Folates: Supplemental Forms and Therapeutic Applications

by Gregory S. Kelly, N.D.

Abstract

Folates function as a single carbon donor in the synthesis of serine from glycine, in the synthesis of nucleotides from purine precursors, indirectly in the synthesis of transfer RNA, and as a methyl donor to create methylcobalamin, which is used in the re-methylation of homocysteine to methionine. Oral folates are generally available in two supplemental forms, folic and folinic acid. Administration of folinic acid bypasses the deconjugation and reduction steps required for folic acid. Folinic acid also appears to be a more metabolically active form of folate, capable of boosting levels of the coenzyme forms of the vitamin in circumstances where folic acid has little to no effect. Therapeutically, folic acid can reduce homocysteine levels and the occurrence of neural tube defects, might play a role in preventing cervical dysplasia and protecting against neoplasia in ulcerative colitis, appears to be a rational aspect of a nutritional protocol to treat vitiligo, and can increase the resistance of the gingiva to local irritants, leading to a reduction in inflammation. Reports also indicate that neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome. (Altern Med Rev 1998;3(3):208-220)

Introduction

Folic acid is a water-soluble vitamin historically used as a treatment for anemia of pregnancy. Folates are abundant in the diet; however, these compounds are readily destroyed by cooking or processing. The best food sources of folates are thought to be green-leafy vegetables. Sprouts, fruits, brewer's yeast, liver, and kidney also contain high amounts of folates. Unlike supplemental forms of folic acid, dietary folic acid is a complex and variable mixture of folate compounds. Because dietary folates can be destroyed readily, and since many individuals do not consume high amounts of folate-rich foods, it is thought that folic acid deficiency is one of the most common nutritional deficiencies.

Biochemistry

Folates function as a single carbon donor in the synthesis of serine from glycine, in the synthesis of nucleotides from purine precursors, indirectly in the synthesis of transfer RNA, and as a methyl donor to create methylcobalamin, which is used in the re-methylation of

Gregory S. Kelly, N.D.—Associate Editor, Alternative Medicine Review; Private Practice, Greenwich, CT. Correspondence address: 56 Lafayette Place, Suite C, Greenwich, CT 06830.

Alternative Medicine Review ♦ Volume 3, Number 3 ♦ 1998



homocysteine to methionine. Synthesis of the active forms of folic acid is a complex process requiring several enzymes, as well as adequate supplies of riboflavin (B2), niacin (B3), pyridoxine (B6), zinc, and serine (see Figure 1).

Folic acid (vitamin B9) is a member of the B-complex family of vitamins. In plants, folic acid is formed from a hetero-bicyclic pteridine ring, para-aminobenzoic acid (PABA), and glutamic acid (see Figure 2). In the diet, folic acid occurs as complex mixtures of polyglutamate (multiple glutamate molecules attached) conjugate compounds. These compounds tend to be resistant to hydrolysis by enzymes in the gastrointestinal tract; however, a group of zinc-dependent intracellular enzymes (folyl polyglutamate hydrolases) are capable of removing the glutamate groups prior to intestinal absorption.¹

Folic acid is generally well absorbed in humans; however, the process of conversion to the metabolically active coenzyme forms is relatively complex. Folic acid is initially deconjugated in the cells of the intestinal wall to the monoglutamate form. In the liver, this compound is subsequently reduced to dihydrofolate and then to tetrahydrofolate via folate and dihydrofolate reductase. Both of these enzymes require NADPH (niacin dependent) as a cofactor. The next step in the activation of the coenzyme requires the amino acid serine to combine with pyridoxal-5'phosphate (B6) in order to transfer a hydroxymethyl group to tetrahydrofolate. This results in the formation of 5, 10-10methylenetetrahydrofolate (5,methyleneTHF) and glycine. Since it is the precursor of the metabolically active 5methyltetrahydrofolate (5-MTHF) utilized in the re-methylation of homocysteine metabolism, 5, 10-methyleneTHF is of central importance. Also precursor a to methylidynetetrahydrofolate (used in purine synthesis), 5, 10-methyleneTHF functions on its own in the generation of thymine side

Alternative Medicine Review ◆ Volume 3, Number 3 ◆ 1998

lates





chains for incorporation into DNA. The formation of 5-MTHF from 5, 10methyleneTHF requires the enzyme methylenetetrahydrofolate reductase (a riboflavin dependent enzyme). After formation of the coenzyme forms of the vitamin in the liver, these metabolically active compounds are secreted into the small intestine with bile (the folate enterohepatic cycle), where they are reabsorbed and distributed to tissues throughout the body.

Folinic acid (5-formylTHF), available supplementally as calcium folinate – also known as leucovorin calcium – is an immediate precursor to 5, 10-methyleneTHF. Oral administration of folinic acid bypasses the deconjugation and reduction steps required for folic acid.

Pharmacology

Although the most common supplemental form of the folates is folic acid, it makes up 10 percent or less of dietary folates. The majority of folates in the diet consist of reduced folates and methyltetrahydrofolates. Although folic acid is generally well absorbed, evidence suggests that reduced folates and methyltetrahydrofolates are absorbed differently than folic acid. In general, intestinal folic acid transport is a saturable process with a pH optimum of 5.5 to 6.0.² Pharmacokinetic studies in pigs indicate oral folic acid results in relatively low bioavailability at high doses and has little effect at increasing the metabolically active forms of folic acid.³ However, human pharmacokinetic studies indicate folic acid has very high bioavailability.^{4,5}

Human absorption kinetic studies of orally administered folinic acid have demonstrated a bioavailability of 92 percent.⁶ Follow-

ing an oral dose of folinic acid, the majority of folates are metabolized to 5-MTHF directly during absorption in the intestine, bypassing the need for deconjugation and subsequent reduction in the liver. The net effect on tissues of providing folinic acid orally is essentially the same as feeding the coenzyme 5-MTHF.⁷ Evidence also suggests a small amount of folinic acid is absorbed systemically when administered as a mouthwash.8 Folinic acid appears to be a more metabolically active form of folate, possibly capable of boosting levels of the coenzyme forms of the vitamin in circumstances, such as psychiatric disorders, where folic acid has little to no effect. Folinic acid might directly cross the blood brain barrier since reduced folates are actively transported into the brain, whereas folic acid is poorly transported to the brain and rapidly cleared from the CNS.9,10

If supplementing with folinic acid, oral administration is preferred, since the area under the curve of the active metabolite after intravenous administration is only half that of an oral dose.¹¹ Although oral supplementation of folinic acid is a reliable manner of increasing tissue levels of biologically active folates, intestinal absorption of folinic acid is a saturable process. At doses above 20-25 mg of folinic acid, the oral and intravenous

Alternative Medicine Review ♦ Volume 3, Number 3 ♦ 1998

bioavailabilities of folinic acid do not appear to be comparable, with oral administration demonstrating diminished bioavailability when compared to intravenous dosing.¹² Therefore, for doses significantly higher than 25 mg of folinic acid, intravenous administration might be preferable.

Folinic acid is prepared pharmaceutically from L-glutamic acid, resulting in a calcium salt with equal amounts of diastereoisomers.¹¹ Most commercially available folates are racemic mixtures of R and S isomers about pteridine-carbon 6. Currently, reports are equivocal as to whether unnatural stereoisomers (R isomers) are inert in vivo or whether they modify specific aspects of folate metabolism.¹³ High doses of intravenous and oral folinic acid result in different profiles of circulating reduced folates. Oral administration appears to be the favored route of administration for stereoselective drug delivery to the systemic circulation, since intravenous administration is associated with high amounts of both 6S folinic acid and 5-MTHF, as well as 6R folinic acid. Oral folinic acid, on the other hand, has the potential advantage of providing sustained plasma concentrations of 5-MTHF in the absence of significant accumulations of 6R folinic acid.14

A number of drugs can interfere with the pharmacokinetics of folic acid. Sulfasalazine, cimetidine and antacids appear to reduce folate absorption.¹⁵ Several drugs, such as aminopterin, methotrexate, pyrimethamine, trimethoprim, and triamterene act as folate antagonists. Although the mechanism is unclear, anticonvulsants, antituberculosis drugs, alcohol, and oral contraceptives produce low serum and tissue concentrations of folate.¹⁶

Folic Acid Deficiency

Folic acid deficiency is considered to be one of the most common nutritional deficiencies. The following may contribute to a deficiency of folic acid: a deficient food supply; a defect in utilization, as in alcoholics and individuals with liver disease; malabsorption; increased needs in pregnant women, nursing mothers, and in cancer patients; metabolic interference by drugs; folate losses in hemodialysis; and an enzyme or cofactor deficiency needed for the generation of active folic acid.^{17,18} Absorption of folic acid appears to be significantly impaired in HIV disease, irrespective of the stage of the disease.¹⁹ Signs and symptoms of folate deficiency might include macrocytic anemia, fatigue, irritability, peripheral neuropathy, tendon hyper-reflexivity, diarrhea, weight loss, and cerebral disturbances.20

Folic Acid and the Treatment of Elevated Homocysteine

A significant component in the pathogenesis, prevention, and treatment of heart disease involves the amino acid homocysteine. Increased blood levels of homocysteine are correlated with significantly increased risk of coronary artery disease (CAD),²¹⁻²⁴ myocardial infarction,^{25,26} peripheral occlusive disease,^{27-³⁰ cerebral occlusive disease,^{27,30} and retinal vascular occlusion.³¹ Elevated levels of homocysteine have also been correlated with a variety of other clinical conditions, such as neural tube defects (NTD), nervous system disorders, diabetes, rheumatoid arthritis, and alcoholism.³²}

Decreased plasma folate levels are correlated with increased levels of homocysteine, and a subsequent increased incidence of CAD. In a fifteen-year Canadian study of CAD mortality in 5,056 men and women 35-79 years of age, lower serum folate levels were correlated with a significantly increased risk of fatal CAD.³³ In a cohort from the Framingham Heart Study, Selhub et al found concentrations of folate and P5P were inversely related to homocysteine levels and the risk of extracranial carotid-artery stenosis.²⁷

Several studies utilizing folic acid, B6, B12, and betaine, either alone or in combination, have demonstrated the ability of these nutrients to normalize homocysteine levels.^{28,29,34-36} In a 1994 placebo-controlled clinical study of 100 men with hyperhomocysteinemia, oral therapy with 650 mcg folic acid, 400 mcg vitamin B12, 10 mg vitamin B6, or a combination of the three nutrients was given daily for six weeks. Plasma homocysteine was reduced 41.7 percent (p<0.001) during folate therapy and 14.8 percent (p<0.01) during B12 therapy, while 10 mg B6 did not reduce plasma homocysteine significantly. The combination worked synergistically to reduce homocysteine levels 49.8 percent.³⁷ In 68 patients with recent myocardial infarction, 18 percent had increased plasma homocysteine. Oral folate therapy (2.5 mg) reduced this hyperhomocysteinemia in 94 percent of treated patients (mean decrease 27%).²⁵

Folic Acid and Neural Tube Defects

A low dietary intake of folic acid increases the risk for delivery of a child with a neural tube defect, and periconceptional folic acid supplementation reduces the occurrence of NTD.³⁸⁻⁴⁴ Research also indicates supplemental folic acid intake results in increased infant birth weight and improved Apgar scores, along with a concomitant decreased incidence of fetal growth retardation and maternal infections.⁴⁵⁻⁴⁸

Recent work indicates that homocysteine metabolism is likely to be the affected pathway where folic acid works to prevent NTD, since significantly higher homocysteine levels have been detected in women carrying affected fetuses than in control women. Evidence also suggests women with a history of NTD-affected pregnancies have altered folic acid metabolism.⁴⁹⁻⁵² Patients with a severe congenital deficiency of the enzyme methyltetrahydrofolate reductase, which is needed for the formation of 5-MTHF, have reduced levels of both methionine and Sadenosylmethionine in the cerebrospinal fluid and show demyelination in the brain and degeneration of the spinal cord.⁵³⁻⁵⁴ Because of its direct impact in the activation of folic acid to its methyl derivative, a milder version of this enzyme defect is strongly suspected to increase the incidence of NTD.⁵⁵

Cervical Dysplasia

Numerous clinical studies have pointed to an association between folate status in adults and cervical dysplasia,⁵⁶⁻⁵⁸ suggesting that folic acid supplementation might play a role in the prevention of cervical dysplasia. It is thought that low red blood cell folate levels enhance the effect of other risk factors for cervical dysplasia and, in particular, that of human papilloma virus-16 infection.⁵⁹⁻⁶¹ Although folate deficiency might play a role in the initiation of cervical dysplasia, folic acid supplements do not appear to be very effective in altering the course of established disease.

One report suggested folate supplementation might reverse cervical dysplasia in women taking oral contraceptives. Forty-seven young women with mild or moderate dysplasia of the uterine cervix were treated with 10 mg of folic acid orally, or a placebo (ascorbic acid, 10 mg) daily for three months. All women had used a combination-type oral contraceptive agent for at least six months prior to initiation of treatment and continued contraceptive use during the study. Butterworth et al reported biopsy and PAP smear scores improved in the women receiving the folic acid supplementation.⁶²

However, several more recent studies have not shown folic acid supplementation to be an effective approach for reversal of cervical dysplasia.⁶³⁻⁶⁴ In one study, 154 subjects with grade 1 or 2 cervical intraepithelial neoplasia were randomly assigned either 10 mg of folic acid or a placebo daily for six months.

Alternative Medicine Review ♦ Volume 3, Number 3 ♦ 1998

No significant differences were observed between supplemented and unsupplemented subjects regarding dysplasia status, biopsy results, or prevalence of human papillomavirus type-16 infection.⁶⁴

Inflammatory Bowel Disease

Evidence suggests folate supplementation might protect against neoplasia in ulcerative colitis. Patients with inflammatory bowel disease (ulcerative colitis and Crohn's) commonly have decreased folate levels, partially due to the use of sulfasalazine, a competitive inhibitor of folate absorption. Lashner et al reported folic acid supplementation was associated with a 62 percent lower incidence of neoplasia compared with individuals not receiving supplementation. The authors subsequently recommended folate be supplemented during sulfasalazine administration to minimize dysplasia or cancer in ulcerative colitis.⁶⁵

In a more recent report, Lashner et al reviewed the records of 98 patients with ulcerative colitis. Folate use was associated with an adjusted relative risk (RR) for neoplasia of 0.72. Supplementation appeared to have a dose-dependent effect at reducing the odds of neoplasia, with a dose of 1 mg/day reducing the RR to 0.54.⁶⁶

In order to evaluate the efficacy of oral administration of a pharmacological dose of folic or folinic acid to prevent folate deficiency in patients with inflammatory bowel disease treated with salicylazosulfapyridine, Pironi et al gave 15 mg/day of either folic or folinic acid for one month to two groups of 15 patients with inflammatory bowel disease. Although both folic and folinic acid increased body stores of folates, folinic acid appeared to be more efficient. After one month the mean increase in red blood cell folate concentration was significantly greater after folinic acid therapy than after folic acid therapy (910 +/-383, versus 570 +/- 212 ng/ml; p less than 0.01).67

Folic Acid and Gout

Although some *in vitro* evidence suggests folate compounds are potent inhibitors of xanthine oxidase activity,⁶⁸ it appears that pterin aldehydes, a photolytic breakdown product of folic acid, is responsible for the observed inactivation of xanthine oxidase.⁶⁹

Because of the ability of the photolytic breakdown product, pterin 6-aldehyde, to inactivate xanthine oxidase, theoretically folic acid might have some benefit in the treatment of gout; however, results to date are limited and unimpressive. Folic acid administered in doses up to 1000 mg orally a day did not significantly lower serum urate concentration nor decrease urinary urate or total oxypurine excretion in five hyperuricemic subjects.⁷⁰

Anemia

Folic acid has a long history of use, in conjunction with vitamin B12, for treatment of macrocytic anemia. Recently, several studies demonstrated the efficacy of folinic acid for the treatment of nutritional anemia. Thirty patients (20 adults and 10 children) suffering from nutritional anemia were given oral folinic acid for 15 days (4-8 mg daily). Supplementation resulted in significant increases in the number of red cells, and in folic acid content both in the serum and in the erythrocytes. A decrease of mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular hemoglobin (MCH) was also observed.⁷¹ Lucchi et al gave 4-8 mg of folinic acid daily for 25 days to 30 elderly patients suffering from macrocytic anemia. They reported a significant decrease of mean corpuscular volume (MCV) and MCH.72

Vitiligo

In some individuals, administration of folic acid appears to be a rational aspect of a nutritional protocol to treat vitiligo. Montes et al observed repigmentation in eight of 15 subjects following prolonged oral

Alternative Medicine Review ♦ Volume 3, Number 3 ♦ 1998

administration of folic and ascorbic acid, with simultaneous parenteral administration of vitamin B12.⁷³

Juhlin and Olsson conducted a twoyear study to determine the efficacy of the combination of folic acid, vitamin B12, and sun exposure for the treatment of vitiligo. One hundred patients with vitiligo were treated, with repigmentation occurring in 52. Total repigmentation was seen in six patients, and the spread of vitiligo was halted in 64 percent of patients. Repigmentation was most evident on sun-exposed areas.⁷⁴

Periodontal Disease

Results indicate folic acid can increase resistance of the gingiva to local irritants and lead to a reduction in inflammation.⁷⁵ Pack and Thomson conducted two double-blind studies to evaluate the effects of systemic and topical folate on gingival inflammation during pregnancy. They found folate mouthwash produced significant improvement in gingival health.⁷⁶⁻⁷⁷

A mouthwash containing 5 mg of folate per 5 ml of mouthwash used twice daily for 4 weeks, with a rinsing time of 1 minute, appears to be the most effective manner of application, since the effect of folate on gingival health appears to be moderated largely if not totally through a local influence.⁷⁸

Folate levels should be checked and supplementation with folic acid considered in patients on long-term anticonvulsant therapy.⁷⁹ There have been some reports that folic acid mouthwash inhibits phenytoin-induced gingival hyperplasia.⁸⁰ However, systemic oral administration of folic acid does not demonstrate significant efficacy as the sole therapeutic agent in the reduction of phenytoin-induced gingival hyperplasia.^{81,82}

Psychiatric Applications

Reports indicate neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome.^{83,84} Significant deficiencies in folate are also common in the elderly population, and can contribute to a decline in cognitive function.⁸⁵⁻⁸⁷

Patients with major depressive disorder often demonstrate lower serum and RBC folate concentrations. Lower serum folate concentrations are also associated with greater severity of depression.⁸⁸ Some evidence indicates low folate levels can predict poorer response to antidepressant treatment with selective serotonin reuptake inhibitors.89 Fava et al found subjects with low folate levels were more likely to have melancholic depression and were less likely to respond favorably to treatment with fluoxetine.⁹⁰ Wesson et al reported patients with higher serum folate levels responded more favorably the antidepressant medicine to desmethylimipramine. They also noted low red-cell folate was correlated with the severity of depression.⁹¹

Clinical recovery in depressed patients with low folate levels has been shown to improve when 5-MTHF is used in conjunction with standard psychotropic medication. Evidence also suggests 5-MTHF can reduce depressive symptoms in patients with normal folate status. Passeri et al compared the effectiveness of an oral dose of 5-MTHF (50 mg/ day) and trazodone on depressive symptoms and cognitive status in normofolatemic elderly patients with mild to moderate dementia and depression. After eight weeks of treatment, similar reductions in the Hamilton Depression Rating Scale were observed in the two groups.⁹²

Alternative Medicine Review ♦ Volume 3, Number 3 ♦ 1998

Godfrey et al found that 41 of 123 patients (33%) with acute psychiatric disorders (DSM III diagnosis of major depression or schizophrenia) had borderline or definite redcell folate deficiency. Following a six-month treatment regimen with 15 mg of 5-MTHF or placebo, in addition to standard psychotropic treatment, a greater improvement in outcome scores was observed in the patients receiving 5-MTHF.⁹³

Findings suggest reduced red-cell folate occurs in both phases of bipolar disorders.⁹⁴ Limited evidence also implies supplemental folic acid might positively effect morbidity of some patients placed on lithium prophylaxis.⁹⁵

Botez et al believe unrecognized and treatable folate deficiency might be the basis of a well-defined syndrome of neurologic, psychiatric and gastrointestinal disorders, with restless legs syndrome representing the main clinical expression of folate deficiency in adults. Neuropsychiatric manifestations might appear as mild depression, permanent muscular and intellectual fatigue, mild symptoms of restless legs, depressed ankle jerks, diminution of vibrational sensation in the legs, stocking-type hypoesthesia, and long-lasting constipation. Their experience indicates an oral dose of 5-10 mg of folic acid for 6-12 months can eliminate or control these symptoms.⁹⁶⁻⁹⁸

Because the costs and risks associated with supplementation of low doses of folic or folinic acid are relatively small, these nutrients should be considered as adjunctive therapies in the treatment of patients with depression, schizophrenia, unipolar or bipolar affective disorders, and for geriatric patients with mild dementia. Although many of these patients will have limited or no response to the additional folate, a significant minority might have folate-responsive conditions.⁸⁴

Nutrient Interactions

Experimental evidence indicates high doses of retinol enhance the folate-dependent oxidation to CO, of formate and histidine, and activity reduces the of hepatic methylenetetrahydrofolate reductase, resulting in decreased 5-methyltetrahydrofolate synthesis. The net result of this interaction could potentially result in decreased ability to regenerate homocysteine to methionine.99 Animal experiments indicate diets sufficient in methionine have a sparing effect on folates.¹⁰⁰ Use of pancreatic enzymes might impair absorption of folic acid, so it is probably wise to supplement folic acid away from these enzymes if both are being used therapeutically.¹⁰¹

Safety and Toxicity

Folic and folinic acid are generally regarded as not toxic for humans; however, some concern exists that supplementation might mask a vitamin B12 deficiency resulting in neurological injury secondary to undiagnosed pernicious anemia. Several authors have suggested folic acid supplements might interfere with intestinal zinc absorption; however, the preponderance of evidence does not support this assertion. At doses as high as 5-15 mg of folic acid daily, folic acid does not appear to have any significant effect on zinc status in healthy nonpregnant subjects.¹⁰²

Information is limited on the antagonism of drug effects of folates in individuals treated with anti-folate medications. Since these medications are used to treat a wide range of malignant and nonmalignant disorders, cavalier use of folates should be avoided until further investigations are conducted. Folates can impact seizure control in drug-treated epileptic patients, so they should be administered with caution to these individuals.^{102,103}

Conclusion

The two supplemental forms of folate are folic acid and folinic acid. While many practitioners are aware of folic acid, folinic acid has largely been reserved as an agent to be utilized for methotrexate rescue. Folinic acid has several advantages over folic acid which might, under some circumstances, offer a therapeutic advantage. It bypasses several steps in the conversion of folic acid to 5-MTHF, is more readily transported into the central nervous system than folic acid, has a longer half-life in the body, and it appears to be a more metabolically active form of folate, capable of boosting levels of the coenzyme forms of the vitamin in circumstances where folic acid has little to no effect. The major disadvantage of folinic acid is its increased cost to the consumer.

The two most widely accepted uses of folic acid are in the lowering of homocysteine levels and the prevention of NTD. Several studies utilizing folic acid alone, or in conjunction with B6, B12, and betaine, have demonstrated the ability of these nutrients to normalize homocysteine levels. The use of supplemental folic acid has become a common practice in pregnancy. Most prenatal vitamins now contain adequate levels of folic acid to statistically reduce the occurrence of NTD.

Clinical studies have pointed to an association between folate status in adults and cervical dysplasia. While folic acid supplementation might play a role in the prevention of cervical dysplasia, several recent studies have not shown folic acid supplementation to be an effective approach for reversal of existing dysplasia. It is unknown whether folinic acid might produce a response; however, because it has been shown to have activity in some cases where folic acid is not effective, it is worth investigation.

Evidence suggests folate supplementation might protect against neoplasia in ulcerative colitis. Based on the limited available information, it appears folinic acid might have a therapeutic edge over folic acid in inflammatory bowel disease; however, more research is required to definitively establish if an advantage exists.

In some individuals, administration of folic acid appears to be a rational component of a nutritional protocol to treat vitiligo. Results also indicate folic acid can increase the resistance of the gingiva to local irritants and lead to a reduction in inflammation. This activity appears to be a result of a local action, since systemic administration of folic acid has not been shown to be effective, while the use of folic acid mouth rinse has shown efficacy.

Reports indicate neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome. Based on available information, it seems prudent to instigate a therapeutic trial of folate supplementation in any patient with neuropsychiatric disease. Since folinic acid appears to cross the blood-brain barrier more readily than folic acid, in these disorders it might be a more effective form of folate supplementation.

References

- 1. Wei MM, Bailey LB, Toth JP, Gregory JF 3rd. Bioavailability for humans of deuteriumlabeled monoglutamyl and polyglutamyl folates is affected by selected foods. *J Nutr* 1996;126:3100-3108.
- 2. Russell RM, Golner BB, Krasinski SD, et al. Effect of antacid and H2 receptor antagonists on the intestinal absorption of folic acid. *J Lab Clin Med* 1988;112:458-463.
- 3. Kokue E, Sekiya T, Shimoda M, Natsuhori M. Pharmacokinetics and bioavailability of folic acid and plasma levels of bioactive folates after folic acid administration to pigs. *Vet Q* 1994;16:91-94.

- 4. Schuster O, Weimann HJ, Muller J, et al. Pharmacokinetics and relative bioavailability of iron and folic acid in healthy volunteers. *Arzneimittelforschung* 1993;43:761-766. [Article in German]
- 5. Gregory JF 3d, Bhandari SD, Bailey LB, et al. Relative bioavailability of deuterium-labeled monoglutamyl tetrahydrofolates and folic acid in human subjects. *Am J Clin Nutr* 1992;55:1147-1153.
- 6. McGuire BW, Sia LL, Leese PT, et al. Pharmacokinetics of leucovorin calcium after intravenous, intramuscular, and oral administration. *Clin Pharm* 1988;7:52-58.
- Whitehead VM, Pratt R, Viallet A, Cooper BA. Intestinal conversion of folinic acid to 5methyltetrahydrofolate in man. *Br J Haematol* 1972;22:63-72.
- 8. Fiore JJ, Kemeny NE, Mehta BM, et al. Systemic absorption of a leucovorin mouth wash: a pharmacologic study. *Cancer Invest* 1987;5:109-111.
- Levitt M, Nixon F, Pincus JH, Bertino JR. Transport characteristics of folates in cerebrospinal fluid; a study utilizing doubly labeled 5-methyltetrahydrofolate and 5formyltetrahydrofolate. J Clin Invest 1971;50:1301-1308.
- Spector R. Cerebrospinal fluid folate and the blood-brain barrier. In: Botez MI, Reynolds EH. Folic Acid in Neurology, Psychiatry, and Internal Medicine. New York: Raven Press; 1979:187.
- 11. Greiner PO, Zittoun J, Marquet J, Cheron JM. Pharmacokinetics of (-)-folinic acid after oral and intravenous administration of the racemate. *Br J Clin Pharmac* 1989;28:289-295.
- 12. McGuire BW, Sia LL, Haynes JD, et al. Absorption kinetics of orally administered leucovorin calcium. *NCI Monographs* 1987;5:47-56.
- 13. Bills ND, Jones AD, Clifford AJ. Biological activity of racemic folate mixtures fed to folate-depleted rats. *J Nutr* 1991;121:1643-1648.
- 14. Schilsky RL, Ratain MJ. Clinical pharmacokinetics of high-dose leucovorin calcium after intravenous and oral administration. *J Natl Cancer Inst* 1990;82:1411-1415.
- 15. Russell RM, Golner BB, Krasinski SD, et al. Effect of antacid and H2 receptor antagonists on the intestinal absorption of folic acid. *J Lab Clin Med* 1988;112:458-463.

- 16. Lambie DG, Johnson RH. Drugs and folate metabolism. *Drugs* 1985;30:145-155.
- Sarazaga A, Garcia de Lorenzo A, Montanes P, Culebras JM. Folates in human nutrition. Different clinical situations in which folate deficiencies exist. *Nutr Hosp* 1991;6:207-226. [Article in Spanish]
- Halsted CH. The intestinal absorption of dietary folates in health and disease. J Am Coll Nutr 1989;8:650-658.
- 19. Revell P, O'Doherty MJ, Tang A, Savidge GF. Folic acid absorption in patients infected with the human immunodeficiency virus. *J Intern Med* 1991;230:227-231.
- Botez MI. Folate deficiency and neurological disorders in adults. *Med Hypotheses* 1976;2:135-140.
- 21. Hopkins P, Wu L, Wu J, et al. Higher plasma homocyst(e)ine and increased susceptibility to adverse effects of low folate in early familial coronary artery disease. *Arterioscler Thromb Vasc Biol* 1995;15:1314-1320.
- 22. Loehrer F, Angst C, Haefeli W, et al. Low whole-blood S-adenosylmethionine and correlation between 5-methyltetrahydrofolate and homocysteine in coronary artery disease. *Arterioscler Thromb Vasc Biol* 1996;16:727-733.
- 23. Boushey C, Beresford S, Omenn G, Motulsky A. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 1995;274:1049-1057.
- 24. Robinson K, Mayer E, Miller D, et al. Hyperhomocysteinemia and low pyridoxal phosphate. Common and independent reversible risk factors for coronary artery disease. *Circulation* 1995;92:2825-2830.
- 25. Landgren F, Israelsson B, Lindgren A, et al. Plasma homocysteine in acute myocardial infarction: homocysteine-lowering effect of folic acid. *J Int Med* 1995;237:381-388.
- 26. Chasan-Taber L, Selhub J, Rosenberg I, et al. A prospective study of folate and vitamin B6 and risk of myocardial infarction in US physicians. *J Am Coll Nutr* 1996;15:136-143.
- 27. Selhub J, Jacques P, Bostom A, et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *N Engl J Med* 1995;332:286-291.

Alternative Medicine Review ♦ Volume 3, Number 3 ♦ 1998

- 28. van den Berg M, Boers G, Franken D, et al. Hyperhomocysteinaemia and endothelial dysfunction in young patients with peripheral arterial occlusive disease. *Eur J Clin Invest* 1995;25:176-181.
- 29. van den Berg M, Stehouwer C, Bierdrager E, Rauwerda J. Plasma homocysteine and severity of atherosclerosis in young patients with lower-limb atherosclerotic disease. *Arterioscler Thromb Vasc Biol* 1996;16:165-171.
- Franken D, Boers G, Blom H, et al. Treatment of mild hyperhomocysteinaemia in vascular disease patients. *Arterioscler Thromb Vasc Biol* 1994;14:465-470.
- 31. Wenzler E, Rademakers A, Boers G, et al. Hyperhomocysteinemia in retinal artery and retinal vein occlusion. *Am J Ophthalmol* 1993;115:162-167.
- Miller AL, Kelly GS. Homocysteine metabolism: Nutritional modulation and impact on health and disease. *Alt Med Rev* 1997;2:234-254.
- Morrison H, Schaubel D, Desmeules M, Wigle D. Serum folate and risk of fatal coronary heart disease. *JAMA* 1996;275:1893-1896.
- 34. Wilcken DE, Dudman NP, Tyrrell PA. Homocystinuria due to cystathionine betasynthase deficiency–the effects of betaine treatment in pyridoxine-responsive patients. *Metabolism* 1985;12:1115-1121.
- 35. Dudman N, Wilcken D, Wang J, et al. Disordered methionine/homocysteine metabolism in premature vascular disease. Its occurrence, cofactor therapy, and enzymology. *Arterioscler Thromb* 1993;13:1253-1260.
- Wilcken DE, Wilcken B, Dudman NP, Tyrrell PA. Homocystinuria–the effects of betaine in the treatment of patients not responsive to pyridoxine. N Engl J Med 1983;309:448-453.
- 37. Ubbink J, Vermaak W, van der Merwe, et al. Vitamin requirements for the treatment of hyperhomocysteinemia in humans. *J Nutr* 1994;124:1927-1933.
- MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991;338:131-137.
- 39. Vergel RG, Sanchez LR, Heredero BL, et al. Primary prevention of neural tube defects with folic acid supplementation: Cuban experience. *Prenat Diag* 1990;10:149-152.

- 40. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *JAMA* 1989;262:2847-2852.
- 41. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;327:1832-1835.
- 42. Bower C, Stanley FJ. Dietary folate as a risk factor for neural tube defects: evidence from a case-controlled study in Western Australia. *Med J Aust* 1989;150:613-619.
- 43. Werler MM, Shapiro S, Mitchell AA. Periconceptional folic acid exposure and risk of occurrent neural tube defects. *JAMA* 1993;269:1257-1261.
- 44. Shaw GM, Schaffer D, Velie EM, et al. Periconceptional vitamin use, dietary folate, and the occurrence of neural tube defects. *Epidemiology* 1995;6:219-226.
- 45. Tamura T, Goldenberg R, Freeberg L, et al. Maternal serum folate and zinc concentrations and their relationships to pregnancy outcome. *Am J Clin Nutr* 1992;56:365-370.
- 46. Scholl TO, Hediger ML, Schall JI, et al. Dietary and serum folate: their influence on the outcome of pregnancy. *Am J Clin Nutr* 1996;63:520-525.
- 47. Frelut ML, deCoucy GP, Christides JP, et al. Relationship between maternal folate status and foetal hypotrophy in a population with a good socio-economical level. *Int J Vitamin Nutr Res* 1995;65:267-271.
- 48. Goldenberg RL, Tamura T, Cliver SP, et al. Serum folate and fetal growth retardation: a matter of compliance? *Obstet Gynecol* 1992;79:719-722.
- 49. Wild J, Seller MJ, Schorah CJ, Smithells RW. Investigation of folate intake and metabolism in women who have had two pregnancies complicated by neural tube defects. *Br J Obstet Gynaecol* 1994;101:197-202.
- Wild J, Schorah CJ, Sheldon TA, Smithells RW. Investigation of factors influencing folate status in women who have had a neural tube defect-affected infant. *Br J Obstet Gynaecol* 1993;100:546-549.
- 51. Yates JR, Ferguson-Smith MA, Shenkin A, et al. Is disordered folate metabolism the basis for the genetic predisposition to neural tube defects? *Clin Genet* 1987;31:279-287.

- 52. Lucock MD, Wild J, Schorah CJ, et al. The methylfolate axis in neural tube defects: in vitro characterisation and clinical investigation. *Biochem Med Metabol Biol* 1994;52:101-114.
- 53. Lussier-Cacan S, Xhignesse M, Piolot A, et al. Plasma total homocysteine in healthy subjects: sex-specific relation with biological traits. *Am J Clin Nutr* 1996;64:587-593.
- 54. Kluijtmans LA, van den Heuvel LP, Boers GH, et al. Molecular genetic analysis in mild hyperhomocysteinemia: a common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor in cardiovascular disease. *Am J Hum Genet* 1996;58:35-41.
- 55. Whitehead AS, Gallagher P, Mills JL. A genetic defect in 5,10 methylenetetrahydrofolate reductase in neural tube defects. *QJM* 1995;88:763-766.
- 56. Christensen B. Folate deficiency, cancer and congenital abnormalities. Is there a connection? *Tidsskr Nor Laegeforen* 1996;116:250-254.
- Liu T, Soong SJ, Wilson NP, et al. A case control study of nutritional factors and cervical dysplasia. *Cancer Epidemiol Biomarkers Prev* 1993;2:525-530.
- Grio R, Piacentino R, Marchino GL, Navone R. Antineoblastic activity of antioxidant vitamins: the role of folic acid in the prevention of cervical dysplasia. *Panminerva Med* 1993;35:193-196.
- 59. Butterworth CE Jr, Hatch KD, Macaluso M, et al. Folate deficiency and cervical dysplasia. *JAMA* 1992;267:528-533.
- 60. Kwasniewska A, Tukendorf A, Semczuk M. Folate deficiency and cervical intraepithelial neoplasia. *Eur J Gynaecol Oncol* 1997;18:526-530.
- 61. Bernardi P, Pace V. Correlations between folic acid, human papilloma virus (HPV) and cervix neoplasms. *Minerva Ginecol* 1994;46:249-255. [Article in Italian]
- 62. Butterworth CE Jr, Hatch KD, Gore H, et al. Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. *Am J Clin Nutr* 1982;35:73-82.
- 63. Butterworth CE Jr, Hatch KD, Soong SJ, et al. Oral folic acid supplementation for cervical dysplasia: a clinical intervention trial. *Am J Obstet Gynecol* 1992;166:803-809.

- 64. Zarcone R, Bellini P, Carfora E, et al. Folic acid and cervix dysplasia. *Minerva Ginecol* 1996;48:397-400. [Article in Italian]
- 65. Lashner BA, Heidenreich PA, Su GL, et al. Effect of folate supplementation on the incidence of dysplasia and cancer in chronic ulcerative colitis. A case-control study. *Gastroenterology* 1989;97:255-259.
- 66. Lashner BA, Provencher KS, Seidner DL, et al. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. *Gastroenterology* 1997;112:29-32.
- 67. Pironi L, Cornia GL, Ursitti MA, et al. Evaluation of oral administration of folic and folinic acid to prevent folate deficiency in patients with inflammatory bowel disease treated with salicylazosulfapyridine. *Int J Clin Pharm Res* 1988;8:143-148.
- 68. Lewis AS, Murphy L, McCalla C, et al. Inhibition of mammalian xanthine oxidase by folate compounds and amethopterin. *J Bio Chem* 1984;259:12-15.
- 69. Spector T, Ferone R. Folic acid does not inactivate xanthine oxidase. *J Bio Chem* 1984;259:10784-10786.
- Boss GR, Ragsdale RA, Zettner A, Seegmiller JE. Failure of folic acid (pteroylglutamic acid) to affect hyperuricemia. *J Lab Clin Med* 1980;96:783-789.
- 71. De Michelis AG, Rabbia F, Sacchetta AC, Chiandussi L. The calcium salt of folinic acid for the treatment of deficiency anemia. *Minerva Med* 1991;82:97-100.
- 72. Lucchi R, Crisera A, Ferrari MG, Sacchetta AC. Folinic acid in the treatment of elderly patients with macrocytic anemia. *Clin Ter* 1990;133:159-163.
- 73. Montes LF, Diaz ML, Lajous J, Garcia NJ. Folic acid and vitamin B12 in vitiligo: a nutritional approach. *Cutis* 1992;50:39-42.
- 74. Juhlin L, Olsson MJ. Improvement of vitiligo after oral treatment with vitamin B12 and folic acid and the importance of sun exposure. *Acta Derm Venereol* 1997;77:460-462.
- 75. Vogel RI, Fink RA, Schneider LC, et al. The effect of folic acid on gingival health. *J Periodontol* 1976;47:667-668.
- Pack AR, Thomson ME. Effects of topical and systemic folic acid supplementation on gingivitis in pregnancy. *J Clin Periodontol* 1980;7:402-414.

Alternative Medicine Review ♦ Volume 3, Number 3 ♦ 1998

- 77. Thomson ME, Pack AR. Effects of extended systemic and topical folate supplementation on gingivitis of pregnancy. *J Clin Periodontol* 1982;9:275-280.
- Pack AR. Folate mouthwash: effects on established gingivitis in periodontal patients. J Clin Periodontol 1984;11:619-628.
- 79. Backman N, Holm AK, Hanstrom L, et al. Folate treatment of diphenylhydantoin-induced gingival hyperplasia. *Scand J Dent Res* 1989;97:222-232.
- Drew HJ, Vogel RI, Molofsky W, et al. Effect of folate on phenytoin hyperplasia. J Clin Periodontol 1987;14:350-356.
- 81. Brown RS, Di Stanislao PT, Beaver WT, Bottomley WK. The administration of folic acid to institutionalized epileptic adults with phenytoin-induced gingival hyperplasia. A double-blind, randomized, placebo-controlled, parallel study. *Oral Surg Oral Med Oral Pathol* 1991;71:565-568.
- 82. Poppell TD, Keeling SD, Collins JF, Hassell TM. Effect of folic acid on recurrence of phenytoin-induced gingival overgrowth following gingivectomy. *J Clin Periodontol* 1991;18:134-139.
- Audebert M, Gendre JP, Le Quintrec Y. Folate and the nervous system. *Sem Hop* 1979;55:1383-1387. [Article in French]
- Young SN, Ghadirian AM. Folic acid and psychopathology. *Prog Neuropsychopharmacol Biol Psychiatry* 1989;13:841-863.
- Metz J, Bell AH, Flicker L, et al. The significance of subnormal serum vitamin B12 concentration in older people: a case control study. J Am Geriatr Soc 1996;44:1355-1361.
- Quinn K, Basu TK. Folate and vitamin B12 status of the elderly. *Eur J Clin Nutr* 1996;50:340-342.
- 87. Fine EJ, Soria ED. Myths about vitamin B12 deficiency. *South Med J* 1991;84:1475-1481.
- Abou-Saleh MT, Coppen A. Serum and red blood cell folate in depression. *Acta Psychiatr Scand* 1989;80:78-82.
- 89. Alpert JE, Fava M. Nutrition and depression: the role of folate. *Nutr Rev* 1997;55:145-149.
- 90. Fava M, Borus JS, Alpert JE, et al. Folate, vitamin B12, and homocysteine in major depressive disorder. *Am J Psychiatry* 1997;154:426-428.

- 91. Wesson VA, Levitt AJ, Joffe RT. Change in folate status with antidepressant treatment. *Psychiatry Res* 1994;53:313-322.
- Passeri M, Cucinotta D, Abate G, et al. Oral 5'methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicenter study. *Aging* (Milano) 1993;5:63-71.
- 93. Godfrey PS, Toone BK, Carney MW, et al. Enhancement of recovery from psychiatric illness by methylfolate. *Lancet* 1990;336:392-395.
- 94. Hasanah CI, Khan UA, Musalmah M, Razali SM. Reduced red-cell folate in mania. *J Affect Disord* 1997;46:95-99.
- 95. Coppen A, Chaudhry S, Swade C. Folic acid enhances lithium prophylaxis. *J Affect Disord* 1986;10:9-13.
- 96. Botez MI, Cadotte M, Beaulieu R, et al. Neurologic disorders responsive to folic acid therapy. *Can Med Assoc J* 1976;115:217-223.
- 97. Botez MI, Fontaine F, Botez T, Bachevalier J. Folate-responsive neurological and mental disorders: report of 16 cases. Neuropsychological correlates of computerized transaxial tomography and radionuclide cisternography in folic acid deficiencies. *Eur Neurol* 1977;16:230-246.
- 98. Botez MI, Peyronnard JM, Berube L, Labrecque R. Relapsing neuropathy, cerebral atrophy and folate deficiency. A close association. *Appl Neurophysiol* 1979;42:171-183.
- 99. Fell D, Steele RD. Modification of hepatic folate metabolism in rats fed excess retinol. *Life Sci* 1986;38:1959-1965.
- 100. Potier de Courcy G, Bujoli J. Effects of diets with or without folic acid, with or without methionine, on fetus development, folate stores and folic acid-dependent enzyme activities in the rat. *Biol Neonate* 1981;39:132-140.
- Russell RM, Dutta SK, Oaks EV, et al. Impairment of folic acid absorption by oral pancreatic extracts. *Dig Dis Sci* 1980;25:369-373.
- 102. Butterworth CE Jr, Tamura T. Folic acid safety and toxicity: a brief review. *Am J Clin Nutr* 1989;50:353-358.
- 103. Campbell NR. How safe are folic acid supplements? Arch Intern Med 1996;156:1638-1644.

Copyright©1998 Thorne Research, Inc. All Rights Reserved. No Reprint Without Written Permission