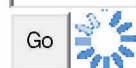




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Effect of Various Regimens of Vitamin B₆ and Folic Acid on Mild Hyperhomocysteinaemia in Vascular Patients

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Mild hyperhomocysteinaemia is associated with peripheral, cerebral or coronary arterial occlusive disease and thromboembolism (Boers et al 1985; Mudd et al 1989; MAC470-01270286

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Page 2

presence of thermolabile 5-methylenetetrahydrofolate reductase are possible causes of the mild hyperhomocysteinaemia. Pyridoxal phosphate, the active form of vitamin B₆, is required as a cofactor for cystathionine synthase. Methyltetrahydrofolate, one of the active forms of folic acid, donates its methyl group in homocysteine remethylation (Mudd *et al* 1989).

The effect of vitamin B₆ and/or folic acid treatment in vascular patients with mild hyperhomocysteinaemia has been poorly studied (Boers 1988; Brattström *et al* 1990). Moreover, the most effective homocysteine-lowering treatment has not yet been described. The aim of the present study was to assess the efficacy of oral treatment with either vitamin B₆ in a daily dose of 50 mg or 250 mg, or a combination of vitamin B₆ and folic acid.

METHODS AND PATIENTS

In 30 patients with documented premature arterial occlusive disease or thromboembolism, mild hyperhomocysteinaemia was established by means of a standardized methionine loading test (Boers *et al* 1983). In the fasting state and 6 hours after methionine loading, blood samples were drawn to determine the total (free plus protein-bound) homocysteine concentration by an HPLC method according to Fiskerstrand *et al* (1993). Vitamin B₆, vitamin B₁₂ and folic acid, all involved in methionine metabolism, were determined in blood in the fasting state. All patients were under the age of 55 years, and none was known to have other risk factors for vascular disease such as diabetes, hyperlipoproteinaemia or hypertension. Ten patients were treated with vitamin B₆ (pyridoxine hydrochloride), in a dose of 50 mg daily. Another 10 patients received vitamin B₆ in a dose of 250 mg daily. A third group of 10 patients were treated with the combination of vitamin B₆ 250 mg daily and folic acid 5 mg daily. The effects of these regimens on the homocysteine concentration were evaluated by performing a second methionine loading test after 6 weeks of treatment. The post-load total homocysteine levels were considered to be normalized if these concentrations had decreased below the level of the mean plus two standard deviations (SD) in normal controls.

RESULTS

After 6 weeks of treatment, the blood concentrations of vitamin B₆ had increased at least 5-fold compared to the pretreatment concentration in 29 out of the 30 treated patients. All patients receiving folic acid treatment showed at least a 5-fold elevation of the folate concentration in serum. The concentration remained unchanged in patients treated with vitamin B₆ alone, as did the serum vitamin B₁₂ concentration in all 30 patients ($p > 0.05$; Wilcoxon signed rank test).

Vitamin B₆ treatment, 50 mg daily, resulted in a slight increase of the mean fasting homocysteine concentration of 8% (from 15.1 $\mu\text{mol/L}$ to 16.3 $\mu\text{mol/L}$; $p > 0.05$), but decreased the mean post-load concentration by 21% (from 59.6 $\mu\text{mol/L}$ to 46.9 $\mu\text{mol/L}$; $p < 0.02$). The post-load homocysteine levels after treatment were normalized in 6 out of 10 patients (Figure 1).

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Page 3

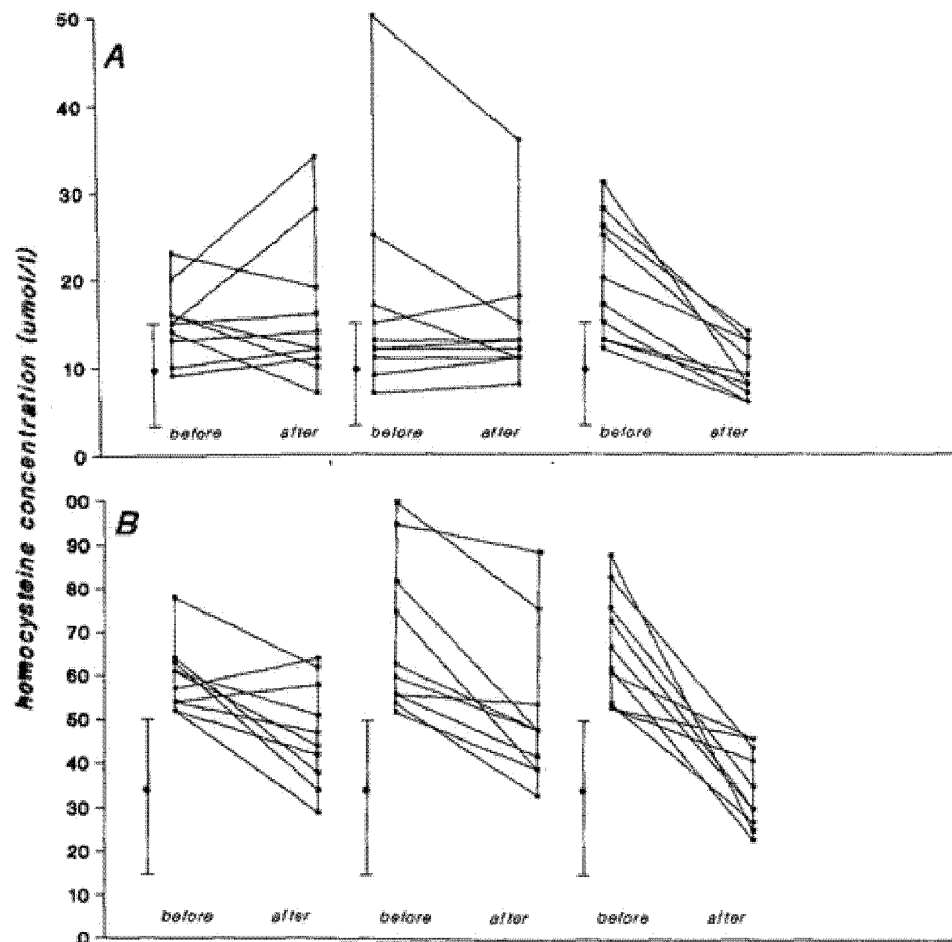


Figure 1 Individual fasting (A) and post-load (B) homocysteine concentrations ($\mu\text{mol/L}$), before and after 6 weeks of treatment with vitamin B₆, 50 mg daily (left), vitamin B₆ 250 mg daily (centre), or vitamin B₆ 250 mg daily plus folic acid 5 mg daily (right) in 30 vascular patients with mild hyperhomocysteinaemia. The mean \pm 2SD of normal controls is indicated

to $14.8 \mu\text{mol/L}$. The mean post-load homocysteine concentration after therapy was 25% lower than for the pretreatment state (decreased from $69.7 \mu\text{mol/L}$ to $51.5 \mu\text{mol/L}$; $p < 0.006$). Seven out of 10 patients normalized their post-load level after therapy.

The mean fasting and post-load homocysteine levels in the patients who received combined treatment decreased markedly compared to the respective mean pretreatment values, from $19.9 \mu\text{mol/L}$ to $9.4 \mu\text{mol/L}$, $p < 0.006$ (a 53% decrease), and from $66.3 \mu\text{mol/L}$ to $33.7 \mu\text{mol/L}$, $p < 0.006$ (a 49% decrease). Normalization of the post-load homocysteine concentration after the combined treatment was achieved in all these patients.

DISCUSSION

Mild hyperhomocysteinaemia in patients with premature arterial occlusive disease

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Page 4

fasting homocysteine concentrations after treatment with vitamin B₆ in a dose of 50 mg or 250 mg daily. However, the mean post-load homocysteine concentrations showed a considerable reduction by the vitamin B₆ regimens, resulting in a normalization of the post-load homocysteine concentrations in 60% and 70% of the patients with vitamin B₆ treatments, as reported earlier (Boers 1988; Brattström et al 1990). In the present study the combined treatment with vitamin B₆ and folic acid resulted in a dramatic decrease of both the mean fasting and post-load homocysteine concentrations, leading in all patients to a normalization of their fasting and post-load homocysteine levels.

None of the patients in this study complained of side-effects associated with the homocysteine-lowering treatment. Long-term adverse effects of vitamin B₆ and folic acid at daily dosages of 250 mg and 5 mg, respectively, have been reported only sporadically (Schaumburg et al 1983; Parry and Bredensen 1985). In our hospital none of about 30 homozygotes for cystathionine synthase deficiency receiving vitamin B₆ and folic acid in a daily dose of 750 mg and 5 mg, respectively, for many years showed any adverse effects such as sensory neuropathy.

We conclude that in vascular patients with mild hyperhomocysteinaemia the combined treatment with vitamin B₆ and folic acid is far more effective than only vitamin B₆ therapy. More studies will be necessary to determine the lowest required dosage of vitamin B₆ and folic acid to normalize the hyperhomocysteinaemia in patients suffering from vascular disease.

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Mild hypohomocysteinemia is associated with peripheral, cerebral or coronary arterial occlusive disease and thromboembolism (Boers et al 1985; Mudd et al 1989; Kang et al 1992). Disarrangements either of homocysteine metabolism or a deficiency of the co-factors methionine or 5-methyltetrahydrofolate can lead to a deficiency of the co-factors methionine or 5-methyltetrahydrofolate.

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