Does Pantoprazole Inhibit the Activation of Clopidogrel?

1. Does pantoprazole sodium interfere significantly with clopidogrel's ability to reduce cardiovascular and cerebrovascular morbidity/mortality?

Question submitted by: Dr. Alan Ong, Toronto, Ontario

Clopidogrel bisulfate is a prodrug that must be metabolized in two or more steps to reach its active form. Cytochrome P450 2C19 (CYP2C19) catalyzes the first and most important reaction. Roughly 3 to 21% of people have a genetic polymorphism in CYP2C19 that reduces activation of clopidogrel and is associated with more thrombotic events.[1] In 2008, Gerbel and Lau observed that omeprazole, an inhibitor of CYP2C19, inhibits the antiplatelet effect of clopidogrel.[2]

Subsequent large observational studies suggested that omeprazole, rather than pantoprazole (which does not inhibit CYP2C19), is associated with more re-admissions for thrombotic events in patients prescribed clopidogrel.[3] A recent mechanistic study supports the hypothesis that pantoprazole does not inhibit activation of clopidogrel.[4] All in all, the combination of clopidogrel and pantoprazole is likely safe and effective.

References
1. Simon T, Verstuyft C, Mary-Krause M, et al: Genetic Determinants of Response to Clopidogrel and Cardiovascular events. N Engl J Med 2009; 360(4):363–375.
2. Gurbel PA, Lau WC, Tantry US: Omeprazole: A Possible New Candidate Influencing the Antiplatelet Effect of Clopidogrel. J Am Coll Cardiol 2008; 51(3):261–263.
3. Juurlink DN, Gomes T, Ko DT, et al: A Population-based Study of the Drug Interaction Between Proton Pump Inhibitors and Clopidogrel. CMAJ 2009; 180(7):713–718.
4. Ferreiro JL, Ueno M, Tomasello SD, et al: Pharmacodynamic Evaluation of Pantoprazole Therapy on Clopidogrel Effects: Results of a Prospective, Randomized, Crossover Study. Circ Cardiovasc Interv 2011; 4(3):273–279.

Answered by:
Dr. Thomas W. Wilson

Brugada Syndrome

2. Please comment on the Brugada syndrome (arrhythmia).

Question submitted by: Dr. T. R. Carscadden, Lively, Ontario

Brugada syndrome is a rare inherited disorder characterized by ST elevation in the anterior ECG leads (predominantly in leads V1 to V2) and an increased risk of ventricular fibrillation, syncope, and sudden death. The presence of the ECG findings without cardiac events is termed a Brugada sign.

The diagnosis of Brugada syndrome should be considered in a patient with syncope or resuscitated cardiac arrest with anterior precordial ST elevation in the absence of evidence of coronary artery disease or underlying cardiomyopathy. The majority of patients are male, and the average age of symptom onset is 40-years. The Brugada sign is present in 1:4,000 to 1:10,000 patients and is more common in Asian populations. However, it has been described in a wide range of ethnic backgrounds including First Nations Persons.

The underlying defect leading to Brugada syndrome in approximately 20% of cases is a mutation in the SCN5A gene resulting in a loss of function defect in the cardiac sodium channel. Additional genes that have been implicated involve mutations that encode the α1- (CACNA1C) and ß- (CACNB2b) subunits of the L-type cardiac calcium channel.

Genetic testing is available, and detects a mutation in 20% of patients with Brugada syndrome and a positive family history and in less than 5% of patients without a family history.

Patients with resuscitated cardiac arrest or syncope suggestive of an arrhythmia are typically managed with an implantable cardioverter defibrillator (ICD). Drug therapy with quinidine showed promise in one series, but ß blockers and amiodarone have not been shown to be beneficial. Asymptomatic carriers should avoid drugs with sodium channel blocking effects, including tricyclic antidepressants, certain antibiotics, local anaesthetics, propofol, lithium, cocaine, and several antiarrhythmic agents.

Answered by:
Dr. Brett Heilbron

Is Warfarin Recommended in a Nonagenarian Female with Atrial Fibrillation?

3. *Would you continue warfarin in a nonagenarian female with intermittent atrial fibrillation, who has valvular heart disease and difficulty with epistaxis?*

Question submitted by: Anonymous

The prudent recommendation of Hippocrates that "The physician must have two special objects in view with regards to disease, namely, to do good or to do no harm," is sage counsel when managing complex cases like this one. While atrial fibrillation increases the risk of thromboembolic stroke in general, elderly patients over the age of 80-years-old are at a very high risk for atrial fibrillation-related cerebrovasular events and benefit the most from closely managed warfarin therapy. Whether atrial fibrillation is intermittent or persistent makes no difference; the stroke risk is the same for those patients with paroxysmal atrial fibrillation as for those in chronic "delirium cordis." The presence of valvular heart disease can further add to the risk of stroke in atrial fibrillation. In particular, patients with rheumatic mitral stenosis and atrial fibrillation have an 18 times the risk of stroke without adequate anticoagulation therapy. By contrast, degenerative, senile aortic valve stenosis (the most common variety in North American nonagenarians) more often causes calcific microemboli, which do not reduce with anticoagulation. The key clinical management issue at hand here is the epistaxis. Warfarin is contraindicated in the setting of active bleeding – epistaxis included – and must be withheld until the bleeding has been rectified. Once the nosebleed has been definitively dealt with, warfarin therapy, with a goal international between 2.5 and 3.0, would be recommended to reduce her substantial stroke risk.

Resources
1. Hylek EM: Antithrombotic Prophylaxis in Elderly Patients with Atrial Fibrillation. Semin Thromb Hemost 2009; 35(6):548–553.
2. Chandrashekhar Y, Westaby S, Narula J: Mitral Stenosis. Lancet 2009; 374(9697):1271–1283.
3. Völler H: Antithrombotic Therapy in Native Heart Valve Disease. J Heart Valve Dis 2004; 13(3):325–328.

Answered by:
Dr. Theodore K. Fenske