Titration of betaine therapy to optimize therapy in an infant with 5,10-methylenetetrahydrofolate reductase deficiency

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Abstract Betaine therapy was given for 2 years to a 2-year-old boy with 5,10-methylenetetrahydrofolate reductase deficiency. Used as a methyl donor to lower homocysteine levels through methylation of methionine, betaine has been reported to be effective in treating homocystinuria. Satisfactory biochemical and clinical responses were obtained with the following regimen: betaine started in the newborn period at increasing doses to reach 1 g given six times a day. It is suggested that frequent administration of a moderate dose may provide clinical and biochemical benefit.

Keywords Betaine · 5,10-Methylenetetrahydrofolate reductase deficiency · Daily dose frequency

Abbreviations

MTHFR methylenetetrahydrofolate reductase
tHcy total plasma homocysteine

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Introduction

Methylenetetrahydrofolate reductase (MTHFR) converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which donates a methyl group to homocysteine to form methionine. MTHFR deficiency results in elevated homocysteine and low methionine levels [6]. Betaine, a methyl donor, has been shown to successfully lower plasma homocysteine and normalize methionine in MTHFR patients of varying age and disease severity [1–4, 12]. In this paper, we report an infant successfully treated with betaine, with emphasis on the frequency of administration.

Case report

A 4-kg male, the third child of consanguineous parents, was delivered at 40 weeks of gestation after an uncomplicated pregnancy. Two siblings died 28 and 16 days; the latter having a positive urinary nitroprusside reaction. Subsequently, the mother received intramuscular cyanocobalamin (1 mg every 2 weeks) and folic acid (5 mg/day) during pregnancy.

On day 2, the patient developed hyperbilirubinemia, hypotonia, and lethargy. Total plasma homocysteine (tHcy) was elevated (155.5 $\mu\text{mol/L}$ [5–15 $\mu\text{mol/L}$]) and methionine was reduced (13.1 $\mu\text{mol/L}$ [7.9–55.3 $\mu\text{mol/L}$]). Urinary homocystine (102 mmol/mol creatinine [0.2–4 mmol/mol creatinine]) and cystathionine (89 mmol/mol creatinine [0.1–3 mmol/mol creatinine]) were increased and urinary nitroprusside testing was positive. Plasma cobalamin, erythrocyte folate, and organic acid profile were normal. The metabolite pattern suggested a remethylation defect and folic acid (10 mg/day), pyridoxine (100 mg/day), hydroxycobalamin (1 mg/day), and carnitine (300 mg/day;

Carnitine%30, Santa Farma) were initiated. At 2 months, betaine anhydrous (100 mg/kg/day, given every 2 h; Cystadane®, Orphan Europe) was introduced.

No enzyme activity was detectable in fibroblasts (0 nmol methyl tetrahydrofolate/h/mg protein), confirming a severe MTHFR deficiency and betaine was increased weekly in 50 mg/kg increments to 3 g/day. Each dose, mixed with formula, was given nine times per day via nasogastric tube. From 9 months to 2 years, 6 g betaine/day was administered orally with meals in six divided doses, mixed with food, milk, or juice. The effects of reducing the frequency to three per day and of increasing the dose to 9 g/day, given three or six times, on plasma tHcy and methionine were evaluated (Fig. 1). Reducing the frequency to three per day increased tHcy from 45 $\mu\text{mol/L}$ (5–15.5 $\mu\text{mol/L}$) to around 90 $\mu\text{mol/L}$ and decreased methionine levels. Increasing to more than six per day led to difficulties in administration; 6 g/day of betaine given in six doses provided adequate control in this patient.

Physical development was normal; however, language development and motor development were retarded by 3 to 6 months. No vaso-occlusive or thromboembolic events occurred.

Discussion

The efficacy of betaine treatment in MTHFR deficiency is established. However, dosage and frequency of administration are still controversial. One study in patients with MTHFR deficiency showed peak betaine concentration after 1 and 2 h with an apparent elimina-

tion half-life of 1 h [7]. A comparison between 12 healthy males and three patients revealed an increased total plasma betaine clearance in patients, suggesting that, due to accelerated distribution and elimination kinetics, patients may require more frequent dosing to maintain plasma concentrations [8]. In this paper, mean tHcy levels of 45 $\mu\text{mol/L}$ (5–15.5 $\mu\text{mol/L}$) were achieved by administration at short intervals. This is in contrast with data indicating minimal benefit from exceeding twice-daily dosing in six patients with classical homocystinuria [5]. In healthy individuals, betaine concentrations are not affected by age and gender. However, in patients with MTHFR deficiency and classical homocystinuria, this may not be the case. Patient age, primary diagnosis, metabolic status, and duration of treatment may explain such discrepancies. There is a need for further studies of betaine in MTHFR deficiency to optimize treatment modalities.

Additionally, one therapeutic action of betaine is to increase brain methionine uptake [11]. Increasing plasma methionine concentration via optimizing betaine therapy may enhance transportation into the brain [9, 10].

In conclusion, more frequent administration of moderate doses of betaine in patients with MTHFR deficiency may provide clinical and biochemical benefits and should be evaluated further.

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Conflict of interest We have no conflict of interest.

Fig. 1 The mean total homocysteine and methionine in plasma in relation to daily dose and frequency of betaine treatment (blood samples were collected prior to administration of betaine during the last week of the each month)

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