Sustained reduction of hyperhomocysteinaemia with folic acid supplementation in predialysis patients

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Abstract

Background. Moderate hyperhomocysteinaemia, as occurs in chronic renal failure patients, is an established independent risk factor for atherosclerotic arterial occlusive accidents, the incidence of which is abnormally high in such patients. Folic acid supplementation has been shown to reduce plasma homocysteine level in end-stage renal disease patients treated with haemodialysis or peritoneal dialysis, but its long-term effects in predialysis patients had not been assessed.

Methods. We prospectively treated a total of 78 predialysis patients with folic acid for at least 1 year (range 12–74 months) together with oral pyridoxine and vitamin B12 supplements. Of the patients, 67 received 5 mg folic acid three times per week, whereas the other 11 patients who were treated with recombinant erythropoietin received 5 mg/day. Plasma fasting total homocysteine concentration was determined at baseline, after 3 months and at the end of follow-up.

Results. Mean (±SD) plasma total homocysteine level decreased from 21.2 ± 6.4 μmol/l at baseline to 14.2 ± 4.6 at 3 months and remained at 12.8 ± 3.7 μmol/l at the end of follow-up (average duration 2.8 years), whereas plasma creatinine rose from 268 ± 129 to 399 ± 234 μmol/l. Mean plasma folate concentration rose from 19 ± 12 to 47 ± 13 nmol/l and mean plasma vitamin B12 rose from 237 ± 119 to 347 ± 191 pmol/l from baseline to end of follow-up.

Conclusions. Moderate folic acid supplementation (2.15 mg/day) allows a substantial (40% as a mean) and sustained (up to 6 years) reduction of plasma total homocysteine level in predialysis uraemic patients without any detectable side effect. Folic acid supplementation may thus contribute to lower the risk of accelerated atherosclerosis in such patients.

Key words: chronic renal failure; folic acid; hyperhomocysteinaemia; predialysis

Introduction

Homocysteine (Hcy) was recently recognized as a risk factor for the development of atherosclerotic arterial occlusive accidents. Moderate hyperhomocysteinaemia has been shown to be associated with premature coronary or cerebrovascular accidents [1,2] and a strong relationship was found between plasma homocysteine level and cardiovascular mortality in patients with coronary artery disease [3].

Plasma total homocysteine concentration is elevated in chronic uraemic patients from the early stage of chronic renal failure (CRF) [4–6]. Chronic uraemic patients exhibit a markedly higher mortality and morbidity from atherosclerotic arterial complications than subjects of same age and gender in the general population [7,8]. Moreover, an association was found between elevated homocysteine level and the risk of myocardial infarction in predialysis patients [9]. This has also been observed in renal transplant recipient patients with moderately altered renal function [10] and recently in end-stage renal disease (ESRD) patients on dialysis [11].

In view of the atherogenic role of hyperhomocysteinaemia, attempts have been made to lower homocysteine accumulation in uraemic patients. Pharmacological folate supplementation was expected to decrease homocysteine accumulation by enhancing the remethylation pathway from homocysteine to methionine, which uses 5-methyltetrahydrofolate (from folic acid) as the methyl donor and methylcobalamin (from vitamin B12) as the coenzyme [6]. Folic acid supplementation was shown to lower plasma homocysteine level by about 30% in predialysis CRF patients, whereas pyridoxine supplementation alone had no significant effect [12,13]. A similar decrease in plasma homocysteine concentration was observed in dialysis patients using 2.5–15 mg/day folic acid supplement [14–16]. Recent studies have shown that folic acid, 1 mg/day or 5 mg/day had a sustained homocysteine-lowering effect for at least 1 year in haemodialysis patients [17] and also in peritoneal dialysis patients [18], but the long-term effects of folic acid therapy in
predialysis patients had not been assessed. In this paper, we report the results observed in 78 predialysis patients who received long-term, i.e. for at least 1 year (and up to 6 years), moderate folic acid supplementation together with pyridoxine and vitamin B12 supplementation.

Patients and methods

Patients

The study was prospective. All 78 patients (49 males, 29 females, all Caucasian) were ambulatory, in good general and nutritional condition and were managed as outpatients. Their ages ranged from 28 to 87 years (mean ± SD: 60.6 ± 13.7 years). No patient was on dialysis or had been transplanted. Serum creatinine (Scr) ranged from 131 to 638 µmol/l. Primary nephropathy was chronic glomerulonephritis in 14, chronic interstitial nephritis in 21, polycystic kidney disease in 13, angiomegalo-Prosclerotic kidney disease in 23, diabetic nephropathy in four and other or unknown in four. Body mass index (BMI) was ≥ 20 kg/m² and serum albumin was > 35 g/l in all patients at the start of follow-up.

Of the 78 patients, 67 received oral supplementation with folic acid (5 mg three times per week, or 2.15 mg/day as a mean) together with pyridoxine (250 mg twice per week) and vitamin B12 (1 mg twice per week). Eleven patients who required recombinant erythropoietin therapy received 5 mg/day folic acid with the same vitamin B6 and B12 supplementation.

Plasma total homocysteine concentration was determined in the fasting state together with plasma vitamin B12 and folate concentration at baseline (To), after three months (T3) and at the end of follow-up (Tf), i.e. at start of maintenance dialysis or by December 1997. All patients underwent regular clinical surveillance and serial serum creatinine determinations. Follow-up duration ranged from 12 to 74 months (mean 33.8 ± 19.3 months).

Methods

Plasma total (free + protein bound) homocysteine was measured using the rapid-enzymatic method of Refsum et al.[19] as modified by Chadefaux et al. [20]. The normal value for total homocysteine concentration in 45 healthy controls was 8.2 ± 2.2 µmol/l (upper limit: 14.1 µmol/l). Plasma vitamin B12 and folate levels were determined by radioimmunoassay. The normal range for plasma folate concentration was 7–34 nmol/l and 150–750 pmol/l for vitamin B12. Creatinine clearances were assessed using the Cockcroft and Gault formula [21] which has been shown to apply to subjects with impaired renal function [22].

Results

Mean plasma levels of total homocysteine and creatinine at baseline (To), after 3 months (T3) and at the end of follow-up (Tf), together with plasma vitamin B12 and folate levels, are given in Table 1 for the whole series. Mean plasma total homocysteine concentration decreased from 21.2 ± 6.4 to 14.2 ± 4.6 µmol/l (P < 0.001) between To and T3 (a 33% decrease) and to 12.8 ± 3.7 µmol/l (P < 0.001) at Tf (a 40% decrease), whereas mean plasma creatinine value rose from 268 ± 129 to 399 ± 234 µmol/l and creatinine clearance declined from 28.4 ± 12.7 to 21.2 ± 12.6 ml/min/1.73m² from To to Tf. Plasma homocysteine level was in excess of 14.1 µmol in 95% of patients at baseline, and in only 37% at 3 months and 31% at Tf (P < 0.01). The per cent decline in homocysteine level between To and Tf did not differ between the 11 patients who received EPO therapy with 5 mg/day folic acid (−37%) and in the 67 patients who received 2.15 mg/day folic acid (−40%).

Plasma vitamin B12 level at baseline was <150 pmol/l (the lower limit of normal values) in 28% of patients and in the lower quartile of normal values (150–300 pmol/l) in 42% of patients. Plasma folate level was subnormal in no patient, but was in the lower quartile of normal values (7–14nmol/l) in 47% of patients. Mean plasma vitamin B12 and folate concentrations rose significantly from To to T3 and remained at the same level until Tf. In particular, plasma folate concentration ranged between 34 nmol/l (the upper limit in healthy subjects) and 60 nmol/l in all supplemented patients. No side-effect which could be attributed to folic acid supplementation was observed.

Discussion

In view of the growing prevalence of hyperhomocysteinemia with progression of chronic renal failure, and of its deleterious atherogenic effects, attempts to reduce homocysteine levels from the earliest stage of CRF would be strongly indicated.

This large cohort study is the first to provide evidence that long-term moderate folic acid supplementation (2.15 mg/day) allows a substantial (40% as a mean) and sustained (up to 6 years) reduction in plasma total homocysteine level in predialysis CRF patients. It is of note that throughout the entire follow-up period plasma total homocysteine remained at the level to which it had decreased after 3 months, although renal function declined markedly in the meantime. Previous studies in predialysis patients are few and have been only short-term. Wilcken et al. [12] reported a significant decline in plasma homocysteine in 21 predialysis uremic patients following a 2-week course with 5 mg/day folic acid. We observed a 40% decrease in plasma total homocysteine level after 3 months on 10 mg/day folic acid in 37 predialysis patients, whereas pyridoxine supplementation had no significant effect [13], however, long-term effects were not assessed in this preliminary trial.

Subnormal or low-normal plasma levels of vitamin B12, folic acid and/or pyridoxine are associated with an elevated plasma homocysteine level in the general population, particularly in elderly subjects [23]. Some degree of folic acid and/or vitamin B6 deficiency is known to be present in ESRD patients and may
aggravate hyperhomocysteinaemia [24]. Therefore, a supplement including pyridoxine (10 mg/day), cobalamin (6 µg/day) and folic acid (1 mg/day) has conventionally been recommended to compensate for insufficient dietary intake and losses through the dialysate fluid [25].

The choice of a moderate folic acid supplement (5 mg three times per week) in our patients for long-term treatment was based on the results of a preliminary (unpublished) study showing that the decrease in plasma total homocysteine level achieved with 5 mg of folic acid three times per week was of similar magnitude to that obtained with 10 mg/day as used in our earlier trial [13]. A significant and sustained homocysteine-lowering effect was similarly observed with either 5 mg/day or 1 mg/day folic acid in dialysis patients [17,18]. As we observed that the baseline vitamin B12 plasma level was below the lower limit of normal or in the lower quartile of normal values in 70% of our patients we added regular vitamin B12 supplementation. Of note, all of our patients were already routinely supplemented with pyridoxine. When treatment with recombinant erythropoietin was needed, folic acid supplement was increased to 5 mg/day with the same vitamin B12 and pyridoxine supplementation.

Because we did not use a control group, we are not able to assess whether the incidence of atherosclerotic arterial accidents was reduced as a result of sustained lowering of total plasma homocysteine level, but this important issue deserves further evaluation. In conclusion, moderate folic acid supplementation appears to be an easy, cheap and safe means of substantially reducing hyperhomocysteinaemia in predialysis CRF patients, with a sustained effect in the long-term. In view of the potential deleterious atherogenic effects of hyperhomocysteinaemia, folic acid supplementation should be considered in the management of predialysis patients, in order to lower homocysteine accumulation and, hopefully, reduce the risk of accelerated atherosclerosis. However, prospective randomized studies are needed to evaluate the potential beneficial effects of such supplementation on cardiovascular events in uremic patients.

**References**


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