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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 20, 2004. 3 drugs were added in the *Formulary* and 3 drugs were deleted and designated not available.

◆ ADDED

Ezetimibe
(Zetia® by Merck/Schering-Plough)

Aripiprazole
(Abilify® by Bristol-Myers Squibb)

Papain-Urea Ointment
(Accuzyme® by Healthpoint)

◆ DELETED

Chlorpromazine Suppositories
(Thorazine® by SmithKline Beecham Co)*

Respiratory Syncytial Virus Immune Globulin
(Respigam® by Medimmune Inc)*

Collagenase Ointment
(Santyl® by Knoll)*

*Nonformulary and Not Available

Ezetimibe was added in the *Formulary*. It is the first agent in a new class of antihyperlipidemic agents, the cholesterol-absorption inhibitors. It is indicated for use as monotherapy or in combination with HMG-CoA-reductase inhibitors to treat dyslipidemias. It produces modest reductions in LDL cholesterol. It can be used as add-on therapy in patients who do not achieve LDL goals with statins and cannot tolerate dose increases or other adjuvant therapies.

Ezetimibe was effective in clinical trials in lowering total cholesterol (TC), LDL, and Apo-B both as monotherapy and in conjunction with statins. No comparative trials are available to date, and it is

(continued on next page)

IV THERAPY

MVI-12 versus "MVI-13"

Effective immediately, the parenteral multivitamin product (MVI) listed in the *Formulary* will contain vitamin K. This will make the current procedure of supplemental vitamin K given in TPN on every Monday no longer necessary and this practice will be stopped. Instead of containing 12 vitamins (ie, MVI-12), the new product (Infuvite®) will contain 13 vitamins, including 150 mcg of vitamin K in each 10-mL daily dose.

◆

The parenteral multivitamin product listed in the *Formulary* contains vitamin K. Caution must be used when Infuvite® is administered to patients on warfarin. Monitoring prothrombin times is essential in determining the appropriate dosage of warfarin therapy.

It is debatable whether patients receiving parenteral nutrition need supplemental vitamin K. Most adult patients on TPN receive lipids, which contain vitamin K (ie, IV 20% lipid contains approximately 60 mcg vitamin K/100 mL). Patient laboratory results are routinely monitored for vitamin K deficiency.

These changes are the result of a long-term governmental evaluation of which vitamins are needed for parenteral supplementation. On September 17, 1984, the FDA announced the conditions for marketing an effective parenteral multivitamin preparation. An effective 12-vitamin formulation (MVI-12) was proposed after being clinically evaluated based on a guideline recommended by the American Medical Association in 1975. In 1985, a workshop further evaluated the use of MVI-12. They found that the dosage of vitamins B, C, and folic acid needed to be increased and that vitamin K should be added to the formulation to make a 13-vitamin formulation.

After this evaluation, a notice was published in the *Federal Register* to change the 12-vitamin formulation to include vitamin K. Additional changes included the indications, contraindications, and labeling of MVI.

The new regulations require the official labeling to state that this formulation is indicated as a daily multivitamin maintenance dosage for adults and children aged 11 and above receiving parenteral nutrition. The indications include conditions where IV administration is needed.

More contraindications were added to the labeling (eg, patients known to be hypersensitive to any of the vitamins or excipients in the product). Allergic reactions have occurred following intravenous administration of thiamine and vitamin K. The 13-vitamin formulation is also contraindicated before blood sampling for detection of megaloblastic anemia. Caution must be used when Infuvite® is administered to patients on warfarin. Monitoring prothrombin times is essential in determining the appropriate dosage of warfarin therapy.

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unknown if ezetimibe provides superior outcomes compared to other agents when used in combination with statins. However, it does not appear to be associated with the same intolerable adverse effects of other agents.

The only FDA-approved dose of ezetimibe is 10 mg once daily. Although hepatically metabolized, ezetimibe is not an inducer or inhibitor of the P-450 system. Overall, ezetimibe appears to be well-tolerated. Levels of ezetimibe are increased in patients with liver dysfunction; therefore, it should not be used in patients with moderate-to-severe hepatic impairment (Child-Pugh Score >7).

Aripiprazole is a new atypical antipsychotic that has been added in the *Formulary*. Although classified as an atypical antipsychotic, aripiprazole's mechanism of action differs from the other agents in this class. It acts as a partial agonist at D2 and 5-HT1A receptors, and as an antagonist at 5-HT2A receptors. This unique mechanism has led to its designation as a "third-generation" atypical antipsychotic agent. These agents are also referred to as "dopamine-serotonin system stabilizers."

Its effectiveness has been demonstrated in 3 published studies. It was equally as effective in treating positive symptoms as haloperidol, but like other atypical antipsychotics, demonstrated superiority in treating negative symptoms of schizophrenia. In another published study, aripiprazole demonstrated it was at least as effective as risperidone in treating schizophrenia and schizo-affective disorder.

Benefits of using aripiprazole include less weight gain compared to olanzapine, no QT-wave prolongation, no increase in prolactin levels, and few EPS adverse effects. Typical doses range from 10 to 15 mg per day. Aripiprazole is a substrate for CYP2D6 and CYP3A4 and, therefore, is subject to many drug interactions. When CYP2D6 or 3A4 inhibitors are used, the dose of aripiprazole should be reduced by 50%. Doses should be doubled when patients are taking CYP3A4 inducers.

Accuzyme®, or **papain-urea ointment**, has permanently replaced collagenase (Santyl®) in the *Formulary*. Papain is a proteolytic enzyme derived from the fruit of Carica papaya and is a potent digestant of nonviable protein matter, but is harmless to viable tissue. When used alone, papain is ineffective as a debriding agent because it requires the presence of activators to exert its digestive function. The combination of urea with papain provides 2 supplementary chemical actions: exposing activators of papain, which are not always accessible in nonviable tissue or debris, and denaturing the nonviable protein matter in lesions and rendering it more susceptible to enzymatic digestion.

Accuzyme® has a labeled indication for the debridement of necrotic tissue and liquefaction of slough in acute and chronic lesions, such as pressure ulcers, varicose and diabetic ulcers, burns, postoperative wounds, pilonidal cyst wounds, carbuncles, and miscellaneous traumatic or infected wounds. The limited published evidence suggests that papain-urea ointment is superior to collagenase.

The manufacturer of **chlorpromazine suppositories** discontinued its production in 2002. Currently there are no other suppliers marketing the product. No suppositories have been dispensed from the pharmacy in over a year. Therefore, chlorpromazine suppositories were deleted from the *Formulary*.

The manufacturer of **respiratory syncytial virus immune globulin (RSV-IVIg)** has announced that this product has been discontinued permanently and is no longer available. It has been deleted from the *Formulary*. Alternative therapy for RSV prophylaxis is palivizumab (Synagis®).

by Wendy D. Smith, PharmD

PRESCRIBING

Initiating warfarin therapy

The use of anticoagulants is indicated for the management of deep vein thrombosis (DVT) and pulmonary embolism (PE). All anticoagulant regimens are considered prophylactic in this regard because they only interrupt progression of the thrombotic process but do not actively resolve it.[1] Treatment regimens for DVT and PE are similar and include the initial use of unfractionated or low molecular weight heparin (LMWH) and warfarin.[2]

Warfarin exerts its anticoagulant effects by inhibiting hepatically produced, Vitamin K-dependent clotting factors (ie, II, VII, IX, and X). Warfarin also depresses the activity of proteins C and S, which have anticoagulant properties themselves. Levels of these proteins may be lowered before the other coagulation factors, resulting in a potentially hypercoaguable state. To avoid this hypercoaguable state, warfarin should be initiated at the same time as heparin or LMWH. It is also recommended that heparin therapy overlap with warfarin once a therapeutic INR is achieved (ie, target 2.5, range 2-3) for 2 days.[1]

The daily maintenance dose of warfarin differs greatly between individuals. The typical dose range is from 0.5 mg per day to 15 mg per day, and often fluctuates over time. The average maintenance dose is 4.5 mg per day, although it is lower in elderly patients. The drug is rapidly and completely absorbed and immediately blocks further hepatic synthesis of the Vitamin K-dependent clotting factors. However, its impact on INR is delayed until preformed coagulation factors are removed, so dose adjustment must allow for these delayed effects.[2]

In the past, a loading dose of 10 mg was initially used. However, this is not usually necessary. A starting dose of 5 mg per day will achieve an INR of 2 in 4-5 days for most patients.[4] Some patients may exhibit sensitivity to warfarin and should receive lower initial doses. Patients over 60 years of age, those with low body weight, impaired hepatic function, heart failure, impaired nutrition, and receiving antibiotics should receive less than a 5 mg per day starting dose.[1-4]

INRs should be measured daily or every other day until 2 therapeutic INRs are achieved at least 24 hours apart. Then, it should be measured 2-3 times per week for 1-2 weeks. The INR should also be monitored when the clinical picture of the patient changes and when interacting medications are started or stopped.[3]

In order to begin therapy with warfarin the clinician must determine which dose of warfarin to use, when to monitor, and finally when the heparin therapy may be stopped. Once a positive diagnosis for a DVT or PE is made, patients should simultaneously be started on heparin and warfarin.[2] Most patients will achieve a therapeutic INR within 5 days receiving 5 mg per day of warfarin. Some patient populations may require a lower starting dose.

by Wendy D. Smith, PharmD

REFERENCES

1. Clinical Practice Guidelines: The use of oral anticoagulants in older people. JAGS 2002; 50:1439-45.
2. Managing Oral Anticoagulant Therapy. Chest 119 (Supplement); January 2001.
3. Gallus, AS, Ross BI, Chong, BH, et al. Consensus guidelines on warfarin therapy: recommendations from the Australasian Society of Thrombosis and Haemostasis. MJA 2000; 172:600-610.
4. Crowther MA, Ginsberg JB, Kearon C, et al. A randomized trial comparing 5 mg and 10 mg warfarin loading doses. Arch Intern Med 1999; 159:46-48.

MEDICATION USE EVALUATION

Evaluation of the heparin protocol

The utility of using weight-based heparin to treat venous and arterial thromboembolism is well established. Using patients' weight to determine heparin dosing (80 units/kg bolus followed by 18 units/kg initial infusion rate) allows patients to rapidly achieve therapeutic activated partial prothrombin times (aPTTs) and avoid prolonged periods of excessive anticoagulation.[1]

The purpose of this medication use evaluation was to evaluate compliance and clinical effectiveness of the current weight-based heparin protocol developed for Shands at UF to treat deep vein thrombosis (DVT) and pulmonary embolism (PE).

A random sample of orders for heparin using the preprinted order sheet titled "*DVT/PE Heparin Protocol*" was obtained by screening orders received by decentralized pharmacists. Patient information was obtained through the hospital and pharmacy information systems and patient chart review.

Thirty orders using the "DVT/PE Heparin Protocol" were evaluated between November 28, 2003 and January 30, 2004. Services using the protocol included: general medicine, surgery, gastroenterology, oncology, trauma/critical care medicine, orthopedics, neurosurgery, and bone marrow transplantation. All but 2 orders were written using the approved preprinted order set.

The most frequent indications for heparin therapy were for treatment of DVT and PE. Other less frequent indications were for anticoagulation prophylaxis until a therapeutic INR was obtained with warfarin, SVC syndrome, and anticoagulation prophylaxis for patients with atrial fibrillation.

Nearly one-third of the preprinted orders had been manually modified or individualized. This practice is not permitted. Preprinted order forms with doses and/or adjustments "scratched out" and different doses written to the side are invalid.

Only one-half of patients received a bolus dose of heparin. Of those, 25% were the incorrect dose. Therefore, two-thirds of patients either did not receive the bolus or received the incorrect dose.

Of the patients who were receiving heparin to treat DVT and PE, 64% of patients did not receive warfarin within 48 hours of the initiation of therapy with heparin. The American College of Chest Physicians Guidelines for Treatment of DVT/PE recommends beginning warfarin simultaneously with heparin therapy and continuing heparin until a therapeutic INR is achieved.[1] In order to insure timely discharge of patients, it is important, whenever possible, to simultaneously begin warfarin therapy with heparin. This will prevent patients from remaining in the hospital in order to achieve therapeutic INRs. All patients had complete blood counts performed within 48 hours of beginning heparin therapy.

Thirty percent of patients' infusions were interrupted within the first 48 hours of treatment. Reasons for interruption of therapy include: blood present in J-Tube, patient going to surgery, presence of DVT ruled out, and supratherapeutic aPTTs.

Overall, 27% of patients received correct doses of the bolus and initial maintenance infusions and did not have their therapy interrupted within 48 hours of starting heparin.

The elapsed time from the start of the infusion until 2 therapeutic aPTTs were obtained ranged from 20 hours to more than 72 hours. In some instances the amount of time until 2 therapeutic aPTTs were achieved was not obtainable because the labs were not ordered as dictated by the protocol. This may have been the case in those patients in which it took longer than 48 hours to reach therapeutic aPTT levels.

The mean time for patients to achieve 2 therapeutic aPTTs in patients who received correct bolus and maintenance doses and who received uninterrupted therapy for the first 48 hours was 32.8 hours [95% CI 20.5-43.5]. Patients who did not receive correct doses and whose therapy was interrupted waited a mean time of 43.5 hours [95% CI 37.2-49.8] until therapeutic aPTTs were obtained. This estimate is likely low because at the time of follow-up (48 hours), many patients were not therapeutic.

Overall, there was a high rate of non-compliance with the *DVT/PE Heparin Protocol*. Examples of non-compliance include: excluding bolus doses, incorrect dosing of boluses and maintenance infusions, modifications of the protocol, lab values obtained at incorrect times, responses to aPTT levels not made in a timely manner, interruption of therapy, and patients not being started on anticoagulation therapy with warfarin. Because of the high rate of non-compliance, it is difficult to answer any questions regarding the clinical appropriateness of the protocol. It is likely that any lack of success of the protocol can, in part, be attributed to non-compliance.

by Wendy D. Smith, PharmD

REFERENCES

1. Gallus, AS, Ross BI, Chong, BH, et al. Consensus guidelines on warfarin therapy: recommendations from the Australasian Society of Thrombosis and Haemostasis. MJA 2000; 172: 600-610.

PRESCRIBING

Pharmacological isomers — Nice to know? Or need to know?

While for most of us, the days of drawing benzene rings and counting carbon bonds have long-since passed, stereochemistry is emerging as an important topic when discussing the development of new medications. Chiral forms of drugs, or enantiomers, contain the same number and type of atom groupings but, analogous to the right and left hand, have different arrangements in space.[1]

Pairs of enantiomers differ in optical activity, with one rotating polarized light to the left ([-] or levorotatory) or to the right ([+] dextrorotatory).[2] Enantiomers may also be described according to their absolute configuration, or the order of the constituents around the chiral center of the molecule, giving the S (or L) or R designation. In contrast to optical activity, which may be influenced by solvent, temperature, or light wavelength used, absolute configuration may only be modified by breaking and reforming chemical bonds.[1] There is no relationship between absolute configuration and optical activity.

Most drugs are produced as racemic mixtures.[2,3,4] Examples of commonly used racemates are atenolol, ibuprofen, and warfarin. These drugs contain a 50:50 mixture of the S and R enantiomers. Enantiomers are non-superimposable mirror-images, or "left- and right-handed" forms of the drug. The interaction between drugs and pharmacological receptors can be likened to placing a hand in a glove. Receptors are often chiral, and "left-handed" drugs will fit only "left-handed" receptors.[4]

Advances in technology over the last decade and the ability to synthesize individual enantiomers have led the pharmaceutical industry to attempt to develop new chemical entities as single isomers.[4] The practice of replacing an already approved racemic mixture of a drug by a single enantiomer is a familiar process to most clinicians. Examples include escitalopram (Lexapro®), esomeprazole (Nexium), and levalbuterol (Xopenex®).

Theoretical advantages of chiral switching include increased potency and selectivity of the drug and

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decreased adverse effects. Some propose that enantiomers offer faster onsets of action and duration of effects and fewer drug-interactions.[2,3,4] However, possibly the largest incentive for chiral switching is many top-selling drugs have been licensed as racemic mixtures, and their substitution with single enantiomers results in patent extension and protection from generic competition with the racemate (eg, desloratadine [Clarinex®]).[4]

For example, manufacturers boast desloratadine's *in vitro* affinity for type 1 histamine receptors is 10-20 times greater than loratadine, the racemic mixture. Desloratadine has also been shown to have 2.5-4 times the antihistaminic properties in animals.[5,6,7] However, desloratadine has never been compared to loratadine, nor any other antihistamine, in clinical trials. It has been shown to be superior only to placebo.

These theoretical pharmacological advantages provide ideal marketing strategies for the pharmaceutical industry. They provide "rationale" for product selection without subjecting the "theory" of their benefits to scientific rigor. In the case of desloratadine, the average wholesale price (ie, AWP) for a 30-day supply is $73.94. A 30-day supply of loratadine, now available over-the-counter, costs around $15. Justification for use of a medication that is 6 times the cost of its racemic mixture should include proof of substantial benefits. This is especially true for drugs that offer no theoretical safety advantages.

Levalbuterol (Xopenex®) is the R-isomer of albuterol. It is approximately 15 times more expensive than albuterol. Levalbuterol is promoted as being a safer alternative to "racemic" albuterol. Claims include that the S-isomer works in opposition to R-albuterol. The theory is that the S-isomer is responsible for tolerance to albuterol, increases airway hyperresponsiveness, the paradoxical bronchospasm seen with albuterol, and the systemic adverse effects seen with albuterol use. However, in this case, scientific evidence disproves these theories. Several well-done reviews refute these possible advantages and conclude that levalbuterol offers no advantage over albuterol.[8]

Differing pharmacological effects resulting from differing enantiomers are beneficial for some drugs. For example, labetolol, which possess both alpha and beta-blocking properties. It was originally thought that both the alpha and beta-blocking properties of labetolol resided in the same molecule. However, examination of its isomers found that one isomer is responsible for the beta-blocking effects and another isomer the alpha-blocking effects. Researchers attempted to market a pure enatiomeric form containing only the isomer with beta-blocking activity. This seemingly ideal alternative, given the name dilevalol, also had partial beta-2 agonist properties and, in addition, did not produce the same orthostatic hypotension sometimes seen with labetolol. However, it never reached the market because it was associated with hepatotoxicity not seen with racemic labetolol.[9]

In conclusion, separation of medications from their racemic mixtures into their individual enantiomers may offer potential therapeutic benefits. However, the development and marketing of these agents should be accompanied by sufficient scientific evidence to support their use, especially when accompanied by increased cost.

By Wendy D. Smith, PharmD

REFERENCES:

1. Lane RM, Baker GB. Chirality and drugs used in psychiatry. Cell Mod Neurobiol 1999; 19:355-72.
2. Baker GB, Prior TI. Stereochemistry and drug efficacy and development: relevance of chirality to antidepressant and antipsychotic drugs. Ann Med; 34:537-43.
3. Coutts RT, Baker GB. Implications of chirality and geometric configuration in some psychoactive drugs and their metabolites. Chirality 1989; 1:99-120.
4. Tucker GT. Chiral switches. Lancet 2000; 355:1085-87.
5. Farkas H. Multicenter study of the effectiveness and tolerability of desloratadine in seasonal allergic rhinitis. Orv Hetil. 2003 May 25;144(21):1021-4.
6. Sabbah A. The place of new antihistamines in allergy management. Apropos of desloratadine. Allerg Immunol (Paris). 2002 Dec; 34(10):377-83.
7. Monroe EW. Desloratadine for the treatment of chronic urticaria. Skin Therapy Lett. 2002 Oct;7(8):1-2, 5.
8. Hatton RC. Formulary Update. Shands Drugs & Therapy Bulletin. Sept 2000; Vol 16(8).
9. Waldeck B. Three-dimensional pharmacology, a subject ranging from ignorance to overstatements. Pharmacology and Toxicology 2003. 93; 203-10.