Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review

Katrina M Wyatt, Paul W Dimmock, Peter W Jones, P M Shaughn O'Brien

Abstract

Objective To evaluate the efficacy of vitamin B-6 in the treatment of premenstrual syndrome.
Design Systematic review of published and unpublished randomised placebo controlled trials of the effectiveness of vitamin B-6 in the management of premenstrual syndrome.
Subjects Nine published trials representing 940 patients with premenstrual syndrome.
Main outcome measures Proportion of women whose overall premenstrual symptoms showed an improvement over placebo. A secondary analysis was performed on the proportion of women whose premenstrual depressive symptoms showed an improvement over placebo.
Results Odds ratio relative to placebo for an improvement in overall premenstrual symptoms was 2.32 (95% confidence interval 1.95 to 2.54). Odds ratio relative to placebo for an improvement in depressive symptoms was 1.69 (1.39 to 2.06) from four trials representing 541 patients.
Conclusion Conclusions are limited by the low quality of most of the trials included. Results suggest that doses of vitamin B-6 up to 100 mg/day are likely to be of benefit in treating premenstrual symptoms and premenstrual depression.

Introduction

The UK Department of Health and the Medical Control Agency have recently published recommendations to restrict the dose of vitamin B-6 available generally to 10 mg and to limit the dose sold by a pharmacist to less than 50 mg.[1] Vitamin B-6 is often used to treat premenstrual syndrome without clear evidence of its efficacy, hence it is timely to re-evaluate vitamin B-6 in the treatment of premenstrual syndrome.

Premenstrual syndrome exists when women complain of regularly recurring psychological or somatic symptoms, or both, which occur specifically during the luteal phase of the menstrual cycle and which are relieved by the onset of, or during, menstruation. Symptoms can be severe enough to disrupt every day life.[2] Mild physiological symptoms occur in approximately 95% of all women of reproductive age. Approximately 5% of symptomatic women complain of such severe symptoms that their lives are completely disrupted.[3]

Somatic symptoms of premenstrual syndrome include bloating, weight gain, mastalgia, abdominal discomfort and pain, lack of energy, headache, and exacerbations of chronic illnesses such as asthma, allergies, epilepsy, or migraine. Commonly reported affective changes are dysphoria, irritability, anxiety, tension, aggression, feelings of being unable to cope, and a sense of loss of control.[4]

Since the original description of the syndrome in 1931[5] numerous hypotheses have been advanced to explain premenstrual syndrome, but to date the pathogenesis remains unclear and speculative.[6] This uncertainty reflects the many treatments available[7]; one reviewer suggested that there were as many as 327 different treatments for premenstrual syndrome.[6] Most interventions, however, have been on the basis of informal observations, retrospective data collection, or inadequately controlled trials.

The recommended dietary allowance for vitamin B-6 is around 2.0 mg/day, depending on age and protein intake,[8] and deficiency of vitamin B-6 is rare.[9] Excessive ingestion (2000-6000 mg) of vitamin B-6 causes peripheral neuropathy,[10–17] and doses of 200 mg/day may cause similar, although probably reversible, effects.[18]

Because the efficacy of vitamin B-6 has not yet been proved, and in light of recent government recommendations, we undertook a systematic review of published and unpublished randomised controlled trials where efficacy of vitamin B-6 was compared with placebo in women with premenstrual syndrome.

Methods

Trials

We found reports of published and unpublished clinical trials by searching medical databases for trials of vitamin B-6 (pyridoxine) in the management of premenstrual syndrome (MeSH terms used were premenstrual syndrome and pyridoxine, together with title and abstract searches for keywords vitamin and pyridoxine, premenstrual syndrome, PMT, LLPDD, and PMDD). We also contacted relevant pharmaceutical companies manufacturing vitamin B-6 preparations. The trials were identified by searching Embase (1988 to 1996), Medline (1966 to 1998), Psychlit (1974 to 1997), Cinahl (1982 to 1997), and the database of

Academic Department of Obstetrics and Gynaecology, North Staffordshire Hospital, Stoke on Trent ST4 6QG
Katrina M Wyatt, *non-clinical lecturer in reproductive endocrinology*
Paul W Dimmock, *researcher*
P M Shaughn O'Brien, *professor*
Department of Mathematics, Keele University, Keele ST5 5BG
Peter W Jones, *professor*
Correspondence to: Dr Wyatt
mea10@keele.ac.uk

BMJ 1999;318:1375–81

the Cochrane Controlled Trials Register. We searched references cited in all included and excluded trials to identify any missing studies. All languages were included. Trials investigating the effect of vitamin B-6 on premenstrual symptoms were included if they were randomised, placebo controlled, double blind, parallel, or crossover studies (where the first treatment period could be treated as a parallel trial) for which data could be acquired. We also included studies investigating the effect of multivitamin supplements on premenstrual symptoms, when the vitamin preparation contained 50 mg or more of vitamin B-6.

Data extraction and outcome measures

We extracted the data from each trial that met the inclusion criteria. When there were insufficient data presented for inclusion, we contacted authors for further details. Data on the dosage and preparation of vitamin B-6 were collected. The main outcome measure was an improvement in overall premenstrual symptoms. Combined or overall symptoms was chosen in an attempt to overcome the clinical heterogeneity concerned with the measurement and scoring of premenstrual symptoms. As a secondary outcome we recorded the improvement in depressive premenstrual symptoms when suitable information was presented. Where possible we also recorded the number of women withdrawing from treatment and those complaining of side effects.

Quality assessment

We assessed the quality of each trial with two different methods. Firstly, we assessed the methodology of each trial with a scale developed by Jadad and colleagues.[19] This scale assesses the randomisation and double blinding and reports of dropouts and withdrawals. Secondly, we developed a second quality scale to assess the trials for study design, reproducibility, and statistical analysis. The eight point scale measured: preliminary diagnosis of premenstrual syndrome for all participants in the trial; confirmation that no other vitamin supplements or oral contraceptives were being concurrently taken; the randomisation procedure described in detail; a power calculation to justify participant numbers, or >65 participants in each arm of the study; a single clearly stated dose of vitamin B-6 only; reproducible measurement of premenstrual symptoms such as use of visual analogue scales or Moos' menstrual distress questionnaire; clear presentation of results; and a description of the number and reason for trial withdrawals. One point was awarded for each category. Each trial was independently scored by KMW and PWD, and any areas of disagreement arbitrated by PMSO. A predetermined criterion for the recognition of the highest quality trials was established. A score of 3 or more was required in the Jadad score (as recommended by Jadad and colleagues[19]) and a score of 6 or more was required in our eight item quality assessment.

Statistical analysis

Where dichotomous data were presented, odds ratios with 95% confidence intervals were generated for the primary and, where possible, secondary outcome in each trial.[20] We calculated odds ratios by categorising patients with a subjective improvement as "better," and those with no change or worse symptoms as "not better." Odds ratios of >1 indicated that an event was more likely to occur in the group receiving vitamin B-6 than in the group receiving placebo. We calculated an overall odds ratio with fixed and random effects models.[20] Homogeneity was tested for with a χ^2 test, with $P<0.05$ indicating significant heterogeneity. For trials using continuous measures of premenstrual symptomology, we calculated a standardised mean difference (or effect size), and converted to an odds ratio using a relation given by Hasselblad and Hedges.[21]

To detect bias (such as publication and location) within the analysed trials, we constructed a funnel plot.[22] To assess quantitatively the asymmetry of the funnel plot we used the method of Egger and colleagues.[22] Briefly, a linear regression of the standard normal deviate defined as the odds ratio is divided by its SE against precision (inverse of the standard error). A regression line which passes through the origin of the plot (within error limits) indicates symmetry and hence the absence of bias.

Results

We identified 25 published trials.[2 18 23–45] Of these, four were excluded because they did not include a placebo group,[34 38 39 43] two were retrospective studies,[40 41] and nine presented quantitative data that could not be analysed,[2 18 23 27 35–37 42 45] leaving 10 placebo controlled trials.[24–26 28–44] Two of the trials had two separate dosing regimens and were effectively treated as four studies. Only one trial contained details of the method of randomisation.[25]

Quality assessment of the trials

Three of the included trials met the Jadad scale cut off point of a score of ≥ 3.[25 26 33] However, only one of the trials included in the meta-analysis scored 6 on our eight point criteria for classification as a high quality trial.[31] Unfortunately this trial had too few subjects to achieve sufficient power and had a low Jadad score. The overall methodology of the trials was poor, with none of the included trials justifying patient numbers with a power calculation. Three of the 10 studies reported the number of withdrawals from a trial, together with reasons, and side effects when taking either vitamin B-6 or placebo.[26 30 33]

Of the nine trials included in the meta-analysis (one trial was excluded owing to statistical heterogeneity), a statement regarding whether women taking oral contraceptives were excluded from the trial was reported in three trials,[25 28 31] three other trials do not mention this as an exclusion criterion,[24 29 30] and one trial excluded women "on medication."[33] Two trials[26 32] included women who were taking the contraceptive pill, but they both flagged those women who did and analysed them separately and found no statistically significant difference between those taking oral contraceptives and those not taking oral contraceptives.

As none of the trials met both our and the Jadad quality criteria, we did not take the quality score into account when considering trials for inclusion. Tables 1 and 2 present the quality scores for included and excluded trials.

We calculated the odds ratios with both fixed and random effects models. Minimal difference was found

Table 1 Characteristics of studies included in meta-analysis of vitamin B-6 in premenstrual syndrome

Study	Participants	Intervention	Outcome measures	Reported results	Withdrawals and side effects*	Jadad (authors') quality score	Comments
Colin 1982[24]	32 with diagnosed mastalgia; 17 given vitamin B-6, 15 given placebo	500 mg/day for 4 months	Mastalgia symptoms worse or better	58% better taking vitamin B-6, 59% better taking placebo	None reported	1(3)	Only studied mastalgia Exclusion of women on oral contraceptives not mentioned
Barr 1984[25]	48; crossover study design	100 mg/day day 10 to day 3 after cycle for 2 months	Depression, irritability, tiredness, headache, stomach ache, and swollen breasts, abdomen, fingers, or ankles	Vitamin B-6 significantly better than placebo	None reported	3 (4)	"Most" women were not on oral contraceptives
Williams et al 1985[26]	434 with diagnosed premenstrual syndrome; 204 given vitamin B-6, 230 given placebo	100 mg/day (55%) 200 mg/day (29%) 50 mg/day (3%)	Depression, irritability, tension, violence, coordination, breast tenderness, bloating, headache, acne rated on a 4 point scale	Significant improvement of global symptoms only for vitamin B-6 over placebo	Owing to side effects 11 women withdrew on vitamin B-6 and 8 withdrew on placebo	3 (4)	Patients included were allowed drugs: 74 psychotropics; 60 analgesics; 33 diuretics; 100 oral contraceptives Only analgesia significantly affected analysis
Chakmakjian et al 1985[28]	31 with diagnosed premenstrual syndrome from hospital and general population; crossover study design	Multivitamin containing 300 mg vitamin B-6/day for 2 × 3 cycles	19 symptoms in 4 subgroups: PMT-A, PMT-C, PMT-D, and PMT-H	Significant effect for symptom groups PMT-A and PMT-C but not for PMT-H and PMT-D	None reported	2 (3)	Women on oral contraceptives excluded
Smallwood et al 1986[29]	42 hospital patients "with severe cyclical mastalgia"; crossover study design	200 mg/day for 2 × 2 cycles	Breast pain and tenderness rated on chart and visual analogue scale	No significant effect	None reported	2 (4)	Only studied mastalgia Exclusion of women on oral contraceptives not mentioned
Stewart 1987[30]*	222 " with premenstrual syndrome symptomology"; 49 given 200 mg vitamin B-6, 70 given placebo 46 given 100 mg vitamin B-6, 58 given placebo	Multivitamin containing 100 mg vitamin B-6 day 1 to day 14 then 200 mg for 4 cycles Multivitamin containing 50 mg vitamin B-6 day 1 to day 14 then 100 mg	19 symptoms in 4 subgroups: PMT-A, PMT-C, PMT-D, and PMT-H rated worse, no better, slightly better, substantially better, or cured	100 mg and 200 mg significantly better than placebo, 50 mg and 100 mg not significantly better than placebo	30 withdrew on placebo, 26 withdrew on vitamin B-6, 5 had side effects on vitamin B-6 and 1 on placebo, 17 withdrew on placebo, 22 withdrew on vitamin B-6, 5 had side effects on vitamin B-6 and 2 on placebo	1 (4)	Exclusion of women on oral contraceptives not mentioned Study blinded to patient only
Kendall and Schnurr 1987[31]	55 (financially reimbursed) with moderate to severe premenstrual mood changes recruited form general population; 29 given vitamin B-6, 26 given placebo	150 mg/day for 2 cycles	Pain, water retention, negative effect, positive effect, control, impaired concentration, behaviour change, autonomic reactions	No significant effect	None reported	1 (6)	Women on oral contraceptives excluded
Doll et al 1989[32]	32 with moderate to severe premenstrual symptoms in previous year recruited from general practitioner; crossover study design	50 mg/day for 3 cycles with one washout cycle between	3 symptom groups: emotional, somatic, and menstrual	Significant effect on emotional symptoms	None reported	2 (5)	Included women on oral contraceptives but data flagged
London et al 1991[33]	44 with self perceived premenstrual syndrome recruited form the general population; 28 given vitamin B-6, 16 given placebo	2 parallel arms Multivitamin containing 300 mg vitamin B-6 or 600 mg vitamin B-6/day for 3 cycles	19 symptoms in 4 subgroups: PMT-A, PMT-C, PMT-D, and PMT-H with London variation	Significant effect observed	Withdrawals: 1 taking placebo, 1 taking 300 mg vitamin B-6, 2 taking 600 mg vitamin B-6, 1 noted "tingling in fingers" at the end of the 600 mg study	3 (5)	Exclusion of women on oral contraceptives not mentioned Women on "medication" excluded

*Neurological side effects reported in 1 of 934 patients while taking 600 mg/day vitamin B-6 as part of multivitamin preparation.[33]

between the two methods, and so the results from the more conservative random effects model were used. The overall odds ratio in favour of vitamin B-6 was 1.57 (95% confidence interval 1.40 to 1.77). One trial caused significant heterogeneity in the overall odds ratio (homogeneity test, $P = < 0.001$),[44] and removal of this trial resulted in homogeneity (homogeneity test, $P = 0.187$). The recalculated odds ratio in favour of vitamin B-6 was 2.32 (1.95 to 2.54). This heterogeneity may be due to an unexpectedly high placebo effect, which resulted in an odds ratio in favour of placebo. It should be noted, however, that the overall odds ratio remained significantly in favour of vitamin B-6 even with the inclusion of this trial. Table 1 lists the nine included trials, and table 2 lists the other 16 trials that were identified. Figure 1 shows the odds ratio and dosage for each of the nine included trials.

We extracted data on the efficacy of vitamin B-6 in treating depressive premenstrual symptoms from five trials.[26 28 31–33] Figure 2 shows the odds ratio for each trial and the term used by those trials to describe depression. The overall odds ratio in favour of vitamin B-6 was 2.12 (1.80 to 2.48; homogeneity test $P < 0.001$). This combined result showed significant heterogeneity with both fixed and random effects models. Exclusion of one trial[31] gave an overall odds ratio of 1.69 (1.39 to 2.06), which was homogeneous (homogeneity test, $P = 0.079$).

Table 2 Characteristics of studies not included in meta-analysis of vitamin B-6 in premenstrual syndrome

Study	No of participants	Intervention	Reason for exclusion	Reported results	Side effects*	Jadad (authors') quality score	Comments
Kerr 1977[34]	70	40-100 mg	Not placebo controlled	Considerable benefit	None observed	0 (1)	
Day 1979[35]	57	100 mg	No detailed data	Improvement in 63% of patients on pyroxidine	No significant side effects observed	0 (3)	
O'Brien 1987[2]	53; crossover study design	100 mg	Data not suitable for meta-analysis	No benefit of drug over placebo	None reported	1 (4)	24 patients preferred pyridoxine *v* 14 taking placebo, but results not significant
Abraham and Hargrove 1980[36]	25	500 mg	Data not suitable for meta-analysis	21 patients showed significant improvement over placebo	None reported	2 (5)	
Mattes and Martin 1982[37]	3	50 mg	Anecdotal study, no assessment of symptoms	Some beneficial effects	None reported	2 (1)	
Goei and Abraham 1983[38]	31	Multivitamin containing 150-600 mg vitamin B-6	Not placebo controlled	Significant decrease in symptoms in all patients	5 patients reported gastrointestinal side effects	1 (5)	Multivitamin
Harrison et al 1984[45]	30	50-150 mg	Sequential design; data not suitable for analysis	No benefit	>100 mg/3 g tryptophan caused drowsiness, nausea, headache, overstimulation	1 (5)	Cointervention each tablet: 50 mg vitamin B-6 + 1.5 g of tryptophan; up to 3 tablets per day
Hagen et al 1985[27]	34	100 mg	Data not suitable for meta-analysis	No significant effect	6 reported nausea: 1 taking vitamin B-6 and 1 taking placebo	3 (5)	Large phase effect: first treatment, whether placebo or vitamin B-6, gave same result Women on oral contraceptives excluded
Fuchs et al 1985[39]	16	Multivitamin containing 300-600 mg vitamin B-6	Not placebo controlled	Beneficial effect	None reported	0 (2)	Multivitamin study centred on analysis of liver enzymes
Malmgren et al 1987[18]	19	300 mg	No data	No significant effect over placebo	None reported	1 (4)	Study centred on uptake of platelet serotonin
Brush et al 1988[40]	630	40-200 mg	Retrospective study, not placebo controlled	40% "good" response 65%-88% partial response depending on dose	7 patients reported indigestion, 5 reported nausea, 3 reported breast soreness No neuropathy reported	0 (1)	Other side effects were termed "coincidental" and included worse premenstrual symptoms and depression
Brush 1988[41]	336	⩽200 mg	Retrospective study, not placebo controlled	70% reported good or partial response	8 patients reported nausea, 5 dizziness, 6 mild tingling or numbness	0 (1)	5 of the patients reporting tingling or numbness were on the highest dose (200 mg)
Van den Berg et al 1989[42]	19	120 mg	Data not suitable for meta-analysis	No beneficial effect	None reported	1 (4)	
Berman et al 1990[43]	28	250 mg	Not placebo controlled	Some favourable trends in improvement of symptoms	None reported	0 (5)	
De Souza et al 1996[44]	44; crossover study design	50 mg every day for 2 × 1 cycle	Statistically heterogeneous	No significant effect	None reported	2 (4)	4 crossovers for magnesium, vitaminB-6, magnesium + vitamin B-6, placebo

*Of 1395 patients taking vitamin B-6, six reported neurological side effects: five patients taking 200 mg/day and one patient taking 100-200 mg/day.

Figure 3 shows a dose response plot of vitamin B-6 dosage against the odds ratio for each of the nine trials. There was no correlation between the amount of vitamin B-6 given and its efficacy.

Figure 4 details a funnel plot of the included trials. Regression analysis of this plot indicated no significant asymmetry (intercept –0.25 (90% confidence interval –0.88 to 0.38) P = 0.49),[22] and thus no evidence of bias.

Discussion

The conclusions that can be drawn from our systematic review are limited. Although the results from the available data suggest that vitamin B-6 is more effective than placebo, there is insufficient evidence of high enough quality to give a confident recommendation for using vitamin B-6 in the treatment of premenstrual syndrome. For example, the evidence from the overall analysis would be more compelling if there were large scale rigorous trials with sufficient power to detect a clinically significant effect. To detect a medium effect size (0.5) at a significance level of 0.05 and 80% power, approximately 65 subjects would be required in each arm, using a two tailed test. Only one of the nine studies included a sufficient number of patients,[26] and all the other trials had low statistical power (< 70%). The methodologies of each trial varied considerably using differing dosage regimens and different outcome measures, which makes intercomparisons difficult. In addition, the possible inclusion of women taking oral contraceptives complicates the overall analysis of the effect of vitamin B-6 on premenstrual syndrome as the vitamin may be treating pill induced premenstrual symptoms or depression.

An overall odds ratio was calculated from the nine included trials. Of these trials, two[24 29] only studied the effect of vitamin B-6 on mastalgia and three[28 30 33] used the multivitamin preparation Optivite (Optimox, Torrance, CA, USA). We believed it was appropriate to

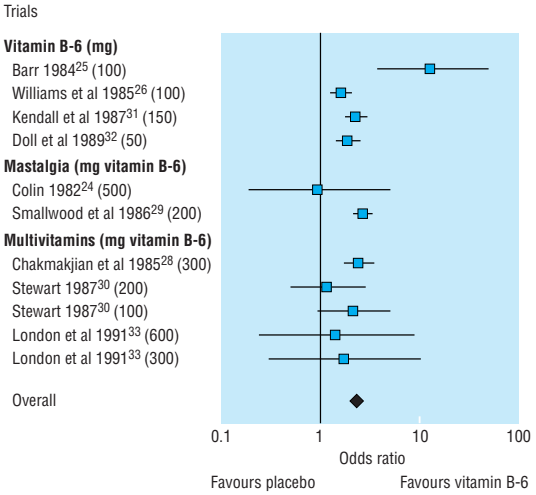

Fig 1 Odds ratios (95% confidence intervals) for proportion of patients showing improvement in overall premenstrual symptoms with vitamin B-6

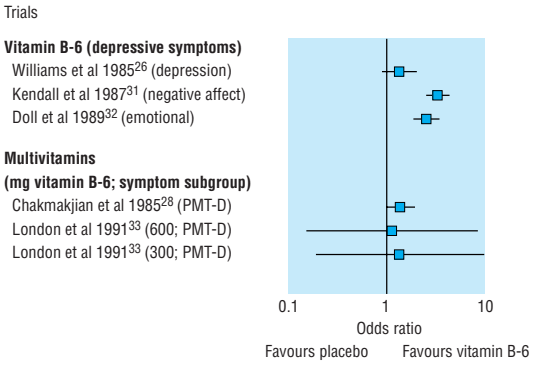

Fig 2 Odds ratios (95% confidence intervals) for proportion of patients showing improvement in depressive premenstrual symptoms with vitamin B-6

include the trials of mastalgia, as breast pain and breast swelling are frequent premenstrual symptoms. As many as 60% of women with premenstrual syndrome report cyclical breast pain as a primary component.[46]

The odds ratios in the four included trials that used only vitamin B-6 and studied premenstrual symptomatology[25 26 31 32] were found to be heterogeneous. The combined odds ratio for the four trials was 2.15 (95% confidence interval 1.79 to 2.59; homogeneity test, P = 0.035), and when one heterogeneous trial was excluded,[25] the recalculated odds ratio was 2.07 (1.72 to 2.50; homogeneity test, P = 0.61).

The use of funnel plots in meta-analysis gives a simple graphical method of assessing bias. A regression analysis to assess quantitatively potential asymmetry of the funnel plot shown in figure 4 indicated no significant asymmetry.[22] The size and quality of the included trials, however, makes any definite statement concerning bias inappropriate.

Depression

One of the rationales behind vitamin B-6 being recommended as a treatment for premenstrual syndrome was the observation that it could ease induced depression in several conditions[47–49] particularly that associated with contraceptive pills high in oestrogen and progesterone.[50 51] The combined odds ratio of the four trials (representing 541 patients) that presented data for depressive symptoms was 1.69 (1.39 to 2.06), and this was homogeneous. This indicates that vitamin B-6 is better than placebo in treating premenstrual depression. It is unlikely, however, that this is the central mode of action of vitamin B-6 in treating premenstrual syndrome, as the odds ratio for overall symptomatology is more favourable than when considering premenstrual depression alone.

Dose response

The lack of a dose response (fig 3) indicates that the amount of vitamin B-6 given has no impact on the efficacy of its use as treatment for premenstrual syndrome, for either vitamin B-6 alone or when given in a multivitamin preparation. This result adds to the misgivings surrounding the use of vitamin B-6 as a treatment. The toxic effects of vitamin B-6 at doses higher than 200 mg/day are well characterised. As the recommended daily allowance of vitamin B-6 is around 2 mg,[8] any

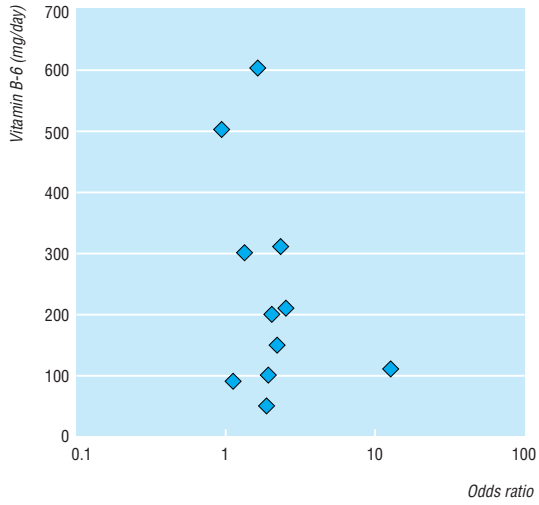

Fig 3 Dose response of vitamin B-6 against individual odds ratios for patients who showed improvement in premenstrual symptoms with vitamin B-6 (when two trials used same dose, data points offset for clarity)

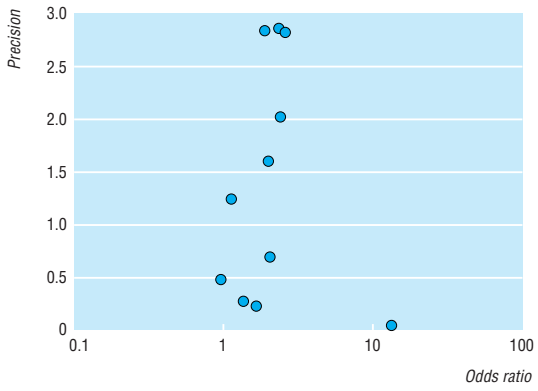

Fig 4 Funnel plot of included studies: precision of study (inverse of SE) against odds ratios

effect of vitamin B-6 on premenstrual symptomatology would be pharmacological. However, there does remain some controversy as to the precise vitamin B-6 requirement in disease states, highlighted by the successful use of vitamin B-6 doses of around 100 mg/day in the management of carpal tunnel syndrome.[52]

Multivitamins

The rationale for including multivitamin treatments in a review on vitamin B-6 is the very large amount of vitamin B-6 in the tablets used, 50 mg per tablet (600 mg/day), which represents over 25 times the recommended daily allowance.[8] Figure 1 shows the results of the published trials on use of multivitamins in the treatment of premenstrual syndrome, with an overall odds ratio of 2.08 (1.55 to 2.78; homogeneity test, $P = 0.61$). The lack of a dose response makes the daily consumption of more than 100 mg of vitamin B-6 inadvisable, and doses in excess of 200 mg/day cannot be recommended in the light of the proved toxic side effects of vitamin B-6, even in a multivitamin preparation.

Side effects

Only one patient of the 940 participating in these trials indicated the presence of any side effects that could be attributed to the neuropathy associated with pyridoxine toxicity.[33] This may be due to the comparatively low doses used and the short duration of the trials. The symptoms, however, may have been missed owing to the lack of assessment by a suitably qualified neurologist. Detailed animal studies on pyridoxine indicate that nerve damage can occur before manifestation of the gross symptoms such as ataxia and neuropathy.[11 12]

Conclusions

Conclusions from this meta-analysis are limited by the quality of the trials. No conclusive evidence of vitamin B-6 toxicity was reported, and there seems to be no dose related response to treatment. We conclude, therefore, that there is no rationale for giving daily doses of vitamin B-6 in excess of 100 mg. Such doses, and possibly doses of 50 mg/day, are likely to be of benefit in relieving premenstrual symptoms.

We believe that this systematic review does highlight the need for a randomised placebo controlled trial, which should be conducted with sufficient subjects and should have the power to detect any significant clinical difference between vitamin B-6 and placebo.

We thank Mrs Cornelia Dean for translating reference 42, and Mrs Olive Ford (National Association for Premenstrual Syndrome) and Ms Ruth Jepson (Cochrane Menstrual Disorders and Subfertility Group) for assistance with literature surveys.

Contributors: PMSO'B originated the idea for the study and coauthored the paper. He also provided the clinical input to the text and resolved any areas of disagreement in the scoring and data extraction from the trials. KMW was the lead author of the paper and extracted and assessed the trial data. She also assisted in the literature searches, reference collation, data entry, and statistical analysis. PWD undertook the literature searches and located the references and assisted KMW in the data extraction and scoring of the trials. He coordinated the data analysis and statistical calculations in collaboration with KMW and under the guidance of the statistical adviser, PWJ. PWJ gave statistical input on the data extraction, validity of statistical tests, conversion of statistical measures, and assessment of the heterogeneity of the collated data. He also performed the power calculations and heterogeneity tests and advised on the statistical methods used in the meta-analysis. PWD and KMW will act as guarantors for the paper.

Funding: None.

Competing interests: PMSO'B has been reimbursed for lectures and conferences by the following companies: Shire Pharmaceuticals, SmithKline Beecham, Eli Lilly, Searle, Sanofi Winthrop, Zeneca, and Solvay Pharmaceuticals. He has also received funds for research staff from Searle, SmithKline Beecham, Eli Lilly, and Sanofi Winthrop. He is married to a member of the research department of Zeneca Pharmaceuticals. KMW, PWD, and PWJ declare no competing interests.

Key messages

- Randomised placebo controlled studies of vitamin B-6 treatment for premenstrual symptoms were of insufficient quality to draw definitive conclusions
- Limited evidence exists to suggest that 100 mg of vitamin B-6 daily (and possibly 50 mg) are likely to be beneficial in the management of premenstrual syndrome
- Vitamin B-6 was significantly better than placebo in relieving overall premenstrual symptoms and in relieving depression associated with premenstrual syndrome, but the response was not dose dependent
- No conclusive evidence was found of neurological side effects with these doses
- A randomised controlled trial of sufficient power and quality is needed to compare vitamin B-6 with placebo to establish definitive recommendations for treatment

1 Joint Food Safety and Standards Group. *Survey of dietary supplements containing vitamin B6*. London: Ministry of Agriculture Fisheries and Food, 1997.
2 O'Brien PMS. *Premenstrual syndrome*. London: Blackwell Scientific, 1987.
3 O'Brien PMS. Helping women with premenstrual syndrome. *BMJ* 1993;307:1471-5.
4 Smith R, Studd J. Premenstrual syndrome. *Clin Rev Gynaecol* 1994;939-47.
5 Frank RT. The hormonal causes of premenstrual tension. *Arch Neurol Psychiatry* 1931;26:1053.
6 Chakmakjian ZH. A critical assessment of therapy for the premenstrual tension syndrome. *J Reprod Med* 1983;28:532-8.
7 O'Brien PMS. The premenstrual syndrome: a review of the present status of therapy. *Drugs* 1982;24:140-51.
8 Driskell JA. Vitamin B6 requirements of humans. *Nutr Res* 1994;14:293-324.
9 Abraham GE. Nutritional factors in the etiology of the premenstrual tension syndrome. *J Reprod Med* 1983;28:446.
10 Antopol W, Thomas M. Experimental study of the effects produced by large doses of vitamin B6. *J Neuropathol Exp Neurol* 1942;1:330-6.
11 Schaeppi U, Krinke G. Pyridoxine neuropathy: correlation of functional tests and neuropathology in beagle dogs treated with large doses of vitamin B6. *Agents Actions* 1982;12:575-82.
12 Krinke G, Naylor DC, Skorpil V. Pyridoxine megavitaminosis: an analysis of the early changes induced with massive doses of vitamin B6 in rat primary sensory neurons. *J Neuropathol Exp Neurol* 1985;44:117-29.
13 Windebank AJ. Neurotoxicity of pyridoxine analogs is related to coenzyme structure. *Neurochem Pathol* 1985;3:159-67.
14 Parry GJ. Sensory neuropathy with low dose pyridoxine. *Neurology* 1985;35:1466-8.
15 Windebank AJ, Low PA, Blexrud MD, Schmelzer JD, Schaumburg HH. Pyridoxine neuropathy in rats: specific degeneration of sensory axons. *Neurology* 1985;35:1617-22.
16 Berger AR, Schaumburg HH, Schroeder C, Apfel S, Reynolds R. Dose response, coasting, and differential fiber vulnerability in human toxic neuropathy: a prospective study of pyridoxine neurotoxicity. *Neurology* 1992;42:1367-70.
17 Schaumburg HH, Kaplan J, Windebank AJ, Vick N, Rasmus S, Pleasure D, et al. Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. *N Eng J Med* 1983;309:445-8.

18 Malmgren R, Collins A, Nilsson CG. Platelet serotonin uptake and effects of vitamin B6-treatment in premenstrual tension. *Neuropsychobiology* 1987;18:83-6.
19 Jadad A, Moore M, Carrol D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomised clinical trials; is blinding necessary? *Control Clin Trials* 1996;17:1-12.
20 Computer programs for epidemiologic analysis: PEPI version 2. Gahlinger PM and Abramson JH. 2. Stone Mountain, GA: USD, 1995.
21 Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. *Psychol Bull* 1995;117:167-78.
22 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
23 Stokes J, Mendels J. Pyridoxine and premenstrual tension. *Lancet* 1972;i:1177-8.
24 Colin C. Studies on the treatment of mastalgia. *Rev Med Brux* 1982;3:605-9.
25 Barr W. Pyridoxine supplements in the premenstrual syndrome. *Practitioner* 1984;228:425-7.
26 Williams MJ, Harris RI, Dean BC. Controlled trial of pyridoxine in the premenstrual syndrome. *J Int Med Res* 1985;13:174-9.
27 Hagen I, Nesheim BI, Tuntland T. No effect of vitamin B-6 against premenstrual tension. A controlled clinical study. *Acta Obstet Gynecol Scand* 1985;64:667-70.
28 Chakmakjian ZH, Higgins CE, Abraham GE. The effect of a nutritional supplement, Optivite for women, on premenstrual tension syndromes. *J Appl Nutr* 1985;37:12-7.
29 Smallwood J, Ah-Kye D, Taylor I. Vitamin B6 in the treatment of pre-menstrual mastalgia. *Br J Clin Pract* 1986;40:532-3.
30 Stewart A. Clinical and biochemical effects of nutritional supplementation on the premenstrual syndrome. *J Reprod Med* 1987;32:435-41.
31 Kendall KE, Schnurr PP. The effects of vitamin B6 supplementation on premenstrual symptoms. *Obstet Gynecol* 1987;70:145-9.
32 Doll H, Brown S, Thurston A, Vessey M. Pyridoxine (vitamin B6) and the premenstrual syndrome: a randomized crossover trial. *J R Coll Gen Pract* 1989;39:364-8.
33 London RS, Bradley L, Chiamori NY. Effect of a nutritional supplement on premenstrual symptomatology in women with premenstrual syndrome: a double blind longitudinal study. *J Am Coll Nutr* 1991;10:494-9.
34 Kerr GD. The management of the premenstrual syndrome. *Curr Med Res Opin* 1977;4:29-34.
35 Day JB. Clinical trials in the premenstrual syndrome. *Curr Med Res Opin* 1979;6:40-5.
36 Abraham GE, Hargrove JT. Effect of vitamin B6 on premenstrual symptomology in women with premenstrual tension syndromes: a double blind crossover study. *Infertility* 1980;3:155-65.
37 Mattes JA, Martin D. Pyridoxine in premenstrual depression. *Hum Nutr Appl Nutr* 1982;36:131-3.
38 Goei GS, Abraham GE. Effect of a nutritional supplement, Optivite, on symptoms of premenstrual tension. *J Reprod Med* 1983;28:527-31.
39 Fuchs N, Hakim M, Abraham GE. The effect of a nutritional supplement, Optivite for women, on premenstrual tension syndromes. *J Appl Nutr* 1985;37:1-11.
40 Brush MG, Bennett T, Hansen K. Pyridoxine in the treatment of premenstrual syndrome: a retrospective survey in 630 patients. *Br J Clin Pract* 1988;42:448-52.
41 Brush MG. Vitamin B6 treatment of premenstrual syndrome. In: Leklem JE, Reynolds RD, eds. *Clinical and physiological applications of vitamin B6*. New York: Liss, 1988: 363-79. (*Current topics in nutrition and disease*, vol 19).
42 Van den Berg H, Schrijver J, Bruinse HW, van der Ploeg HM. Vitamin B6 and premenstrual syndrome. *Voeding* 1989;50:58-62.
43 Berman MK, Taylor ML, Freeman E. Vitamin B-6 in premenstrual syndrome. *J Am Diet Assoc* 1990;90:859-61.
44 De Souza MC, Walker AF, Bolland KM, Robinson PA. A synergistic effect of magnesium and vitamin B6 supplementation for the relief of symptoms of the premenstrual syndrome (PMS). *Proc Nutr Soc* 1996;56:75A.
45 Harrison W, Endicott J, Rabkin JG, Nee J. Treatment of dysphoric changes: clinical outcome and methodological implications. *Psychol Bull* 1984;118-22.
46 Blue J, Harman J. *Mastalgia review*: St Marks Breast Centre. *NZ Med J* 1998;111:34-7.
47 Villegas-Salas E, Ponce dL, Juarez-Perez MA, Grubb GS. Effect of vitamin B6 on the side effects of a low-dose combined oral contraceptive. *Contraception* 1997;55:245-8.
48 Bernstein AL. Vitamin B6 in clinical neurology. *Ann NY Acad Sci* 1990;585:250-60.
49 Stewart JW, Harrison W, Quitkin F, Baker H. Low B6 levels in depressed outpatients. *Biol Psychiatry* 1984;19:613-6.
50 Adams PW, Rose DP, Folkard J, Wynn V, Seed M, Strong R. Effects of pyridoxine hydrochloride upon depression associated with oral contraceptives. *Lancet* 1973;:897-904.
51 Winston F. Oral contraceptives, pyridoxine, and depression. *Am J Psychiatry* 1973;130:1217-21.
52 Folkers K, Ellis J. Successful therapy with vitamin B6 and vitamin B2 of the carpal tunnel syndrome and need for determination of RDAs for vitamins B6 and B2 for disease states. *Ann NY Acad Sci* 1989;295-301.

(Accepted 11 March 1999)

Influence of hospital and clinician workload on survival from colorectal cancer: cohort study

F Kee, R H Wilson, C Harper, C C Patterson, K McCallion, R F Houston, R J Moorehead, J M Sloan, B J Rowlands

Abstract

Objective To determine whether clinician or hospital caseload affects mortality from colorectal cancer.
Design Cohort study of cases ascertained between 1990 and 1994 by a region-wide colorectal cancer register.
Outcome measures Mortality within a median follow up period of 54 months after diagnosis.
Results Of the 3217 new patients registered over the period, 1512 (48%) died before 31 December 1996. Strong predictors of survival both in a logistic regression (fixed follow up) and in a Cox's proportional hazards model (variable follow up) were Duke's stage, the degree of tumour differentiation, whether the liver was deemed clear of cancer by the surgeon at operation, and the type of intervention (elective or emergency and curative or palliative intent). In a multilevel model, surgeon's caseload had no significant effect on mortality at 2 years. Hospital workload, however, had a significant impact on survival. The odds ratio for death within 2 years for cases managed in a hospital with a caseload of between 33 and 46 cases per year, 47 and 54 cases per year, and ≥55 cases per year (compared to one with ≤23 cases per year) were respectively 1.48 (95% confidence interval 1.03 to 2.13), 1.52 (1.08 to 2.13), and 1.18 (0.83 to 1.68).
Conclusions There was no detectable caseload effect for surgeons managing colorectal cancer, but survival of patients treated in hospitals with caseloads above 33 cases per year was slightly worse than for those treated in hospitals with fewer caseloads. Imprecise measurement of clinician specific "events rates" and the lack of routinely collected case mix data present major challenges for clinical audit and governance in the years ahead.

Department of Epidemiology and Public Health, Queen's University of Belfast, Belfast BT12 6BJ
F Kee, *professor*
C C Patterson, *senior lecturer in medical statistics*
Northern Ireland Centre for Clinical Oncology, Belvoir Park Hospital, Belfast BT8 8JR
R H Wilson, *specialist registrar*
R F Houston, *consultant*

continued over

BMJ 1999;318:1381–6

Introduction

In 1995, the then chief medical officer, Sir Kenneth Calman, made recommendations for improving