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BRIEF REPORT

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Treatment of hyperhomocysteinemia in children on dialysis by folic acid

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Abstract Adult patients with renal failure have a high total homocysteine concentration in plasma. Hyperhomocysteinemia is an independent risk factor for cardiovascular diseases. Folic acid lowers the homocysteine concentrations in plasma in hyperhomocysteinemia. Whether this results in a reduced risk for cardiovascular diseases remains to be proven by intervention studies. In the present study we investigated: (1) if homocysteine concentrations are elevated in the plasma of children with renal failure and (2) the influence of folic acid administration on the plasma homocysteine concentration. The plasma homocysteine concentration was measured in 21 children, 9 on hemodialysis and 12 on peritoneal dialysis, before and 4 weeks after treatment with 2.5 mg folic acid daily. Healthy children (234) constituted the control group. In controls the median homocysteine concentration was 9.1 µmol/l (range 4.3–20.0 µmol/l). The median plasma homocysteine concentration in patients before folic acid treatment was 20.0 µmol/l (Q1-Q3 13.7–26.0; Q, quartile). After 4 weeks of folic acid treatment the median plasma homocysteine concentration was 12.0 µmol/l [Q1-Q3 9.8–14.3 (P<0.0001 Wilcoxon signed rank test)]. There was no significant difference between hemodialysis and peritoneal dialysis patients. Children with renal failure treated with hemodialysis or peritoneal dialysis have elevated plasma homocysteine concentrations, but this is significantly reduced after administration of 2.5 mg folic acid daily for 4 weeks. It is suggested that folic acid be added to the treatment of children with renal failure, although a beneficial effect still has to be proven. The required dose needs further study.

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Introduction

In adult patients with chronic renal failure, hyperhomocysteinemia is common [1–5]. The basis for this condition is unclear; it appears to reside more in altered metabolism than in reduced excretion [3]. Recently, a markedly reduced clearance of homocysteine from the plasma of patients with renal failure has been reported [6]. Hyperhomocysteinemia has been reported as an independent risk factor for vascular disease in patients on peritoneal and hemodialysis [3, 7]. It can be effectively treated by the administration of folic acid, although normalization of homocysteine plasma concentrations does not occur [8–10].

For children with endstage renal disease no data are available. The present paper aims to provide data on homocysteine plasma concentrations in children with endstage renal disease, as well as on the effect of folic acid supplementation.

Patients and methods

The study group consisted of 21 children, 9 treated with hemodialysis [mean age 10.6 years, standard deviation(SD) 4.1] and 12 with peritoneal dialysis (mean age 8.5 years, SD 4.5). The mean duration of dialysis was 36 months in the hemodialysis group (SD 21 months) and 28 months in the peritoneal dialysis group (SD 31 months). All patients were on regular vitamin B^6 supplementation (2.0 mg daily). Blood specimens were taken after a light continental breakfast, and before dialysis was started in those patients on hemodialysis. Original diseases were posterior urethral valves (8), hemolytic uremic syndrome (3), focal glomerulosclerosis (3), renal dysplasia (2), nephronophthisis, renal ischemia, cystinosis, diffuse mesangial proliferative glomerulonephritis, and Henoch-Schönlein nephritis.

After a baseline measurement of plasma concentrations of homocysteine and folic acid, oral folic acid supplementation was started at a dose of 2.5 mg daily. After 4 weeks of supplementation, plasma homocysteine and folic acid concentrations were

Table 1 Plasma homocysteine and folic acid concentrations in children on dialysis, before and after 4 weeks of supplementation with 2.5 mg folic acid daily

Patient number	Age (years)	Dialysis modality	Before supplementation		After 4 weeks supplementation	
			Homocysteine (μmol/l)	Folic acid (μmol/l)	Homocysteine (μmol/l)	Folic acid (μmol/l)
1	16.8	HD	24.6	13	18.6	1,400
2	9.3	HD	32.0	14	20.4	510
3	9.1	HD	15.9	23	13.4	920
4	13.1	HD	14.9	22	10.4	120
5	10.4	HD	8.9	42	10.4	400
6	11.8	HD	30.6	8	12.1	370
7	2.4	HD	10.0	220	9.6	3,100
8	11.9	HD	21.5	19	14.6	260
9	10.6	HD	20.0	14	12.0	260
10	10.1	PD	25.1	9	13.7	200
11	10.5	PD	15.5	15	9.6	160
12	9.2	PD	20.0	9	–	–
13	14.7	PD	64.9	8	18.2	160
14	14.7	PD	23.2	12	11.9	55
15	5.8	PD	12.4	13	10.6	320
16	14.0	PD	26.8	10	16.4	160
17	2.6	PD	5.4	16	3.6	400
18	4.3	PD	11.8	10	8.0	120
19	8.8	PD	41.7	6	8.2	130
20	3.7	PD	7.8	32	5.0	1,500
21	3.0	PD	5.7	310	8.7	120

PD, Peritoneal dialysis; HD, hemodialysis

measured again. Plasma homocysteine concentrations were also measured in a control group of 234 healthy children (aged 0–19 years).

Total plasma homocysteine concentrations were determined using high-performance liquid chromatography with fluorometric detection [11]. Folic acid was determined using Dualcount SPD radioimmunoassay (Diagnostic Products, Los Angeles, Calif., USA).

Results

The baseline median homocysteine concentration was 20.0 μmol/l (Q1-Q3 13.7–26.9; Q, quartile) (Table 1). After 4 weeks of folic acid supplementation, the median homocysteine concentration was decreased to 12.0 μmol/l (Q1-Q3 9.8–14.3 μmol/l). This decrease was statistically significant ($P<0.0001$, Wilcoxon signed rank test). In our control population the median homocysteine concentration was 9.1 μmol/l (range 4.3–20.0 μmol/l). Recently published reference values for children give the following figures for a control population: 2 months–10 years, median 5.8 μmol/l, interval 3.3–8.3 μmol/l; 11–15 years, median 6.6 μmol/l, interval 4.7–10.3 μmol/l; 16–18 years, median 8.1 μmol/l, interval 4.7–11.3 μmol/l [12]. There was no significant difference between hemodialysis and peritoneal dialysis patients. Folic acid concentrations were within the normal range according to the manufacturers at the start of the study.

Discussion

Children with endstage renal disease treated with hemodialysis or peritoneal dialysis have elevated homocysteine concentrations in their plasma. These concentrations can be significantly reduced by the administration of folic acid, although complete normalization does not occur. This is similar to the results obtained in adult patients [8–10]. Total as well as free (non-protein-bound) plasma homocysteine concentrations are increased in renal failure [13].

Recent epidemiological studies indicate that a modestly elevated plasma homocysteine concentration predisposes to arteriosclerotic vascular disease and venous thrombosis. The mechanisms of vascular damage are not well understood [14]. An impairment of endothelium-dependent vasodilation is observed in adult hemodialysis patients [15]. A beneficial effect of lowering of homocysteine concentrations in these patients on this impaired vasodilation remains to be proven.

The folic acid dose for optimal treatment still has to be established. In most studies in adult patients 5 mg of folic acid is prescribed daily [8, 10]. Further studies are needed to obtain more information on the optimal dosage. Genetic factors may also influence optimal dose [16].

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LITERATURE ABSTRACTS

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Unfavorable course of minimal change nephrotic syndrome in children with intrauterine growth retardation

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Background Intrauterine growth retardation (IUGR) is associated with higher morbidity and mortality not only in perinatal life but also in later life. The purpose of our study was to determine whether IUGR has any effect on the course of minimal change nephrotic syndrome (MCNS) in children.
Methods Forty children who were between 1 and 16 years old at the onset of MCNS, who have been followed for at least three years and for whom we were able to obtain birth weights and gestational ages, were included. The diagnosis of MCNS was predicted on the basis of clinical and laboratory features, and in 11 children (27.5%) the diagnosis was confirmed by renal biopsy. IUGR was defined as birth weight below the tenth percentile for gestational age.
Results Five children (12.5%) had signs of IUGR at birth. In children with IUGR, we observed a higher mean number of relapses (10.4 vs. 3.3, $P<0.001$) and a higher incidence of steroid dependency (80% vs. 21%, $P<0.02$) than in children without IUGR. Other differences between children with and those without IUGR included more frequent treatment with cytotoxic agents and cyclosporine, and a higher incidence of renal biopsy in children with IUGR.
Conclusions Our study demonstrated an unfavorable course of MCNS in children with IUGR. IUGR could therefore enable early identification of those children who are at risk of becoming frequent relapsers and of developing steroid dependency. This, however, should be confirmed in a larger number of patients.

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Effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its metabolite in healthy volunteers: does the formulation difference matter?

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This study was conducted to determine the effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its major metabolites, M1 and M17, in 12 healthy volunteers. Each subject received two oral doses of microemulsion cyclosporine with water or grapefruit juice. Each subject also received intravenous cyclosporine on a separate occasion. Blood samples were collected for assay of cyclosporine, M1, and M17 during a 24-hour period, and were analyzed by a high-performance liquid chromatography method. Compared with water, administration with grapefruit juice significantly increased peak concentration (Cmax) and area under the concentration-time (AUC) of cyclosporine. Administration with grapefruit juice increased the absolute bioavailability of microemulsion cyclosporine by 45%. For cyclosporine metabolites, administration with grapefruit juice decreased the Cmax and AUC of M1 by 21% and 15%, respectively. These findings suggest that concurrent administration with grapefruit juice increases the bioavailability of microemulsion cyclosporine significantly compared with water in healthy volunteers. The grapefruit juice affects each metabolite formation and its pharmacokinetics differently, which suggests that the major site of its formation is different.