Example 8.3 Palomar Health Newsletter (1 of 4)

encapsulated news
OCT.2013
PHARMACY INFORMATION FOR PHYSICIANS, NURSES AND PHARMACISTS

VTE Prophylaxis: Enoxaparin (Lovenox) Is Out; BID SubQ Heparin Is In

Jeremy Lee, Pharm.D., BCPS

New therapeutic substitution: enoxaparin to subQ heparin in selective populations

Venous Thromboembolism (VTE) prophylaxis with subcutaneous (subQ) unfractionated heparin is a cost effective option for Palomar Health patients.

Palomar Health utilizes both enoxaparin (Lovenox) and subQ heparin for VTE prophylaxis in medical patients. The American College of Chest Physicians (ACCP) guidelines state that both heparinoids are equally effective for VTE prophylaxis in most patient populations, except for the following populations: orthopedic surgery, stroke, trauma and bariatric surgery (in which enoxaparin is recommended). The guidelines also state that twice daily administration of subQ heparin is just as effective as three times daily administration.

Unfractionated Heparin (UFH) is a cost effective option for VTE prophylaxis. The cost of enoxaparin 40mg daily is $5.70 and heparin 5,000 units twice a day is $2.34. Current utilization patterns indicate physicians utilize either heparinoid for VTE prophylaxis. Order sets currently list both medications as an option for VTE prophylaxis and physicians prescribe both medications as well. There is opportunity to utilize subQ heparin in an estimated 60% of patients receiving enoxaparin for VTE prophylaxis. Significant cost savings can be realized with a uniform conversion from enoxaparin to heparin use in VTE prophylaxis. The transition can result in an estimated $20,000 - $40,000 in cost savings, should maintain similar efficacy and complies with the ACCP recommendations for VTE prophylaxis.

Plan

1. **Providers:**
   a. **Utilize subQ heparin 5,000 units twice daily in appropriate patients for VTE prophylaxis.** Physicians may still choose to order 7,500 unit doses or the TID frequency at their discretion. This may be especially appropriate for morbidly obese patients, along with the use of pulsatile ankle stockings (PAS).
   b. **Maintain enoxaparin prophylactic therapy in orthopedic surgery, stroke, trauma and bariatric surgery** patients where there is compelling evidence of either increased efficacy or safety with enoxaparin.
2. **Information Systems: Revise necessary powerplans** to reflect use of subQ heparin as preferred medication option and the BID dosing of subQ heparin. This is underway, but will take time.
3. **Pharmacy: Pharmacy has implemented an automatic therapeutic substitution enabling pharmacists to change orders for prophylactic doses of enoxaparin to heparin subQ 5,000 units BID except in the orthopedic surgery, stroke, trauma and bariatric surgery patient populations.**

NOTE: These changes do NOT apply to the use of "therapeutic" doses of enoxaparin used to TREAT thromboembolic diseases like DVT, PE or MI. Nor does it apply when enoxaparin is used as prophylaxis against stroke (e.g. A-fib, electrophysiology procedures). SubQ heparin is NOT indicated for these conditions.

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For more info about this example contact Olga DeTorres, PharmD at Olga.DeTorres@palomarhealth.org

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4-factor Prothrombin Complex Concentrate (Kcentra) for Reversal of Warfarin

By Michael Kruse, Pharm.D., MBA, BCPS

SUMMARY:
Kcentra is the first 4-factor prothrombin complex concentrate approved in the United States. The product includes more factor VII, protein C, and protein S than the 3-factor products. Overall, studies have found it to be equal in safety and efficacy for reversal or warfarin. There are trends toward increased embolic events but decrease fluid overload. Because of the trends for increased embolic events, there is a Black Box Warning. This warning and the drug cost necessitate reserving the drug for its FDA indication – reversal of warfarin in patients with acute major bleeding. Canadian guidelines also allow for use in patients on warfarin who need urgent surgery (< 6 hours). The product has been added to the formulary with restriction to these two indications. Pharmacists will screen patients to assure appropriate use. This product will replace most FFP for this indication and all factor VIIa (with possible exception for Jehovah's Witness patients). Although made from human blood, the risk of infectious agents is low due to multiple neutralization/sterilization techniques.

PHARMACOKINETICS:
International Normalized Ratio (INR)

In the plasma-controlled RCT in acute major bleeding, the median INR was above 3.0 prior to the infusion and dropped to a median value of 1.20 by the 30 minute time point after start of Kcentra infusion. By contrast, the median value for plasma was 2.4 at 30 minutes after the start of infusion.

EFFICACY:
Overall efficacy in major bleeding was non-inferior hemostasis compared to plasma at 24 hours. However, 62.2% of patients had an INR less than 1.3 at 30 minutes compared to 9.6% in the plasma arm.

SAFETY:
The incidence of thromboembolic (TE) adverse reactions assessed as at least possibly related to study treatment by the investigator or, in the case of serious thromboembolic events, the blinded safety adjudication board (SAB) was 5 (4.9%) in the Kcentra group and 3 (2.8%) in the plasma group.

There were 6 subjects (5.8%, all non-related by investigator assessment) in the Kcentra group who experienced fluid overload in the plasma-controlled RCT in acute major bleeding and 14 (12.8%, 7 events related by investigator assessment) who had fluid overload in the plasma group.

PURCHASE PRICE:
4-factor PCC (Kcentra) costs $1.27 per unit. The price per dose is based on the pre-treatment INR.

Pre-treatment INR	2 – < 4	4 – 6	> 6
Dose of Kcentra (units of Factor IX) / kg body weight	25	35	50
Maximum dose (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000
80 kg patient cost	2000 units = $2540	2800 units = $3556	4000 units = $5080
Maximum dose cost	2500 units = $3175	3500 units = $4445	5000 units = $6350

NEW PROCESSES OR MECHANISMS FOR ORDERING, ADMINISTRATION AND MONITORING:

1. PowerPlan to be released on September 10th that will guide warfarin reversal. Kcentra will only be available within this PowerPlan. New order sentences will be created for vitamin K to balance the need to reverse warfarin but prevent warfarin resistance.
2. Because of the Black Box Warning and cost of the medication, pharmacists will need to screen patients to assure it is only used in acute major bleeding in patients on warfarin OR in patients on warfarin needing urgent (< 6 hours) surgery.
3. Administration: 4-10 vials must be reconstituted with 20 mL of sterile water for each vial. This cumbersome mixing requires mixing in pharmacy and delivered STAT. This will be injected into a 500 mL bag.
4. Alaris: The product should be administered at a rate of 0.12 mL/kg/min (~3 units/kg/min) to a maximum rate of 8.4 mL/min. This calculates to a rate of 400-504 mL/HR. Alaris has been programmed with Guardrails at 400 and 505 mL/HR.
5. Dedicated line: this product requires a dedicated line.
6. Monitoring: any patient administered a reversal agent should be monitored for embolic events.

IV to Oral Azithromycin

By Olga DeTorres, Pharm.D., FASHP, BCPS-ID

Azithromycin is a commonly prescribed antibiotic for the treatment of community-acquired pneumonia, bronchitis and COPD/asthma exacerbation because to its broad bacterial spectrum and anti-inflammatory effects. Patients admitted with community-acquired pneumonia, bronchitis and COPD/asthma exacerbation are kept on IV antibiotics longer than necessary. Early conversion from IV to the PO route has been reported to increase patient safety and comfort, reduce cost and facilitate earlier discharge without compromising medical care. The dosing regimen for oral Azithromycin is the same as IV; 500 mg every 24 hr. Serum and tissue levels after oral administration are similar to those achieved with parenteral azithromycin administration. The cost of an azithromycin 500 mg vial is almost twice that of the oral 500 mg tablets. By implementing an IV-to-PO switch for Azithromycin, Palomar Health could save up to $3,000 per year. Most university medical centers have an automatic IV-to-PO automatic substitution in place for azithromycin. The Antibiotic Sub-Committee recommended that Palomar Health implement a similar procedure. Pharmacy will be performing an automatic substitution for IV Azithromycin to PO whenever patients meet the criteria listed in the "IV to PO - Automatic Substitution by a Pharmacist" Procedure. With the addition of azithromycin to this procedure, we hope to increase patient satisfaction while shortening length of hospital stay.

For more info about this example contact Olga DeTorres, PharmD at Olga.DeTorres@palomarhealth.org

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Example 8.3 Palomar Health Newsletter (continued 3 of 4)

Antimicrobial Prophylaxis for Pacemaker & Defibrillator Insertion – A Success Story!

By Olga DeTorres, Pharm.D., FASHP, BCPS-ID

In 2006 an outbreak of Methicillin-Resistant *Staphylococcus aureus* (MRSA) pocket infections triggered the Cardiology Department to review the measures they used to prevent infection during pacemaker and intra-cardiac defibrillator placement. These infections when they occur can be quite costly. Treatment usually requires that the device be surgically removed and that the patient receive several weeks of parenteral antibiotic therapy. The review found that all patients received antimicrobial prophylaxis prior to pacemaker and intra-cardiac defibrillator placement. A systemic prophylactic antibiotic (cefazolin) was ordered in all cases. The results were reviewed by the Antibiotic Subcommittee of the Palomar Health Pharmacy and Therapeutics Committee. They made the following recommendations:

- To prevent MRSA pocket infections and/or endocarditis from occurring after the placement of pacemakers and intra-cardiac defibrillators, Vancomycin IV should be given in conjunction with cefazolin IV as antimicrobial prophylaxis prior to these procedures.
- Beta-lactam allergic patients should receive Vancomycin IV alone for antimicrobial prophylaxis.

A repeat Medication Use Evaluation (MUE) reviewed the charts of all patients who had undergone a pacemaker or defibrillator insertion during the month of July 2012. The MUE found that 100% of patients received antimicrobial prophylaxis prior to pacemaker or defibrillator insertion. Appropriate antibiotics were ordered in most patients (96.2%). The duration of prophylaxis (< 24 hours) was appropriate in 100% patients. Not one patient experienced a post- procedure infection. The old adage is still true today: "An ounce of prevention is better than a pound of cure." Congratulations to the cardiologists and the cath lab staff for a job well done!

Fluzone High-Dose Influenza Virus Vaccine

By Olga DeTorres, Pharm.D., FASHP, BCPS-ID

The standard adult dose influenza vaccine generates an immunological response in only 44% for patients < 65 years of age and 19% of patients who are 65 years or older. Current adult influenza vaccines provide inadequate coverage against influenza in the elderly resulting in serious morbidity and increased mortality. An influenza vaccine with greater immunogenicity compared with the currently available vaccines was needed. Fluzone High-Dose, an inactivated influenza vaccine was recently added to the Palomar Health formulary. Each 0.5 mL dose contains 60 mcg of hemagglutinin from each of the three influenza strains, subtypes A (H1N1 and H3N2) and type B which is four times greater than the standard vaccine. The vaccine works by inducing the production of neutralizing antibodies. Patients are considered to have seroconverted when they generate hemagglutination inhibition antibody titers that are 1:40.

Contraindications are the same as for other influenza vaccines, e.g. history of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or to a previous dose of any influenza vaccine or history of Guillain-Barre Syndrome. Common side effects include injection site reactions (e.g. tenderness, erythema, swelling, induration, ecchymosis), fever, vomiting, drowsiness, lost appetite and irritability. Patients should be monitored for fever after administration.

Fluzone High-Dose is a welcome addition to our vaccine formulary. Its use will be limited to patients ≥ 65 years of age.

Safety of Ganciclovir & Valganciclovir

By Olga DeTorres, Pharm.D., FASHP, BCPS-ID

Ganciclovir was the first antiviral agent approved for the treatment of cytomegalovirus (CMV) infection. It is widely used for the treatment of CMV infections in patients with poorly controlled and advanced HIV/AIDS, and recipients of solid organ and bone marrow transplantation, who are at high risk for invasive CMV disease. Valganciclovir, an oral prodrug that is rapidly converted to ganciclovir, also plays a major role in the treatment and prevention of CMV infections in immunocompromised hosts. Ganciclovir is commonly associated with a range of serious hematological adverse effects including granulocytopenia, neutropenia, anemia, thrombocytopenia, as well as seizures, pain and phlebitis at injection site (due to high pH), rash, itching, increased serum creatinine and BUN concentrations. It is also considered a potential human carcinogen, teratogen and mutagen. It can potentially cause inhibition of spermatogenesis. Ganciclovir is handled as a cytotoxic drug in the clinical setting. Because of safety concerns, the charts of all patients who received ganciclovir or valganciclovir during the past six months were reviewed.

Our use of ganciclovir and valganciclovir is very low. There were only five patients during the study period. Two patients received the drug for prophylaxis after organ transplantation, one patient received it as empiric therapy for CMV esophagitis, while two patients were treated for CMV retinitis or viremia. Two of the five patients experienced a hematological adverse event during their hospital stay, neutropenia and pancytopenia. The chart review found that renal function and CBC were not monitored in patients who had been receiving these agents as outpatients. Given the risk of bone marrow suppression, patients receiving ganciclovir or valganciclovir should have a complete blood count (CBC) with a differential at least twice a week during induction therapy, then weekly thereafter. In addition, renal function monitoring should be done at least weekly during induction therapy, since a decline in renal function may require adjusting the dose of ganciclovir. More frequent monitoring should be considered in patients at particularly high risk for nephrotoxicity, such as those receiving cyclosporine, tacrolimus, aminoglycosides or amphotericin B. The Antibiotic Sub-Committee recommended that ganciclovir and valganciclovir be added to the Pharmacy Clinical Monitoring Report, allowing pharmacists to order weekly serum creatinine and CBC whenever physicians fail to do so.

In the past, these agents were restricted to use by Infectious Disease specialists; the Antibiotic Sub-Committee recommended that the ganciclovir and valganciclovir restrictions be expanded to include hematologists/oncologists and gastroenterologists as their patients often present with serious CMV infections. The Pharmacy and Therapeutics Committee approved their recommendations.

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Example 8.3 Palomar Health Newsletter (continued 4 of 4)

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Summary of Drugs

SUMMARY OF DRUGS ADDED TO THE FORMULARY WITH RESTRICTIONS...

Generic	Brand	Indication	Class
Prothrombin complex concentrate 4-factor (PCC-4)	Kcentra	Reversal of warfarin in patients with acute major bleeding or the need for urgent surgery within 6 hours.	Hemostatic; Prothrombin Complex Concentrate (PCC)
Influenza virus vaccine	Fluzone High-Dose	Active immunization against influenza virus in adults 65 years and older	Vaccine, Inactivated (viral)

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