Do antidepressants cause folic acid depletion? A pilot study

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SUMMARY. Chronic administration of tricyclic antidepressants is common; folic acid depletion is a potential consequence adversely affecting the mental state. In a pilot study prior to research in the community, serum and red cell folate and serum vitamin B_{12} levels were measured in the following elderly psychiatric inpatients: 14 controls (patients not receiving any drugs with known antifolate activity), 11 receiving tricyclic antidepressants, 13 receiving antipsychotics (phenothiazines) and four receiving an anticonvulsant (carbamazepine). Patients on prolonged treatment with carbamazepine or phenothiazine drugs had lower concentrations of folate in serum and erythrocytes compared with controls; the decrease was statistically significant for the effect of phenothiazines on serum folate levels. Tricyclic antidepressants, which are in widespread use in the community, did not cause folate depletion during the first two years of treatment.

Introduction

LONG term antidepressant therapy is used in both psychiatric outpatient departments and general practice but little is known of the effect of chronic administration. Folic acid depletion is one potential hazard of therapy which is easily missed and may lead to deterioration in the mental state. Dealing with patients who depend on potent psychoactive drugs of all types will become an increasing part of general practice as the number of long stay patients in psychiatric hospitals falls.

Pharmacological induction of the mixed function oxidase system, by way of which many drugs are metabolized, and which uses folic acid as a co-factor, can lead to folate depletion[1] if the drugs are given for a long period.[2] This phenomenon has been well documented for both anticonvulsant and antipsychotic drugs; however, up to the present time it would seem that only seven patients receiving antidepressants alone have been studied. In the study by Labadarios and colleagues[2] both controls and experimental subjects were found to have low red cell folate levels and hence, presumably, low body stores. The calculated folic acid intakes of all the subjects were low, although it must be recognized that there are difficulties in estimating folic acid intake[3] owing to problems in determining the amounts of folic acid in foods.

The importance of folic acid depletion lies in the fact that it causes deterioration in memory[4] and exacerbation of both schizophrenia and dementia.[5,6] In children, low serum and red cell folic acid levels correlate with low IQ, neurotic disturbances and depression.[7] Moreover, it has been suggested that such central effects could impair the patient's response to what would otherwise be adequate drug treatment in non-depleted patients.[5] It has also been suspected that folate depletion must be quite marked in order to produce clinical features; this is already well recognized with vitamin B_{12} deficiency. Another clinically important effect is that the deficiency can be worsened, for example by intercurrent illness or medication with antifolate activity, and the patient may then suffer further loss of drug handling ability, with a consequent rise in serum drug levels and accompanying risk of toxicity.

In this study, red cell folate concentrations (the most reliable index for assessing body stores), serum folate and serum vitamin B_{12} levels were measured in an elderly population of psychiatric inpatients all receiving the same diet, the folic acid content of which was calculated from food tables. Groups of patients taking antidepressant, antipsychotic or anticonvulsant drugs were each compared with a control group.

Method

The subjects in the control and treatment groups were inpatients over 65 years of age at Netherne Hospital, Surrey. The treatment cards of 600 patients were scanned to select 11 patients taking a tricyclic antidepressant drug. The drugs and dosages were as follows: imipramine 75 mg (two patients); lofepramine 70 mg (one); clomipramine 50 mg (one); amitriptyline 75 mg (one); amitriptyline 150 mg (two); dothiepin 50 mg (three); dothiepin 100 mg (one). In addition, 13 patients taking a phenothiazine antipsychotic, four patients taking the anticonvulsant carbamazepine and 14 control patients taking medication with no known antifolate activity were selected. Patients with a history of alcoholism, gastric surgery or malabsorption were excluded, but the use of small doses of benzodiazepines is so common that it could not be a restriction criterion.

Following an overnight fast, a blood sample was taken from each patient for film examination and determination of the blood count and red cell indices by the Coulter method. An aliquot of whole blood containing ethylenediaminetetraacetic acid (EDTA) as anticoagulant and a quantity of serum were kept at −20 °C for determination of red cell folate, serum folate and serum vitamin B_{12} levels. Estimations were performed using the Amersham vitamin B_{12}/folate dual radioassay kit.

The folic acid content of the hospital diet was assessed by detailed examination of the menu which operates over a three-week cycle. The percentage of individuals preferring 'light' rather than 'normal' meals was noted. The likely initial folic acid content of the food was calculated from food composition tables.[8] No quantitative allowance for the probable degree of destruction during cooking and distribution could be made, because of variable effects on the folic acid content of individual foods.[9]

The results were analysed by comparing mean values for the various measurements in the different groups using unpaired t-tests. Where appropriate these tests and also regression analysis

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and evaluation of correlation coefficients were determined using the Minitab program.

Results

The ages, duration of therapy and length of stay in hospital of the patients are summarized in Table 1.

Although serum folate concentrations were lower in the drug treatment groups than in the controls (Table 2), only in the case of the patients on phenothiazines did the difference achieve statistical significance ($P=0.05$). Similar differences were found between red cell folate concentrations in the controls and those in other groups; the differences between the controls and patients on phenothiazines just failed to reach statistical significance ($P<0.07$). The values in patients taking carbamazepine were similar to those taking phenothiazines, but the number of patients involved was small.

The folate levels in patients taking phenothiazines tended to be in the lower half of the normal range (normal range: serum folate >2.5 $\mu g\ l^{-1}$, red cell folate 235–712 $\mu g\ l^{-1}$). The serum vitamin B_{12} levels were scattered throughout the normal range in all groups (normal range: 180–710 $\mu g\ l^{-1}$).

The average time on treatment with an antidepressant was 1.9 years (Table 1); only two patients had been taking tricyclic antidepressants for much longer periods. The red cell folate levels of these two patients were in the middle of the normal range. There was no correlation between red cell folate level and duration of treatment with antidepressants up to six years.

The red cell folate concentrations for all groups were compared with the mean corpuscular volume. Regression analysis showed no correlation in any of the groups. There was no correlation between the mean corpuscular volume and age, but there was a tendency for haemoglobin concentration to fall with age.

Twice as many patients preferred a 'normal' to a 'light' diet. The normal diet for a patient had a calculated folate content of 157±22 μg per day compared with 139±29 μg per day for the light diet.

Discussion

In the present study, the absolute values obtained for serum folate concentration were lower and those for red cell folate higher in all groups than in the study by Labadarios and colleagues.[2] It is tempting to suggest that these differences are due to the different methods used for the assays. In the earlier study, folate was determined by the method of Chanarin and colleagues,[10] whereas in the present investigation we used the radioassay that is now standard in clinical laboratories. We have confirmed that a low serum level of folate is associated with the administration of phenothiazines and, although the difference in the red cell level did not achieve statistical significance, it was, as in the previous study, lower than in the controls. The mean duration of treatment of our subjects on phenothiazines (8.7 years) was shorter than in the previous study (15 years) and this may partly account for the findings that the red cell levels, representing body stores, were not so severely reduced. We studied more patients on tricyclic antidepressant drugs than Labadarios and colleagues, and the patients were older and had been in hospital for longer. However, they had received antidepressants for a slightly shorter time and, contrary to Labadarios's findings, the serum and red cell folate levels in our patients were not significantly affected by the drugs.

The folate content of the normal and light diets in the hospital were both lower than national and international recommended daily intakes. However, the food tables in current use are based on values obtained with the assay using *Lactobacillus casei* and are accepted as being inaccurate.[3] One consequence of this has been that there is a large discrepancy between the observed folic acid intake in apparently healthy people living in the UK and the intake recommended by either the World Health Organization[11] or the Food and Nutrition Board of the US National Academy of Sciences[12] of 200 μg and 400 μg per day respectively. Experiments in folate depletion have even been tried but gave no clear result.[3] In this study we made use of the folate levels reported in tables[8] for cooked dishes where possible but with no allowance made for losses after cooking or how much individuals ate at any given meal. Nonetheless, the controls did not show folate depletion despite an apparently low dietary content of folate.

The results must be interpreted with caution since in addition to their small numbers, the patients were a very heterogeneous group. The controls were mainly, but not exclusively, suffering from dementia, and therefore tended to be very dependent, with little involvement in activity outside the ward. Those on phenothiazines had a variable degree of function, ranging from being severely incapacitated to those who had spent many years within an institution but with a good level of function; similar conditions applied to the small group on carbamazepine. Generally, the antidepressant group had the highest level of function. Again, some had been in hospital for many years owing either to lack of community support structure or to an erroneous label of schizophrenia.

Table 1. Characteristics of control and treated patients (ranges shown in parenthesis).

Treatment groups	Sex	Mean age (years)	Mean period in hospital (years)	Mean period in therapy (years)
Controls	14 female	78.7 (70–88)	33 (0–50)	–
Antidepressants	8 female, 3 male	73.8 (65–87)	12 (0.5–53)	1.9 (0.5–6)
Phenothiazines	13 female	70.6 (65–87)	26 (10–40)	8.7 (0.5–25)
Carbamazepine	4 female	71.0 (59–79)	37 (30–41)	5.0 (3–8)

Table 2. Effect of drug treatment on the serum and red cell folate levels and on serum vitamin B_{12} level.

Treatment	Number of patients	Mean ± SEM		
		Serum folate ($\mu g\ l^{-1}$)	Red cell folate ($\mu g\ l^{-1}$)	Serum vitamin B_{12} ($ng\ l^{-1}$)
Control	14	3.9 ± 0.7	485 ± 69	351 ± 47
Antidepressants	11	3.3 ± 0.4	440 ± 36	326 ± 36
Phenothiazines	13	2.4 ± 0.2*	345 ± 29	351 ± 45
Carbamazepine	4	2.7 ± 0.5	360 ± 50	301 ± 29

* $P = 0.05$ versus control. SEM = standard error of mean.

The demand for folic acid can be increased by pregnancy, enzyme induction by one or more drugs, and by interaction between drugs. Clinically, it is important to recognize the drugs which cause marked enzyme induction. Their effects go beyond the problems raised by competition for hepatic metabolism, as the subsequent folate depletion seems to have an adverse effect on the patient's cerebral function and quality of life. The only way in which folate depletion can be identified with certainty is to carry out routine determinations of red cell folate in 'at risk' patients because, as noted here, deficiency can be found in the absence of macrocytosis. General practitioners deal successfully with large numbers of patients presenting with mild to moderate depression.[13] On the other hand, psychiatrists deal with more severe illnesses, and are also more likely to use higher doses of drugs. In either case, the practitioner must be fully aware that should multiple drug therapy be used (that is for the treatment of more than one physical or mental disorder simultaneously), then there is the risk of compounding any antifolate effect.

This study suggests that tricyclic antidepressants, which are in widespread use in the community, do not cause folate depletion in an elderly inpatient population for the first two years of therapy. However, in view of the observed long term effects of anticonvulsant and antipsychotic treatment, it would seem reasonable that a large number of patients in the community on long term antidepressants should be studied in the future. The number of patients at risk of folate depletion that general practitioners will encounter is likely to increase as more patients are treated within the community.

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