minute. Airway hypoxia was discontinued as soon as possible in each infant who showed this degree of desaturation; it should be remembered that this required the tent to be opened and the gas mixture to be removed from around the baby. No infant remained at ≤80% in 15% oxygen for longer than 126 seconds.

Of the four infants in whom exposure to hypoxia was discontinued early, one infant had a sibling who had died of the sudden infant death syndrome and was already being monitored at home. Oxygen saturation levels in all four infants remained within the normal range during subsequent monitoring. We believed that monitoring the infants for a longer period in hospital would not have been ethically appropriate because they might be exposed to additional risks (for example, the risk of acquiring an infection in hospital). The two infants who had died following an aircraft flight were not monitored so we are unaware of the duration and degree of hypoxaemia to which they might have been exposed.

Although Savulescu's commentary raises the spectre of human or mechanical error, we took every precaution to ensure that the infants were safe. These included the use of a special medical gas mixture of 15% oxygen and 85% nitrogen instead of air diluted with nitrogen, continuous monitoring of the partial pressure of inspired carbon dioxide to identify rebreathing, and continuous monitoring of the partial pressure of inspired oxygen to ensure adequate ventilation of the tent with the gas mixture. The study was done in a room near the intensive care unit. There was also continuous surveillance by an experienced paediatrician of the readings from the pulse oximeter, transcutaneous monitoring of the partial pressure of carbon dioxide, monitoring of respiratory movement, and electrocardiography.

Although Milner reports in his editorial that British Airways identified no deaths on the undisclosed number of flights involving infants, this is low quality information. It is not accurate, as shown by the personal communication cited in our paper. Infant stimulation and the attention paid to an infant during an airline flight may delay potentially serious consequences of the flight until after the plane's arrival. British Airways would not have access to information on infants after arrival and did not seem to know about either of the two cases of the sudden infant death syndrome that were described in our report.

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Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials

Homocysteine Lowering Trialists' Collaboration

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Abstract

Objective: To determine the size of reduction in homocysteine concentrations produced by dietary supplementation with folic acid and with vitamins B-12 or B-6.

Design: Meta-analysis of randomised controlled trials that assessed the effects of folic acid based supplements on blood homocysteine concentrations. Multivariate regression analysis was used to determine the effects on homocysteine concentrations of different doses of folic acid and of the addition of vitamin B-12 or B-6.

Subjects: Individual data on 1114 people included in 12 trials.

Findings: The proportional and absolute reductions in blood homocysteine produced by folic acid supplements were greater at higher pretreatment blood homocysteine concentrations (P < 0.001) and at lower pretreatment blood folate concentrations (P < 0.001). After standardisation to pretreatment blood concentrations of homocysteine of 12 μmol/l and of folate of 12 nmol/l (approximate average concentrations for Western populations), dietary folic acid reduced blood homocysteine concentrations by 25% (95% confidence interval 23% to 28%; P < 0.001), with similar effects in the range of 0.5-5 mg folic acid daily. Vitamin B-12 (mean 0.5 mg daily) produced an additional 7% (3% to 10%) reduction in blood homocysteine. Vitamin B-6 (mean 16.5 mg daily) did not have a significant additional effect.

Conclusions: Typically in Western populations, daily supplementation with both 0.5-5 mg folic acid and about 0.5 mg vitamin B-12 would be expected to reduce blood homocysteine concentrations by about a quarter to a third (for example, from about 12 μmol/l to 8-9 μmol/l). Large scale randomised trials of such regimens in high risk populations are now needed to determine whether lowering blood homocysteine concentrations reduces the risk of vascular disease.

Introduction

Epidemiological studies have consistently reported that patients with occlusive vascular disease have higher blood homocysteine concentrations than

control subjects, and that these differences precede the onset of disease and are independent of other risk factors.[1-5] A meta-analysis of the observational studies of blood homocysteine and vascular disease indicated that a prolonged lowering of homocysteine concentration by 1 µmol/l was associated with about a 10% reduction in risk throughout the range 10-15 µmol/l.[1] Blood concentrations of homocysteine are inversely related to blood concentrations of folate, vitamin B-12, and, to a lesser extent, vitamin B-6.[6] Dietary supplements of these vitamins are used to reduce homocysteine concentrations in subjects with homozygous homocystinuria, who have particularly high blood concentrations of homocysteine.[7] Several randomised controlled trials of the effects of folic acid based supplements on homocysteine concentrations have been conducted. Our study aimed, by a meta-analysis of data from individual participants in these trials, to determine more reliably the size of the reduction in blood homocysteine achieved with different doses of folic acid and with the addition of vitamin B-12 and vitamin B-6. This should help in the design of randomised trials of the effects of lowering homocysteine concentrations on vascular disease.

Methods

Studies included

We aimed to identify all published and unpublished randomised trials that had assessed the effects on blood homocysteine concentrations of folic acid supplements, with or without the addition of vitamins B-12 or B-6. Studies were not eligible if they did not include an untreated control group, assessed treatment after methionine loading, or treated patients for less than 3 weeks.[8-15] Eligible studies were identified by Medline searches (using search terms and widely used variants for folic acid, vitamin B-12, vitamin B-6, and homocysteine, and including the non-English language literature), scanning reference lists, and personal contact with relevant investigators. The 14 trials we identified that fulfilled the eligibility criteria[16-24] included two completed trials (involving 50 and 144 subjects; V Howard, I Brouwer, personal communications) from which data are not available for collaborative analyses until their publication. The 12 available trials included 1114 subjects. Ten of these trials had a parallel group design[16-24] and two had a crossover design[21] (for which, to avoid any carryover effects, we used only data from the first period). The allocated treatment was blinded in all trials except two that had untreated controls.[16 23]

Information collected

For each subject entered in these trials, we sought details of age, sex, smoking habits, history of vascular disease or hypertension, and vitamin use before randomisation, and of their randomly allocated treatment regimen (daily dose of folic acid, vitamin B-12 or vitamin B-6, and scheduled duration) and blood concentrations of homocysteine, folate, vitamin B-12, and vitamin B-6 before treatment and at the end of the scheduled treatment period.

Table 1 Characteristics of the 12 available trials of treatment based on folic acid

Report	No of patients	Mean age (years)	Treatment duration (weeks)	Median pretreatment concentration Homocysteine (µmol/l)	Median pretreatment concentration Folate (nmol/l)
Brattström[16]	53	65	6	14.3	13.0
Den Heijer I[17]	52	56	8	17.2	9.7
Den Heijer II[17]	178	53	8	11.9	12.7
Den Heijer III[17]	92	61	8	13.6	12.1
Ubbink I[18]	91	39	6	24.9	4.7
Ubbink II[19]	26	40	6	20.6	4.7
Naurath[20]	285	75	3	12.4	9.7
Pietrzik I[21]	70	25	12	7.4	23.1
Pietrzik II[21]	128	25	4	7.5	21.3
Woodside[22]	112	40	8	9.8	9.2
Cuskelly[23]	17	23	12	5.6	6.4
Saltzman[24]	10	58	4	14.4	19.9
Total	1114	52	6	11.8	11.6

Statistical analysis

The proportional reductions in blood homocysteine in the treated groups compared with the control groups were determined by extending an analysis of covariance[25] that estimated the differences in post-treatment, log transformed homocysteine values after adjustment for baseline values of homocysteine. The simple model was extended to allow the extent of this adjustment to vary between studies and to take account of factors such as folic acid dose, concomitant vitamin B-12 or vitamin B-6, age, sex, and duration of treatment. More complex models that allowed the effect of folic acid supplementation to differ in individual studies were used to investigate sources of heterogeneity.

Results

Characteristics of individual trials

Among the 1114 subjects in the trials, the mean age was 52 years (range of trial means 23 to 75 years) and the mean duration of treatment was 6 weeks (range 3 to 12 weeks) (table 1). The median pretreatment blood concentration of homocysteine was 11.8 µmol/l and of folate was 11.6 nmol/l, but there were substantial differences between the trials. All of the trials compared folic acid alone versus control or folic acid plus vitamin B-6 or B-12, or both, versus control, although two trials[17 18] also involved within-trial comparisons of folic acid alone versus combination therapy (table 2). A correlation coefficient of 0.87 for homocysteine in pretreatment blood samples collected from 664 of these patients on two separate occasions shows that there was relatively little variation within subjects and that the homocysteine measurements were reliable. Compliance with the study protocols was good, with blood homocysteine measurements at the end of study treatment available from 98% of those randomised.

Exploration of heterogeneity between the results of different trials

The effect of folic acid on blood homocysteine concentrations seemed to differ among the trials. This heterogeneity of the homocysteine lowering effect was not explained by differences in age, sex, or duration of treatment (although the longest duration studied was only 12 weeks). The proportional and absolute reduc-

tions in blood homocysteine concentrations seemed, however, to be influenced by the pretreatment blood concentrations of homocysteine and folate, but not of vitamin B-12. Even after adjustment for differences in the folic acid regimen, the homocysteine lowering effect of folic acid ranged from a proportional reduction of 16% (11% to 20%) among subjects in the bottom fifth of pretreatment blood homocysteine concentrations to a 39% (36% to 43%) reduction among those in the top fifth (fig 1; P for trend < 0.001). Conversely, the blood homocysteine lowering effect of folic acid was greater at lower pretreatment blood concentrations of folate (P for trend < 0.001). These associations of the homocysteine lowering effect with pretreatment concentrations of blood homocysteine and blood folate remained significant (P < 0.001) when both pretreatment measurements were included simultaneously in the model. The model provided no strong evidence that the variation in the homocysteine lowering effect with baseline homocysteine depended on baseline folate or vice versa. Figure 2 shows that the proportional reductions in blood homocysteine concentrations achieved by folic acid supplementation according to pretreatment blood levels of homocysteine and folate under this assumption. (Exclusion of the two trials[18 19] in subjects with very high pretreatment blood homocysteine concentrations did not materially alter these findings, and nor did inclusion of the two small completed but unpublished trials not yet formally available for these collaborative analyses: data not shown.)
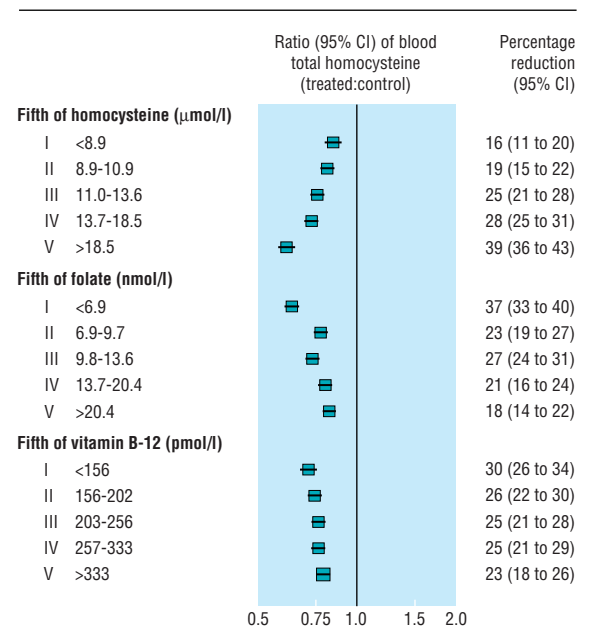
Fig 1 Reductions in blood homocysteine concentrations with folic acid supplements according to pretreatment blood concentrations of homocysteine, folate, and vitamin B-12. Squares indicate the ratios of post-treatment blood homocysteine among subjects allocated folic acid supplements to those of controls; size of square is proportional to number of subjects, and horizontal line indicates 95% confidence interval

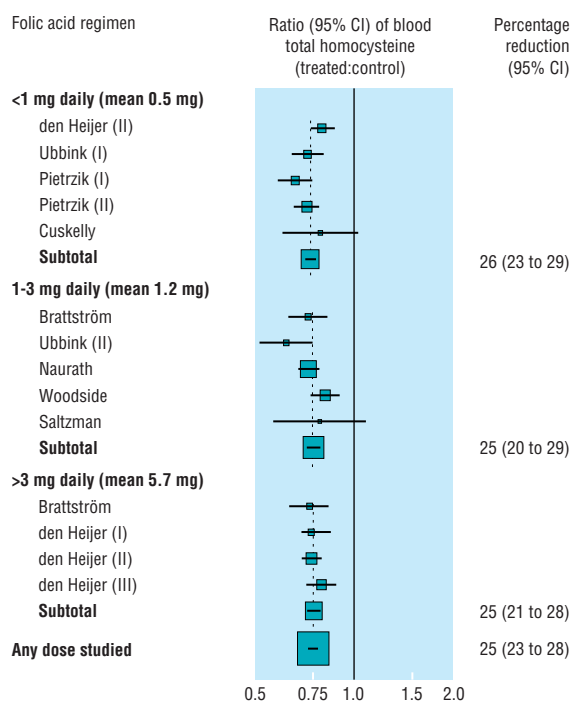**Table 2** Blood concentrations of homocysteine in individual trials

Report	Treatment comparisons with doses of vitamins	No of patients	Mean homocysteine concentration (µmol/l)			
			Pretreatment	Post-treatment	Difference (SD)	Ratio (SD)
Brattström[16]	Untreated control	20	14.5	15.1	0.6 (1.2)	1.0 (0.1)
	2.5 mg folate	16	16.9	12.0	−4.9 (3.9)	0.7 (0.2)
	10 mg folate	17	15.8	11.3	−4.5 (3.5)	0.7 (0.1)
Den Heijer I[17]	Placebo	27	18.9	17.8	−1.1 (5.6)	1.0 (0.2)
	5 mg folate, 0.4 mg B-12, 50 mg B-6	25	18.7	11.3	−7.0 (7.0)	0.7 (0.2)
Den Heijer II[17]	Placebo	36	11.9	11.4	−0.6 (2.7)	1.0 (0.2)
	0.5 mg folate	36	12.4	9.7	−2.8 (2.4)	0.8 (0.2)
	5 mg folate	35	12.1	8.9	−3.2 (2.2)	0.8 (0.1)
	0.4 mg B-12	36	12.6	11.3	−1.3 (2.0)	0.9 (0.2)
	5 mg folate, 0.4 mg B-12, 50 mg B-6	35	12.1	8.3	−3.8 (3.9)	0.7 (0.2)
Den Heijer III[17]	Placebo	46	14.0	14.5	0.5 (5.6)	1.0 (0.4)
	5 mg folate, 0.4 mg B-12, 50 mg B-6	46	15.9	10.3	−5.7 (9.7)	0.7 (0.2)
Ubbink I[18]	Placebo	17	30.0	30.7	−0.7 (9.1)	1.0 (0.3)
	0.6 mg folate	19	28.4	16.8	−11.6 (6.2)	0.6 (0.2)
	10 mg B-6	17	28.2	27.9	−0.3 (9.6)	1.0 (0.4)
	0.4 mg B-12	18	30.6	26.0	−4.6 (9.1)	0.9 (0.3)
	0.6 mg folate, 0.4 mg B-12, 10 mg B-6	20	26.9	13.6	−13.3 (7.3)	0.5 (0.2)
Ubbink II[19]	Placebo	13	23.5	22.1	−1.4 (4.8)	1.0 (0.2)
	1 mg folate, 0.4 mg B-12, 10 mg B-6	13	29.3	11.5	−17.8 (13.8)	0.5 (0.2)
Naurath[20]	Placebo	142	13.9	13.4	−0.5 (2.7)	1.0 (0.2)
	1.1 mg folate, 1 mg B-12, 5 mg B-6	143	12.7	8.4	−4.4 (3.5)	0.7 (0.2)
Pietrzik I[21]	Placebo	37	8.1	8.7	0.6 (1.2)	1.1 (0.1)
	0.4 mg folate, 0.1 mg B-12, 2 mg B-6	33	7.2	5.8	−1.4 (1.3)	0.8 (0.2)
Pietrzik II[21]	Placebo	86	8.1	8.2	0.2 (1.4)	1.0 (0.2)
	0.4 mg folate, 2 mg B-6	42	7.8	6.6	−1.2 (1.2)	0.9 (0.1)
Woodside[22]	Placebo	55	9.9	9.0	−0.9 (1.8)	0.9 (0.2)
	1 mg folate, 0.02 mg B-12, 7.2 mg B-6	57	11.9	7.8	−4.3 (3.4)	0.7 (0.1)
Cuskelly[23]	Untreated control	8	7.0	6.7	−0.2 (0.7)	1.1 (0.1)
	0.4 mg folate	9	5.8	5.0	−0.8 (1.0)	0.9 (0.2)
Saltzman[24]	Placebo	5	11.5	12.2	0.7 (1.5)	1.1 (0.1)
	2 mg folate	5	19.6	15.0	−4.6 (3.5)	0.8 (0.1)

Effects of different folic acid doses on blood homocysteine

After pretreatment blood concentrations of homocysteine and folate were adjusted for, there was no longer much evidence of heterogeneity between the separate blood homocysteine lowering effects in the different trials of daily folic acid doses of <1 mg (mean dose 0.5 mg; P value for heterogeneity=0.15), of 1-3 mg (mean dose 1.2 mg; P=0.05), or of >3 mg folic acid (mean dose 5.7 mg; P=0.69). Nor was there any evidence of differences between the blood homocysteine lowering effects of these different folic acid doses. For individuals with pretreatment blood concentrations of homocysteine of 12 µmol/l and of folate of 12 nmol/l (approximate average concentrations for Western populations), folic acid doses of <1 mg, 1-3 mg, and >3 mg daily were each associated with reductions in blood homocysteine of about one quarter (fig 3).

		Folate concentrations before randomisation (nmol/l)				
		20	15	12	10	5
Homocysteine concentrations before randomisation (µmol/l)	5	10%	13%	15%	16%	23%
	10	19%	21%	23%	25%	30%
	12	21%	23%	25%	27%	32%
	15	23%	26%	28%	29%	34%
	20	27%	29%	31%	32%	37%

Fig 2 Predicted proportional reduction in blood homocysteine concentrations with folic acid supplementation (0.5-5 mg daily)

Fig 3 Reductions in blood homocysteine concentrations with varying doses of folic acid at pretreatment blood concentrations of homocysteine of 12 µmol/l and folate of 12 nmol/l. Squares indicate the ratios of post-treatment blood homocysteine among subjects allocated folic acid supplements to those of controls; size of square is proportional to number of subjects, and horizontal line indicates 95% confidence interval

Effects of adding vitamin B-12 or vitamin B-6 to folic acid

The addition of vitamin B-12 (0.02-1 mg daily; mean 0.5 mg) to folic acid further reduced blood homocysteine concentrations by about 7% (3% to 10%). Hence, among people with pretreatment blood concentrations of homocysteine of 12 µmol/l and of folate of 12 nmol/l, adding vitamin B-12 to folic acid changed the reduction in homocysteine from 25% (23% to 28%) to 31% (27% to 35%). Adding vitamin B-6 (2-50 mg daily; mean 16.5 mg) to folic acid did not lower blood homocysteine any further.

Discussion

Among the vitamins studied in these trials, folic acid had the dominant blood homocysteine lowering effect, and this effect was greater among subjects with higher blood homocysteine concentrations or lower blood folate concentrations before treatment. After standardisation for differences in pretreatment blood homocysteine and folate concentrations, the effect of folic acid was similar for daily doses ranging from 0.5 to 5 mg daily, and vitamin B-12 produced a small additional effect. Supplementation with vitamin B-6 did not seem to have any material effect on blood homocysteine concentrations, but these trials did not assess effects on blood homocysteine after methionine loading, which may be determined to a greater extent by the transsulphuration pathway in which vitamin B-6 is a cofactor.[8]

Our results suggest that a daily dose of at least 0.5 mg of folic acid, along with a similar amount of vitamin B-12, would produce a proportional reduction in blood homocysteine of about a quarter to a third. The addition of about 1 mg daily of oral vitamin B-12 to folic acid would also be expected to avoid the theoretical risk of neuropathy due to unopposed folic acid therapy in patients deficient in vitamin B-12, even those with intrinsic factor deficiency or malabsorption states.[26-28] Studies in the United States and Britain indicate that the average concentration of blood homocysteine in a typical Western population is about 12 µmol/l,[4 6] and so a reduction of about a quarter to a third would correspond to an absolute reduction of about 3-4 µmol/l. A previous meta-analysis of the observational studies suggests that a prolonged lower blood homocysteine concentration of 3-4 µmol/l would correspond to 30-40% less vascular disease.[1] Consequently, even if as much as half of the epidemiologically predicted benefit is achieved within a few years of lowering blood homocysteine (as seems to be the case with cholesterol lowering[29-31]), trials of folic acid supplements may well need to be large, and to include people at high risk, to be able to detect the sort of reductions—15% to 20%—in cardiovascular risk that might realistically be anticipated.

Supplementation with folic acid is a cheap and effective method of lowering blood homocysteine concentrations. If large scale trials in high risk populations do show reliably that blood homocysteine reductions with such supplements can be sustained over time and that this strategy reduces the risk of vascular events (and is safe), this could have important public health implications. Higher dose supplements could be used in people at high risk, and population mean

Key messages

- Higher blood homocysteine concentrations seem to be associated with higher risks of occlusive vascular disease and with lower blood concentrations of folate and vitamins B-12 and B-6

- Proportional and absolute reductions in blood homocysteine concentrations with folic acid supplements are greater at higher pretreatment blood homocysteine concentrations and at lower pretreatment blood folate concentrations

- In typical Western populations, supplementation with both 0.5-5 mg daily folic acid and about 0.5 mg daily vitamin B-12 should reduce blood homocysteine concentrations by about a quarter to a third

- Large scale randomised trials of such regimens in people at high risk are now needed to determine whether lowering blood homocysteine concentrations reduces the risk of vascular disease

concentrations of blood homocysteine could be reduced by fortifying flour with folic acid.[1 32] Introducing fortified flour for the prevention of neural tube defects before trials of folic acid on vascular disease are conducted could, however, complicate the overall assessment of any benefits—or risks—of lowering homocysteine concentrations in this way.

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