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SHANDS at the University of Florida

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Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 16, 2002. 2 drugs were added in the *Formulary* and 2 drugs were deleted. 3 drugs were evaluated, but not added: 2 of these drugs were designated nonformulary and not available. In total, 4 drugs were designated not available.

◆ **ADDED**

Darbepoetin (Aranesp® by Amgen)

Orphenadrine IV (eg, Norflex® by 3M Pharm)

◆ **DELETED**

Plicamycin (Mithracin® by Bayer)

Theophylline ER (Uni-Dur® by Schering Laboratories)

◆ **NONFORMULARY, NOT AVAILABLE**

Hydrocodone + Acetaminophen (Lortab® etc.)

Orphenadrine oral (eg, Norflex®)

Theophylline ER (Theo-24® by UCB Pharma)

Tramadol + Acetaminophen (Ultracet® by Ortho-McNeil)

◆ **EVALUATED, BUT NOT ADDED**

Tizanidine (Zanaflex® by Athena Neurosciences)

Darbepoetin was initially evaluated by the P&T Committee in November 2001. At that time, darbepoetin could not be billed by a hospital-based clinic. There would have been no reimbursement for this expensive agent. There is now

(continued on next page)

PAIN MANAGEMENT

Potential problems of chronic and acute APAP use

The use of acetaminophen (APAP) is pervasive. It is the most commonly prescribed analgesic-antipyretic at Shands at UF. Because APAP is perceived as being void of drug interactions and adverse effects, it is very attractive for the treatment of fever and mild pain. However, uninformed acute or chronic use of APAP can lead to serious and potentially fatal adverse effects.

APAP is available without a prescription in many dosage forms (eg, tablets, capsules, liquid, infant drops, and suppositories). It is commonly found in combination with pseudoephedrine, dextromethorphan, chlorpheniramine, diphenhydramine, or doxylamine. APAP is also available by prescription in combination with codeine, hydrocodone, or oxycodone. The amount of APAP in combination products is often overlooked.

APAP effectively relieves both acute and chronic pain. It is often preferred in elderly patients with osteoarthritis over other NSAIDs because it is associated with fewer adverse effects (ie, gastrointestinal and renal) and drug interactions. The American Geriatrics Society recommends APAP as the analgesic of choice for minor aches and pains in patients > 50 years of age. APAP effectively reduces fevers in adults, adolescents, children, and infants. APAP is the only analgesic that can be used throughout pregnancy.

The safety and effectiveness of APAP contribute to its widespread use. This prevalence has contributed to its potential problems as users are often lulled into a false sense of security. However, the use of APAP does have risks.

Toxicities associated with excessive doses of APAP are hepatotoxiciy and occasionally renal failure. These events have been documented during acute, short-term, and chronic ingestion of APAP at excessive doses. Acute overdoses occur when excessive doses (ie, > 7.5 grams in adults or > 150 mg/kg in children) have been ingested within a 24 hour period. Toxicity has occurred with short-term APAP therapy (ie, less than 10 days) when doses exceed 5 gm/day. Toxicity during chronic therapy (ie, > 10 days of use) has occurred at doses between 2.6 and 4 gm/day. Risk factors that have been associated with toxicity include infants receiving excessive doses for febrile illness, alcoholics, patients taking medications that induce cytochrome P450 (CYP450) enzymes, and patients with preexisting liver disease. There are reports of patients without these risk factors developing APAP toxicity during chronic APAP use.[1]

The labeling for Tylenol® states that the maximum daily dose of APAP is 4 grams per day. Reports of patients developing toxicity at doses less than 4 gm/day have led to the recommendation that daily doses should not exceed 2.6 grams per day during chronic administration, particularly if the patient has other risk factors (eg, alcohol use). This lower daily chronic dose is approximately equivalent to taking 650 mg of APAP 4 times daily or 1000 mg 3 times daily.

An overview of the metabolism and elimination of APAP explains the mechanism of its potential toxicity.

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INSIDE THIS ISSUE

Formulary update, *from page 1*
a reimbursement code for use in the treatment of anemia associated with chronic renal failure, including patients on dialysis and pre-dialysis patients.

Darbepoetin is a long-acting analog of human erythropoietin (EPO). The addition of carbohydrate chains and selective amino acid substitutions result in an increased circulating half-life compared with EPO. Darbepoetin's 2 to 3 times longer half-life permits once-weekly administration compared with 3-times-weekly administration with EPO or every-other-week administration compared with weekly administration. This could result in fewer clinic visits and less personnel time. There is no available evidence to support therapeutic superiority.

Currently, it is not clear whether there will be a cost advantage with this new agent compared with EPO. Darbepoetin should be less expensive with higher doses and more expensive at lower doses. Darbepoetin was not added in the *Formulary* for other uses (eg, anemia associated with cancer treatment) because there still is no reimbursement for this indication.

Intravenous orphenadrine is listed in the *Pain Treatment Algorithm* under acute pain with intensity of 5 to 7 and under chronic pain. In the *Treatment Tables*, orphenadrine is listed for skeletal muscle spasms (pain source) that is cramping or spasming (pain character) for PRN or routine use. IV orphenadrine should only be used for maintenance therapy in chronic pain patients or other patients who require muscle relaxants who are unable to take or tolerate oral medications.

IV orphenadrine is a centrally acting, parenteral, skeletal muscle relaxant. It is an old drug. It was marketed in 1959, before efficacy and safety were required. It has potent anticholinergic effects. Thus, the expected adverse effects include somnolence, dry mouth, blurred vision, dizziness, hallucinations, palpitations, and tachycardia. Its use is not recommended in geriatric patients and is among the list of drugs that are indicators for poor therapy in the elderly.

Considering that orphenadrine has been on the market for more than 40 years, it is striking how little scientific data there is to support the use of this agent. There are no published comparisons with other skeletal muscle relaxants.

Each dose of IV orphenadrine costs about $32. The usage of this agent is expected to be very low.

Oral orphenadrine is not needed and is considered inappropriate. It was designated nonformulary and not available.

Plicamycin was discontinued by its manufacturer. Plicamycin was formerly known under the generic name mithramycin. The generic name was changed from mithramycin to plicamycin to avoid medication errors. The decision to stop manufacturing plicamycin was based on declining demand for it in the US. This is attributed to the introduction of newer therapies for the treatment of malignant hypercalcemia (eg, bisphosphonates).

Uni-Dur® was deleted from the *Formulary* and **Theo-24®** was designated nonformulary and not available. Both of these products are once-daily formulations of theophylline extended-release. Twice-daily dosage forms of theophylline ER remain listed in the *Formulary*.

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All hydrocodone-acetaminophen combinations were deemed nonformulary and not available in August 2001. The P&T Committee reaffirmed this decision.

The use of once-daily theophylline ER products has been very low at Shands at UF. The manufacturer of Uni-Dur® recently stopped making this product. Although there are other once-daily products on the market (eg, Uniphyl®), it was determined that a product was not needed. Theo-24® was designated not available because of its potential to "dose dump" with fatty meals, which could lead to adverse effects.

Hydrocodone + acetaminophen has previously been reviewed by the P&T Committee in August 2001. Hydrocodone-acetaminophen combinations have frequently been requested for nonformulary use by patients who are taking this combination on admission for pain. All hydrocodone-acetaminophen combinations were deemed nonformulary and not available in August 2001. The P&T Committee reaffirmed this decision.

There is no reason to start a patient on hydrocodone-acetaminophen in the hospital. Patients admitted on hydrocodone-acetaminophen can be switched to oxycodone-acetaminophen or oxycodone alone. Hydrocodone is approximately half the potency of oxycodone on a milligram-per-milligram basis. There is no published evidence to support the concept that patients who do not tolerate oxycodone will tolerate hydrocodone, although some patients will relate this experience.

Hydrocodone-acetaminophen combinations are often used to manage moderate pain in a variety of patients. The use of acetaminophen with an opioid allows a lower dose of each agent to be used than if either agent were used alone. However, by using a fixed-dose combination, it limits the prescriber's ability to raise dosages beyond the maximum daily dose of acetaminophen.

Hydrocodone is a semi-synthetic opioid similar to codeine. It is available only in combination with other drugs. It is most commonly used in combination with acetaminophen for pain control. Hydrocodone does not have any therapeutic advantages compared with other opioids, like oxycodone. However, hydrocodone-acetaminophen is a Schedule III controlled substance, while oxycodone-acetaminophen is a Schedule II controlled substance. This quirk in the law allows for more convenient outpatient prescribing of hydrocodone combinations. A Schedule II controlled substance prescription cannot be refilled and it cannot be telephoned into a pharmacy. Since hydrocodone-acetaminophen combinations can be refilled and telephoned into a pharmacy, they are popular. This "advantage" does not apply to the inpatient setting.

As tolerance develops with chronic use, the dosage of hydrocodone-acetaminophen has to be increased to get the same therapeutic benefit. Thus, fixed combinations of hydrocodone with acetaminophen are not a good choice for chronic pain.

Shands' policy does not allow patients to use their own supply of controlled substances. Patients who bring in their own supply of drugs like Vicodin®, Lortab®, or Lorcet® will have their prescriptions sent home with their families or stored securely with their other valuables until their discharge.

Ultracet® is a fixed combination of tramadol 37.5 mg and acetaminophen 325 mg. Tramadol and Ultracet® are popular in the ambulatory setting because prescriptions can be phoned into a pharmacy. Like with hydrocodone-acetaminophen-combinations, this is not an advantage for the inpatient setting. The P&T Committee has previously approved a restriction at Shands at UF to treat tramadol as a controlled substance.

Ultracet® has a labeled indication for short-term (ie, 5 days or less) management of acute pain. The

labeled dosage is 2 tablets every 6 to 8 hours with a maximum of 8 tablets per day (ie, 2.6 grams of acetaminophen and 75 mg of tramadol).

There are few published data on Ultracet®. These data suggest that Ultracet®'s pain relieving ability (ie, 2 tablets) is most similar to over-the-counter doses of ibuprofen (ie, 400 mg) and acetaminophen with codeine (ie, Tylenol® No. 3). It should be considered inferior to higher dosages of NSAIDs (eg, ibuprofen 600 mg & 800 mg) or oxycodone-acetaminophen (eg, Tylox® or Percocet®).

Whether tramadol and tramadol-containing products are acceptable alternatives in patients with drug-seeking behavior is controversial because of warnings regarding this population that are listed in the labeling. Tramadol has been associated with physiological dependence and long-term users should be tapered to avoid withdrawal symptoms.

Tramadol is associated with central nervous system adverse effects. Lower doses of tramadol are used to decrease these adverse effects. However, most patients already receive 50 mg of tramadol, and Ultracet® delivers a larger dose (ie, 75 mg) when the labeled dose is used. There are no published data on a 1-tablet dose for Ultracet®. A dose of tramadol 50 mg with an additional dose of 650 to 1000 mg of acetaminophen would be a reasonable alternative to Ultracet® that could cause less CNS effects. Prescribers using the labeled information (eg, the *PDR*) for Ultracet® would likely use the 2-tablet dose.

Tramadol can cause seizures. Patients with a history of a seizure disorder should not receive tramadol. Patients on drugs that lower the seizure threshold, including antidepressants (SSRIs & MAOIs) and neuroleptics, should not receive tramadol. Since many patients are receiving antidepressants, and since most patients do not have contraindications to NSAIDs or opioids, this limits the number of patients who are good candidates for tramadol.

Ultracet® costs 80 cents a tablet, which is $1.60 per dose. This is 7 times more expensive than Tylenol® No. 3, 18 times more expensive than Tylox®, and 32 times more expensive than ibuprofen 600 mg. Also, in the outpatient setting, Ultracet® is often a "tier 3" drug in most prescription benefit programs, which would require patients to pay high co-pays. This could decrease the use of this product and patient satisfaction.

Tramadol 50 mg with either 650 mg or 1 gram of acetaminophen is a reasonable alternative to Ultracet® in the inpatient setting based on the available evidence. Tramadol (alone) remains in the *Formulary* for use in combination with varying doses of acetaminophen.

Tizanidine was reviewed because it is a frequently used nonformulary drug. Tizanidine is an oral skeletal muscle relaxant that has been available in Europe for many years. The FDA approved it in 1996. The mechanism of action is not known, but its main effects are linked to its alpha-blocking effects. This is the reason that patients may experience a significant decrease in blood pressure (ie, hypotension) with tizanidine. Tizanidine has a short half-life (3 to 4 hours) and is relatively short-acting. The labeling states that it should be reserved for those daily activities and times when the relief of spasticity is most important. The labeled indication is for spasticity.

The Cochrane Database reviewed the use of tizanidine (and other muscle relaxants) in spasticity. They intended to do a meta-analysis, but the heterogeneity of the data did not meet their stringent standards. They did, however, do a systematic review of the available data. This review included 6 trials comparing tizanidine to baclofen and 1 that compared tizanidine to diazepam. Tizanidine has not been compared to cyclobenzaprine. They concluded that the efficacy and tolerability of tizanidine was similar to baclofen and diazepam for the treatment of spasticity. An independent meta-analysis reached the same conclusion. There were some patients who experienced more muscle weakness with baclofen, but these were patients with multiple sclerosis and spinal chord injuries. There is no good comparison data for other indications.

Somnolence and dry mouth are common adverse effects with tizanidine, which is reported more often than with baclofen. At normal dosages, tizanidine is about 30-times more expensive than baclofen.

Skeletal muscle relaxants are only appropriate for short-term use. The main reason to use tizanidine would be to continue outpatient therapy for patients who were recently placed on this drug. Tizanidine remains available through the nonformulary process. Patients can continue using their tizanidine from home under the patient's own medications policy, if they are admitted on this agent and a specific order is written to continue this home medication.

ADVERSE DRUG REACTION PREVENTION

Droperidol warning!

In December 2001, the FDA added a black-box warning to the labeling of droperidol. Droperidol has been on the market for over 30 years and this labeling change was surprising to many practitioners.

The black-box warning was based on multiple reports of patients developing torsade de pointes subsequent to droperidol administration, even at dosages that do not exceed the recommended range. The FDA recommended that droperidol be reserved for use only after alternative therapies have failed because of the potential proarrhythmic effects.

The FDA also recommended that all patients undergo a 12-lead ECG before administration of droperidol and continuing 2 to 3 hours after completion of therapy. Droperidol is now contraindicated in patients with known or suspected QT prolongation and caution is advised for patients at risk of QT prolongation due to existing diseases or concomitant drugs. These new stipulations in the labeling are difficult to implement.

Many institutions removed droperidol from their formularies or are planning to do so. Guidelines for ECG monitoring exist at about 1/3 of hospitals in a recent survey.

E-mail was sent to the medical staff asking for their input on the possible deletion of droperidol. 3 areas of use were identified where the prescribers felt like there is no good alternative: as a sedative during endoscopic procedures, as an adjunct to anesthesia in neurosurgical procedures that localize seizure foci (ie, droperidol does not raise the seizure threshold), and to treat migraine headaches refractory to other therapies. Unlike the use for nausea and vomiting, there may not be acceptable alternatives to droperidol in these indications. Those who felt that droperidol should remain in the *Formulary* for these indications uniformly felt that ECG monitoring is reasonable. However, the P&T Committee did not determine that a monitoring restriction was necessary.

Therefore, droperidol remains in the *Formulary* at Shands at UF. It will be removed from all SureMed® cabinets to limit immediate access.

An insert will be dispensed with each dose of droperidol that summarizes the black-box warning. The use of droperidol for nausea and vomiting is discouraged. When the benefits outweigh the potential risks, ECG monitoring is strongly recommended.

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Prescribing, *from page 1*
Approximately 90% of APAP undergoes hepatic glucuronide and sulfate conjugation to form inactive and harmless metabolites that are eliminated in the urine.

The remaining fraction (5 to 15%) is either eliminated unchanged in the urine or undergoes oxidation by CYP450 to a highly reactive electrophile, N-acetyl-*p*-benzoquinoneimine (NAPQI). NAPQI covalently binds to glutathione and forms a non-toxic complex. In overdoses, these pathways are overwhelmed, resulting in an increased formation of NAPQI, which depletes glutathione stores allowing it to bond covalently with critical cellular proteins proximal to the site of oxidative metabolism. This effect can occur in both the liver and kidneys resulting in cell death and necrosis.

Acetylcysteine is the antidote for acute APAP overdoses.[2] Acetylcysteine's sulfhydryl groups serve as a substrate for NAPQI in place of glutathione in the liver. The sulfhydryl groups bind NAPQI and render it unavailable to react with cellular proteins. Unfortunately, there is no known antidote for chronic APAP toxicity. Avoidance is the only "antidote."

The undesired toxicities of chronic APAP use can only be avoided by limiting the daily dose to < 4 grams during short-term therapy and < 2.6 grams daily during chronic therapy. APAP administered as single-entity products and combination products must be considered.

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The undesired toxicities of chronic APAP use can only be avoided by limiting the daily dose to < 4 grams during short-term therapy and < 2.6 grams daily during chronic therapy. APAP administered as single-entity products and combination products must be considered.

Shands at UF has several combination products containing APAP listed in the *Formulary*. These products include Tylox® capsules (oxycodone 5 mg-APAP 500 mg), Roxicet® Elixir (oxycodone 5 mg-APAP 325mg per 5 mL), and Tylenol® No.3 (codeine 30 mg-APAP 300 mg and codeine 12 mg-APAP 120 mg per 5 mL).

It is important to know a patient's current use of APAP before prescribing combination products containing APAP. Instructions should be given to hold a "PRN" APAP dose (eg, for fever) if an APAP-containing combination product has already been given (eg, for pain).

In the outpatient setting, patients should be given specific instructions on the dose and frequency of APAP. The American Academy of Pediatrics has published a position statement that parents be given written instructions on the dose and frequency of APAP for infants and children.

The US Pharmacopeia recommends up to 4 grams of APAP daily for short-term use. For chronic therapy, up to 2.6 grams daily can be used unless chronic treatment with higher doses is prescribed and monitored by a physician.[3] It is especially important to limit chronic doses of APAP to < 2.6 grams per day for patients with known risk factors for developing APAP toxicity. These steps can help to decrease APAP toxicity.

by Jay Weaver, PharmD

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