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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 on August 19, 2003. 3 drugs were added in the *Formulary*. 3 drugs were deleted and 9 products were designated not available. A previously approved therapeutic interchange has been implemented based on the results of bidding these products.

◆ ADDED

Aprepitant* (Emend® by Merck)

Restricted

Atazanavir (Reyataz® by Bristol-Myers Squibb)

Ramipril (Altace® by Wyeth)

◆ DELETED

Bosentan (Tracleer® by Actelion)

Methyltestosterone (generic)

Tocainide (Tonocard® by AstraZeneca)

◆ NONFORMULARY AND NOT AVAILABLE

Benazepril (Lotensin® by Novartis)

Bortezomib (Velcade® by Millennium)

Fosinopril (Monopril® by Bristol-Myers Squibb)

Moexepril (Univasc® Schwarz Pharma)

Moxifloxacin (Avelox® by Bayer)

Perindopril (Aceon® by Solvay)

Pioglitazone (Actos® by Lilly)

Quinapril (Accupril® by Pfizer)

Trandolapril (Mavik® by Knoll)

◆ THERAPEUTIC INTERCHANGES

Rosiglitazone (Avandia®) for **Pioglitazone** (Actos®)

(continued on next page)

POLICIES AND PROCEDURES

More invalid abbreviations

Effective October 5, 2003, there will be 5 more (now a total of 10) unacceptable abbreviations that will make an order invalid. Prescribers will be contacted for order clarifications for all orders with unacceptable abbreviations. The elimination of these abbreviations are recommended by the Institute for Safe Medication Practices (ISMP).

MSO4 and MgSO4 can be confused. Getting a dose of magnesium instead of morphine is an avoidable error. Mistakenly receiving a dose of morphine can lead to respiratory depression and have tragic consequences.

Most people cannot even remember what "cc" stands for. Instead of cubic centimeter, the correct unit is milliliter (mL). When handwritten, "cc" can be mistaken for zeros or the abbreviation for units.

The original 5 unacceptable abbreviations listed above also make an order invalid. In order to avoid the need to rewrite an order, please do not use these abbreviations.

	INAPPROPRIATE ABBREVIATION	APPROPRIATE ABBREVIATION
EFF. 10/5	QD or OD	Spell "daily" instead.
	< or >	Spell "less than" or "greater than."
	MSO4	Spell "Morphine."
	MgSO4	Spell "Magnesium sulfate."
	cc	Use "mL" instead.
ORIGINAL	U	Spell "Units" instead.
	IU	Spell "International Units" or "Units" instead.
	µ (Greek mu symbol)	Use "mcg" for micrograms.
	doses less than 1 unit	Use leading zero (eg, 0.1 mg).
	doses greater than 1 unit	Do not use trailing zero (eg, 1 mg).

Obviously, the more legibly orders are written, the better. However, even with carefully written orders, abbreviations have been associated with problems.

The abbreviation for daily (QD) can be mistaken for the abbreviation for 4 times a day (QID). This can lead to a 4-fold overdose. Therefore, QD must not be used. The abbreviation for once daily (OD) can be confused with the abbreviation for "right eye" (OD = oculus dexter) and can result in the administration of oral medications in the eye.

The symbols for less than (<) or greater than (>) are commonly misinterpreted. The "less than" symbol is interpreted as "greater than" and vice versa. This can lead to overdosing or underdosing. Both can cause significant patient harm.

INSIDE THIS ISSUE

◆ Drug allergies

◆ Imipenem use evaluated

Formulary update, *from page 1*

Aprepitant is an oral "add-on" therapy for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. It is a selective antagonist of substance P receptors. Clinical trial data suggest it is beneficial in improving the percentage of patients who have no nausea or vomiting after receiving highly emetogenic chemotherapy. However, published data may exaggerate the treatment effect since clinical trials do not include the usual therapy for delayed nausea and vomiting (ie, metoclopramide). Aprepitant's improvement of delayed chemotherapy-induced nausea and vomiting accounts for most of its benefits.

Data suggest that aprepitant has a low incidence of common adverse effects. However, the overall safety profile is unknown, since published data are limited. Aprepitant does have the potential to interact with many drugs patients could be receiving concomitantly, including chemotherapy and other antiemetics.

Aprepitant is expensive with a typical 3-day course of therapy costing approximately $250. Off-label use and overuse is a concern. Thus, aprepitant's use was restricted to approval by an oncology pharmacist. The criterion for approval will be for use in patients receiving highly emetogenic chemotherapy who have failed standard antiemetics in their first treatment cycle. A medication use evaluation (MUE) will be done after 6 months have passed to monitor the use of aprepitant.

Atazanavir is the first once-a-day protease inhibitor with a labeled indication for the treatment of HIV-1 in combination with other antiretroviral agents. With the emphasis of giving fewer doses per day (ie, decreased pill burden) to improve compliance, atazanavir will be considered for antiretroviral regimens along with 2 nucleoside reverse transcriptase inhibitors.

Antiretroviral drugs are usually added in the *Formulary* to ensure continuity of care. A delay in therapy could contribute to drug resistance. Drug regimens are being selected by genotyping and phenotyping and, thus, continuing the same drug is critical in this patient population.

Ramipril was added in the *Formulary* when the angiotensin converting enzyme (ACE) inhibitors were reviewed. Ramipril has been a frequently requested nonformulary drug. Ramipril's addition was based on the data published in the Heart Outcomes Prevention Evaluation (HOPE) trial.

Although it is generally believed that ACE inhibitors are similar, not all prescribers agree with this viewpoint. The HOPE trial provided unique data showing benefit for the use of ramipril in reducing cardiovascular complications in patients 55 years of age or older and who are at risk for these complications, but who do not need an ACE inhibitor for heart failure, uncontrolled hypertension, diabetes, or renal disease. Therefore, ramipril was added in the *Formulary* for this narrow indication.

Captopril, enalapril, and lisinopril are the ACE inhibitors that have been and remain listed in the *Formulary*. Captopril and enalapril are often used in pediatric patients. Lisinopril is the preferred once-daily ACE inhibitor listed. Lisinopril is available as a generic and is an inexpensive option in the category. In the outpatient setting, patients will pay less for lisinopril than other once-daily ACE inhibitors, whether they are insured and pay a co-pay or if they pay cash for their prescriptions.

The remaining 6 oral ACE inhibitors on the market (**benazepril**, **fosinopril**, **moexepril**, **perindopril**, **quinapril**, **trandolapril**) will no longer be available through a nonformulary request, effective October 1, 2003. When these drugs are prescribed in September, prescribers will be contacted and alerted to this pending change. Pharmacists will be prepared to offer an approximate equivalent dosage of lisinopril. A dosage equivalent chart is available on the Shands intranet at http://intranet.shands.org/pharm/ACEI_Convert.pdf.

Bosentan is an endothelin antagonist that is used as an oral alternative to intravenous epoprostenol (Flolan®) for the treatment of pulmonary hypertension. It was added in the *Formulary* in October 2002.

Recently, Shands at UF was notified that the hospital can no longer stock this drug. The manufacturer stated that the FDA mandated that bosentan be limited to only a restricted distribution program because of concerns about hepatotoxicity. Since bosentan can no longer be stocked, it was deleted from the *Formulary* and designated a "high-priority" nonformulary drug. Patients will have to provide their own supply for use during their hospitalization.

Methyltestosterone tablets are not used in the inpatient setting. There has been no use of methyltestosterone in the past 2 years. Therefore, it was deleted from the *Formulary*

Tocainide is an oral, local anesthetic-type antiarrhythmic agent similar to mexiletine. It has been used only to treat life-threatening arrhythmias.

Serious adverse effects have been associated with tocainide and have limited its usefulness. Bone marrow suppression and pulmonary fibrosis are rare, but serious, adverse effects associated with the use of tocainide.

AstraZeneca will stop making tocainide tablets on December 31, 2003. In anticipation of this drug being discontinued, the use of this agent was evaluated. Tocainide has not been used at Shands in the last 2 years; therefore, it was deleted from the *Formulary*.

Bortezomib is a potent, selective, and reversible inhibitor of the 26S proteasome in mammalian cells. It induces apoptosis in a wide variety of cancer-cells. Bortezomib has a labeled indication for the treatment of multiple myeloma in patients who have received at least 2 prior therapies and have demonstrated disease progression on the last therapy.

The official labeling of the product states no trials have demonstrated a clinical benefit, such as an improvement in survival; however, secondary outcomes in a Phase 2 trial suggest patients responding to bortezomib therapy demonstrated an improved survival rate.

The most commonly reported adverse events associated with the use of bortezomib are asthenia (fatigue, malaise, and weakness), nausea, diarrhea, decreased appetite, constipation, thrombocytopenia, peripheral neuropathy, pyrexia, vomiting, and anemia. However, the causality of these reported adverse effects is difficult to assess. Multiple myeloma and the concomitant therapies used to treat it also contribute to these adverse effects.

The cost implications of bortezomib are complex. One course of treatment will cost approximately $24,000. Currently, bortezomib has no outpatient reimbursement code for a hospital-based clinic.

Previously, the P&T Committee has not added drugs in the *Formulary* that did not have an outpatient reimbursement code. In these situations, however, there were alternatives available (eg, Aranesp® vs EPO). The alternative in this situation is to refer patients to community physicians, who can bill for this therapy (as a physician operated clinic). Until bortezomib's reimbursement issues are resolved, it will not be available in the inpatient setting nor from any Shands-based clinic.

Rosiglitazone and **pioglitazone** are thiazolidinedione oral antidiabetic agents. These drugs are sometimes referred to as insulin sensitizers or "glitazones." This category was reviewed because of

the high volume of nonformulary requests for pioglitazone.

The published evidence suggests that rosiglitazone and pioglitazone have similar effects on blood glucose, and, thus, hemoglobin A_{1C} concentrations. The only minor differences between these agents appear to be in the adverse effects associated with their use. Rosiglitazone was selected because it is less expensive than pioglitazone.

Pioglitazone appears to have a more favorable effect on blood lipids (ie, cholesterol and triglycerides), but it is associated with more reported weight gain and peripheral edema. For the short time that patients are hospitalized on these agents, these differences were not considered clinically relevant.

An automatic interchange has been approved for the conversion of pioglitazone to rosiglitazone. The conversion is as follows: rosiglitazone 2 mg will be dispensed for pioglitazone 15 mg; rosiglitazone 4 mg will be dispensed for pioglitazone 30 mg; and, rosiglitazone 8 mg will be dispensed for pioglitazone 45 mg. Most patients are expected to receive 4 or 8 mg of rosiglitazone. Pioglitazone will no longer be available through the nonformulary system.

MEDICATION ERROR PREVENTION

Preventing allergic reactions to drugs

Documenting and reporting drug allergies is a multidisciplinary process involving several steps. During the patient's initial assessment, the physician questions the patient about his allergy history. Further probing may be warranted to understand the reaction better.

Additionally, nursing conducts an initial patient assessment. If an allergy is noted, the nurse places a red wristband on the patient. This assists other hospital staff in identifying patients with allergies. The nurse also provides allergy documentation to the unit clerk. The unit clerk enters the information into the hospital information system (HIS). The information in the HIS is sent to the pharmacy computer system. Pharmacists can then screen for drug allergies. These steps are essential in preventing allergic reactions in the hospital setting.

Patients often do not understand the difference between allergies and adverse effects. Common adverse effects may be falsely recorded as allergies, which may limit therapeutic options. For example, a patient who experiences vomiting while receiving morphine is not "allergic" to morphine. Also, patients often mistake a histamine-induced rash as an allergic reaction after the administration of morphine. Previous exposure to similar medications or descriptions of the reaction may help to clarify allergy histories.

Accurately reporting and communicating allergy information during a patient's hospitalization is as critical as the initial assessment. Physicians can write orders to add or delete allergies from a patient's profile into HIS. If this communication does not occur, the patient's safety may be at risk.

For example, a nurse may notify the physician about an allergic reaction. The reaction would be treated appropriately, and the medication discontinued. If the HIS is not updated appropriately, pharmacy may dispense a similar drug at a later date, which could cause a similar event. Updating the allergy information could have prevented this second event from occurring.

The diagnosis of allergic reactions can be challenging. The presentations of allergic reactions vary. Manifestations may include rashes, vasculitis, anaphylactic reactions, and Stevens-Johnson syndrome. These varied presentations make it difficult to link a reaction with a medication. Physicians are left with the dilemma of interpreting and managing the reaction.

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Accurately reporting and communicating allergy information during a patient's hospitalization is as critical as the initial assessment.

A helpful tool in identifying the causative medication includes the time period between initiating the medication and the immune reaction — or temporal relationship. Allergic reactions typically present within several minutes to several days after initiating a medication. It is unlikely a medication initiated 2 weeks ago would elicit a drug allergy. This temporal relationship is key in assessing the causality of a reaction.

Additionally, it makes sense to know the medications that are most often associated with allergic reactions. Beta-lactam antibiotics, sulfonamide medications, heparin, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid-containing medications are commonly associated with "allergic" reactions.

Although commonly reported as drug allergies, many of these medications do not produce true or typical allergic reactions. Heparin may cause antibody formation, which targets and destroys platelets. This is commonly referred to as heparin-induced thrombocytopenia (HIT). Heparin should be avoided in the future in these patients. NSAIDs inhibit the production of prostaglandins, which may produce symptoms of shortness of breath. Even though this is not a typical "allergy," it is serious and should be recorded as an allergy so the patients will not receive NSAIDs in the future. Beta-lactam antibiotics can produce classic IgE-mediated reactions or anaphylactic reactions.

Although the reactions may differ from patient to patient, several characteristics are common with allergic reactions. First, allergic reactions occur after repeated use of the medication. Second, a small dose, or "test" dose, can cause a manifestation. Third, the manifestation should diminish over time once the medication is discontinued. If rechallenged with the medication, a similar reaction can occur.

Treatment of allergic reactions depends on the nature and severity of the reaction. The medication should be discontinued unless the benefits outweigh the risk of using the medication. Epinephrine and maintaining the patient's airway are first-line therapies for severe, anaphylactic reactions. Conversely, patients with a minor rash may be treated appropriately with antihistamines and systemic corticosteroids. Histamine-mediated reactions, like often reported with opioids, can be managed by pretreatment with antihistamines.

At the time of discharge, any allergy changes should be explained in detail to the patient. The patient can provide this information to pharmacies in the community and his primary care physician to help ensure accurate allergy documentation…and to help avoid future reactions.

by Todd Correll, PharmD

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MEDICATION USE EVALUATION

Imipenem streamlining is useful

Imipenem was a relatively high volume antibiotic at Shands at UF in 2002, particularly in the intensive care units. In March 2003, the manufacturer issued information regarding a decrease in imipenem manufacturing and distribution due to manufacturing difficulties. The projected restricted distribution was expected to last a few months; however, it is difficult to rely on these estimates. In order to prevent a critical shortage, the Anti-Infective Subcommittee established use criteria to try to limit imipenem use to the most critical patients. Criteria were developed with input from the major prescribers of this agent.

These criteria were accompanied by a procedure for ongoing review. A clinical pharmacist evaluated all imipenem orders within 72 hours following the antibiotic initiation. Patients were evaluated based on the indication for use, culture and sensitivity reports, and site-source of infection. If imipenem use did not meet the approved criteria, alternative antibiotics were recommended to the primary medical team.

Imipenem use was considered appropriate if the any of the following criteria were met:

- Serious nosocomial infections due to multi-drug resistant gram-negative bacilli
- Necrotizing pancreatitis
- As monotherapy for patients with complicated intra-abdominal infection when other beta-lactam antibiotics are not appropriate (ie, allergies, antibiotic failure, culture/sensitivities)
- Intra-abdominal infection with failure of primary therapy (ie, cefepime + metronidazole, ciprofloxacin + metronidazole, Timentin®)
- Intra-abdominal infection with the presence of at least 1 organism that is resistant to other beta-lactam antibiotics
- Intra-abdominal sepsis in patients without documented infectious source at the time of decompensation
- As monotherapy for complicated skin and soft tissue infections with multiple organisms involved, 1 of which is resistant to other beta-lactam antibiotics.

A formal evaluation was done for 53 patients who received imipenem over 5 weeks from May 12, 2003 to June 13, 2003. 1 patient expired within the 48 hours of receiving imipenem and was excluded from the results. One patient received 2 treatment courses of imipenem and was counted as 2 separate occurrences to evaluate appropriate imipenem utilization. 32 patients (60.3%) received imipenem for indications consistent with the P&T-approved criteria for use. 21 patients (39.6%) did not meet the P&T-approved criteria for imipenem use. 4 of these 21 patients were changed to alternative therapy before the prescribers were contacted. Of the remaining 17 patients, 12 were successfully converted to alternative therapy.

This evaluation found that most prescribers reserved imipenem for complicated infections or multiply-drug-resistant organisms. Most of the patients who received a carbapenem for uses not listed in the approved criteria were converted successfully to an alternative agent. These results provide support for other possible antibiotic streamlining efforts.