OSF Saint Francis Medical Center
Department of Pharmacy

FYDI

Fall 2009

℞.....For Your Drug Information.....℞

Therapeutic Consults and Controversies

Prasugrel Approval and Comparison to Clopidogrel

In July 2009, the FDA approved an agent similar to Plavix® (clopidogrel). The new drug, Effient™ (prasugrel), is a platelet aggregation inhibitor that has been shown to reduce the rate of a combined endpoint of nonfatal myocardial infarction (MI), nonfatal stroke, and cardiovascular (CV) death in comparison to clopidogrel. Treatment differences were derived predominantly by a decrease in nonfatal MIs (with prasugrel treatment), with little difference in CV death and no difference in strokes.[1]

Prasugrel is indicated to reduce the rate of thrombotic cardiovascular events, including stent thrombosis, in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI). Patients comprising the indicated population include those with non-ST-elevation myocardial infarction (NSTEMI), unstable angina (UA), and ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.[1] To initiate therapy, a single loading dose of 60 mg prasugrel should be administered, followed by a maintenance dose of 10 mg once daily. Prasugrel is currently available in 5 mg and 10 mg tablets and can be administered with or without food. Patients taking prasugrel should additionally take aspirin (75 mg-325 mg) daily to further decrease their risk of cardiovascular events.[2]

Prasugrel is a thienopyridine prodrug that is metabolized to both active and inactive metabolites. Once converted to its active metabolite (R-138727), prasugrel irreversibly binds the $P2Y_{12}$ component of ADP receptors on platelets. Consequently, platelet activation and aggregation is inhibited.[1,3] Following hydrolysis by esterases, conversion to prasugrel's active metabolite requires a single CYP-450-dependent oxidative step, whereas clopidogrel requires two consecutive CYP-450-dependent steps to form an active metabolite.[3] Due to this more proficient conversion to an active metabolite, prasugrel has approximately ten times greater potency than clopidogrel.[4]

When compared to approved and higher loading doses of clopidogrel, prasugrel has been shown to achieve faster onset of greater extent as well as more consistent inhibition of platelets.[5] Despite greater efficacy and lower risk of major cardiovascular events when compared to clopidogrel treatment following PCI, treatment with prasugrel has been associated with an increased risk of significant bleeding.[1,3] The FDA has required prasugrel labeling to include a Medication Guide as well as a black box warning addressing prasugrel's risk of significant, sometimes fatal bleeding.

The bleeding risk warning states that prasugrel is contraindicated in patients with active pathological bleeding or a history of transient ischemic attack or stroke. Additionally, prasugrel is not recommended in patients $\geq$ 75 years of age due to an increased risk of fatal and intracranial bleeding and uncertain effectiveness. In certain high-risk situations (such as in patients with a history of prior MI or diabetes), however, prasugrel use in patients $\geq$ 75 years may be considered. Patients less than 60 kg are also at an increased risk of bleeding if treated with prasugrel due to an increased exposure to the active metabolite of prasugrel. In such patients, lowering the maintenance dose to 5 mg daily is recommended, although safety and effectiveness of the 5 mg dose have not been prospectively studied. An additional risk factor for bleeding includes the concomitant use of medications that increase the risk of bleeding (e.g. warfarin, heparin, chronic NSAID use, fibrinolytics, etc.). Furthermore, prasugrel should not be started in patients likely to undergo urgent coronary artery bypass graft surgery (CABG), and whenever possible,

prasugrel should be discontinued at least seven days prior to any type of surgery. Should a bleeding event associated with an invasive procedure occur, withholding a dose of prasugrel would not be sufficient to restore hemostasis. Prasugrel inhibits platelet aggregation for the lifetime of a platelet (7-10 days), so the administration of exogenous platelets may be needed. However, platelet transfusions within six hours of a prasugrel loading dose or four hours of a maintenance dose may be less effective.[1]

In conclusion, prasugrel possesses superior inhibition of platelet activation and aggregation in comparison to clopidogrel. However, prasugrel use is associated with higher rates of clinically significant bleeding. Understanding the risks and benefits of prasugrel treatment is imperative so that its use is limited to appropriate patients and circumstances.

Submitted by Jamie Shelly, PharmD Candidate

References:

1. Effient™ [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
2. Prasugrel. Lexi-Drugs Online. Lexi-Comp Online. Lexi-Comp, Inc. Hudson, OH. Available at: http://online.lexi.com/crlonline. Accessed August 3, 2009.
3. Prasugrel. Online Factsandcomparisons. Wolters Kluwer Health, Inc. Conshohocken, PA. Available at: http://online.factsandcomparisons.com. Accessed August 3, 2009.
4. Niitsu Y, Sugidachi A, Ogawa T, Jakubowski JA, Hashimoto M, Isobe T, et al. Repeat oral dosing of prasugrel, a novel P2Y12 receptor inhibitor, results in cumulative and potent antiplatelet and antithrombotic activity in several animal species. *Eur J Pharmacol* 2008; 579: 276-82.
5. Li YG, Ni L, Brandt JT, Small DS, Payne CD, Ernest CS 2nd, et al. Inhibition of platelet aggregation with prasugrel and clopidogrel: an integrated analysis in 846 subjects. *Platelets* 2009; 20:316-27.

Drugs in Review

Dronedarone (Multaq®)

Added to formulary November 2009

Similar products on formulary: Amiodarone

Dronedarone (Multaq®) is a newly antiarrhythmic drug that is structurally similar to amiodarone.[1] It has properties from all four Vaughan-Williams antiarrhythmic classes, including sodium channel blockade, beta-blockade, potassium channel blockade, and calcium channel blockade.

Although it shares chemical similarities with amiodarone, certain changes were made to its molecular structure in an effort to decrease some of the toxicities seen with amiodarone.[2] While amiodarone's efficacy for the treatment of atrial fibrillation and other arrhythmias is well-documented, its long half life and its potential for pulmonary and thyroid toxicities present safety issues. Specifically, iodine was removed from dronedarone in order to decrease the risk of thyroid-related toxicity. A methane-sulfonyl group was also added, which shortened dronedarone's half-life to less than 24 hours. These structural changes are also thought to decrease the risk of pulmonary toxicity with dronedarone. To date, none of the clinical studies for dronedarone have shown an increase in either thyroid or pulmonary toxicity with the use of this drug.

Dronedarone undergoes hepatic metabolism via the CYP3A4 enzyme. It is primarily eliminated by the liver; therefore, renal dosage adjustment is not necessary for this drug. While no dosage adjustment is necessary in patients with moderate hepatic impairment, dronedarone is contraindicated in patients with severe liver failure. Dronedarone has a half life of 13-19 hours.[1,3]

In addition to being a substrate of CYP3A4, dronedarone also inhibits CYP3A4 and CYP2D6 enzymes. It also inhibits P-glycoprotein transport. These factors increase dronedarone's potential to interact with other medications. The table below summarizes some of the major drug interactions associated with dronedarone.

Common side effects of dronedarone include diarrhea, asthenia, nausea, skin reactions, abdominal pain, bradycardia, vomiting, and dyspepsia. The labeling for dronedarone does contain a black box warning stating that the drug is contraindicated in patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart

failure clinic. This warning was added based on the findings of the ANDROMEDA trial, which was a double-blind, placebo-controlled, randomized, parallel-group trial involving 627 adults with new or worsening heart failure (NYHA Class III or IV).[4] The primary efficacy endpoint was death from any cause or hospitalization for worsening heart failure. The trial was stopped early due to an increase of deaths associated with the use of dronedarone. A total of 37 patients died during the shortened study period; 25 of these occurred in the dronedarone group.

Dronedarone is pregnancy category X and should not be used in pregnant patients. However, there have been no reports of increased risks for pregnant caregivers who handle this product and it is not considered a hazardous medication. Breast milk excretion of dronedarone is unknown.

Dronedarone is available in 400 mg oral tablets. The approved dosing regimen for atrial fibrillation/atrial flutter in adults is 400 mg PO twice daily with meals.

Daily Cost: $6.97 (AWP)
Monthly Cost: $48.79 (AWP)

References

1. Multaq package insert. Bridgewater, NJ: Sanofi-Aventis; 2009 July.
2. Hohnloser S, Crijns HJGM, van Eickels M, et al. Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation. NEJM. 2009; 360: 668-78.
3. Lexi-Comp Online. Hudson, Ohio: Lexi-Comp, Inc.
4. Kober L, Torp-Pedersen C, McMurrya JJV, et al. Increased Mortality after Dronedarone Therapy for Severe Heart Failure. NEJM. 2008; 358: 2678-87

Dronedarone Drug Interactions[3]		
Drug	**Net Effect**	**Mechanism of Action**
Digoxin	Increased levels of digoxin	Inhibition of P-gP transporter
Verapamil & Diltiazem	Increased effect of dronedarone	CYP3A4 inhibition caused by verapamil and diltiazem
Beta-blockers	Increased bradycardia	Duplicate effect
Ketoconazole	Increased effect of dronedarone	CYP3A4 inhibition caused by ketoconazole
Grapefruit juice	Increased effect of dronedarone	CYP450 enzyme inhibition caused by grapefruit juice
Rifampin	Decreased effect of dronedarone	CYP3A4 induction
Phenobarbital	Decreased effect of dronedarone	CYP3A4 induction
Carbamazepine	Decreased effect of dronedarone	CYP3A4 induction
Phenytoin	Decreased effect of dronedarone	CYP3A4 induction
St. John's Wort	Decreased effect of dronedarone	CYP3A4 induction
Simvastatin	Increased effect of simvastatin	CYP3A4 inhibition/ P-gP inhibition caused by dronedarone
Tacrolimus	Increased effect of tacrolimus	CYP3A4 inhibition caused by dronedarone
Sirolimus	Increased effect of sirolimus	CYP3A4 inhibition caused by dronedarone
Propranolol	Increased effect of Propranolol	CYP2D6 inhibition caused by dronedarone
Warfarin (S enantiomer)	Increased effect of warfarin	CYP3A4 inhibition caused by dronedarone

Medication Safety Notes

Food-Drug Cross-Sensitivities

When patients with food allergies come into the hospital, pharmacists are often questioned about cross-sensitivities with medications. This poses a challenge to pharmacists because this information can be difficult to find. Most of the commonly used drug information resources do not contain pre-formulated charts or lists with this information. Many computer systems (including IDX) do not flag drugs that are cross-sensitive to foods. Therefore, dealing with food-drug cross-sensitivities requires a customized approach.

When dealing with patients with food allergies, the best initial course of action is to get a

detailed history of the patients' allergies. This history should include a description of allergic reactions as well as a list of allergens. Some patients' self described food allergies may be food intolerances and not true IgE-mediated allergic reactions. If a patient's food allergy is determined to be a true allergy, any medication that they may need to receive during their hospital stay needs to be closely examined.

Most reactions that occur in food allergic patients after drug ingestion are caused by inert ingredients in the drug formulation, and not the active ingredient. For this reason, it is important to determine exactly which product the patient will receive. For example, if the patient is to receive the brand name product, then this is the product that needs to be investigated. The generic version of that drug may have different excipients and therefore may not have the same cross-sensitivity considerations as the branded product. Food derived excipients serve a variety of uses in drug formulation, including manufacture/identification, stability/preservation, taste improvement, drug delivery, and improvement of efficacy.[1] Any intentionally added ingredients are disclosed in the package insert. Additionally, any ingredient derived from one of the eight most common allergens (peanuts, tree nuts, soybeans, wheat, milk, egg, fish, or shellfish) are usually disclosed by source from the manufacturer. However, manufacturers may not always declare sources of less common allergens, such as corn, tomato, or strawberry. Some products may also be unintentionally contaminated with food derived products during the manufacturing process. This type of contamination may not be stated on the drug label.

Often the best sources of information regarding food derived ingredients are the package insert and the drug manufacturer. If the package insert does not explicitly state a food source for a drug ingredient, the drug information department of the manufacturer can be contacted for clarification. The table below provides a list of drugs that the potential to cause reactions in patients with specific food allergies. (Keep in mind that this table is not all inclusive.)

Handling food-drug cross-sensitivities requires extra work on the part of pharmacists and other healthcare providers. As the incidence of food allergies in the general population continues to increase, this issue will become more important.

References:

1. What are excipients doing in medicinal products? DTB. 2009;47(7):81-84.
2. Baxter. Personal Communication. October 6, 2009.
3. Hofer KN, McCarthy MW, Buck ML, et al. Possible Anaphylaxis after Propofol in a Child with Food Allergy. Ann Pharmacother. 2003;37:398-401.
4. Hospira. Personal Communication. October 6, 2009.
5. Lexi-Comp Online. Hudson, OH: Lexi-Comp, Inc. 2009.

Food and Drug Cross-sensitivities [2-5]

Food	Affected Medications
Egg	Fat emulsion, Influenza vaccine, Interferon alfa-n3,measles and mumps vaccines, MMR vaccine, Propofol, Verteporfin, Yellow fever vaccine
Fish	Protamine, Omega-3-acid ethylesters (Lovaza®)
Iodine	Amiodarone, Potassium iodide
Papaya	Crotalidae polyvalent immune Fab, digoxin immune Fab (ovine)
Peanut	Dimercaprol,Combivent® MDI*, Progesterone in oil capsules (Prometrium), Soy isoflavones*, Fluocinolone oil (Derma-Smoothe/FS®, DermaOtic®), Diphenhydramine orally disintegrating tablets (Benadryl® Children's Allergy Fastmelt®*
Sesame	Dronabinol, Fluphenazine decanoate, Haloperidol decanoate, Nandrolone decanoate, Progesterone in oil injection, Pipotiazine (Piportil®)
Soy lecithin	Liposomal doxorubicin, Fat emulsion, Combivent® MDI, Propofol, Soy isoflavones, Diphenhydramine orally disintegrating tablets (Benadryl® Children's Allergy Fastmelt®)
Corn	Dextrose solutions, Fentanyl citrate

*Contains soy which may cause allergic reactions in hyper-sensitive peanut allergic patients

FDA New Molecular Entity Approvals

Generic (Trade)	Manufacturer	Approval Date	Indication
Dronedarone (Multaq)	Sanofi Aventis	7/2009	A new anti-arrhythmic agent approved for atrial fibrillation or atrial flutter.
Prasugrel (Effient)	Eli Lilly	7/2009	A new platelet inhibitor approved for use in patient with unstable angina, non-ST-segment elevation MI, or ST elevation MI undergoing percutaneous coronary intervention (PCI)
Pitavastatin (Livalo)	Kowa	8/2009	A new HMG-CoA Reductase Inhibitor approved for use in patients with hyperlipidemia.
Asenapine (Saphris)	Organon USA	8/2009	Anti-psychotic agent approved for acute treatment of schizophrenia, acute mania, or mixed episodes of bipolar I disorder.
Vigabatrin (Sabril)	Lundbeck	8/2009	GABA inhibitor approved for treatment of infantile spasms and refractory complex partial seizures.
Bepotastine Besilate (Bepreve)	ISTA	9/2009	Eye drop approved for treatment of itching associated with allergic conjunctivitis
Telavancin Hydrochloride (Vibativ)	Theravance	9/2009	Antibiotic approved for treatment of skin and skin structure infections caused by gram positive organisms.
Pazopanib Hydrochloride (Votrient)	GlaxoSmithKline	10/2009	Vascular endothelial growth factor inhibitor approved for the treatment of advanced renal cell cancer.
Romidepsin (Istodax)	Gloucester Pharmaceuticals	11/2009	A new histone deacetylase inhibitor approved for the treatment of cutaneous T-cell lymphoma.

Frontline DI

Is 500 mg IV q6h an Appropriate Dose of Thiamine for Wernicke's Encephalopathy?

The theory behind the higher doses and increased frequency is as follows: 1) Patients with alcohol induced Wernicke's encephalopathy may have such severe thiamine deficiency from chronic malabsorption of thiamine to warrant higher doses 2) Blood thiamine levels fall to baseline values between 6 and 24 hours, which provides rationale for giving it more frequently—(ie 2-3 times per day). Whether or not q6h dosing is necessary has not been determined. The duration of high dose therapy has not really been spelled out, either. It seems that many patients may not need to continue the higher dose therapy beyond the first couple days. After that, they could potentially be switched to a lower dose. This may vary from patient to patient.

The biggest side effect to watch for with the IV form (which is recommended for acute encephalopathy) is anaphylaxis. The risk for this is increased in patient receiving larger doses if they are administered too quickly.

Reference:

1. Ambrose ML, Bowden SC, Whelan G. Thiamin Treatment and Working Memory Function of Alcohol-Dependent People: Preliminary Findings. Alcoholism: Clinical and Experimental Research. 2001;25(1):112-116

Is Prior Use of NPH Insulin a Risk Factor for Protamine Anaphylaxis?

Because NPH insulin contains 0.35 to 0.45 mg protamine/100 units of insulin, diabetics who use this type of insulin may become sensitized to it over time. This amount of protamine is small enough that it may not cause an allergic reaction in most patients; however, it may trigger the development of memory cells which could in turn lead to an anaphylactic reaction when larger amounts of protamine are given.

Interestingly, history of vasectomy was also listed as a risk factor for protamine allergy. Apparently, vasectomized men systemically absorb sperm, which contains protamine, thus leading to stimulation of antibody production. Approximately 35% of

vasectomized men have antiprotamine IgE in their serum compared with 0% in non-vasectomized controls.

Reference:

1. Porsche R, Brenner ZR. Allergy to Protamine Sulfate. Heart Lung. 1999;28:418-28.

Why Must IV/IM Toradol be Given Prior to PO Toradol?

The package insert recommends that PO Toradol® (ketorolac) should only be given after parenteral Toradol® because the PO Toradol® does not work as well if IV or IM is not given first. The parenteral form is meant to be similar to a loading dose. The problem with starting off on PO only is that physicians and patients tend to want to extend therapy beyond 5 days because it does not control pain as well when administered this way. This misuse can increase the potential for adverse effects, such as renal toxicity.

Reference:

1. Personal Communication. Ethex Laboratories. October 6, 2009