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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 16, 2006. 2 drugs were added in the *Formulary* and 2 drugs were deleted. The age-of-use criterion for 1 drug was modified.

◆ ADDED

Cetuximab*
(Erbitux® by Bristol-Myers Squibb)

Cholestyramine Light in Aquaphor® (compounded)

**Restricted to credentialed chemotherapy prescribers*

◆ DELETED

Amyl nitrite (generic)

Doxacurium
(Nuromax® by Abbott)

◆ CRITERIA FOR USE

Promethazine
(Phenergan® & generics)*

**Cannot be used in children less than 2 years of age*

Cetuximab is a recombinant, human-mouse chimeric monoclonal antibody that binds to epidermal growth factor receptors (EGFR). Overexpression of EGFR on cancer cells has been associated with a poor prognosis, decreased survival, and a higher incidence of metastasis. Cetuximab currently has labeled indications for the treatment of metastatic colorectal cancer intolerant to irinotecan-based chemotherapy and in combination with radiation therapy for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) or as a single agent for the treatment of recurrent or metastatic SCCHN in patients who have failed platinum-based therapy. It was evaluated for addition in the *Formulary* because it is an injectable oncology

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NEWS

Prescribing generics improves compliance

A recent study published in the *Archives of Internal Medicine* suggests that compliance (adherence) is 60% better for generics than nonpreferred brand name drugs.[1] In this study, which was done in relatively young patients with a third-party prescription drug program and a 3-tiered formulary, compliance was best with generic drugs, less with brand-preferred drugs, and worst with nonpreferred brand name drugs. These compliance estimates were based on refill data and may actually underestimate the difference in compliance between inexpensive generics and more expensive brand name drugs. If a patient refused to fill the initial prescription because of cost, then it would not have been included in this study's estimate of compliance.

Tiered formularies are designed to steer patients towards prescriptions that are less expensive for the employer or other agency that provides the prescription benefit. With 3-tiered formularies, a patient's co-pay or "out-of-pocket" expenditures increases with each tier. Generic co-pays are always the least expensive. Preferred brands are often chosen because manufacturers provide rebates to third-party payors. Nonpreferred brands are more expensive or are not deemed medically necessary in the benefit plan (eg, lifestyle drugs). This study did not state the co-payments that patients were required to pay for each tier and did not give examples of the types of drugs in the third tier. Although not proven in this study, the implications are that patients' compliance rates increase when they have to pay less "out of pocket" even when they have a prescription drug benefit.

In this study, the compliance rate was lowest for inhaled corticosteroids (ie, 20.6%). The importance of compliance for the treatment of asthma is well known for the prevention of acute exacerbations, which can be extremely serious and require hospitalization. The study also showed that older patients and patients with higher incomes were more compliant. The estimate of 60% greater compliance with generic drugs was adjusted for drug class and age.

Unfortunately, most prescribers do not know what the preferred brands are in a patient's prescription drug plan.[2] Therefore, it is always a good option to choose a generic when there are equally effective agents in a therapeutic category. A list of selected generic choices within some therapeutic categories can be found on our intranet site at http://intranet.shands.org/pharm/Drugs%20Available%20As%20Generics.pdf.

It is recommended that prescribers ask patients if they have difficulty paying for their prescriptions and to determine if there are less expensive alternatives, when needed.[3,4] Pharmacists can help prescribers determine what options exist in a patient's prescription benefit plan.

With the establishment of Medicare Part D, there are now many more patients who have a prescription benefit plan. It is difficult to keep up with the preferred drugs in each plan. Thus, the use of generics is a good option when there is a generic alternative within a category. Lack of patient response to drug therapy may be a reflection of their lack of compliance because of their inability to pay for their prescriptions.[4]

References available upon request to the editor.

INSIDE THIS ISSUE

Formulary update, *from page 1*
drug that may require use in the inpatient setting.

Normal human epithelial cells, such as skin and hair follicles express EGFR, a transmembrane glycoprotein that is a type I tyrosine kinase receptor. Human cancer cells of the head and neck, colon, and rectum may express EGFR. Cetuximab is an EGFR inhibitor that interferes with the tyrosine kinase cascade and arrests cell growth.

When used as a single agent or in combination with irinotecan in irinotecan-refractory metastatic colorectal carcinoma, cetuximab has been shown to increase overall partial response and time to progression. In patients with SCCHN, response rates, time to progression, and overall survival were increased with the addition of cetuximab to either radiation or platinum-containing chemotherapy.

Cetuximab has a black-box warning about the potential to cause a severe infusion reaction, which is defined as rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension, and/or cardiac arrest. This reaction has been reported in 3% of patients, and these reactions were sometimes fatal (ie, less than 1 patient in 1000 patients). Due to the potential for cardiopulmonary arrest associated with infusion, caution is recommended in patients who have a history of cardiac disease. Profound hypomagnesemia and hypocalcemia have also been reported based on postmarketing surveillance experiences; thus, cetuximab requires continuous monitoring. Another more common adverse effect associated with cetuximab is an acneform rash. There has been a positive correlation between response rates and rash in patients with colorectal carcinoma.

Patients are usually treated with intravenous diphenhydramine before each cetuximab dose. Dexamethasone pre-treatment has also been used. If patients experience a mild to moderate infusion reaction, the infusion rate is decreased by 50%. Cetuximab should be immediately stopped when more serious infusion reactions occur. Treatment must also be stopped when patients develop a serious rash. There are dosage reduction recommendations when the rash is less severe.

Each vial of cetuximab costs approximately $470 and a typical course of therapy costs approximately $3000 per cycle. The inpatient use of cetuximab is anticipated to be modest.

Cetuximab was added for use for its labeled indications when patients cannot tolerate treatment in the outpatient setting and when patients are admitted for another medical problem and their cetuximab treatment is due.

Cholestyramine is a resin that binds bile acids. When given orally, the binding of bile acids in the intestine indirectly decreases serum cholesterol. Cholesterol is a precursor for bile acids. Cholestyramine stimulates cholesterol synthesis to replace the bile acids eliminated in the feces, but shunts cholesterol into the bile acid synthesis pathway. This causes the liver to increase cholesterol uptake and decreases serum cholesterol. Cholestyramine Light is sugar-free (eg, contains aspartame), while regular cholestyramine contains sucrose.

Aquaphor® (white petrolatum) is used alone as a topical protectant. Pharmacists use Aquaphor® to compound many topical products because it easily forms emulsions with aqueous solutions and oily substances.

Cholestyramine Light in Aquaphor® has been a commonly requested nonformulary mixture for use as a "butt paste" in patients with treatment-resistant diaper dermatitis. It was evaluated because of its high volume of use.

Good hygiene (eg, prompt removal of stool and urine), cleansing with warm water and a mild soap, and completely drying the area (eg, before re-applying a diaper) are very important in the treatment of diaper dermatitis. Zinc oxide is the most commonly used protectant.

In reviewing the evidence regarding the mixture of Cholestyramine Light in Aquaphor®, no randomized trials documenting efficacy were found. There are, however, case reports supporting this mixture. 2 case series showed resolution of refractory skin irritation in patients with ostomies who failed traditional therapies. There is also 1 published case report of resolution of diaper dermatitis in a patient who was refractory to all other therapies. The Dermatology Division supports the use of this product for resistant diaper dermatitis and supports its addition in the *Formulary.* Also, several pediatric practitioners support its addition. The rationale for this mixture is that topical cholestyramine binds bile acids that are irritating to the skin.

Therefore, the P&T Committee added compounded Cholestyramine Light in Aquaphor® in the *Formulary.* Orders written for "Butt Paste" will not be honored and will require a clarification (ie, orders must be for "Cholestyramine Light in Aquaphor").

Amyl nitrite is an inhaled nitrite that was once used for the treatment of angina. There are, however, no contemporary uses for amyl nitrite, except as part of the Cyanide Kit, which is listed in the *Formulary.*

Amyl nitrite was deleted from the *Formulary* because it is never used as a single agent. It has not been stocked in the Pharmacy for many years, but was not formally deleted from the *Formulary* until now.

Amyl nitrite is in Cyanide Kits along with injectable forms of sodium nitrite and sodium thiosulfate. Patients exposed to cyanide require rapid treatment including decontamination, airway management, and oxygen therapy. The nitrites are used based on the theory that they induce methemaglobinemia, which provides ferric ions in hemoglobin to bind cyanide and prevents its binding to cellular iron, which causes cellular toxicity. Inhaled amyl nitrite is only used until intravenous sodium nitrite can be given. Sodium thiosulfate is given so that cyanide will form thiocyanate, which can then be safety excreted.

Doxacurium is a long-acting, nondepolarizing, neuromuscular blocking agent that has been discontinued by its manufacturer (ie, Abbott). Since it is no longer marketed, it was deleted from the *Formulary* and designated nonformulary and not available. Pancuronium is the long-acting nondepolarizing neuromuscular blocking agent still available in the *Formulary.* There are also several other intermediate- and short-acting skeletal muscle relaxants available.

Promethazine is a phenothiazine with antihistamine properties (ie, a H1-blocker) that has been on the US market since 1951. It is used for its anticholinergic, sedative, and antiemetic effects.

Recently, the FDA issued a labeling change that states that promethazine is contraindicated in children less than 2 years of age because of potential to cause fatal respiratory depression. Postmarketing cases of respiratory depression in this patient population have resulted in fatalities. Therefore, promethazine use in children less than 2 years of age is prohibited at Shands at UF.

COST-EFFECTIVE DRUG THERAPY

Starting warfarin therapy early shortens LOS

There is a bed shortage within our institution causing patients to wait to receive care. As healthcare professionals, we are currently seeking innovative ways to increase bed availability. A way to "add beds" is to efficiently treat patients, thereby minimizing length of stay (LOS). Early initiation of oral anticoagulants is an efficient method of treating deep venous thrombosis (DVT) and pulmonary embolism (PE). By starting patients' anticoagulation early, they will stabilize sooner, which could allow earlier discharge and increase available beds.

The most recent guidelines for the treatment of venous thrombosis recommends concomitant administration of heparin and warfarin at the time of diagnosis of DVT or PE (ie, both drugs started on day 1).[1] In addition, day 1 initiation of warfarin is recommended for patients with a known protein C deficiency or other thrombophilic states.[1,3]

Despite the guideline's recommendation for simultaneous oral anticoagulation at time of DVT/PE diagnosis, there may be a problem with day 1 warfarin treatment. The main controversy surrounding same-day initiation of warfarin and heparin is the theoretical risk of creating a period where the patient is hypercoaguable.

The risk of a hypercoaguable state is based on the rapid depletion of protein C due to its half-life of 6–8 hours.[3] Warfarin's mechanism of action is through inhibition of vitamin K-dependent clotting factors.[3] In addition, protein C and protein S, which are natural anticoagulants, are also depressed due to their vitamin K dependence.[3] Anticoagulant effects occur sooner with unfractionated heparin (UFH) and low molecular weight heparins (LMWHs) due to their short half-lives (ie, rapid steady state) and the short half-lives of the factors they inhibit.[2]

It may take 4 to 6 days for a patient to become therapeutic when warfarin is used as a single agent.[3] This is due to the variability of the half-lives of the clotting factors and warfarin's long half-life. Upon initiation of warfarin, protein C is quickly depleted, leaving the patient naturally and therapeutically at risk for thrombosis. However, published literature does not support this risk.

Studies have shown that recurrence of thrombosis occurs at the same rate, despite early or late warfarin initiation with concurrent heparin. Hull and colleagues showed that 5 days of intravenous heparin with early initiation of warfarin on day 1 of treatment (short-course) was as effective as 10 days of heparin with day-5 initiation of warfarin (long-course).[4] They determined that the recurrence of thrombosis was 7.0% in the long-course therapy compared to 7.1% with the short-course group.[4] Gallus and colleagues assessed day-1 warfarin treatment compared to day-7 warfarin treatment and also found similar rates of recurrence for both groups, 3.6% and 4.7%, respectively.[2] Thus, these data do not support an increased risk of thrombosis recurrence when beginning warfarin on day 1 with heparin therapy in the setting of a controlled clinical trial.

In addition, numerous studies have documented a shortened LOS with early initiation of warfarin. One small, retrospective study assessed LOS with warfarin started within 24 hours of heparin compared to starting 24 hours after heparin and determined that LOS was decreased by 2 days for the early start group.[5] A similar study showed a 2.2-day decrease in LOS with early initiation of warfarin.[2]

A caveat to applying the results of the above studies is that in a controlled setting patients may be adequately anticoagulated with UFH sooner due to strict observance of treatment protocols. Current data collected at Shands at UF suggests that roughly 50% of patients receiving the institution-approved DVT/PE UFH weight-based treatment protocol do not acheive timely therapeutic anticoagulation (ie, within 24 hours) due to inappropriate protocol adjustments. Before initiating day-1 warfarin and heparin treatment, we first need to improve day-1 therapeutic UFH use by being more compliant with the UFH protocol. Another option for day-1 treatment would be to combine warfarin with therapeutic doses of LMWHs, which achieve therapeutic anticoagulation after the first dose. However, the drawbacks with this treatment approach are the lack of known dosage adjustments for renal failure and the prolonged duration of effect when overdoses are given.

A second concern about the early initiation of warfarin with UFH for DVT or PE is insufficient duration of heparin administration. The guidelines recommend that UFH be discontinued when the INR is stable and above 2, which typically occurs within 5 to 7 days of concomitant anticoagulation therapy.[1,3] The theory supporting the use of at least 5 days of overlapping UFH is that warfarin's anticoagulant effects are typically delayed for 4 days until all clotting factors are therapeutically depressed.[3] By continuing UFH until warfarin has depressed the vitamin K-dependent clotting factors, (ie, 5 to 7 days), it ensures that patients are adequately anticoagulated.

In order to set a goal discharge of 5 days post DVT/PE diagnosis, warfarin must be started on treatment day 1 to achieve 2 therapeutic INRs before discharge. However, improved compliance with the heparin protocol is needed before this can be instituted. Then, early administration of warfarin for thrombosis treatment could decrease LOS and provide hospital beds for needy patients.

By Erin McCann, PharmD

References available upon request to the editor.

POLICIES AND PROCEDURES

Automatic approval for "Patient May Take Own Meds"

When a patient is admitted, the admitting physician continues those home medications that are needed during the patient's hospitalization. If the drug is listed in the *Formulary,* the drug is dispensed. If the drug is not listed in the *Formulary,* but we have a supply from a previous nonformulary request, the drug is dispensed. However, there are nonformulary medications that are not available.

Rather than go through the complete nonformulary process, the easiest solution to continue a patient's home medication is to use their own supply, if they brought their prescriptions from home. In the past, a pharmacist had to page the prescriber, describe the situation, and get an order for the patient to continue his or her own supply of medication. Since this is universally approved, the P&T Committee approved a "P&T-Authorized" order to allow the patient to use his or her own supply of medication in this circumstance.

In order for this process to be implemented, a complete order must be written (eg, drug, strength, route, and frequency). Orders like, "May take home meds" will not be accepted.

Like all orders allowing patients to take their own supply of medication, the product will have to follow the "Patient Medications Brought Into Shands at the University of Florida" policy (http://intranet.shands.org/licacc/Intranet/Patient%20Care/PM02-37.pdf). A pharmacist has to be able to verify that the contents of the prescription vial are the same as the drug listed on the label of the vial. Patients cannot use their own supply of a controlled substance. If these products cannot be switched to a product listed in the *Formulary, then*

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POLICIES AND PROCEDURES

Dietary supplement use in the hospital

The policy that allows physicians to prescribe dietary supplements for their inpatients has been modified based on recent developments regarding the certification of these products. Currently, there are no dietary supplements listed in the *Formulary,* and patients may only use their own supply from a sealed container. Inpatient supplement use requires a written order so that these products are listed with the patient's medications on the medication administration record (MAR), and so they can be screened for potential drug interactions.

Until recently, there has been no way to assure the contents of a dietary supplement container were safe. However, there are now USP-verified dietary supplements that have been rigorously tested and meet the United States Pharmacopoeia's standards. Supplements meeting these standards contain the supplement(s) listed on the label in the amount listed (ie, integrity). These supplements do not contain harmful levels of contaminants (ie, purity). This certification also documents that the product will break down appropriately for absorption in the body (ie, dissolution) and is made under good manufacturing processes (ie, safe manufacturing). Products meeting these standards will have the USP-verified dietary supplement seal on each bottle.

This is a major change for dietary supplements. Over the last decade, despite widespread use of these products, consumers have had no legitimate assurance that the product being taken was the product and amount listed on the label. There are numerous reports in the literature of products not containing any of the labeled product and/or containing contaminants. For this reason, the P&T Committee would not consider the addition of any dietary supplement in the *Formulary.* These products were deemed unsafe.

Now that there is a list of products that are USP-verified, these products could be considered for addition in the *Formulary.* However, there will have to be sufficient published evidence of safety and efficacy.

In order for patients to continue to use dietary supplements in the inpatient setting, patients will have to continue to use their own supply (ie, from a sealed container) unless they are listed in the *Formulary.* Further, if there is a USP-verified product available, 1 of these products must be used.

Currently, the list of USP-verified dietary supplements is small. The following products are available: alpha lipoic acid, coenzyme Q10, fish oil, Echinacea (purpurea), ginseng, L-lysine, lutein, and methylsulfonylmethane (MSM). The USP web site lists brands of USP-verified supplements (http://www.usp.org/USPVerified/dietarySupplements/resources.html).

A good source of evidence-based information on the use of these dietary supplements can be found on the web at http://www.nlm.nih.gov/medlineplus/druginformation.html.

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a nonformulary request will have to be made. Nonformulary schedule II controlled substances are difficult to obtain because of regulatory requirements and a significant delay should be expected.

In general, patients' own supplies of injectables, liquids, and topical products cannot be used (unless explicitly allowed by the policy cited). It is difficult to identify these products and assure safe use.