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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 16, 2010. 2 drugs were added in the *Formulary*, and 2 products were deleted. 5 products were designated nonformulary and not available. 1 interchange was temporarily approved and the criteria for use for 1 drug was changed.

◆ ADDED

Bendamustine (Treanda® by Cephalon)*

**Restricted: 1st cycle or high-risk for tumor lysis syndrome*

Gadobenate Dimeglumine (Multihance® by Bracco Diagnostics)

◆ DELETED

Benzocaine Lozenges (Chloraseptic® Lozenges)†

†Nonformulary and not available

Benzocaine Spray (Hurricaine® Spray)‡

‡Nonformulary and not available June 1, 2010

◆ NONFORMULARY AND NOT AVAILABLE

Collagenase Clostridium Histolyticum (Xiaflex®)

Lamotrigine ER (Lamictal® XR)

Trazodone ER (Oleptro®)

◆ INTERCHANGES

Phenytoin Injection for **Fosphenytoin**§

§Only effective during the fosphenytoin shortage

◆ CRITERIA-FOR-USE CHANGES

Iron Dextran (InFed®)¶

¶Restricted: neonates only

(continued on next page)

PRESCRIBING

Individualized dosing of Warfarin? Why so complicated?

The September 2009 issue of the *Drugs & Therapy Bulletin* published detailed *Warfarin Dosing Guidelines* designed for use at Shands at UF. The guidelines are complicated since they include multiple INR goals, multiple recommendations for dose changes, a standard dosing protocol, and a low-dose protocol. The guidelines also included the admonition to wait 2 days after any dose change before considering the next dose change. All of this leads to the question, "Why is the dosing of warfarin so complicated?"

...it [takes] up to six days to see the full effect of any dose change of warfarin on the resulting INR.

The following case may help provide some answers. A patient has been taking warfarin 2.5 mg daily for the past 7 days (17.5 mg weekly) without missing any doses; the observed INR today is 1.4. This INR is below the desired therapeutic goal for this patient (2.0 to 3.0) and a dose increase of warfarin is warranted. Would it be appropriate to double this dose of warfarin and be reasonably assured that the resulting INR would be 2.8, which would be within this patient's goal of therapy?

The answers to both of these questions lie in an understanding of how warfarin works (its mechanism of action), as well as how warfarin is disposed of by the body (its pharmacokinetics).

Warfarin works by limiting the formation of activated clotting factors, which, in turn, are responsible for the eventual formation of a fibrin clot. One implication from this mechanism is that the full effect of warfarin is dependent on the depletion of multiple activated clotting factors (ie, II, VII, IX, and X) and their respective half-lives. The longer the half-life, the longer it takes to deplete the clotting factor. Some consider the depletion of factor Xa most responsible for any subsequent change in INR response to warfarin. Since the half-life of factor Xa is 24 to 40 hours, this means that it would take up to six days to see the full effect of any dose change of warfarin on the resulting INR. The disposition of activated clotting factors is one reason for the delay needed between changes in warfarin dose.

Another reason relates to the disposition of warfarin itself. Warfarin is cleared predominantly by the liver through a process that may become saturated. Since the half-life of warfarin (36 to 42 hours) is very similar to that of Factor Xa, it may also take the same 2 to 6 days before its effects are maximized. Also, since the hepatic clearance of warfarin is saturable, a small dose increase would very likely result in a very large change in the resulting INR. Using our patient as an example, if the dose of warfarin were increased to 5 mg daily (from 2.5 mg daily), it is very likely that the resulting INR would be greater than 4.0. To prevent this from occurring, a dose increase of 10% to 20% of the weekly dose would be preferred. Such a dose might be 3.75 mg Monday and Thursday and 2.5 mg daily on all remaining weekdays (ie, a 14% increase).

A delay of several days is needed after a dose change of warfarin to accommodate the prolonged half-lives of both warfarin and the primary clotting factor affected by warfarin, factor Xa. Aggressive dose changes of warfarin are usually avoided due to the likelihood of an exaggerated INR response in association with the non-linear disposition of warfarin.

by Larry Lopez, PharmD

INSIDE THIS ISSUE

Formulary update, *from page 1*

Bendamustine is a dual mechanism chemotherapy drug with properties of both an alkylating agent and a purine anti-metabolite. It has labeled indications for use in chronic lymphocytic leukemia (CLL) and treatment-resistant non-Hodgkins lymphoma (NHL).

Bendamustine has been used in Europe since the 1970s; only recently, trials examining its safety and efficacy have been published. Bendamustine is included in the 2010 National Comprehensive Cancer Network (NCCN) guidelines for first-line monotherapy and refractory/relapsed therapy with or without rituximab in CLL, first- and second-line therapy in combination with rituximab in follicular lymphoma, and induction and second-line therapy with or without rituximab in mantle cell lymphoma.

Limited clinical trials exist comparing the efficacy of bendamustine to first-line therapeutic options. Efficacy and safety have largely been demonstrated in phase II trials and trials without active comparators. Bendamustine has shown increased response rates compared to chlorambucil in CLL and has an effect on relapsed and rituximab-refractory NHL, but no randomized active comparator studies have been performed to examine its role in relapsed or refractory follicular lymphoma or relapsed or refractory mantle cell lymphoma. Chlorambucil is generally considered a poor choice for a comparison for the treatment of CLL since there are regimens with better response rates.

Major adverse effects for bendamustine include myelosuppression, infections, infusion reactions, tumor lysis syndrome, and skin reactions. Studies indicate that a lower dose may be necessary when used as a second-line therapy for CLL.

Bendamustine-containing regimens are expensive. Usually bendamustine is at least 50% more expensive than alternatives. Reimbursements often do not cover this increased cost.

Bendamustine was added in the *Formulary* for first-cycle therapy or at other times when patients are at risk for tumor-lysis syndrome. Usually, this drug will be administered in the outpatient setting. Bendamustine is already listed in the *Chemotherapy Policy,* requiring that it be ordered using a *Chemotherapy Order Form.*

Gadobenate dimeglumine is a gadolinium-based contrast agent. Gadoben-ate is a paramagnetic agent that develops a magnetic moment when placed in a magnetic field. This magnetic moment results in a large local magnetic field that enhances the relaxation rates of water protons in its vicinity leading to an increase of signal intensity (brightness) of tissue. Gadobenate has labeled indications for use in MRIs of the CNS in adults to visualize lesions with abnormal blood-brain barriers or to visualize abnormal vascularity of the brain, spine, and associated tissues.

Gadobenate has 2 characteristics that distinguish it from other gadolinium-based contrast agents currently available in the US. A small percentage is excreted via the hepatobiliary system in addition to its renal excretion, whereas other gadolinium-based contrast agents are strictly renally eliminated. This is marketed as providing better safety and tolerability; however, there is no comparative evidence to support this claim. The agent also has a nearly 2-fold increase in T1 relaxivity compared with other gadolinium-based contrast agents due to its weak and transient protein binding with serum macromolecules (eg, albumin). This is thought to provide enhanced visualization of lesions.

Recent trials have demonstrated gadobenate's ability to enhance MRI studies when compared to gadodiamide (eg, lesion border delineation, definition of disease extent, lesion internal morphology, and lesion contrast enhancement). These improved measurments could yield better clinical outcomes (increased detection rates). Also, better characterization of disease extent and morphology could lead to treatment that is more effective. However, better outcomes have not been demonstrated with gadobenate.

Gadobenate has a safety profile similar to other gadolinium-based contrast agents. Most adverse events are transient, self-resolving, and mild in intensity. In clinical trials, adverse events were reported in less than 0.5% of subjects, with headache, nausea, dizziness, and taste perversion the most commonly reported adverse events.

The most serious adverse effect associated with the use of gadolinium-based contrast agents is nephrogenic systemic fibrosis (NSF). Patients with NSF develop tight and rigid skin, which makes it difficult to bend joints. Extensive fibrosis of organs can lead to death. Most patients who develop this serious adverse effect have impaired renal function. Whether there is a different incidence of this reaction among the gadolinium-based contrast agents is unknown.

Gadobenate is considerably more expensive than gadodiamide. If it replaced gadodiamide, it could increase radiological expenditures several hundred thousand dollars. Therefore, the Department of Radiology is developing criteria for use to determine the appropriate niche for this product. Utilization of gadobenate and gadodiamide will be monitored.

Benzocaine is an ester-type, short-acting local anesthetic. Benzocaine is widely available in topical products (eg, Hurricaine® Spray) and is most commonly used in the hospital to anesthetize mucosal membranes.

Because of the risk of methemoglobinemia associated with the mucosal use of benzocaine, the spray and lozenges were deleted from the *Formulary* and designated nonformulary and not available for safety reasons. Nationally, the Department of Veterans Affairs eliminated the mucosal use of benzocaine in 2006. Atomized lidocaine 4% is the recommended alternative to benzocaine spray. Menthol-containing lozenges (without benzocaine) like Cepacol® Lozenges are an alternative to Chloraseptic® Lozenges.

Local anesthetics can oxidize hemoglobin to methemoglobin through their amine metabolites. Benzocaine is a more potent oxidizer than lidocaine. The potential for benzocaine to cause methemoglobinemia is widely known. Two studies done in animals, one in sheep and one in macaques, have shown that benzocaine causes methemoglobinemia in a dose-dependent fashion, whereas lidocaine is much less likely to do so.

A 2009 article that analyzed all reported cases of methemoglobinemia due to topical anesthetics reviewed 242 episodes of methemoglobinemia in 233 patients between 1949 and 2007. 97 of these were published since 2000. Of the 242 episodes, 12 were attributed to lidocaine and 7 of these patients were taking an additional drug that has oxidative activity. Only 3 patients developed methemoglobinemia after appropriate therapeutic use of lidocaine. Most (158) of the cases were attributable to benzocaine. The authors made a case for abandoning the use of benzocaine because it appears that some patients develop methemoglobinemia with even low doses of benzocaine.

There have been cases of methemoglobinemia reported with the use of topical lidocaine products. However, the risk for methemoglobinemia is much less than the risk associated with benzocaine.

Lidocaine 4% topical solution spray is given in 1- to 5-mL doses (40-200 mg lidocaine) sprayed with a tracheo-laryngeal atomizer (MADgic®) or applied with a cotton applicator. The maximum adult dose is 10 mL of 4% solution. Sterile lidocaine 4% will be stocked where benzocaine spray is now stocked. The MADgic® tracheo-laryngeal atomizer devices will be stocked in the supply rooms with other devices. For more information on how to use these devices, go to http://www.wolfetory.com/madgic.php. We will be stocking the MAD 600 device, because it is the most versatile and comes with a syringe.

In order to allow a transition from benzocaine to lidocaine, there will be a 2-month overlap (April and May 2010) when both products will be available. Users will be notified of the impending removal and nonformulary and not available status of benzocaine. This will allow users to become familiar with atomized lidocaine during the transition period.

Collagenase clostridium histolyticum is the first drug with a labeled indication

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Formulary update, *from page 2*
for the treatment of Dupuytren's contracture; surgery is an alternative treatment. Dupuytren's contracture affects a person's ability to straighten and properly use their fingers. Collagen clostridium histolyticum is injected into collagen cords of the hand and breaks down excessive build-up of collagen in the hand. It is injected into collagen cords up to 3 times at approximately 4-week intervals.

The use of collagen clostridium histolyticum is an outpatient procedure; therefore, it was designated nonformulary and not available for inpatient use.

Lamictal® XR is a once-daily version of anti-seizure medication lamotrigine immediate-release (IR), which is now available from multiple companies as a generic drug. Lamictal® XR has labeled indications for primary generalized tonic-clonic seizures and partial onset seizures with or without secondary generalization in patients greater than or equal to 13 years of age.

Lamictal® XR's labeling states that the conversion from the IR to the ER should use the same daily dose. Therefore, Lamictal® XR was designated nonformulary and not available. Patients can continue to use their own supply from home, if they have it, or be converted to lamotrigine IR.

Oleptro® is the once-daily version of the antidepressant trazodone; IR trazodone is available as a generic from multiple companies. Oleptro® has a labeled indication for the treatment of major depressive disorder. Oleptro® was designated nonformulary and not available. Patients can continue to use their own supply from home, if they have it.

Intravenous phenytoin was deleted from the *Formulary* and was designated nonformulary and not available in August 2008. After that decision, orders were automatically changed to fosphenytoin, a water-soluble prodrug of phenytoin with some advantages over parenteral phenytoin (eg, less irritating to veins and can be administered more rapidly).

A recent **shortage of fosphenytoin** has required the re-addition of IV phenytoin in the *Formulary*, and, temporarily (during the shortage), fosphenytoin orders can be automatically interchanged to phenytoin. It appears that the shortage occurred when the brand name product (Cerebyx® was discontinued) and generic manufacturers were no longer able to meet demand. Supposedly, this shortage will be resolved by mid-May, but the resolutions of shortages are always difficult to predict.

Since IV fosphenytoin is widely used, it would be very difficult to contact all fosphenytoin prescribers to change patients to phenytoin IV, when needed. Also, there are situations (eg, IM administration, loading doses of fosphenytoin in small children) when fosphenytoin is preferred, and we will be attempting to reserve fosphenytoin for these uses. However, it is possible that we will exhaust all fosphenytoin before the shortage is resolved.

The automatic interchange to IV phenytoin will use the same "Phenytoin-Equivalent (PE)" doses. The phenytoin will be diluted in normal saline and administered at the appropriate rate (25 mg/min). All phenytoin IV solutions should be filtered through a 0.22-micron filter.

Iron dextran is 1 of the 4 forms of parenteral iron supplements on the US market (ie, ferumoxytol [Feraheme®], iron dextran, iron sucrose [Venofer®], and sodium ferric gluconate [Ferrlecit®]. Iron dextran and sodium ferric gluconate are listed in the *Formulary*. Ferrlecit® is the primary parenteral iron product listed in the *Formulary*, while iron dextran is now restricted to use in only neonatal TPN. There are no data to support the use of sodium ferric gluconate complex [Ferrlecit®] in TPN. However, the Adult TPN Service does not use iron in TPN.

On September 25, 2009, the box warning for iron dextran was modified. A test dose is now recommended prior to the first dose. This is to monitor for anaphylactic-type reactions during administration. Fatal reactions have occurred despite the patient tolerating the test dose. Patients with a history of multiple drug allergies appear to be at greater risk for this reaction.

Iron dextran is the only injectable iron product with documented use in neonates. It is also the only product with dosing recommendations in *NeoFax*, the primary reference used for neonatal drug dosing. *NeoFax* also states that iron dextran can be used in neonatal TPN if there is sufficient amino acid content (2%). Neonates rarely experience anaphylactic (anaphylactoid) reaction and the labeled iron dextran test dose would be higher than what is given to neonates; and, therefore, a test dose will not be used in this population. There is no recommended test dose for neonates.

PRESCRIBING

Naloxone 101 – A fresh look at an old drug

Health care practitioners do not use naloxone in everyday practice, so some may have forgotten how to use it. Most know it is an opioid antagonist used to reverse respiratory depression, but they may not remember much more than that. To feel confident using any drug, practitioners should understand when it is appropriate to use the drug, what the dose is, how it is administered, precautions of its use, and its potential adverse effects. Hopefully, a quick review of these things will serve as a refresher on the use of naloxone.

Naloxone is an opioid antagonist used primarily for partial or complete reversal of respiratory depression induced by opioids.[1] It has FDA approval in adults and children for this indication, in addition to its use in suspected or known acute opioid overdose. Off-label uses of naloxone include opioid-associated pruritus and constipation.[2]

Naloxone comes in 1-mL vials at a concentration of 0.4 mg/mL.[1] In most situations, the contents of one vial should be diluted with 9 mL of normal saline to a concentration of 40 mcg/mL. This concentration facilitates the delivery of smaller doses (20-40 mcg). Doses may then be administered intravenously (IV), intramuscularly (IM), subcutaneously (SQ), or intraosseously (IO) in case of an emergency. Onset is most rapid (2 to 3 minutes) with IV administration but may take up to 15 minutes when used IM or SQ. Per ACLS guidelines, doses 2-2.5 times the normal dose may also be administered endotracheally (ET).[2]

When using naloxone, it is important to understand that respiratory depression occurs at a higher μ-receptor occupancy than analgesia.[3] In clinical practice, when a patient first shows signs of respiratory depression (less than 8 breaths per minute or oxygen saturation less than 80-90%), a single low dose of naloxone may be enough to reverse the respiratory depression but not the analgesia. With this concept in mind, doses should start low and then be increased or repeated until adequate ventilation or alertness has been achieved without causing significant pain or discomfort.

The labeling for naloxone lists doses from 100-200 mcg for opioid-induced respiratory depression.[1] On the Shands at UF *Adult PCA Order Form,* doses are much lower: 20 mcg (0.5 mL of 40 mcg/mL concentration) IV push, repeated every 1-2 minutes as needed. The adult epidural infusion order form utilizes a higher dose of naloxone: 100 mcg (2.5 mL of 40 mcg/mL concentration), repeated until the desired effect has been achieved. Similar doses may be used to treat opioid-induced pruritus.[2] When dosing naloxone, consider the severity of a patient's underlying pain and the extent of their respiratory depression. Small doses can effectively improve ventilation without reversing analgesia, so it is better to start low and increase until there is a response.

For acute reversal of respiratory depression in children, the American Academy of Pediatrics Committee on Drugs (AAPCD) recommends naloxone

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Prescribing, from page 3

1-15 mcg/kg/dose IV/IM repeated until a response is achieved.[2] On the PCA order form at Shands Children's Hospital, the dose is 2-5 mcg/kg/dose IV, with a maximum of 200 mcg/dose. The order form also has an option to order a slow naloxone infusion for PCA-associated pruritis; the recommended dose is 0.25-2 mcg/kg/hr.

For urgent treatment of known or suspected opioid overdose, the doses are higher: 0.4-2 mg IV/IM/SQ.[1] For these situations 10 mL, 1-mg/mL vials are available for use. Doses should be repeated until adequate ventilation is observed. If the total dose reaches 10 mg with no response, the diagnosis of opioid overdose should be questioned. In the same clinical situation, the dose for children, per AAPCD, is 100 mcg/kg IV/IM for children less than 5 years old or less than 20 kg, and 2 mg IV/IM for children 5 years and older or 20 kg and above.[2]

Naloxone's half-life in adults is only about 30 minutes, so situations of "renarcotization" may occur if the underlying opioid has a longer half life (eg, morphine or hydromorphone).[4] For this reason, repeat doses of naloxone in 1- to 2-hour intervals may be necessary to maintain respiratory status. Starting a naloxone infusion is another way to overcome this phenomenon. An infusion should be made by adding 2 mg of naloxone to a 500 mL bag of normal saline or 5% Dextrose. The rate of administration should then be titrated to the patient's response.[1]

While there is no available formulation of oral (PO) naloxone, this route of administration has been studied and used for treatment of opioid-induced constipation. At Shands at UF, our pharmacy compounds a naloxone liquid (0.4 mg/mL) from our injectable product. The dose studied was 3 mg PO three times daily titrating up to 12 mg three times daily by the fourth day.[2]

Like most drugs, there are a number of precautions to consider before giving naloxone. Naloxone should not be used in situations of non-opioid-induced respiratory depression (eg, benzodiazepines, barbiturates), and it may create only a partial response in patients taking partial opioid-receptor agonists (eg, buprenorphine).[1] In patients with known or suspected physical dependence to opioids, naloxone should be used cautiously since withdrawal symptoms may occur within minutes of administration. Newborns born to mothers suspected of long-term opioid use should not be administered naloxone due to the risk of seizures and/or acute withdrawal symptoms. Naloxone is metabolized by the liver, so caution should also be used in patients with hepatic dysfunction.

Use of naloxone for opioid reversal has caused serious and life-threatening adverse effects like pulmonary edema, cardiac arrhythmias, hypertension, and cardiac arrest.[1-3] The cause of these complications is thought to be due to a massive release of catecholamines after naloxone administration.[3] This sympathetic over-stimulation may result in arrhythmias and vasoconstriction. Vasoconstriction can then contribute to pulmonary edema by causing fluid to shift from the systemic circulation into the pulmonary vasculature.

Other adverse effects that may occur after opioid reversal with naloxone include nausea, vomiting, restlessness, diaphoresis, tachycardia, seizures, or tremor.[2] When naloxone is given at low doses and titrated to effect, it is generally considered safe and well-tolerated in children and adults.

To summarize, naloxone is an opioid antagonist used for reversal of opioid-induced respiratory depression, pruritus, and constipation. In non-emergent situations, naloxone doses should start low and be titrated to effect. High doses should be used cautiously since they may reverse analgesia and cause the breakthrough of severe underlying pain. Practitioners should also always consider cardiovascular complications and the recurrence of sedation and respiratory depression when treating a patient with naloxone.

by Danielle Wallace, PharmD

REFERENCES

1. International Medication Systems, Limited. Naloxone hydrochloride injection package labeling. So. El Monte, Ca 91733. Revised Aug 2001.
2. Micromedex® 2.0. Naloxone Drug Monograph. Accessed March 18, 2010.
3. Dahan A, Aarts L, Smith TW. Incidence, Reversal, and Prevention of Opioid-Induced Respiratory Depression. Anesthesiology 2010;112:226-38.
4. Fakuda K. Miller: Miller's Anesthesia. 7th ed. Churchill Livingston, 2009. Accessed through MD consult on March 18, 2010.