

Enhancement of recovery from psychiatric illness by methylfolate

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41 (33%) of 123 patients with acute psychiatric disorders (DSM III diagnosis of major depression or schizophrenia) had borderline or definite folate deficiency (red-cell folate below 200 µg/l) and took part in a double-blind, placebo-controlled trial of methylfolate, 15 mg daily, for 6 months in addition to standard psychotropic treatment. Among both depressed and schizophrenic patients methylfolate significantly improved clinical and social recovery. The differences in outcome scores between methylfolate and placebo groups became greater with time. These findings add to the evidence implicating disturbances of methylation in the nervous system in the biology of some forms of mental illness.

Lancet 1990; **336**: 392–95.

Introduction

About two-thirds of patients with megaloblastic anaemia due to deficiency of vitamin B₁₂ or folate have treatable neuropsychiatric complications.^{1,2} The importance of low serum concentrations of vitamin B₁₂ or folic acid in psychiatric patients in the absence of anaemia or macrocytosis is less certain. Less than 5% of psychiatric patients have low serum vitamin B₁₂ concentrations³ but low serum folate has been reported in 10–33% (mean 22.5%).^{4,5} Serum folate concentrations can vary greatly in response to day-to-day changes in dietary folate intake, but the red-cell folate concentration reflects the folate status over the previous 3 months or longer and may be normal in states of acute recent folate depletion.³ We⁶ reported significantly lower than normal red-cell folate concentrations and a correlation between serum and red-cell folate concentrations in psychiatric patients with or without epilepsy and have since found borderline or definite red-cell folate deficiency in 31% and 12%, respectively, of 285 patients consecutively admitted to the psychiatric unit at Northwick Park hospital.⁷

We have undertaken a double-blind, placebo-controlled trial of folate replacement in patients with depression or schizophrenia referred as outpatients or for acute admission at King's College Hospital. The patients were screened for borderline or definite folate deficiency by red-cell folate assays. A close association between depression and folate deficiency has been reported^{4,8–10} and there is also much interest in methylation and schizophrenia.^{9,11} In this study we used the methyl derivative of folate for treatment as it is this form which is actively transported across the blood-brain barrier and which is detectable in the cerebrospinal fluid in concentrations three times greater than in serum.^{12,13}

Patients and methods

123 adult patients admitted or referred as new outpatients to the psychiatric unit of King's College Hospital with a DSM III diagnosis of major depression or schizophrenia were screened with a red-cell folate assay for borderline (below 200 µg/l) or definite

(below 150 µg/l) folate deficiency. Patients with a red-cell folate level below 200 µg/l entered the double-blind, placebo-controlled trial of treatment with methylfolate 15 mg daily for 6 months, after stratification into the two diagnostic groups (depression and schizophrenia). Folate or placebo was added to the standard psychotropic drugs deemed appropriate by the consultant psychiatrist responsible for the patient. The trial was approved by the hospital ethical committee and patients gave informed consent.

Exclusion criteria were pregnancy, significant cognitive impairment, alcoholism, severe physical illness, vitamin B₁₂ deficiency, or the ingestion of drugs known to deplete folate (eg, anticonvulsants).

TABLE 1—CHARACTERISTICS OF TREATMENT GROUPS

| — | n | Mean (range) age (yr) | Male/female |
|----------------------|----|-----------------------|-------------|
| <i>Depression</i> | | | |
| Methylfolate | 13 | 45 (24–64) | 6/7 |
| Placebo | 11 | 46 (20–70) | 5/6 |
| <i>Schizophrenia</i> | | | |
| Methylfolate | 9 | 42 (24–63) | 4/5 |
| Placebo | 8 | 46 (28–65) | 5/3 |

Day 0 was the date of entry to the trial and the start of methylfolate or placebo treatment. It did not usually coincide with the start of other treatment, which in many cases, and depending on clinical circumstances, had to be initiated before the result of the folate assay was known; the average delay was 10 days. All patients entering the trial were rated on the clinical rating scale,¹⁴ the 17-item Hamilton depression inventory, and the Beck depression self-rating scale on day 0 and after 1, 3, and 6 months. In addition, all patients were rated on an overall clinical outcome scale at 1, 3, and 6 months: 1 = symptom-free/socially recovered; 2 = residual symptoms/socially recovered; 3 = pronounced impairment without full social recovery; 4 = slight or no improvement.

Blood count and measurement of serum and red-blood-cell folate and serum vitamin B₁₂ were repeated at 3 months and at 6 months but the results were not available until the end of the trial. Blood count was measured on a Coulter S counter, folate levels with *Lactobacillus casei*, and serum vitamin B₁₂ by a radioisotope method.

Results

41 (33%) of the 123 patients screened had red-cell folate levels below 200 µg/l and entered the trial of methylfolate. There were 24 patients with depression (31% of 76 depressed patients screened) and 17 patients with schizophrenia (36% of 47 schizophrenic patients screened). 22 patients were randomly allocated to the group receiving methylfolate and 19 to the placebo group (table 1). There were no significant differences in haemoglobin, mean cell volume, serum or red-cell folate, or serum vitamin B₁₂

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TABLE II—CONCOMITANT PSYCHOTROPIC MEDICATION

| | Placebo | Methylfolate |
|-----------------------------|---------|--------------|
| Depression | | |
| Tricyclic antidepressant | 6 | 9 |
| Monoamine oxidase inhibitor | 0 | 2 |
| Lithium | 2 | 0 |
| None | 3 | 2 |
| Schizophrenia | | |
| Oral neuroleptics | 4 | 5 |
| Depot neuroleptics | 4 | 4 |

TABLE III—CLINICAL OUTCOME AND RATING SCORES

| | Mean (SE) score | | |
|------------------------------------|-----------------|-------------|--------------|
| | 1 mo | 3 mo | 6 mo |
| Clinical outcome scores | | | |
| Placebo (n = 19) | 2.5 (0.2) | 2.6 (0.2) | 2.6 (0.2) |
| Methylfolate (n = 22) | 2.1 (0.2) | 1.8 (0.1)* | 1.6 (0.1)† |
| Clinical rating scale | | | |
| Depressed placebo (n = 11) | 3.64 (1.11) | 2.63 (0.65) | 3.90 (0.85) |
| Depressed methylfolate (n = 13) | 2.54 (0.50) | 2.31 (0.59) | 2.15 (0.65) |
| Schizophrenic placebo (n = 8) | 5.63 (1.57) | 6.12 (1.96) | 5.87 (2.00) |
| Schizophrenic methylfolate (n = 9) | 5.22 (1.93) | 3.44 (1.08) | 2.22 (0.72) |
| Hamilton rating scale | | | |
| Depressed placebo (n = 11) | 8.00 (2.20) | 8.18 (2.06) | 11.27 (2.24) |
| Depressed methylfolate (n = 13) | 9.62 (2.11) | 8.46 (1.97) | 8.31 (2.04) |

For differences between methylfolate and placebo: *p < 0.01; †p < 0.001.

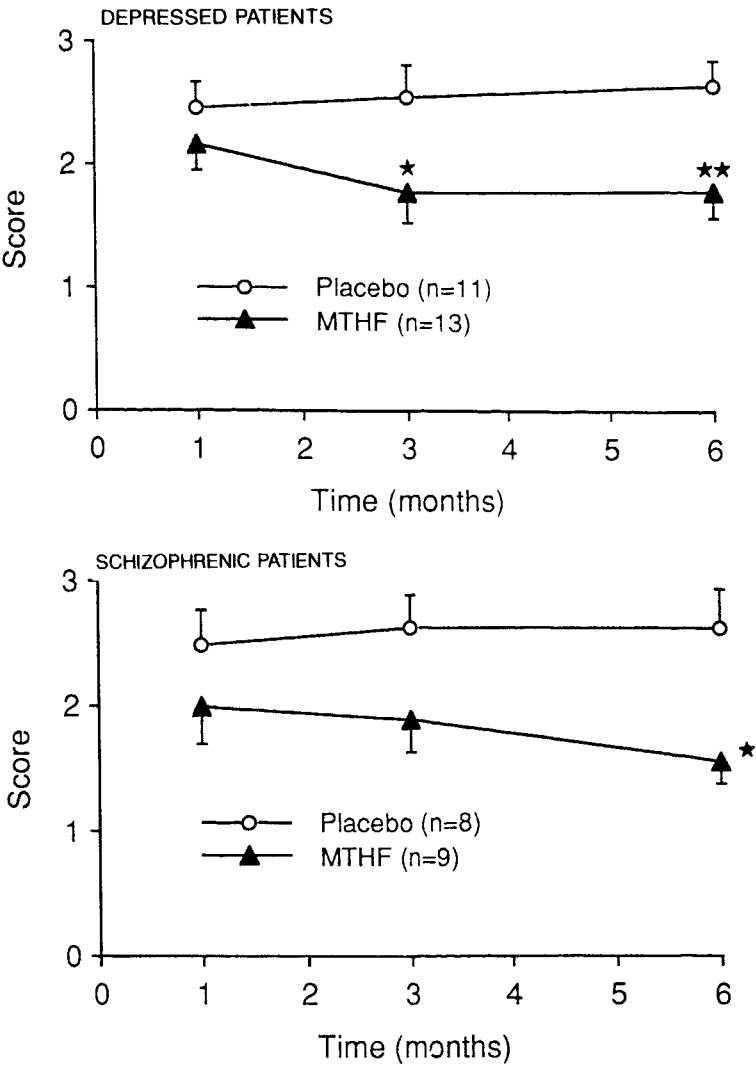
between the treatment groups. 1 patient in each group was anaemic and 4 patients in each group had macrocytosis (mean cell volume greater than 98 fl). 9 of 22 patients in the methylfolate group and 8 of 19 patients in the placebo group had red-cell folate concentrations below 150 µg/l (definite folate deficiency) at baseline. There were no significant differences in the distribution of the various psychotropic drugs given between the groups (table II).

All 41 patients completed the 6-month trial. Comparisons between the placebo and folate groups were made at 1, 3, and 6 months by means of the Mann-Whitney U test (table III). The mean clinical outcome score was significantly lower in the methylfolate than in the placebo group at 3 months (p < 0.01) and 6 months (p < 0.001) for the whole study group (table III). There were also significant differences between the treatment groups among patients with depression at 3 and 6 months and among schizophrenic patients at 6 months (see accompanying figure). The significance of differences between the methylfolate and placebo groups increased with time.

Of the rating scales used, the clinical rating scale correlated most closely with the clinical outcome scores at all time points both among the depressed patients (r = 0.55–0.69; p < 0.02–0.01) and among schizophrenic patients (r = 0.65–0.80; p < 0.01–0.001). The Hamilton rating scale also correlated closely with clinical outcome among the depressed patients (r = 0.51–0.72; p < 0.05–0.01) but not

TABLE IV—SERUM AND RED-CELL FOLATE AND SERUM VITAMIN B₁₂ CONCENTRATIONS

| | Mean (SD) | | |
|--------------------------------------|-----------|-----------|-----------|
| | Baseline | 3 mo | 6 mo |
| Serum folate (µg/l) | | | |
| Placebo | 5.3 (3.2) | 8.7 (5.4) | 7.2 (5.3) |
| Methylfolate | 6.5 (4.5) | > 18.0 | > 18.0 |
| Red-cell folate (µg/l) | | | |
| Placebo | 143 (45) | 226 (116) | 271 (148) |
| Methylfolate | 150 (45) | > 800 | > 800 |
| Serum vitamin B ₁₂ (ng/l) | | | |
| Placebo | 388 (171) | 344 (119) | 333 (132) |
| Methylfolate | 322 (130) | 301 (128) | 347 (142) |



Clinical outcome scores (mean and SE) in depressed and schizophrenic patients receiving methylfolate (MTHF) or placebo.

*p < 0.05, **p < 0.01, for differences between treatment groups.

among the schizophrenic patients. Beck scores correlated poorly with clinical outcome in both disorders. Clear trends in favour of methylfolate were found in the clinical rating scale in both the depressed and schizophrenic subgroups at 3 and 6 months, and for the Hamilton scale among depressed patients at 6 months (table III). In the depressed subgroup rating scores tended to rise at 6 months in patients on placebo, whereas scores were stable or falling in patients receiving methylfolate.

There were no significant differences in baseline folate or vitamin B₁₂ concentrations between the methylfolate and placebo groups (table IV). After 3 and 6 months' treatment with methylfolate, serum and red-cell folate concentrations were above the upper limit of the assay, but serum vitamin B₁₂ was unchanged. In the placebo group there were slight rises in serum and red-cell folate concentrations at 3 and 6 months and again no change in serum vitamin B₁₂.

Discussion

The proportion of patients with depression or schizophrenia who had borderline or definite folate deficiency (33%) is almost identical to that in a larger series at Northwick Park Hospital.⁷ Since only 2 of the patients in this study were anaemic and 20% had macrocytosis, few of the 41 patients in the clinical trial would have been identified without the screening procedure.

In this study we have not addressed the question of what causes borderline or subnormal folate concentrations,

although this question needs further investigation. It is widely assumed that the low folate concentrations are the result of a poor diet secondary to the mental illness. However, attempts to prove this assumption have not been successful.¹⁵⁻¹⁷ In the Northwick Park Hospital study,⁷ patients with depression had similar folate concentrations to a group with alcoholism, although the depressed patients were not obviously as malnourished as the alcoholic patients. None of the patients in this study was alcoholic or taking drugs known to reduce folate concentrations. The possible role of malabsorption of folate has not been investigated in a psychiatric population, although Botez and colleagues¹⁸ described a syndrome of depression responsive to folic acid associated with functional gastrointestinal disease.

Whatever the cause of the low folate concentrations, the results of treatment with methylfolate suggest that low folate is clinically relevant to the underlying mental disorder. In the whole study group of 41 patients the administration of methylfolate was clearly associated with a better overall symptomatic and social recovery; the benefits over placebo became more significant with time, in keeping with the view that the response of the nervous system to folate may occur slowly.⁸ The enhanced clinical and social recovery on methylfolate treatment was seen in both depressed and schizophrenic patient subgroups. Of the rating scales used, the clinical rating scale, which is suitable for both depression and schizophrenia, correlated best with clinical outcome and showed clear trends in favour of methylfolate in both subgroups.

The vitamin assays done during the trial confirmed that compliance with methylfolate treatment was good. Serum and red-cell folate levels in the placebo group were slightly higher at 3 and 6 months than at baseline, which may perhaps be attributable to better appetite and folate intake associated with clinical improvement on standard psychotropic treatment.

It has long been suspected that folate deficiency, whether or not associated with megaloblastic anaemia, is involved in some psychiatric disorders, especially depression.^{1,4,8-10} The most common neuropsychiatric complication of folate-deficient/megaloblastic anaemia is a reversible affective disorder.² The association of low serum folate levels and depression has been noted in psychiatric, neurological, psychogeriatric, and epileptic patients.^{4,5,6,9,10,15} Whether it is a primary or secondary phenomenon and, if secondary, whether a vicious circle like aggravation of the mental state occurs, have never been resolved. In a retrospective survey²⁰ psychiatric patients treated with folic acid spent less time in hospital and made significantly better social recoveries than those in whom low serum folate levels were not treated. Folic acid had beneficial effects on mood, drive, and sociability in epileptic patients with low serum folate in a 1-year open study,⁸ but subsequent double-blind, placebo-controlled studies for up to 3 months did not show any effect of the vitamin on cognitive measures of mental function.^{5,21} In patients with depression associated with gastrointestinal disorder folic acid significantly improved various neuropsychological measures, especially mood, compared with placebo.²² In patients with affective disorder on prophylactic treatment with lithium, plasma folate was negatively correlated with residual affective morbidity;²³ small doses of folic acid (200 µg daily) reduced the affective morbidity in these patients in a double-blind, placebo-controlled trial.²⁴ Our trial of methylfolate, the form of the vitamin transported into the nervous system, provides the

most compelling evidence yet that, whether primary or secondary, low folate levels may be important for the underlying mental state, replacement therapy resulting in an enhanced clinical response to standard psychotropic treatment.

The effect of folic acid on mental function, especially mood, is reinforced by the effect of S-adenosylmethionine (SAM) in depression.^{9,25-27} SAM is the sole methyl donor in many methylation reactions in the nervous system, involving neurotransmitters (including monoamines), membrane phospholipids, proteins, and nucleoproteins. SAM obtains its methyl group for these methyltransferase reactions from methylfolate, by way of the synthesis of methionine. The facts that depression is the commonest neuropsychiatric complication of severe folate deficiency and that SAM may have antidepressant properties suggest that methylation in the nervous system is important in the expression of mood and is implicated in some affective disorders.^{9,28} Both folic acid and SAM affect the turnover of monoamines, including serotonin and dopamine, which links methylation with monoamine theories of affective disorder.^{9,28}

Was the effect of methylfolate on mood and mental function in this study due to correction of folate deficiency, as we originally postulated, or could it have a more direct pharmacological action, irrespective of folate status, as has been reported for SAM? Studies of methylfolate used as sole treatment in patients with and without folate deficiency would be required to answer this question.

We thank Bioresearch, Milan, for supplies of methylfolate.

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Do changes in pattern of breast usage alter the baby's nutrient intake?

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Twelve mother/baby pairs took part in a study of the difference in effect of two patterns of breast feeding—either feeding at one breast or at two breasts during a feed. Baseline measures were taken at 4 weeks, and the test patterns of feeding were followed for a week each, in random order. The two patterns of feeding led to differences in milk volume intake and mean feed fat concentration, but not in the baby's net fat intake per 24 h. The results indicate that the breast-fed baby can regulate his fat intake quickly and thus mothers should be encouraged to practise "baby-led" feeding.

Lancet 1990; **336**: 395-97.

Introduction

The secretory output of human mammary epithelial cells is consistent when studied in vitro.¹ However, since milk is a stored product, there is scope for inconsistency between the composition of the milk synthesised and that which the infant derives by suckling. Thus, during the course of a breast-feed there is a conspicuous increase in the fat concentration of the milk.²⁻⁴ Hytten's plausible explanation for this pattern of change was based on a physical model of breast emptying;² no secretory explanation has yet been proposed.

It may be inferred from Hytten's proposal that the more completely the breast is emptied, the higher is the fat concentration of the milk—a view supported by experiments showing that the fat concentration at the end of a breast-feed is directly related to feed length and feed volume.⁵ This finding underlies the hypothesis⁶ that with incomplete breast emptying (as might be caused by premature termination of feeds or poor positioning of the baby at the breast) the milk that the infant receives will, within weeks, become progressively lower in fat, so that the baby could become calorie deprived and fail to thrive. Here we describe how we tested this hypothesis in a within-subject, repeated measures, randomised, crossover study in which each mother acted as her own control. This design is sensitive to small experimental effects. The study has

implications for the estimation of the breast-fed baby's energy intake: if completeness of breast emptying affects the milk fat concentration, then estimates of nutrient intake will be influenced by feed management policies that affect breast emptying.

Methods

Subjects

Twelve mother/baby pairs provided complete data during the baseline and both experimental periods. The mothers (seven primiparous, five multiparous) were enlisted through the National Childbirth Trust. The babies (eight female, four male) were all born at term, and their mean birthweight was 3.465 kg (SD 0.35).

Data collection

Breast milk output was assessed by weighing the infant before and after every feed taken during a period of 24 h (8 am to 8 pm). The babies were weighed with a 'Sartorius 3826-MP8' balance with data-averaging keyboard (74401-AWK) (Sartorius Ltd, Epsom). Milk samples expressed by mothers (at least 5 drops) before and after the feed (from the breast offered over the 12 hours from 8 am to 8 pm were analysed for fat content) by use of the creamatocrit technique by one investigator (J. C. I.); coefficient of variation for repeated samples was 1.1%. The fat concentration of the milk taken at each feed was defined as the mean of the pre-feed and post-feed fat values. This definition is based on the assumption that breast milk fat changes in a linear manner during the feed. The theoretical issues underlying this assumption have been addressed previously^{4,7} and it is generally accepted to be a reasonable approximation.^{8,9} An adjustment for non-linearity has recently been suggested,¹⁰ but when applied to the present data it did not materially affect the outcome (largely due to the within-subject study design employed).

Net fat intake at a feed was taken as the product of feed volume and the fat concentration of the milk taken at that feed; total daytime (8 am-8 pm) fat intake was taken as the sum total of the individual feed values. Night-time (8 pm-8 am) fat intake was estimated as the product of the night-time volume intake and the mean of all

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