Colloquium: Homocyst(e)ine, Vitamins and Arterial Occlusive Diseases

Vitamins as Homocysteine-Lowering Agents[1]

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ABSTRACT Moderate hyperhomocysteinemia is, today, considered an established risk factor for cardiovascular disease. A graded dose-response relationship between plasma homocysteine concentration over its full range and cardiovascular risk strongly supports causality. Therefore, intervention studies with homocysteine-lowering vitamins are needed. This mini review shows that supplementation with folic acid not only markedly reduces elevated plasma homocysteine concentrations but also reduces normal homocysteine concentrations. Folic acid doses of <1 mg/d may be effective. Supplementation with a combination of folic acid and cyanocobalamin will secure full homocysteine-lowering effect and prevent occurrence of vitamin B-12 deficiency during the course of therapy. J. Nutr. 126: 1276S–1280S, 1996.

INDEXING KEY WORDS:

- *homocysteine* • *folate* • *folic acid*
- *vitamin B-12* • *vitamin B-6*

There is rapidly accumulating evidence that moderate hyperhomocysteinemia is an independent risk factor for cardiovascular disease (Boushey et al. 1995, Selhub et al. 1995, Stampfer et al. 1992, Ueland et al. 1992). To date, all but a few of over 75 studies, including a total of more than 15,000 investigated patients and controls, support this issue (full reference list on request). Both basal hyperhomocysteinemia and hyperhomocysteinemia unmasked by a methionine load are markers for increased cardiovascular risk (Ueland et al. 1992). Moreover, the findings of a dose-response relationship between plasma homocysteine concentration, over its full range, and the relative risk for (Arnesen et al. 1995, Malinow et al. 1993, Pancharuniti et al. 1994, Robinson et al. 1995, Perry et al. 1995) the prevalence of (Selhub et al. 1995) or the severity of cardiovascular disease (Ubbink et al. 1991) strongly supports causality. Now, we must focus on intervention studies to establish whether homocysteine lowering with vitamins reduces cardiovascular risk (Stampfer and Malinow 1995).

The dietary vitamins B-6, B-12 and folate and their synthetic oral counterparts, pyridoxine hydrochloride, cyanocobalamin and folic acid, serve as precursors of the cofactors for homocysteine metabolism, pyridoxal 5-phosphate, methylcobalamin and methyltetrahydrofolate, respectively (Ueland et al. 1992). In humans, vitamin B-6 deficiency does not result in basal hyperhomocysteinemia (Miller et al. 1992). In contrast, folate and vitamin B-12 deficiency may result in considerable hyperhomocysteinemia, which is rapidly normalized after replenishment with the deficient vitamin (Allen et al. 1990, Brattström et al. 1988a, Kang et al. 1987, Stabler et al. 1988). Even within their normal ranges, the levels of serum or red cell folate and serum vitamin B-12 are strong determinants of plasma homocysteine concentration (Andersson et al. 1992, Brattström et al. 1994, Selhub et al. 1994, Ueland et al. 1993).

In untreated young cases of genetically caused severe hyperhomocysteinemias (homocystinurias), life-threatening cardiovascular events are frequent (Erbe 1986, Mudd et al. 1989). In most cases, treatment with cofactors for homocysteine metabolism result in considerable decreases of plasma homocysteine concentration (Mudd et al. 1989, Ueland et al. 1992). In pyridoxine-responsive hyperhomocysteinemia it was statistically confirmed that homocysteine lowering reduces the number of cardiovascular events (Mudd et al. 1985). The lack of reports on vascular events in cases of non-pyridoxine-responsive hyperhomocysteinemias on effective homocysteine-lowering therapy with betaine, folic acid and/or vitamin B-12 suggests that homocysteine lowering also in these cases reduces cardiovascular risk.

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Vitamins for lowering basal homocysteine concentration

Renal insufficiency results both in moderate hyperhomocysteinemia and accelerated atherosclerosis (Wilcken et al. 1988). Several studies have consistently shown that oral treatment with folic acid (5–10 mg/dy) reduces renal hyperhomocysteinemia by a mean of 30–60% (Arnadottier et al. 1993, Chauveau et al. 1994, Janssen et al. 1994, Wilcken et al. 1981, Wilcken et al. 1988). Oral pyridoxine has no homocysteine-lowering effect (Arnadottir et al. 1993, Wilcken et al. 1981).

In two studies, including a total of 28 nonvitamin-deficient healthy subjects with mostly normal plasma homocysteine concentrations, we tested the homocysteine-lowering effect of folic acid (5 mg/d for 2–4 wk) (Brattström et al. 1985, Brattström et al. 1988b). All but two with low homocysteine concentrations responded to folic acid, with reductions on average >30% and were most marked in those with high homocysteine concentrations. Oral treatment over 2 wk with pyridoxine (40 mg/d) or cyanocobalamin (1 mg/d) had no homocysteine-lowering effect (Brattström et al. 1988b). In another study, pyridoxine (120 mg/d for 6 wk) had no effect on plasma homocysteine concentration in 16 healthy subjects (Brattström and Hultberg unpublished). On the basis of these observations, we proposed that the homocysteine-lowering effect of folic acid in nonfolate-deficient subjects is that excess folic acid after conversion to methyltetrahydrofolate increases the rate by which homocysteine is remethylated to methionine. In contrast, excess vitamin B-12 and pyridoxine will not decrease plasma homocysteine unless deficiency is present because these vitamins serve as coenzymes and not as cosubstrates as does methyltetrahydrofolate (Brattström et al. 1988b).

Subsequently, we studied the effect of folic acid and pyridoxine in 20 moderately hyperhomocysteinemic patients with cardiovascular disease (Brattström et al. 1990). After pyridoxine (240 mg/d, for 2 wk) plasma homocysteine tended to increase, but after another 2 wk on pyridoxine with the addition of folic acid (10 mg/d) all patients showed reduced homocysteine concentrations, with 57% mean reduction. We also failed to show a homocysteine-lowering effect of high dose pyridoxine (300 mg/d for 12 wk) in 37 stroke patients (Lindgren, Brattström and Hultberg unpublished). In two recent studies of patients with vascular disease and hyperhomocysteinemia (Glueck et al. 1995, van den Berg et al. 1994) and in one study of normal normohomocysteinemic subjects (Haglund et al. 1993), the combination of pyridoxine (100–250 mg/d) and folic acid (5–10 mg/d) reduced plasma homocysteine by a mean of 51, 38, and 30%, respectively.

In groups of consecutive patients with acute myocardial infarction of whom most were normohomocysteinemic and all of whom had normal serum folate concentrations, we found that 2.5 and 10 mg of folic acid over 6 wk had similar homocysteine-lowering effect; in both groups plasma homocysteine was reduced by a mean of 27% (Landgren et al. 1995). Reductions were seen in all but two patients, both with low homocysteine values. With a few exceptions the response to folic acid was proportional to the pretreatment homocysteine levels. These exceptional patients were hyperhomocysteinemic and had low or low normal serum vitamin B-12 concentrations. In one with a subnormal vitamin B-12 concentration and a partial response to folic acid, oral treatment with cyanocobalamin (2 mg/d for 2 wk) normalized plasma homocysteine.

Hyperhomocysteinemia due to vitamin B-12 deficiency does not respond to folic acid therapy (Allen et al. 1990). It is likely, that even in subjects with low normal vitamin B-12 concentrations full response to folic acid cannot be achieved unless vitamin B-12 is given concomitantly (Landgren et al. 1995). This view is supported by recent studies by Ubbink et al. (1993a, 1993b, 1994). It was shown that men with moderate hyperhomocysteinemia (>16.3 μmol/l) in most cases had suboptimal plasma vitamin B-12 (<200 pmol/l) and folate (<5 nmol/l) concentrations (Ubbink et al. 1993a). Such men were in a 6-wk trial given either folic acid (0.65 mg/d), pyridoxine (10 mg/d), cyanocobalamin (0.4 mg/d) or the combination of these vitamins (Ubbink et al. 1994). Most but not all responded to folic acid, with the mean homocysteine concentration decreased from 28.8 to 16.8 μmol/l (−42%), a posttreatment value, however, still above normal. Pyridoxine had no homocysteine-lowering effect, whereas cyanocobalamin decreased plasma homocysteine by a mean of 15%. In contrast, all responded to the combination by a mean homocysteine reduction of 50% although homocysteine values were not normalized in all subjects during this short trial. Because the majority of these men probably had suboptimal vitamin B-12 status, homocysteine lowering could have been better if a higher cyanocobalmin dose had been used or if the treatment period had been extended for several weeks. There are recent results showing that high dose parenteral administration of cobalamin decreases plasma homocysteine in subjects with normal vitamin B-12 levels (Araki et al. 1993, Nilsson et al. 1994).

Vitamins for lowering postmethionine load hyperhomocysteinemia

Several studies have shown that patients with premature cardiovascular disease frequently respond to oral methionine loading tests (100 mg/kg body weight) with abnormally high increases in plasma homocysteine concentrations (Ueland et al. 1992). There is evidence to suggest that an abnormal response to methionine loading indicates impaired pyridoxal 5-phosphate–dependent homocysteine catabolism, whereas an abnormally high basal homocysteine concentration

mainly reflects impaired vitamin B-12 and folate-dependent homocysteine remethylation (Brattström et al. 1990, Christensen and Ueland 1993, Miller et al. 1994). In accordance with this and in contrast to the lack of effect of pyridoxine on basal homocysteine concentrations, several studies have shown that pyridoxine (100–250 mg/d) improves abnormal methionine loading tests in many but not all patients (Brattström et al. 1990, Dudman et al. 1993, Franken et al. 1994). However, when the combination of pyridoxine (100–250 mg/d) and folic acid (5–10 mg/d) was administered, all patients responded and the abnormality was mostly normalized (Brattström et al. 1990, Dudman et al. 1993, van den Berg et al. 1994). It has recently been demonstrated that methionine-rich meals normally cause slight increases in plasma homocysteine concentration (Guttormsen et al. 1994). It is quite possible that subjects with abnormal methionine loading tests also respond abnormally to methionine-rich meals leading to transient periods of hyperhomocysteinemia, which could be normalized with combined pyridoxine and folic acid therapy. This, however, warrants further study.

Discussion and recommendations

What doses and what combination of vitamins should be recommended for long-term homocysteine lowering? For several reasons, it seems wise to combine folic acid and cyanocobalamin. First, folic acid seems to reduce almost all but low homocysteine levels. Second, cyanocobalamin will probably secure full folic acid responsiveness. Third, in vitamin B-12 deficiency, erroneous treatment with folic acid may correct the hematological abnormalities but elicit and deteroriate vitamin B-12 neuropathy (Chanarin 1994). Therefore, before start of therapy, vitamin B-12 deficiency must be excluded, and the combination must contain a dose of cyanocobalamin high enough to prevent the occurrence of vitamin B-12 deficiency, even if complete intrinsic factor deficiency develops during the course of therapy. Of oral administered cyanocobalamin only about 1% is passively absorbed to the blood (Berlin et al. 1968). The normal daily intrinsic factor receptor-mediated uptake of vitamin B-12 is <2 μg, which means that at least 0.2 mg of cyanocobalamin have to be administered (Adams et al. 1971).

There are recent data that suggest that modest doses of folic acid (<1 mg/d) are sufficient for homocysteine lowering (Ubbink et al. 1994). We found that subjects regularly taking multivitamins containing, among other vitamins, only 0.2–0.4 mg folic acid had significantly lower plasma homocysteine levels (−22%) than subjects not taking multivitamins (Brattström et al. 1994). Hitherto, unpublished results from the European Community Concerted Action Project on Homocysteinemia and Vascular Disease are confirmative. Moreover, in survivors of the original Framingham Heart Study cohort, Selhub et al. (1994) found a mean of 5.3 μmol/l lower (−36%) plasma homocysteine concentrations in those with a high dietary intake of vitamins B-6, B-12 and folate than in those with a low intake of these vitamins.

For intervention studies in cardiovascular disease patients, a combination of 1 mg folic acid and 0.4 mg cyanocobalamin is probably sufficient for effective homocysteine lowering. This combination will be an innocuous means that not only normalizes hyperhomocysteinemia in most patients but also will reduce normal homocysteine values, leading to a shift of the entire homocysteine distribution toward lower values. The latter is important because results of several studies have shown a dose-response relationship between plasma homocysteine concentration over its full range and risk for cardiovascular disease. At present, there are not sufficient data to recommend intervention also against postmethionine load hyperhomocysteinemia with high dose pyridoxine therapy.

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