by the Food & Drug Administration would require a 6-injection series before exposure. However, the literature reports that the ability of any vaccine to protect humans in the event of biologic terrorism has not been determined. Also, this vaccine has not been evaluated for safety and efficacy in children less than 18 years of age or adults greater than 60 years old.

Intravenous administration of antibiotics is recommended in the literature for patients with clinical evidence of cutaneous, gastrointestinal, or inhalational anthrax infections. However in a mass casualty setting, oral therapy is obviously recommended due to exhaustion of equipment and antibiotic supplies. The Working Group on Civilian Biodefense recommends ciprofloxacin 400 mg IV q12h for initial therapy or penicillin G 4 mu IV q4h or doxycycline 100 mg IV q12h for susceptible strains. In vitro studies have suggested using ofloxacin or levofloxacin in place of ciprofloxacin. The FDA approved ciprofloxacin as the first medication labeled for use after anthrax exposure from bioterrorism. Other antibiotics are recommended to be used only if the previously mentioned antibiotics are not available or if the anthrax strain is resistant to the recommended antibiotics.

by Carol Raschke, PharmD

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News, *from page 1*
from Purdue Pharma. The manufacturer is working on developing a combination product that would contain an opiate antagonist such as naloxone. This formulation would decrease the effects of oxycodone when injected, thereby deterring abuse and misuse. This product, however, will not be available for a couple of years.

In order to help reduce reimbursement costs and abuse of OxyContin®, Florida's Medicaid program has recently placed restrictions on the monthly quantity of tablets that are dispensed per prescription. Without Medicaid approval, the State will not pay for a prescription for a patient receiving more than 120 OxyContin® in a month. Florida Medicaid is also requiring Schedule II medications be written on pre-printed, counterfeit-proof prescription pads. Pharmacies must show compliance with this regulation or they may not be reimbursed for those medications not written on the correct prescription blank. Currently, OxyContin® is available in 4 strengths: 10 mg, 20 mg, 40 mg, and 80 mg. Due to many deaths, the 160-mg tablet was removed from the market in May 2001.

Restrictions on patients' ability to get OxyContin® through Medicaid are already in place in 4 states: Maine, West Virginia, Ohio, and South Carolina. Vermont is the first state that has discontinued paying for OxyContin® prescriptions for individuals receiving prescriptions through Medicaid. In Pulaski, Virginia, a fingerprinting system has been implemented for legally prescribed OxyContin® prescriptions. This system requires patients to dip their forefinger in invisible ink and then press it on a special paper. The paper is then attached to the prescription and kept on file at the pharmacy. The fingerprint is used to identify patients involved with stolen or falsified prescriptions. Some psychiatrists in Louisiana are currently using the fingerprint system when dispensing narcotics from their offices. This system may be utilized in pharmacies for other narcotic prescriptions as well.

by Kristen Greenwood, PharmD

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MEDICATION ERROR PREVENTION

Lente or Lantus?

Poor handwriting can result in medication errors. Poorly written orders can result in misinterpretations and patient harm. The order in the figure below is for Lantus® Insulin (insulin glargine). This long-acting insulin is currently NOT listed in the *Formulary* at Shands at UF. The order in the figure comes from another hospital where it was misinterpreted as "Lente" insulin.

Insulin orders that are prescribed daily will be questioned to determine whether they are "Lente" or "Lantus." Clearly written orders will help minimize the potential for error. Consider printing these orders.

by Laura Tipton, RPh, MBA