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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 20, 2001. 4 drugs or dosage forms were added in the *Formulary* and 3 drugs or dosage forms were deleted.

◆ ADDED

Albuterol nebulization solution (unit dose ampules by Nephron)

Anti-inhibitor coagulant complex, human-drived (FEIBA® VH Immuno by Baxter)

Diphtheria and Tetanus toxoids and acellular Pertussis vaccine (Tripedia® by Aventis Pasteur)

Rosiglitazone (Avandia® by SmithKline Beecham)

◆ DELETED

Albuterol nebulization solution (multi-dose vials containing benzalkonium chloride)

Diphtheria and Tetanus toxoids and acellular Pertussis vaccine (Acel-Imune® by Lederle)

Urine diagnostic strips (Albustix, Glucostix, Ketostix)

Albuterol is a moderately selective beta2-receptor agonist that is commonly administered by oral inhalation, through an inhalation device such as a nebulizer. Albuterol is widely used as a bronchodilator in the management of exacerbations of asthma or other chronic obstructive airway diseases.

A recently published study conducted at the University of Florida College of Pharmacy showed that certain preservatives commonly found in commercially available albuterol nebulization solutions can themselves cause bronchospasm. Benzalkonium chloride (BAC),

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PRESCRIBING

When should you use Ultram®?

Pain management is increasingly recognized as an important aspect of patient care, especially in the face of new healthcare standards and regulations. When working with patients who need pain control, the range of choices for treatment can be confusing. Tramadol (Ultram®) is a novel pain-relieving medication that has a specific area in pain management where it may be useful.

Tramadol is taken orally and can be used for moderate-to-severe, chronic pain. The parent compound (tramadol) and a primary metabolite (M1) are both active and have a unique, 2-fold mechanism of action.[1] Both are agonists at μ-opioid receptors.[2] It is at this site where the drug acts like other opiate agonists (eg, morphine) to produce a "central" pain-relieving effect. Tramadol and M1 have a low affinity for the μ-opioid receptor compared with other opiate agonists. Tramadol and M1 also inhibit norepinephrine and serotonin reuptake in the central nervous system, which is thought to contribute to pain relief.

Tramadol is available only with a prescription. It is not a controlled substance. This non-controlled status may contribute to its overuse. It may also promote some misconceptions about its efficacy and its adverse effects—or perceived lack of adverse effects. These misperceptions can lead to inappropriate prescribing.

Tramadol is not useful for acute pain. Studies comparing tramadol to other pain relieving medications (including morphine, codeine, meperidine and hydrocodone) show that tramadol is significantly less effective in relieving acute or chronic pain.[3–5] This is especially true for severe or post-operative acute pain. Studies show equal or more adverse effects associated with tramadol when compared with other traditional pain medications.[3–6]

A particularly important aspect of tramadol that is often ignored is the dosage titration that is recommended when initiation therapy. This dosage titration will help to decrease, and potentially avoid, adverse effects that are typically associated with tramadol use. Tramadol should be started at a low dosage (ie, 25 mg once daily), then increased every 3 days by 25-mg-per-day increments (given as a separate dose). The target dose is 100 mg per day (ie, 25 mg 4 times daily). If adequate pain relief is not achieved with 100 mg per day, the dose can be increased by 50 mg every 3 days, as tolerated, up to 200 mg per day (ie, 50 mg 4 times daily). After titration, doses of 50 to 100 mg every 4 to 6 hours as needed (with a maximum dose of 400 mg per day) may be given. This titration does not provide rapid pain relief, but it allows for better tolerability. When tramadol is used for treatment of acute pain, doses are not titrated, resulting in an increased incidence of adverse effects.

Because of tramadol's low affinity for μ-opioid receptors, it would be expected to have a lower incidence of adverse effects compared with other opiate agonists. Respiratory depression is a concern with opiates.[3] Studies comparing the effects of tramadol to morphine on oxygen saturation and respiratory rate found both had similar effects. Tramadol and morphine did not decrease respiratory function to a clinically significant degree, but the rate of respiratory decline was similar for both drugs.

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INSIDE THIS ISSUE

Formulary, *from page 1*

1 of the preservatives studied, was found to cause significant bronchospasm that could potentially interfere with the effectiveness of a bronchodilator in an emergency. This prompted a review of the albuterol nebulization products that are commonly stocked and used at Shands at UF. The multi-dose vials of albuterol nebulization solution used at Shands contained BAC. The multi-dose vials of albuterol nebulization solution were deleted from the *Formulary*. A preservative-free unit-dose albuterol product, by Nephron Pharmaceutical Corporation, was added in the *Formulary*.

FEIBA® is an anti-inhibitor coagulant complex (AICC) derived from human plasma. AICC is similar to prothrombin complex concentrates (PCCs or factor IX complexes), but AICC has undergone *in-vitro* activation, resulting in an increased amount of activated and precursor vitamin K-dependent clotting factors (factors II, VII, IX, and X). FEIBA® VH Immuno contains factors II, IX, and X, which are mainly inactivated, and factor VII, which is mainly activated. A 1999 review of coagulation factors by a multidisciplinary Hematology/Pharmacy group recommended that FEIBA® be in the *Formulary.* At that time FEIBA® was routinely stocked and used in the hospital; however, it had not been formally added in the *Formulary.*

Acel-Imune® and **Tripedia**® are Diphtheria/Tetanus toxoids and acellular Pertussis (DTaP) vaccines. These products contain various pertussis antigens (isolated from *Bordetella pertussis*) in combination with diphtheria toxoid (isolated from *Corynebacterium diphtheriae*) and tetanus toxoid (isolated from *Clostridium tetani*). Acel-Imune® was the first DTP product approved that contained acellular pertussis. Acellular pertussis vaccine has a significantly lower incidence of local and systemic adverse reactions and better efficacy when compared to vaccines that contain whole cell pertussis (DTwP). Vaccination with DTP is indicated for all children from 2 months to 7 years of age and for close contacts of persons with pertussis. Previously, DTP vaccines were indicated only for children 15 months and older, and acellular products (DTaP) were indicated only for the final 2 booster doses of the childhood immunization schedule; however, DTaP is now approved for the entire immunization schedule. Acel-Imune® is no longer available from the manufacturer; therefore, Tripedia® will replace Acel-Imune® in the *Formulary*.

Rosiglitazone is an oral antidiabetic agent. It is in the group of antidiabetic agents known as thiazolidinediones (commonly referred to as glitazones) that act as "insulin sensitizers." Rosiglitazone is not chemically or functionally related to the alpha-glucosidase inhibitors (eg, acarbose), the biguanides (eg, metformin), or sulfonylureas (eg, glipizide). The glitazones specifically target insulin resistance, which is thought to be central to the development of type 2 diabetes and some of the complications of the disease. Rosiglitazone monotherapy results in improvements in glycemic control, indicated by reductions in fasting plasma glucose and hemoglobin A1c compared with baseline and relative to placebo.

Rosiglitazone decreases hyperglycemia by reducing insulin resistance and improving insulin sensitivity at target tissues. Enhancing sensitivity to insulin, it increases insulin-mediated glucose uptake in the liver, adipose tissue, and muscle. In addition to decreased blood glucose, a decrease in blood insulin is seen.

The initial dose of rosiglitazone is 4 mg daily, which is given as a single daily dose or in 2 divided doses. The dose can be increased after 12 weeks to the maximum daily dose of 8 mg daily. No dosing adjustments are necessary for patients with renal impairment. Dosing adjustments may be required for patients with hepatic impairment, although no specific recommendations are available. Patients with existing hepatic impairment, as evidenced by active liver disease or serum transaminase (ALT) levels 2.5 times the upper limit of normal, should not use rosiglitazone.

Rosiglitazone can be used alone or in conjunction with metformin or a sulfonylurea for the treatment of type 2 diabetes. Patients who are inadequately controlled on metformin should have rosiglitazone added to therapy, rather than being switched to rosiglitazone alone. Patients who will have rosiglitazone added to their sulfonylurea regimen should be instructed to closely monitor their blood glucose levels, as they may experience hypoglycemia. Sulfonylurea doses may need to be decreased if hypoglycemia occurs.

Adverse effects most commonly reported for rosiglitazone include upper respiratory tract infection, injury and headache. The 1st glitazone available for use, troglitazone, was removed from the market because of several cases of death associated with troglitazone-induced hepatotoxicity. This led to concern regarding whether hepatotoxicity is a class-effect. Thus far, there is no evidence that rosiglitazone is hepatotoxic.

Rosiglitazone has been added in the *Formulary*, while pioglitazone (the other currently marketed glitazone) will remain a nonformulary drug. Pioglitazone can be switched to a comparable dose of rosiglitazone while patients are hospitalized, based on initial and maximum dosage of the 2 drugs. For example, patients who receive 30 mg of pioglitazone per day could be switched to 4 mg of rosiglitazone per day during their hospitalization.

By Jamie Reinke, PharmD

NEWS

Updated HIV treatment guidelines released

The *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* was updated and released in February. Specific changes in the *Guidelines* are in the following sections: Considerations for Initiating Therapy in the Patient with Asymptomatic HIV Infection; Adherence to Potent Antiretroviral Therapy; Highly Active Antiretroviral Therapy (HAART)-Associated Adverse Clinical Effects; and The Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection.

A critical issue for clinicians and patients is when to start antiretroviral therapy. Starting therapy early has several associated risks that can decrease the patient's quality of life. Antiretrovirals can cause short-term toxicities associated with serious morbidity and mortality, including nucleoside-related lactic acidosis, nevirapine-related rash or hepatotoxicity, and abacavir-related hypersensitivity.

When patients start treatment too early, short-term toxicities are not the only concern. Poor adherence and long-term antiretroviral exposure can lead to viral resistance.

Treatment with antiviral drugs has proven to be very effective. Many patients with HIV have long life expectancies. HIV is now considered

(continued on page 3)

NEWS

OxyContin® abuse on the rise

Over the past month-and-a-half, several Gainesville pharmacies have been robbed; a few times even at gunpoint. The thief's objective in each instance…to get OxyContin®, the sustained-release form of oxycodone. This is consistent with a growing national trend, the abuse of OxyContin®. Also referred to as OC, Oxy, oxycotton, and killers, OxyContin® is abused by chewing or grinding up these sustained-release tablets. Some abusers snort or inject the ground tablets.

The Florida Department of Law Enforcement issued a safety alert in February 2001 because of a number of deaths from OxyContin®. Reports along the East Coast from Maine to Florida show a similar pattern. OxyContin® is obtained by various sources, but a disturbing trend of armed robberies of pharmacies has been reported. OxyContin® reportedly sells for as much a $100 a tablet on the illicit drug market. The New York Times reports that drug dealers have used legitimate patients, as well as "fakers," to obtain OxyContin®

Pointing out the abuse problem with OxyContin® is important and prescribers should be aware of it. However, these reports hopefully will not have a negative impact on the pain management of patients who need aggressive pain therapy.

OxyContin® is only 1 choice among many good drugs that can be used for pain management. OxyContin® was added in the *Formulary* for chronic pain that lasts for more than a few days as an alternative to regular-release oxycodone, oxycodone combinations (eg, Tylox®), and extended-release morphine (eg, Oramorph®) for chronic pain conditions like cancer or sickle cell disease.

Oxycodone is an opioid analgesic similar to morphine. Like morphine, oxycodone stimulates the μ-opioid receptor and alters pain perception at the spinal cord level and higher levels of the central nervous system. On a mg-per-mg basis, oxycodone is more potent than oral morphine. Oxycodone causes analgesia, sedation, and euphoria. Like other opioids, oxycodone does not exhibit a ceiling effect, and the dose can be increased to achieve a targeted effect. Other pharmacologic effects include miosis, respiratory depression, pruritus, and impaired gut wall peristalsis (ie, constipation). Respiratory depression is associated with excessive doses that have not been titrated.

Oxycodone has good oral bioavailability. OxyContin® has biphasic absorption. The initial release of oxycodone results in pain relief within 1 hour; however, it is slower than other regular-release oral opioids. After the initial release, Oxycontin's controlled-release of oxycodone persists over the next several hours. The labeled dosing for OxyContin® lists a dosage interval of every 12 hours. If a higher dose is needed to control a patient's pain, an increased dose is recommended—as opposed to a more frequent interval (ie, every 8 hours).

Clinical studies show that OxyContin® is as effective as regular-release oxycodone and sustained-release morphine at equipotent doses. For the opioid-naïve patient or the patient stabilized on a dose of extended-release morphine, OxyContin® offers no obvious therapeutic advantage. At Shands at UF, OxyContin® is 25-times more expensive than Oramorph® and 5-times more expensive than oxycodone-acetaminophen combinations.

Although sustained-release morphine (Oramorph®) is the drug-of-choice when an extended-release opioid is needed, certain patients may better tolerate OxyContin®. Inter-patient variability in responses may account for differing efficacy between oral extended-release morphine and oxycodone; however, this should be rare. OxyContin® is not recommended for the management of acute pain (eg, post-operative pain).

News, *from page 2*

to be a "chronic" disease and, unfortunately, this is associated with long-term antiretroviral toxicities. Some long-term antiretroviral toxicities are lipodystrophy and protease inhibitor-related lipid disturbances.

Starting therapy late puts patients at risk for HIV disease progression and loss of immune function. If therapy is delayed too long, the chance of adequate viral suppression can be decreased, and the rate of adverse effects and toxicities can increase.

The Panel on Clinical Practices for the Treatment of HIV Infection is the expert panel that develops and updates the *Guidelines*. The panel took these risks into consideration when they updated the recommendations. The *Guidelines* now recommend starting antiretroviral therapy in asymptomatic patients when CD4+ T-cell counts fall below 350 cells per cubic milimeter (mm^3), where the previous guidelines suggest starting therapy at <500 cells/mm^3. For asymptomatic patients with CD4+ T-cell counts higher than 350 cells/mm^3, treatment should be considered when HIV plasma levels reach >30,000 copies/mL using branched DNA testing or >55,000 copies/mL using RT-PCR test. Previous guidelines suggested starting therapy at much lower HIV plasma levels (10,000 copies/mL by branched DNA or 20,000 copies/mL by RT-PCR). The updated *Guidelines* are conservative when starting antiviral therapy, but the panel is trying to balance short-term risks with long-term benefits when initiating medical therapy.

The drug-specific recommendations made in the updated *Guidelines* include 2 new additions to the "strongly recommended" category of anti-HIV drug treatment. These new additions are Kaletra® (a co-formulation of ritonavir and lopinavir) and the combined use of ritonavir and indinavir.

The importance of adherence to therapy has been revised in the *Guidelines*. This section now links strict adherence to antiviral drug regimens with control over HIV replication and, thus, the potential prevention of viral resistance.

The updated section that addresses the expanding scope of antiretroviral drug toxicities is an important addition, especially with the increased life span of HIV-infected individuals who are maintained on antiviral drugs. Of particular concern are the alterations in fat metabolism seen with long-term drug therapy. More and more patients are presenting with dangerously high cholesterol and triglyceride levels, which puts them at risk for premature coronary disease. There are no specific recommendations for treating elevated cholesterol and triglyceride levels in HIV-positive patients. The effectiveness of lifestyle modifications and drug therapy are not clear. Extreme caution should be used with HMG Coenzyme A reductase inhibitors (ie, statins) in patients taking protease inhibitors (PI's). PI's may inhibit the metabolism of statins, which could increase the risk of statin associated myopathy and rhabdomyolysis.

The updated *Guidelines* can be found at the HIV/AIDS Treatment Information Services (ATIS) Web site, http://www.hivatis.org.

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Prescribing, *from page 1*

Even though tramadol is a weak opioid receptor agonist, it still causes constipation. Other gastrointestinal effects have also been seen, including nausea, vomiting, and dry mouth. In clinical trials, nausea has been reported in 40% of patients and vomiting in 20%.

CNS effects are the most common side effects seen with tramadol. Drowsiness, dizziness, fatigue, and headache are commonly reported. The most concerning CNS effect is the increased risk of seizures. Fortunately, there is a relatively low frequency of seizures associated with tramadol use, and this adverse effect often can be avoided. Patients at higher risk for seizures include those who have a history of seizures or a seizure disorder, recent head trauma, metabolic disturbances, alcohol or drug withdrawal, or CNS infection. Other factors that can predispose patients to seizures with tramadol use include concomitant administration of tricyclic antidepressants and other tricyclic compounds (eg, cyclobenzaprine), selective serotonin-reuptake inhibitors (SSRIs), anorexants, monoamine oxidase inhibitors, and neuroleptics. Overdoses of tramadol are associated with an increased seizure rate, and the administration of naloxone (commonly used to reverse the effects of an opiate overdose) will make the risk for tramadol-induced seizure even higher.

Elderly patients seem to be more sensitive to the adverse effects associated with tramadol. A study by Rauk and colleagues compared tramadol to acetaminophen with codeine in patients older than 65 years with chronic pain.[7] There was a significantly higher dropout rate in the tramadol group due to adverse effects. There was no difference in pain relief between the groups, and neither group had significant relief from their pain (compared to baseline) at normal recommended doses of each medication.

It was predicted that dependence and abuse would not be an issue with tramadol, because of its low affinity for μ-opioid receptors. There have been reports, however, that both dependence and abuse occur with tramadol. Many reports of abuse have been associated with individuals who have a history of drug abuse. Dependence, to the point of withdrawal reactions, has been reported — and not just in individuals with a history of drug abuse.[8] Tramadol is abused by healthcare professions who do not have access to controlled substances. For these reasons, tramadol is handled like a controlled substance at Shands at UF.

Tramadol is no more effective than combination opiate products for mild-to-moderate pain. It is not as effective as more potent analgesics for more severe acute pain, such as post-operative and cancer pain. Tramadol may be useful for the treatment of chronic, moderate-to-severe pain. It is best tolerated when the dosage is slowly increased. Patients not taking other medications that interact with tramadol are the best candidates for tramadol use. Although not a controlled substance, tramadol may be misused.

By Jamie Reinke, PharmD

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