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SHANDS
at the University of Florida

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Drugs & Therapy
B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 15, 2001. 3 drugs or dosage forms were added in the *Formulary* and 3 drugs were deleted. 3 drugs were designated nonformulary and not available.

◆ ADDED

Estradiol tablets (generic of Estrace®)

Estradiol transdermal (Climara® by Berlex)

Pantoprazole injection (Protonix® Injection by Wyeth-Ayerst)

◆ DELETED

Anthralin cream (Drithrocreme® by Dermik)

Guanethidine (Ismelin® by Novartis)

Rapacuronium (Raplon® by Organon)

◆ NONFORMULARY AND NOT AVAILABLE

Conjugated estrogens + medroxyprogesterone (PremPro® by Wyeth-Ayerst)

Esterified estrogens (Estratab® by Solvay or Menest® by SmithKline Beecham)

Estropipate (Ogen® by Upjohn)

It is impractical to list every estrogen product and/or estrogen combination product in the *Formulary* in order to continue therapy that patients are taking as outpatients. However, the P&T Committee made changes that extend the listing of the estrogen products in the *Formulary,* while designating a few products nonformulary and not available.

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SHORTAGES

Shortage of Benadryl® Injection ≠ IV hydroxyzine

Drug shortages have become a way of life. Prescribers are trying to figure out what to do when something is not available or when it has limited availability. It is hard to believe, but injectable diphenhydramine (ie, Benadryl® injection) has been difficult to get. Hopefully, by the time this article is published, this shortage will be resolved. During the shortage of injectable diphenhydramine, prescribers have to determine the best alternative to an injectable antihistamine.

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Alternatives to injectable diphenhydramine include **oral** diphenhydramine or hydroxyzine, **intramuscular** hydroxyzine, intravenous promethazine, and injectable corticosteroids. Although not listed in the *Formulary*, injectable dimenhydrinate would be another alternative, if the diphenhydramine shortage persists.

The onset of action is slower for oral diphenhydramine or hydroxyzine; however, the oral route is usually the best option. Oral hydroxyzine is more potent and is preferred to diphenhydramine. In patients who cannot take oral medications, intramuscular hydroxyzine or an alternative injectable H1-blocker may be used. Intravenous corticosteroids or epinephrine are needed for patients experiencing anaphylaxis or urticaria.

Why intramuscular hydroxyzine? Why can't hydroxyzine be given IV? When given intramuscularly, the onset of action is approximately the same as the oral. Therefore, the only reason to use this route would be when nothing, including oral hydroxyzine liquid, can be given orally.

Injectable hydroxyzine is not recommended for intravenous administration. The most recent labeling (ie, revised 1993) for Vistaril® Injection states in the Contraindications section, "Hydroxyzine hydrochloride intramuscular solution is intended only for intramuscular administration and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously." Because this is in the Contraindications section of the labeling, it would be risky to use intravenous hydroxyzine under any circumstances. Further, the Precautions section of the labeling it states, "As with all intramuscular preparations, Vistaril® Intramuscular Solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage."

The reasons for these warnings are not well-known. Before 1970, the labeling for parenteral hydroxyzine included the intravenous route of administration. In 1970, the intravenous route of administration was removed after several reports of thrombosis and gangrene were associated with the IV route of administration. These unfor-

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INSIDE THIS ISSUE

Formulary update, *from page 1*

Only conjugated estrogen (Premarin®) tablets, injection, and cream have been listed in the *Formulary*. Several other forms of estrogens are commonly used as hormone replacement therapy in postmenopausal women. Some women refuse to take conjugated estrogens because they have ethical issues with the method of collecting the urine from pregnant horses. The urine of pregnant mares is the raw material used to produce equine conjugated estrogens.

Estrogens are commonly used as hormone replacement therapy in postmenopausal women. The benefits in postmenopausal women include relief of moderate-to-severe vasomotor symptoms, decreased risk of osteoporosis, decreased vulvovaginal signs and symptoms, and possibly decreased cardiovascular disease. Hormone replacement therapy may also be used in female hypogonadism, castration, or primary ovarian failure.

Estradiol tablets and transdermal patches were added in the *Formulary*. Estradiol tablets and patches are frequently requested nonformulary products. These requests are usually to continue therapy that has been started on outpatients.

Estradiol tablets were added as a synthetic alternative to conjugated estrogens. Estradiol is the major hormone produced by a female's ovaries. Although 6 different natural estrogens have been isolated from the human female, only 3 are present in significant quantities (ie, 17-beta-estradiol, estrone, and estriol). Estradiol is rapidly and reversibly oxidized to estrone. Both of these can be converted to the much weaker estriol.

Due to almost complete first-pass metabolism, estradiol must be given in a micronized oral dosage form to ensure therapeutic effect. Estradiol is extensively metabolized in the gastrointestinal mucosa during absorption. The liver also extensively metabolizes it. Micronization of oral estradiol tablets slows oral absorption and decreases 1st-pass metabolism by the liver. Absolute bioavailability of micronized estradiol is roughly 5 to 10% of an administered dose.

Some clinicians prefer transdermal estradiol. The advantages of transdermal estrogen (compared with oral) include less interpatient variability in blood levels achieved (ie, oral estrogens undergo extensive first-past metabolism and enterohepatic recirculation) and less liver exposure to estrogens. Oral estrogens present high levels to the liver and stimulate increased synthesis of triglycerides, transcortin, sex hormone-binding globulin and angiotensinogen. Transdermal estrogens may be preferred in women with hypertension, hypertriglyceridemia, or a history of increased risk of cholelithiasis.

The major disadvantage of transdermal estrogen is the risk of skin irritation (rash). This can be alleviated by rotating applications sites (ie, never use the same site twice in a row) and applying the patch on the buttocks. Moisture under the patch is also a problem and may contribute to the incidence of rash.

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The major disadvantage of transdermal estrogen is the risk of skin irritation (rash). Moisture under the patch is also a problem and may contribute to the incidence of rash.

Federal Law requires that patients receiving estrogen products be informed of possible risks associated with their use via written patient package inserts, which meet federal requirements, **before** the administration of the first dose and every 30 days thereafter as long as therapy continues. This statute neither applies to estrogen products used for contraception, nor does it apply if the agent in question is being used to treat cancer. Whenever possible, transdermal estrogens should be placed prior to a patient's admission when the admission is elective. This may avoid the legal requirement to provide the patient with the estrogen patient package insert while they are in the hospital. For more information, refer to hospital policy PM 02-04.

The approved patient information leaflets describe when and how to use estrogens and the risks of estrogen treatment. The information is designed for patients and contains a discussion on the risk of cancer (ie, breast and uterus), gallbladder disease, pancreatitis, abnormal clotting, and endometrosis. It explicitly warns against using estrogens in pregnancy and in the post-partum period…not only because of the possible effects on women (ie, abnormal clotting), but because of the possible effects on the fetus (ie, possible birth defects and cancer later in life).

Conjugated estrogens plus medroxyprogesterone (ie, PremPro®) is a fixed combination product that was designated nonformulary and not available. Orders written for PremPro® will be automatically substituted with the individual ingredients that are listed in the *Formulary*. PremPro® orders will be changed to orders for Premarin® 0.625 mg and medroxyprogestrone 2.5 mg with the designation: *P&T-Authorized Change*.

If there are other fixed combinations of nonformulary estrogens, the prescriber will be contacted to prescribe the individual constituents. When the ingredients of combination products are not listed in the *Formulary*, the prescriber may substitute the closest formulary alternatives or the product can be requested by the nonformulary process.

Esterified estrogens contain 75% to 85% sodium estrone sulfate and 6% to 15% sodium equilin sulfate. It was designated nonformulary and not available. Patients can be switched to either estradiol tablets (1 mg estradiol = 0.625 mg esterified estrogens) or conjugated estrogens (0.625 mg = 0.625 mg).

Estropipate is crystalline estrone solubilized as the sulfate and stabilized with piperazine. It was also designated nonformulary and not available. Patients can be switched to either estradiol tablets (1 mg estradiol = 0.625 mg estropipate) or conjugated estrogens (0.625 mg = 0.625 mg).

Pantoprazole injection is the only injectable proton-pump inhibitor (PPI) currently on the US market. We liberally use an extemporaneously compounded omeprazole liquid in patients who cannot take oral capsules or tablets. Also, an injectable PPI could displace the use of injectable H2-blockers, which cost anywhere from 5% to 25% of the cost of pantoprazole injection. If injectable pantoprazole is not used responsibly, it could have a dramatic impact on pharmaceutical expenditures. Therefore, the use of pantoprazole will be tracked for the 1st 6 months that it is available.

Injectable pantoprazole was approved as a 2nd-line agent for gastroesophageal reflux in patients unable to take oral medications. Injectable pantoprazole should be discontinued as soon as the patient is able to resume treatment with oral therapy, which is emphasized in the labeling. Therefore, pantoprazole was added to the IV-to-PO policy. Taking other oral medications or oral solid feedings is the primary criteria for automatic switching.

(continued on next page)

Formulary update, *from page 2*

The following criteria for use are considered appropriate for injectable pantoprazole:

- ICU patients with clinically-active GI bleeding.
- Patients s/p gastric surgery.
- Patients with post-op ileus meeting the criteria for an oral proton-pump inhibitor.
- Combination therapy with an IV H2-blocker should only be for patients with refractory ulcer healing with nocturnal breakthrough bleeding (PPI in AM, H2-blocker in PM).
- Maximum duration 14 days.
- IV to PO when patient is eating solid food.

Intravenous pantoprazole must be used with an in-line filter. The filter is supplied with each dose of injectable pantoprazole.

Anthralin cream is a topical antipsoriatic agent. This product has not been used in the last year at Shands at UF. The manufacturer has discontinued it; therefore, it was deleted from the *Formulary.*

Guanethidine is a postganglionic adrenergic blocking agent that was used for the treatment of hypertension. It was approved by the FDA in 1960 and is rarely used today. It causes depletion of norepinephrine in the synapse, causing reductions in total peripheral resistance and producing reductions in blood pressure. Guanethidine has a significant side effect profile, specifically pronounced postural hypotension. It has not been used in the last year at Shands at UF. The manufacturers of guanethidine no longer make this product. Therefore, it was deleted from the *Formlary.*

Rapacuronium is a nondepolarizing neuromuscular blocking agent that was used as an adjunct to general anesthesia, for endotracheal intubation, and for neuromuscular blockade during short surgical procedures. The onset of action of rapacuronium is similar to succinylcholine and it has a short duration of effect.

On March 29, 2001 the FDA announced that Organon is voluntarily withdrawing rapacuronium from the market. This action was based on reports associating rapacuronium with bronchospasm. 5 deaths have been associated with its use.

Succinylcholine is an alternative, but it is in short supply. There is a nationwide back-order on succinylcholine because the manufacturer has had difficulty acquiring the raw material to make it.

SHORTAGES

Controls not recommended with PPD testing

Candida, mumps, and tetanus toxoid are in the *Formulary* at Shands at UF. These skin tests are frequently ordered with PPD testing with the clinician's intent of using these as controls with the PPD test for tuberculosis.

In the early 1990s, the Centers for Disease Control (CDC) recommended the use of controls when testing for tuberculosis in HIV infected patients and persons who have an increased risk for tuberculosis infection (ie, intravenous drug users and those persons from countries endemic for tuberculosis). However, while the PPD skin test has been extensively studied and validated, anergy tests have not been standardized and the utility of anergy skin testing in helping to interpret results of a negative PPD has not been validated.

The most recent CDC recommendations for screening for tuberculosis infection do not recommend that anergy testing be routinely performed in high risk patients. This recommendation is based on the lack of standardization of the products and the lack of validation of this practice

The Anti-Infective Subcommittee of the P&T Committee discussed whether or not these skin tests should be removed from the *Formulary.* Although skin tests are not recommended to be used as controls for PPD skin testing, some physicians use these agents in testing for anergy. Shands at UF currently spends $15,000 per year on the candida, mumps, and tetanus skin tests.

The Anti-infective Subcommittee recommends that these agents not be used as controls for PPD testing. In addition, due to the shortage of tetanus toxoid and tetanus diphtheria toxoid (see below), tetanus toxoid will no longer be dispensed at Shands at UF when "controls" are ordered.

By Joanne J. Orrick, PharmD

REFERENCE

1. Anon. Screening for Tuberculosis and Tuberculosis Infection in High-Risk Populations Recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR September 8, 1995, 44(RR-11);18-34.

SHORTAGES

Tetanus-diphtheria toxoids and tetanus toxoid shortage

Shands at UF is being impacted by a severe shortage of tetanus and diphtheria toxoids (Td) and tetanus toxoid (TT). We were first alerted about this shortage in November 2000 and, until recently, had been able to keep enough product in stock to meet the needs of Shands at UF and the facilities that the Shands at UF Pharmacy serves. This shortage is expected to last another 12 months.

Per CDC recommendations, the following are the criteria with the highest priority for use during this shortage:

1. Persons traveling to a country where the risk of diphtheria is high (Td);
2. Persons requiring tetanus vaccination for prophylaxis in wound management (Td or TT);
3. Persons who have received fewer than 3 doses of any vaccine containing Td; and
4. Pregnant women who have not been vaccinated with Td during the preceding 10 years.

In a recent Notice to Readers, the CDC reinforced the need to reserve the use of Td and TT for the priority indications listed above. Effective immediately, **clinicians should discontinue the use of Td and TT for routine booster vaccinations.** To assure vaccine availability for priority indications, all routine Td boosters in adolescents and adults should be delayed until 2002.

During this shortage, each clinic that the Shands at UF Pharmacy serves will be restricted to ordering 1 multi-dose vial of TT or Td at a time. This vial should only be used for the above priority indications.

By Joanne J. Orrick, PharmD

REFERENCE

1. Anon. Deferral of Routine Booster Doses of Tetanus and Diphtheria Toxoids for Adolescents and Adults. MMWR Weekly May 25, 2001/50(20); 418, 427.

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Shortages, *from page 1*

tunate adverse events were actually associated with inadvertent intra-arterial administration.

When an injectable H1-blocker is needed, intravenous hydroxyzine is NOT an option. The shortage of diphenhydramine could lead to unfortunate adverse drug events, if these precautions are not known.

There are limited alternatives to injectable diphenhydramine. Injectable promethazine (eg, Phenergan®) does have antihistaminic activity, but it has rarely been used for this pharmacologic property. It also can be irritating when injected IV, so it should only be used with caution. Although the intravenous route of administration is not contraindicated, the labeling for Phenergan® Injections states, "The preferred parenteral route of administration for Phenergan® Injection is by deep intramuscular injection. The proper intravenous administration of this product is well tolerated, but use of this route is not without some hazard. It is not for subcutaneous administration. INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY. SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS. Injection into or near a nerve may result in permanent tissue damage. When used intravenously, Phenergan® Injection should be given in a concentration no greater than 25 mg/mL at a rate not to exceed 25 mg per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily."

It is expected that the shortage of injectable diphenhydramine will be resolved soon; however, there are some lessons we can learn from this shortage. Oral hydroxyzine is an excellent alternative. Injectable promethazine may be a reasonable alternative in patients who require an injectable antihistamine.

Histamine binds more avidly to receptors than antihistamines. Therefore, pre-treatment with an oral antihistamine is always preferred to an injectable antihistamine given after a reaction has already begun.