Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Pyridoxine (Vitamin B_6)***
-February 2016-

Background:
Vitamin B_6 was first identified in 1932 by Paul Gyorgy, MD. It is a group of chemically-related compounds that are interconverted in biological systems. Pyridoxine hydrochloride is the form utilized as the vitamin B_6 supplement. It is converted into pyridoxal 5'-phosphate, the active form. Vitamin B6 is a cofactor for synthesis of neurotransmitters (serotonin, dopamine, epinephrine, norepinephrine, and GABA), histamine, serine, methionine, selenium forms, the function of transaminases and the conversion of tryptophan to niacin. It is also involved in glycogenolysis, gluconeogenesis, sphingolipid synthesis, hemoglobin synthesis and function, and certain aspects of gene expression. Recommended daily allowances vary based on gender, age, pregnancy, and lactation status, ranging from 1.3-2.0 mg/day. It is readily available in many plant and animal food sources and is highly absorbed in the jejunum and ileum. Pyridoxine hydrochloride is FDA approved for prevention and treatment of vitamin B_6 deficiency, a rare condition. Off label uses include the treatment of gyromitrin-containing mushroom overdose/toxicity, nausea and vomiting of pregnancy, and prevention/treatment of isoniazid (INH)–associated peripheral neuropathies.

Discussion:
Nausea and vomiting of pregnancy (NVP) appears to be a normal physiological response of the first trimester, occurring in ~ 90% of pregnancies. Severe NVP, termed hyperemesis gravidarum, is associated with weight loss of >5% of the prepregnancy weight and occurs in 0.3-3.0% of pregnancies. Etiological causes are theorized to be related to psychologic factors, hormonal changes (esp. hCG), abnormal GI motility, and *Helicobacter pylori*. Treatments encompass dietary modifications, avoidance of triggers, non-pharmacologic, herbal (ginger), supplement (pyridoxine), and other pharmacologic therapies.

Pyridoxine was first referenced for the treatment of NVP in 1942. In 1956, Bendectin® (doxylamine succinate/pyridoxine hydrochloride/dicyclomine hydrochloride) was FDA-approved for the treatment of NVP. This product was reformulated in 1976 after review under the Drug Effectiveness Study Implementation (DESI) showed no effectiveness for NVP associated with the dicyclomine component. In 1977, a lawsuit was filed (Mekdeci case) alleging a link between Bendectin® as a teratogen associated with Poland syndrome, a hypoplasia of the pectoral muscles. Although the lawsuit was defeated, reports surfacing in popular media of the day led to a flurry of lawsuits over the ensuing years. Despite a 1980 FDA panel finding no evidence for an association between Bendectin® and birth defects, Merrell Dow Pharmaceuticals (MDP) ceased production in 1983. In 1989, a US Federal judge combined pending cases into a single lawsuit. The jury found in favor of MDP. This verdict upheld under two appeals, however, cases continued to follow. In 1993, Dr. William Griffith McBride, an Australian OB-GYN credited with the discovery of the association of thalidomide with birth defects and an expert witness on several highly publicized Bendectin® cases, was convicted of medical fraud for falsifying data related to the "Debendox* experiment". Two meta-analyses, Einarson, et al. (1988) and McKeigue, et al. (1994) failed to show any increased risk for major malformations associated with this product. *Drugs in Pregnancy and Lactation* notes "the preponderance of data supports the assessment that the fixed combination of doxylamine/pyridoxine is safe for human pregnancy, including in the first trimester." In 2013, Diclegis® (delayed-release doxylamine succinate/pyridoxine hydrochloride) was FDA approved in the US.

Clinical Trials:
Two clinical trials provide the most recent data in regards to the use of Vitamin B_6 vs. placebo in the treatment of NVP.[1,2] Vutyavanich, et al. (1991) conducted a double-blinded, randomized, placebo-controlled trial (RPCT) involving 336 pregnant women, with the active treatment arm receiving pyridoxine 25mg/day. Mean nausea scores were reduced after 5 days (Mean Difference (MD) = 2.9 ± 2.2 vs. 2.0 ± 2.7, p=0.008), but there was no difference in the number of vomiting episodes. Sahakian, et al. (1994) conducted a double-blinded, RPCT involving 59 pregnant women, with the active treatment arm receiving

*Debendox was a British drug composed of doxylamine 10 mg/dicylomine 10mg/pyridoxine 10 mg.

pyridoxine 75 mg/day. Women with severe nausea had less nausea at 72 hours (MD= 4.3 ± 2.1 vs. 1.8 ± 2.2, p≤ 0.01), but with no significant reduction in nausea scores for women with mild to moderate nausea. However, there was a reduction in vomiting for the pyridoxine group (number of women still vomiting at 72 hours, 8/31 vs. 15/28; p≤ 0.05).

In 2010, Koren, et al. conducted a double-blinded, RPCT of pyridoxine hydrochloride 10 mg/doxylamine succinate 10 mg delayed-release (Canadian-brand Diclectin®). The clinical trial included 256 pregnant women treated for 14 days. The Pregnancy Unique Quantification of Emesis scale was used to assess response. The treatment arm showed significant reduction in symptoms compared to placebo (-4.8 ± 2.7 vs. -3.9 ± 2.6; p=0.006) and improved quality of life.[3]

Systematic Reviews:
In 2010, Cochrane conducted a review of a variety of treatments for NVP. The same 2 RCTs noted above involving the use of vitamin B_6 vs. placebo in the treatment of NVP were identified by Cochrane. The two combined studies included 416 women and used standard symptom questionnaires to assess response. The authors concluded that the results favored vitamin B_6 for reduction of nausea after 3 days (MD = 0.92; 95% CI: 0.40-1.44). No strong evidence was shown for reduced vomiting (average RR 0.76, 95% CI: 0.35-1.66). The reviewers noted a high degree of heterogeneity in available studies and recommended caution in interpretation.[4]

Guidelines:
The American College of Obstetricians and Gynecologists (ACOG) published an ACOG Practice Bulletin on NVP in 2015. They note that treatment of NVP with vitamin B_6 or vitamin B_6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy.[5]

Findings:
The IHS NPTC notes that vitamin B_6 is an essential nutrient readily available through dietary sources. Pyridoxine ± doxylamine is recommended as the first-line pharmacologic treatment for nausea and vomiting of pregnancy. Clinical trials show marginal improvements in nausea with variable reductions in vomiting. Pyridoxine is recommended as a standard of care for co-administration with isoniazid (INH) to prevent (10-50 mg/day) or treat (100-200 mg/day) INH-associated neuropathy. The NPTC **added pyridoxine** to the National Core Formulary.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References

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