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Folic Acid

Updated: February 6, 2018.

OVERVIEW

Introduction

Folic acid is a water soluble vitamin found in many foods and particularly in leafy green vegetables that is essential for the critical biosynthetic pathways involving transfer of methyl groups to organic compounds. There is no evidence that folic acid, in physiologic or even super-physiologic, high doses, causes liver injury or jaundice.

Background

Folic acid (fo' lik a' cid) is the critical water soluble vitamin that plays an essential role in many biosynthetic pathways largely as a major donor of one-carbon molecules such as methyl groups. Folic acid is a pteroylglutamic acid, but it exists in several related congeners such as tetrahydrofolic acid (the activated form of the vitamin) as well as methyltetrahydrofolate, methenyltetrahydrofolate, and folinic acid which have different concentrations in foods, degrees of bioavailability and levels of activity. These related molecules are collectively referred to by the generic term folate. Folate deficiency is characterized by weakness, macrocytic anemia, diarrhea, cheilosis and glossitis. Folate is found in many foods and particularly in fresh green vegetables, liver and some fruits. Grain products and cereals are fortified with folic acid, and its deficiency is now rare in the United States, found largely in patients with small bowel malabsorption syndromes, severe malnutrition or chronic alcoholism. Normal plasma folate levels in adults are 2 to 20 ng/mL (4.5 to 45 nmol/L) and red cell folate, a better indicator of chronic intake, 140 to 628 ng/mL (317-1422 nmol/L). The recommended daily allowance of folate in adults is 400 µg for both men and women, higher intakes being recommended during pregnancy and in the elderly. Folate supplements are taken by a large proportion of the American population, driven partially by the belief that higher doses of folate may improve metabolic fitness and decrease the risk of aging related conditions, such as atherosclerosis, cancer and dementia. These benefits of increased folate intake, however, have not been shown in prospective controlled trials. Folic acid is available in multiple, over-the-counter forms in concentrations of 200 to 1000 µg, and it is a component of virtually all multivitamin preparations usually at levels of 200 to 400 µg. Oral intake of more than 1000 µg daily is not recommended. Parenteral forms of folic acid are also available including leucovorin, which is an approved prescription drug used to reverse the effects of folate antagonists such as methotrexate, trimetrexate and pemetrexed. Oral forms of folic acid have few if any side effects and there are no proven adverse events associated with high doses. Injectable forms of folic acid have been implicated in rare instances of hypersensitivity reactions.

Hepatotoxicity

Neither normal nor excessively high intakes of folate are associated with liver injury or liver test abnormalities. In long term clinical trials, serum enzyme and bilirubin elevations were no more frequent with folic acid therapy than with placebo. Use of high doses of folic acid (up to 15 mg daily) has not been associated with appreciable adverse reactions, ALT elevations or hepatotoxicity.

Likelihood score: E (unlikely cause of liver injury).

Mechanism of Injury

It is not clear how folate might cause liver injury. Folate is stored in the liver, but it is metabolized in many tissues and has no effects on the hepatic microsomal enzyme systems.

Drug Class: Vitamins

Other Drugs in the Class: Vitamin A, Vitamin B, Vitamin C, Vitamin D, Vitamin E, Vitamin K, Niacin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Folic Acid – Generic, Combination Products (some include leucovorin)

DRUG CLASS

Vitamins

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

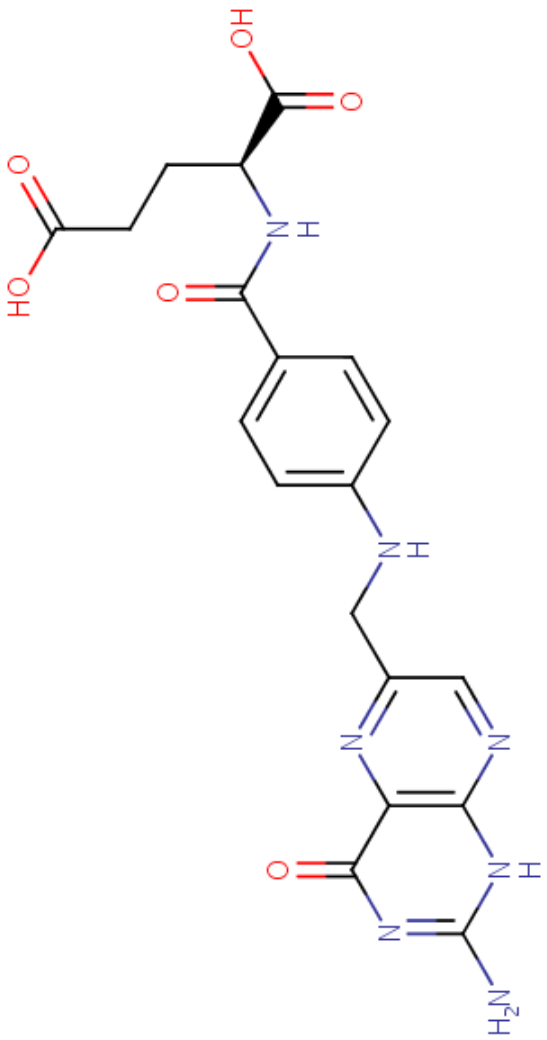
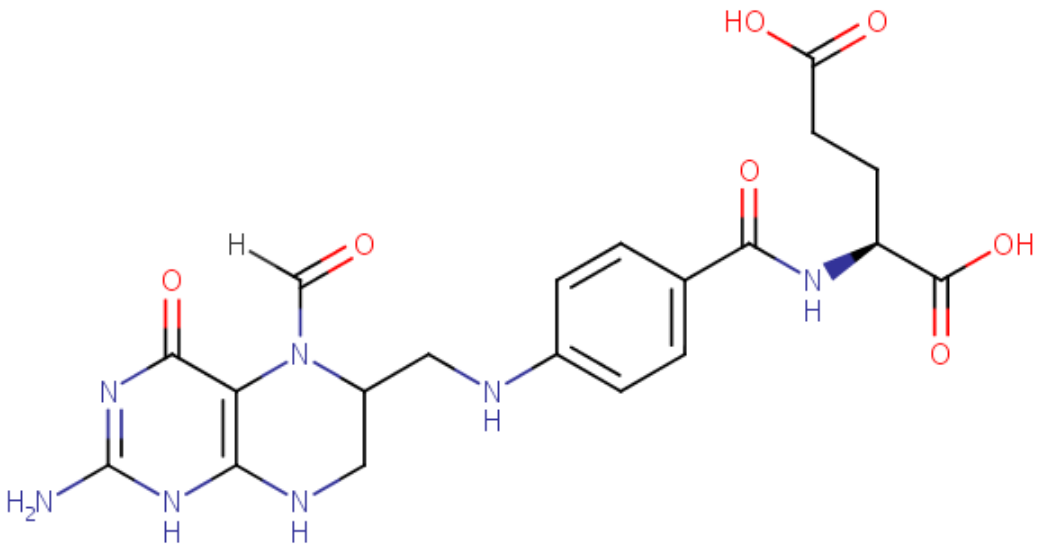
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Folic Acid	59-30-3	C19-H19-N7-O6	

Table continued from previous page.

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Leucovorin	58-05-9	C20-H23-N7-O7	

ANNOTATED BIBLIOGRAPHY

References updated: 06 February 2018

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Expert review of hepatotoxicity published in 1999; does not discuss folate).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp, 631-57.

(Review of hepatotoxicity of dietary supplements; does not discuss vitamins and minerals).

Kaushansky K, Kipps TJ. Hematopoietic agents: growth factors, minerals and vitamins. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1067-1100.

(Textbook of pharmacology and therapeutics).

Herbert Victor. Folic acid. In, Shils ME, Olson JA, Shike M, Ross AC, eds. Modern nutrition in health and disease. 9th ed. Baltimore: Williams & Wilkins, 1998; pp 433-46.

(Textbook of nutrition).

Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline. Washington DC: National Academy Press, 1998.

(Reports from the Food and Nutrition Board of the Institute of Medicine on dietary reference values for vitamin intake; replacing the previously published Recommended Dietary Allowance).

https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ (Fact sheet on folate maintained and regularly updated by the Office of Dietary Supplements, National Institutes of Health).

https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ (Fact sheet on folate maintained and regularly updated by the Office of Dietary Supplements, National Institutes of Health).

Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, et al; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006; 354: 1567-77. PubMed PMID: 16531613.

(Among 5522 adults with vascular disease or diabetes treated with folate [2.4 mg daily] with vitamins B6 and B12 vs placebo for an average of 5 years, active vitamin supplementation did not reduce overall, cardiovascular or cancer death rates; no mention of ALT elevations or hepatotoxicity).

Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, et al.; Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007; 297: 2351-9. PubMed PMID: 17551129.

(Among 1021 adult patients with colorectal adenomas treated with folic acid [1 mg daily] vs placebo with or without aspirin for up to 8 years, the rate of recurrent adenomas was not reduced with either folate or aspirin; no mention of ALT elevations or hepatotoxicity).

Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. JAMA 2008; 299: 2027-36. PubMed PMID: 18460663.

(Among 5442 adult women treated with folic acid and vitamins B6 and B12 vs placebo for an average of 7.3 years, vitamin supplementation had no effect on overall cardiovascular disease event rates [14.9% vs 14.3%]; no mention of ALT elevations or hepatotoxicity).

Ebbing M, Bønaa KH, Nygård O, Arnesen E, Ueland PM, Nordrehaug JE, Rasmussen K, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA 2009; 302: 2119-26. PubMed PMID: 19920236.

(In a combined analysis of two studies with extended follow up in 6837 Norwegian adults with ischemic heart disease who were treated with B vitamins and folate [0.8 mg daily] vs placebo, cancer rates [particularly lung cancer] were slightly higher in the supplemented group [10% vs 8.4%]; no mention of adverse events, ALT elevations or hepatotoxicity).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed Citation

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to folate, niacin or the water soluble vitamins).

Andreeva VA, Touvier M, Kesse-Guyot E, Julia C, Galan P, Hercberg S. B vitamin and/or ω-3 fatty acid supplementation and cancer: ancillary findings from the supplementation with folate, vitamins B6 and B12, and/or omega-3 fatty acids (SU.FOL.OM3) randomized trial. Arch Intern Med 2012; 172: 540-7. PubMed PMID: 22331983.

(Among 2511 adults treated with combination of B vitamins and folate versus placebo for average of 4.7 years, vitamin supplementation had no effect on cancer incidence or mortality; no mention of adverse events, ALT elevations or hepatotoxicity).

Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, Armitage J, et al.; B-Vitamin Treatment Trialists' Collaboration. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet 2013; 381 (9871): 1029-36. PubMed PMID: 23352552.

(In a metaanalysis of 13 controlled trials of folate supplementation vs placebo in 46,969 adult patients followed for an average of 5.2 years, folate had no effect on overall cancer incidence or on site specific cancer rates [including liver]; no mention of ALT elevations or hepatotoxicity).

Shea B, Swinden MV, Ghogomu ET, Ortiz Z, Katchamart W, Rader T, Bombardier C, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. J Rheumatol 2014; 41: 1049-60. PubMed PMID: 24737913.

(Metaanalysis of 6 controlled trials of folate [folinic or folic acid] vs placebo supplementation during methotrexate therapy of rheumatoid arthritis found that folate decreased the rates of ALT elevations [5.6% vs 20.8%] and drug discontinuations without changing evidence for efficacy of methotrexate).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 7 were attributed to niacin, but none were attributed to any other vitamin including folic acid).

Biesalski HK, Tinz J. Multivitamin/mineral supplements: Rationale and safety - A systematic review. Nutrition 2017; 33: 76-82. PubMed PMID: 27553772.

(Review of safety of multivitamins stresses the lack of information on adverse events in trials of vitamin supplementation, but concludes that multivitamins are safe at physiological doses in the short and long term).

Field MS, Stover PJ. Safety of folic acid. Ann N Y Acad Sci. 2017 Nov 20. [Epub ahead of print] PubMed PMID: 29155442.

(Review of long term safety of folate supplementation summaries two government-supported expert panel reviews that concluded that there is no evidence for adverse effects of folic acid fortification of food).