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Pharmacy & Therapeutics

Update

Drug Information for Health Care Professionals

January 2007

Use of Folic Acid, Vitamin B_6, and Vitamin B_{12} to Lower Homocysteine Concentrations

By: Julie Long, PharmD Candidate

Homocysteine is an amino acid derived from the dietary amino acid methionine. Elevations in homocysteine have been associated with endothelial dysfunction, vascular smooth muscle growth, arterial stiffening, procoagulant activity, reduction in arterial vasodilation, proinflammatory responses, and oxidative stress. In 1969, it was proposed that homocysteine caused atherosclerosis. The Homocysteine Studies Collaboration suggested a 25% reduction in homocysteine is associated with an 11% lower risk of ischemic heart disease and 19% lower risk of stroke.

Patients with hyperhomocysteinemia have an inherent inability to metabolize homocysteine, which causes an increase in serum homocysteine concentrations. This increase in homocysteine may result in mental retardation, ectopic lenses, skeletal abnormalities, premature atherosclerosis, and premature thrombosis. Three enzymes and three cofactors are involved in the breakdown of homocysteine, cystathione β-synthase using vitamin B_6, methionine synthase using vitamin B_{12}, and methylene tetrahydrofolate reductase using folic acid. By providing exogenous cofactor, the amount of homocysteine can be reduced by increasing its metabolism.

Foltx® is a medical food containing folic acid (2.5 mg), vitamin B_6 (25 mg), and vitamin B_{12} (2 mg) that is approved for the dietary management of hyperhomocysteinemia. It has been hypothesized that lowering homocysteine concentrations may be extrapolated to patients with normal to mild elevations in homocysteine to reduce the risk of cardiovascular (CV) disease. Several clinical trials have been conducted to test this hypothesis.

The Norwegian Vitamin Trial (NORVIT) was a randomized, double-blind, placebo-controlled trial that evaluated the potential benefit of B vitamins in 3749 men and women after a myocardial infarction (MI). Participants were randomized to one of four groups: (1) 0.8 mg folic acid, 0.4 mg vitamin B_{12}, and 40 mg vitamin B_6; (2) 0.8 mg folic acid and 0.4 mg vitamin B_{12}; (3) 40 mg vitamin B_6; or (4) placebo. The primary end-

point was a composite of nonfatal and fatal MI or, and sudden cardiac death. Patients were followed up to 2.5 to 3 years.

In groups that received folic acid, homocysteine concentrations were reduced by approximately 26%; however, this did not affect the primary endpoint. At the end of 3 years, treatment with folic acid, with or without B vitamins, did not significantly reduce event rates. The combination of folic acid, vitamin B_{12}, and vitamin B_6 actually increased the risk of an event, with a hazard ratio of 1.2 (95% CI 1.02 to 1.41, p=0.03). Treatment with vitamin B_6 was associated with a 17% increase in the risk of myocardial infarction (p=0.05), and the combination of all 3 vitamins was associated with a 30% increase in the risk of nonfatal myocardial infarction (p=0.05). However, these data were not adjusted for multiple comparisons. The NORVIT authors concluded that treatment with folic acid with or without B vitamins is not recommended because it did not lower the risk of recurrent CV disease in patients following an MI.

The Heart Outcomes Prevention Evaluation (HOPE-2) trial was a randomized, double-blind, placebo-controlled trial that evaluated the potential benefit of B vitamins in 5522 patients at high risk of major vascular events. Patients were included if they had a history of coronary, cerebrovascular or peripheral vascular disease, or diabetes and an additional risk factor for atherosclerosis were randomized to receive the combination of folic acid (2.5 mg), vitamin B_{12} (1 mg), and vitamin B_6 (50 mg), or placebo. Serum homocysteine concentrations were measured at baseline, 2 years, and 5 years. The treatment arm achieved a 25% reduction in homocysteine concentrations. However, the primary endpoint (ie, composite of death from cardiovascular causes, MI, or stroke) did not reach statistical significance. However, the secondary endpoint (ie, incidence of stroke) did achieve a 25% decrease in relative risk (p=0.03). Hospitalization for unstable angina was associated with a 24% increase in relative risk (p=0.02). The results were not adjusted for multiple comparisons, and were difficult to explain biologically. Therefore, the authors do not recommend treatment with folic acid and B vitamins to lower the incidence of composite CV death.

The Vitamin Intervention for Stroke Prevention (VISP) study was a randomized, double-blind trial to evaluate the potential benefit of B vitamins in 3680 patients after a nondisabling cerebral infarction. Patients were randomized to high dose (2.5 mg folic acid, 0.4 mg vitamin B_6, 25 mg vitamin B_{12}) or low dose (20 mcg folic acid, 0.2 mg vitamin B_6, 6 mcg vitamin B_{12}) vitamin combination. After 2 years, there was no statistically significant difference between the treatment groups in the risk of stroke, coronary heart disease event, or death.

The Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) was a randomized, double-blind, placebo-controlled clinical trial that evaluated 315 patients with chronic renal failure. Participants were randomized to treatment with 15 mg folic acid or placebo and followed for an average of 3.5 years. Despite a 19% reduction in homocysteine concentration in the folic acid group, there were no statistically significant differences in cardiovascular event rates, leading the authors to conclude that treatment with folic acid is not recommended to improve cardiovascular morbidity and mortality in patients with chronic renal failure.

Four trials that assessed similar, but varied patient populations all reached the same conclusion. Homocysteine concentrations were lowered, but treatment with folic acid, vitamin B_6, and vitamin B_{12} was not the anticipated solution to prevent cardiovascular disease. Several hypotheses have been suggested by Loscalzo to explain the treatment failure. Homocysteine may not be a cause of atherosclerosis. Homocysteine may be a surrogate marker for another species that cause atherosclerosis or therapy with folic acid and the B vitamins may produce adverse effects that offset the homocysteine lowering benefit.

There are 3 potential biochemical mechanisms by which exogenous folic acid and B vitamins may be detrimental. First, folic acid promotes cell proliferation through the synthesis of thymidine, which may occur in an atherosclerotic plaque. Second, when homocysteine metabolism is increased using the B vitamin cofactors, s-adenosylmethionine concentra-

tions are increased, leading to an increase in methylation reactions in the cell. Methylation of DNA appears to play a role in atherosclerosis. Third, as the methylation potential in the cell increases, l-arginine is converted to dimethylarginine, which inhibits the activity of nitric oxide synthase, increasing the risk of vascular disease.

Treatment with folic acid and B vitamins does lower homocysteine concentrations, but does not reduce cardiovascular morbidity and mortality, and should therefore not be recommended. The American Heart Association (AHA) does not recognize hyperhomocysteinemia as a major risk factor for CV disease. Additionally, AHA does not recommend the widespread use of folic acid and B vitamins to reduce the risk of heart disease and stroke.

References are available upon request

Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy Associated with Contrast Agents

By: Kathryn Noyes, PharmD
Pharmacy Practice Resident

Nephrogenic Systemic Fibrosis/ Nephrogenic Fibrosing Dermopathy (NSF/NFD) is a newly diagnosed disease state that is potentially associated with the administration of gadolinium-containing contrast agents.

NFD is a sclerotic cutaneous condition presenting in patients with end-stage renal disease and is characterized with the appearance of sclerotic plaques, histologically resembling sclero-myxedema-like features, on the distal extremities and trunk. The skin plaques may result in severe contractions and limited mobility.[1,2] NSF is characterized as a variation of NFD that involves fibrosis of other organs (eg, lungs, liver, and heart). NSF/ NFD is a debilitating and potentially fatal disease.

The Centers for Disease Control identified 49 patients with NFD between 1997 and 2002.[2] In a small case control study of these patients, common risk factors were not uncovered.[2] It has been suggested that because NFD had not been described prior to 1997 that the sudden occurrence of this disease may be likely caused by a new agent or technique of examination.[4] While severe kidney disease predisposes patients to NFD/NSF only a small amount of patients develop the condition, suggesting that there is another factor involved in the etiology of this disease.

Since June 2006, the Food and Drug Administration (FDA) has been reviewing reports detailing patients who developed NSF/ NFD after they received a gadolinium-based contrast agent during a magnetic resonance imaging scan (MRI) or magnetic resonance angiography (MRA). As of December 21, 2006, 90 individuals with NSF/NFD had been reported to FDA. All patients had moderate (GFR < 60 mL/min/1.73m^2) to end-stage renal disease (GFR < 15 mL/ min/1.73m^2) prior to their MRI or MRA with a gadolinium-based contrast agent. The NSF/NFD began 2 days to 18 months after undergoing a contrast-enhance MRI or MRA. Many of these patients received a dose of gadolinium-based contrast agent exceeding product labeling recommendations. Researchers have detected gadolinium deposits in skin biopsies from patients with NSF/ NFD.[4,5]

Currently, the approved gadolinium-containing products include gadodiamide (Omniscan®), gadopentetate dimeglumine (Magnevist®), gadoteridol (Prohance®), gadobenate dimeglumine (Multihance®), and gadoversetamide (OptiMARK®). None of these agents have been approved by FDA for MRA and the dose of gadolinium-containing products used in MRA may be up to 3 times higher than the approved dose for MRI.[6] These agents are all excreted via the kidney and have similar pharmacokinetics profiles.[8]

The possible connection between NFD and gadolinium-containing contrast has been theorized with a possible mechanism related to the poor solubility of free gadolinium ions and their likelihood of forming precipitates with phosphate, carbonate, or hydroxyl, which are deposited in the skin, muscle, bone, liver and other organs.[4] The presence of gadolinium in areas of calcium phosphate deposition in the blood vessels of one NFD patient was identified in a case report by Boyd and colleagues.[9]

Physicians should carefully assess the need for gadolinium-based

contrast agents in this patient population when performing an MRI or MRA. FDA recommends that physicians weigh the benefits and risks of performing an MRI or MRA with contrast in patients with moderate to end-stage renal disease. An alternative imaging method and/or contrast agents should be considered. Additionally, dialysis may be considered in these patients; however, there are no published data to support the utility of dialysis to prevent or treat NSF/NFD.

For more information please visit the FDA Web page at www.fda.gov/cder/drug/infopage/gcca/default.htm.

Med•U•Way to Focus on Pandemic Influenza

The next MED•U•WAY Conference will focus on pandemic influenza and the use of neuraminidase inhibitors. The program will be held on Thursday, January 18, 2006, at 12:00 PM, in 2 West Amphitheater.

The featured speakers will be Michael Schmidt, PHD, Department of Microbiology and Immunology; Deborah Stier Carson, PharmD, FCCP, Professor, College of Pharmacy; Robert Ball, MD, MPH, Infectious Disease Consultant and Epidemiologist, SCDHEC.

Attendees will receive 1 credit hour of continuing education, and lunch is provided.

MED•U•WAY is sponsored by the Pharmacy and Therapeutics Committee.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the actions listed below, which were effective on December 18, 2006 unless otherwise stated.

Additions with Restrictions:
Sildenafil (Revatio®)
Prescribing is restricted to patients who have pulmonary arterial hypertension.
20-mg tablet

Gadobenate dimeglumine (Multihance®)
Prescribing is restricted to adult patients undergoing contrast-enhanced MRI of the CNS, adult patients undergoing hepatobiliary contrast-enhanced imaging for metastatic detection or a subset of MRCP (ie, evaluation of the intrahepatic biliary tree), or patients who have end-stage renal disease requiring dialysis.
529-mg/mL vials

Addition:
Polyethylene glycol (generic)
17-gram, unit-dose packets
Automatic Therapeutic Substitution (ATS) Change
The ATS for polyethylene glycol will be updated to reflect the addition of the pre-packaged polyethylene glycol doses. The updated ATS protocol is located on the on the *Formulary and Drug Information Resources* Web page.

Restriction NOT Changed:
Aprepitant (Emend®)
The request to extend the restriction to the anesthesiology service for post operative nausea and vomiting (PONV) was not approved due to the lack of evidence of superiority to other agents and the substantial cost difference as compared with ondansetron.

Restriction Removed:
Effective date to be assigned for March 2007
Meropenem (Merrem®)
The formulary restriction will be removed with the deletion of imipenem/cilastatin. The formulary active date has been extended to create appropriate use and dosing guidelines for meropenem and to provide appropriate education.

Deletion
Effective date to be assigned for March 2007
Imipenem/cilastatin (Primaxin®)

Line extensions
Pantoprazole (Protonix®)
20-mg tablet

Levetiracetam (Keppra®)
500-mg/5-mL injection

Leuprolide acetate (Lupron®)
7.5-, 22.5-, and 30-mg injection

Updated Chart
The *Formulary Medications Requiring Filtration Prior to Administration at MUSC-MC* chart has been revised to reflect any changes in the formulary since September 2005. The changes include the addition of cetuximab (Erbitux®) and updated references for each medication. The chart was reviewed and approved by the Medication Cycle Improvement Group and is available on the *Formulary and Drug Information Resources* Web page.