

Drugs & Therapy

B ♦ U ♦ L ♦ L ♦ E ♦ T ♦ I ♦ N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 21, 2002. 2 drugs were added in the *Formulary* and 2 drugs were deleted. 1 drug was evaluated, but not added: it was designated nonformulary and not available. In total, 5 drugs were designated not available.

◆ ADDED

Arsenic trioxide
(Trisenox[®] by Cell Therapeutics)

Dimercaprol
(BAL in Oil by Akorn)

◆ DELETED

Ergonovine injection
(generic by Bedford Labs)

Tolazoline (Priscoline[®] by Ciba)

◆ EVALUATED, BUT NOT ADDED

Dexmedetomidine*
(Precedex[®] by Abbott)

*Nonformulary and not available

◆ NONFORMULARY, NOT AVAILABLE

Desloratadine
(Clarinet[®] by Schering)

Fentanyl PCA Cartridges
(generic)†

Meperidine Oral & PCA
(generic)

Octreotide Depot
(Sandostatin LAR[®] Depot by
Novartis)

†50 mcg/mL the only strength still available

Arsenic trioxide is an inorganic metal used for the treatment of leukemia. The labeled indication for *continued on page 2*

PAIN MANAGEMENT

Ode to the Sphincter: The comparative effects of morphine and meperidine

Acute pancreatitis is a clinical syndrome characterized by severe acute abdominal pain, vomiting, and elevations in serum amylase and lipase concentrations. It is most commonly associated with alcohol ingestion and gallstones. Medical teaching has been that morphine

out the facts.¹

In 1 study identified in this review, Coelho and colleagues evaluated the effects of morphine, meperidine, and other narcotic analgesics on the biliary pressure of opossums (the chosen animal model for biliary studies).² Although biliary pressure was higher in animals that had undergone cholecystectomy, the difference between morphine and meperidine was not significant. Furthermore, in animals with a gallbladder, the increase in biliary pressure was not significant, regardless of whether morphine or meperidine was administered.

In a human trial by Economou and Ward-Mcquaid, 31 patients were given morphine, meperidine, or another narcotic agonist after cholecystectomy.³ Although biliary pressures were increased significantly from baseline in both the morphine and meperidine groups, there was no difference between the agents.

Pitfalls of early trials include the method by which biliary pressures were measured. Early studies used a T-tube, which is considered an indirect measurement that is more prone to error than modern methods of bile duct pressure measurement via ERCP. In a 1990 study by Thune and colleagues, morphine was compared to meperidine via direct manometry of *continued on page 4*

◆ Studies of narcotic effects on the sphincter of Oddi and bile duct pressures indicate that there is no difference between morphine and meperidine for acute pain relief in patients with pancreatitis.

should not be used for treatment of pain associated with pancreatitis because of the potential for inducing spasms in the sphincter of Oddi.

Meperidine was purported not to induce these spasms; therefore, it was the preferred opioid in this patient population. This was an irrational justification for the continued use of meperidine as a pain medication.

There is no head-to-head study comparing morphine and meperidine that shows any difference in pain-relief. Studies of the narcotic effects on the sphincter of Oddi and bile duct also suggest there is no difference between these agents.

Several investigators have examined the issue of narcotic analgesic effects in patients with acute pancreatitis. A review of clinical trials comparing various narcotic analgesics and their effects on biliary pressure helps sort

◆ INSIDE THIS ISSUE

- ◆ Tessalon[®] Pearl
- ◆ Dietary supplement safety

Formulary update, from page 1 arsenic trioxide is for the induction of remission and consolidation of acute promyelocytic leukemia (APL) in patients who are refractory to or have relapsed from retinoid and anthracycline chemotherapy and whose APL is characterized by the presence of the t(15;17) translocation of the PML/RAR-alpha gene expression. APL is a subset of acute myelocytic leukemia with this specific chromosomal abnormality. Although the exact mechanism of arsenic trioxide is not known, it appears to target the specific chromosomal abnormality present in APL cells.

Current therapy for newly diagnosed APL includes all-trans retinoic acid (ATRA) in combination with anthracyclines for consolidation, then ATRA for maintenance. Although most patients respond to standard therapy, about a third of patients that achieve remission will relapse.

Patients with APL who relapse are treated with stem cell transplantation (SCT), when an HLA-compatible donor is available. Arsenic trioxide offers an alternative to SCT. The response rate depends on the patient's previous treatment status, but more than half of the previously treated patients responded in clinical trials.

Treatment with arsenic trioxide is associated with serious adverse effects. There is a black-box warning about APL differentiation syndrome and QT prolongation. APL differentiation syndrome is characterized by fever, dyspnea, weight gain, pulmonary infiltrates, and pleural or pericardial effusions. This syndrome can be fatal. Arsenic trioxide can also cause QT interval prolongation and complete atrioventricular (AV) block. QT prolongation can result in torsade de pointes. Therefore, factors that increase the risk of QT prolongation (eg, hypokalemia and hypomagnesemia) must be considered and increased monitoring is required.

A typical induction and consolidation course of therapy will cost nearly \$36,000 and each additional consolidation course will cost \$11,000. Arsenic trioxide usually will be administered in the inpatient setting. Current reimbursement schemes will not cover this increased cost; therefore, patient selection will be important. The use of this agent in the inpatient setting is expected to be very low.

Dimercaprol is a chelator of heavy metals that is used as an antidote for arsenic, gold, lead, and mercury toxicities. It is given intramuscu-

larly—never intravenously. The 'oil' vehicle for dimercaprol is peanut oil, which should be considered in patients allergic to peanuts.

Dimercaprol must be available when arsenic trioxide is given. It is also used for rare, but serious, environmental toxicological exposures. Therefore, it has been stocked in the Pharmacy, although not officially listed in the *Formulary*. Dimercaprol was listed in the *Formulary* for these potentially life-threatening toxicities.

Ergonovine injection was a parenteral ergot alkaloid that was primarily used by cardiologists to induce vasospasm and diagnose angina (ie, the ergonovine provocation test). This has fallen out of favor and the manufacturer of injectable ergonovine has stopped making this drug.

Tolazoline was a parenteral direct peripheral vasodilator with moderate

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alpha-adrenergic blocking activity. It was recently discontinued by the manufacturer and is now unavailable. It was used by radiologists for special procedures. Nitroglycerin has replaced the use of tolazoline.

Dexmedetomidine is a relatively selective alpha-2-adrenergic receptor agonist with centrally mediated sedative effects. The sedative, analgesic, and anxiolytic properties of dexmedetomidine are attributed to decreased central noradrenergic activity. It has a labeled indication for short-term (ie, <24 hours) sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. There are no published data to support the use of dexmedetomidine for other indications.

There are few published data on dexmedetomidine for the labeled indication. Of the 3 major evaluations used for FDA approval, only 1 has been published. All of these trials compare dexmedetomidine to placebo and evaluate the need for supplemental sedatives to achieve a target sedation scale (ie, Ramsay score). Secondary variables include time to extubation, and total use of opioids, propofol, and benzodiazepines. Patients treated with dexmedetomidine did use less morphine and midazolam, but other benefits were not demonstrated.

One abstract showed a significantly shorter time to extubation, but the quality of these data could not be assessed.

Hypotension is the main adverse effect associated with the use of dexmedetomidine. Other adverse events include hypertension and nausea. In a study that assessed patient satisfaction, patients complained that they were undersedated on dexmedetomidine, despite appearing comfortable. Patients may also exhibit signs of withdrawal (nervousness, agitation, headaches, and increased blood pressure) if dexmedetomidine is stopped abruptly.

Based on the pharmacology of dexmedetomidine, there is interest in its use as a sedating agent in non-intubated, neurologically impaired patients who need to lie still for a procedure (eg, MRI). In this situation, it would provide sedative effects, but would not decrease respiratory function. However, dexmedetomidine does decrease blood pressure in about a third of patients. Also, dexmedetomidine could be used in the operating room (OR) for intravenous anesthesia and provide morphine-sparing effects, yet have no effect on respiration.

A particularly interesting niche for dexmedetomidine could be the facilitation of extubation. Other sedatives can cause respiratory depression, which can make extubation more difficult. Unfortunately, there are no published data to support the use of dexmedetomidine for off-labeled indications. Further, there are no published data that showed more rapid extubation, shorter ICU stays, or lower costs in the ICU when dexmedetomidine is used. Although there are theoretical pharmacologic advantages of dexmedetomidine, there is insufficient evidence that these pharmacologic differences result in better patient outcomes.

Dexmedetomidine costs about \$275 per day, which is nearly twice the cost of propofol and 7 times the cost of midazolam. There are no proven offsetting cost benefits.

Dexmedetomidine was not added in the *Formulary* and was designated nonformulary and not available. Should additional data be published supporting the use of dexmedetomidine, it will be re-evaluated by the P&T Committee.

Desloratadine is a nonsedating antihistamine. It is a metabolite of loratadine, which is the nonsedating antihistamine listed in the *Formulary*. Desloratadine has a labeled indication for the treatment of allergic rhinitis and chronic urticaria in patients at least 12 years old.

In October 2000, loratadine was designated the only nonsedating antihistamine in the *Formulary* and orders for cetirizine and fexofenadine are automatically interchanged to loratadine. There is no evidence that desloratadine offers any advantage over the other nonsedating antihistamines, including loratadine. Therefore, desloratadine was designated nonformulary and not available and will be automatically interchanged to loratadine (ie, 10 mg loratadine = 5 mg desloratadine).

Fentanyl PCA syringes were standardized. Having multiple concentrations of PCA syringes can lead to medication errors and, possibly, adverse patient outcomes. Rather than produce nonstandard concentrations of PCA syringes, increasing the basal rate of opioid is preferable. Therefore, 1 standard fentanyl PCA syringe (50 mcg/mL) is now listed in the *Formulary*. All other concentrations are nonformulary and not available.

Meperidine oral and PCA syringes are no longer available at Shands at UF. Meperidine is a synthetic, short-acting opioid. Because it is short acting, it often provides insufficient pain control. Post-operative agitation and other central nervous system adverse effects, such as seizures, are attributed to the normeperidine metabolite. This metabolite is problematic in patients with impaired renal function, but can also cause problems in patients with good renal function. The only appropriate uses of meperidine recommended by the Pain Committee are for the treatment of drug-induced rigors and for sedation and analgesia in short procedures.

Octreotide depot injection is a once-a-month dosage form of octreotide. Octreotide is used to treat acromegaly, carcinoid tumors, vasoactive intestinal peptide tumors (VIPomas), and various off-labeled indications. Octreotide injection is listed in the *Formulary* and costs approximately 97.5% less than the depot dosage form, which costs between \$1200 and \$1900 per dose. This incremental cost increase is not covered by current inpatient reimbursement schemes. Therefore, octreotide depot injection was designated nonformulary and not available for inpatient use.

NONFORMULARY DRUG USE

Clinical Pearl: Don't use Tessalon® Perles

Nonformulary drugs prescribed at Shands at UF are reviewed each month. One goal of this review is to discourage the use of unnecessary drugs. There is often little scientific evidence to justify listing these drugs in the *Formulary*. One approach is to designate these drugs not available. These drugs will not be obtained through the nonformulary system. However, it is preferable to use education to discourage the use of these products.

Benzonatate (Tessalon® Perles) is an example of a nonformulary drug with questionable benefit. Benzonatate is considered a "low priority" nonformulary drug. It will be acquired, but the acquisition is not urgent, since its efficacy is questionable.

Benzonatate is a long-chain polyglycol derivative chemically related to procaine. It has been used as an antitussive since 1958. Most references discourage the use of benzonatate. There are no randomized, controlled studies that assess the efficacy of benzonatate compared to placebo or other drugs.

Opioids have the most data showing antitussive effectiveness. According to the Chest Guidelines for Managing Cough as a Defense Mechanism and a Symptom, 1st-line therapy includes codeine and all phenanthrene alkaloid narcotics related to codeine, dextromethorphan, antihistamines, and NSAIDs for specific indications.¹ These medications have proven efficacy for the treatment of nonproductive cough in randomized, clinical controlled trials. Adverse effects and therapeutic dosages have been well studied.

Since opioids are effective in relieving nonproductive cough when the cause of the cough cannot be determined, opioids are 1st-line therapy in most clinical situations.¹⁻³ Dextromethorphan is also used, particularly

for over-the-counter therapy. However, opioids are usually preferable for severe, nonproductive cough.

There are 3 published cases where benzonatate was used to treat opioid resistant cough in terminal cancer patients.⁴ All of the patients received 10 mg of hydrocodone every 4 hours, with no relief of their symptoms. In 2 of the 3 patients, hydrocodone was discontinued and benzonatate 200 mg 3 times daily was added. The 3rd patient also had benzonatate 200 mg 3 times daily added, but continued to receive hydrocodone. In all 3 patients, the cough was relieved. These case reports suggest a possible niche for benzonatate, but this small case series represents a low level of evidence.

There is 1 published study that compares benzonatate with a lidocaine translaryngeal block in patients undergoing intubation.⁵ Benzonatate capsules (200 mg) provided rapid and reliable anesthesia for awake intubation; however, these patients also received 4 mL of lidocaine translaryngeally in both "treatment" groups. Whether benzonatate alone would be useful was not answered.

Evidence shows that opioids and dextromethorphan are effective for the treatment of cough. These alternatives should be used in place of benzonatate. There is insufficient evidence to use benzonatate for opioid-resistant cough or as a topical anesthetic to facilitate awake intubation.

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- Type of reaction
- Whether the reaction was: — probable, possible, or definite
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Pain management, from page 1 the sphincter of Oddi.⁴ Although the effects of phasic wave frequency were different for the 2 agents, there was no significant change from baseline in basal pressure, amplitude, or wave propagation direction.

This study, when considered with studies available for other narcotic agents, suggests that narcotics affect the sphincter of Oddi through altering the wave frequency of sphincter contractions, not through direct pressure effects. It has been hypothesized that because morphine and meperidine both affect phasic frequency, they affect the "filling" phase of the sphincter of Oddi, leading to an increase in biliary pressure indirectly, but not increasing the basal sphincter pressure.

Other potential concerns when deciding to use morphine or meperidine in treatment of moderate to severe pain are inherent in the pharmacology of the agents. Meperidine is metabolized to a neurostimulant (ie, normeperidine). This can potentially increase the risk for occurrence of adverse CNS events, including seizures. Also, duration of pain relief is generally shorter for meperidine than morphine, requiring a more frequent dosing interval when meperidine is used.

When choosing an opioid to treat

pain associated with acute pancreatitis, analgesic efficacy is the greatest concern. Morphine may be a useful pain reliever for some patients. Meperidine is not a good choice because it offers no beneficial effect on the sphincter of Oddi and is inferior from an efficacy and safety perspective.

By Rebecca Melin, PharmD

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QUOTABLE QUOTES

Safety of Dietary Supplements

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"In essence, [dietary] supplements exist in a 'data-free world.' In the United States, the public spends almost \$4 billion yearly on supplements, with little or no data on what they can expect. We rely on the market to prove efficacy and safety, a strategy that failed before with prescribed drugs and resulted in the establishment of the FDA. We should learn from our experiences. Perhaps the time has come to hold the manufacturers of any product with a health claim to the same standards as the pharmaceutical industry."

James D. Lewis, MD, MSC
Brian L. Strom, MD, MPH

From: Balancing Safety of Dietary Supplements with the Free Market. *Ann Intern Med* 2002;136:616-8. April 16, 2002.