Pyridoxine (vitamin B_6) and the premenstrual syndrome: a randomized crossover trial

HELEN DOLL

SUSAN BROWN

AMANDA THURSTON

MARTIN VESSEY

SUMMARY. A randomized double-blind crossover trial was conducted to study the effects of pyridoxine (vitamin B_6) at a dose of 50 mg per day on symptoms characteristic of the premenstrual syndrome. Sixty three women aged 18–49 years, identified by means of a general practice based survey of menstrual patterns in the community, entered the trial. All of the women had noticed moderate to severe premenstrual symptoms during the previous year.

The women kept a daily menstrual diary which graded the severity of nine individual symptoms from zero to three. After completing a diary for an initial month the women were randomized to receive either drug or placebo for three months, after which the treatments were crossed over for a further three months. Thirty two women completed the full seven months of the study. In these women a significant beneficial effect ($P<0.05$) of pyridoxine was observed on emotional type symptoms (depression, irritability and tiredness). No significant effect was observed on premenstrual symptoms of any other type.

Introduction

THE literature surrounding the premenstrual syndrome dates back to 1931 when Frank first described the disorder, attributing it to oestrogen excess.[1] Since then, many aetiologies and treatments have been proposed, though to date none of these has been confirmed. This is largely a result of the multifactorial nature of the syndrome and the wide overlap of the disorder with other gynaecological and psychiatric complaints.

There is no precise medical definition of the premenstrual syndrome, there being no consensus as to which of a number of physical and psychological symptoms are necessary for its diagnosis.[2] Clare considers that the syndrome does not constitute a single entity but that various symptom profiles occur, in different combinations, with a predictable relationship to menstruation.[3] He points out that these symptoms are not uncommon but occur intermittently in women of childbearing age, and that evidence of premenstrual exacerbation of the symptoms which may be present during other cycle phases is sufficient to diagnose premenstrual syndrome.[4] Dalton, on the other hand, considers that the symptoms should only be present premenstrually,[5] and, similarly, O'Brien specifies that a symptom free week should follow the regression of symptoms during menstruation.[6]

One of the most popular treatments used in the premenstrual syndrome is pyridoxine (vitamin B_6); this followed on from use of the vitamin for the treatment of depression in oral contraceptive users.[7,8]

Pyridoxine was originally thought to correct aberrant oestrogen metabolism in the premenstrual syndrome,[9] but it is now considered that a role in the regulation of brain monoamine production is more likely.[10]

As with many of the other treatments used in the premenstrual syndrome, pyridoxine has appeared useful when tested in open, uncontrolled trials.[11] This finding is largely accounted for by the high placebo response (generally around 40%) of women with the syndrome. Despite its widespread use and frequent acclaim on the basis of open studies, we know of only five randomized controlled trials which have described the use of pyridoxine in the premenstrual syndrome. Of these, three concluded that pyridoxine had no beneficial effect[12-14] (although one did report an improvement in non-depressive symptoms[14]), while two showed a favourable response.[15,16] Additionally, other reports have suggested that pyridoxine may have toxic effects, even when used in relatively low doses.[17-19]

The equivocal nature of the literature concerning the effectiveness of pyridoxine in the treatment of the premenstrual syndrome prompted the research presented in this paper. The study was designed to test two hypotheses: first, that pyridoxine is effective in the treatment of the premenstrual syndrome; second, that it is feasible to supervise a trial of a simple treatment like pyridoxine by mail. The differing views about the definition of the premenstrual syndrome led to the use of a questionnaire which asked about the most commonly described physical and psychological symptoms associated with the premenstrual syndrome; allowed women to describe in their own words any additional symptoms they had experienced; and collected the data throughout the menstrual cycle so that changes in symptom clusters and symptom severity between the different menstrual cycle phases could be analysed.

Method

The treatment trial was part of a community based postal survey of the menstrual patterns of over 2000 women aged 18–49 years registered with two general practices.[20]

Planning difficulties

The study was planned to be a randomized double-blind crossover trial of 200 mg pyridoxine daily, conducted entirely by post, with the exception of telephone conversations (approximately three per woman) with one of us (A.T.) to ensure compliance with the study requirements. A number of difficulties, however, were encountered in the planning stage of the study:

First, the approval of the local ethical committee had been sought, and immediately given, for the postal community survey. The committee, however, initially withheld approval for the treatment trial. This was mainly on the basis that the study participants had not been subjected to a mental health screen. The committee considered that the heterogeneity of the participants might obscure an assessment of any response to treatment. One of us (S.B.) met the committee members and defended the study on the grounds that it would be unreasonable to expect general practitioners to screen patients with suspected premenstrual syndrome in routine clinical practice using a mental health

H. Doll, BSc, research scientist, S. Brown, MRCOG, MRCGP, senior registrar, A. Thurston, research assistant, and M. Vessey, FRCP, FRCGP, professor, Department of Community Medicine and General Practice, Oxford.

© *Journal of the Royal College of General Practitioners*, 1989, 39, 364-368.

questionnaire, and that our protocol was therefore a pragmatic one. The committee was convinced by this argument and gave its approval.

Secondly, during the interval that passed between seeking the approval of the two groups of general practitioners for the study, and the time that we were ready to start, the medical and the national press reported some examples of pyridoxine neuropathy. This publicity arose out of a study which, following a local television report, identified 16 patients with reversible pyridoxine neuropathy, one of whom reported having taken as little as 200 mg per day.[18] As a consequence of this publicity a number of women sought reassurance from their general practitioner about the safety of pyridoxine 200 mg daily. One of the two groups of general practitioners involved in our study then insisted that the treatment trial should use a daily dose of pyridoxine which would not exceed 50 mg.

Finally, although the second group of general practitioners still approved the use of pyridoxine 200 mg daily in the trial, they requested that one of us (S.B.) should carry immediate clinical responsibility for the study participants. This was felt to be impracticable and so the 150 patients registered with this practice were excluded from the treatment trial.

Study entrants

Women were eligible to join the trial if they indicated that they had noticed moderate to severe premenstrual symptoms during the previous year which were alleviated with the onset of menses. Other entry criteria for inclusion in the study were absence of any illness requiring medical treatment, and absence of current medication for the premenstrual syndrome. The study design included women using the oral contraceptive pill, but their records were flagged so that they could be analysed separately from other subjects.

Although 220 women were originally eligible for the study, after the exclusion of the women from the larger practice only 70 women were invited to join the study. Two women were excluded on the basis of their current medication and five failed to return the initial diary.

Study

After a full explanation of the study, each subject kept a daily menstrual diary which graded the severity of individual symptoms (depression, irritability, tiredness, breast discomfort, swollen abdomen, swollen hands/feet, headache, stomach cramps, backache, and other menstrual symptoms) from zero to three thoughout the seven menstrual cycles of the study period. The 63 women kept an initial record for the first menstrual cycle, and they were then randomized to receive either pyridoxine 50 mg per day (group A) or placebo tablets (group B) for three months, after which the treatments were crossed over for the remaining three months. Of these 63 women, one failed to complete the first month after randomization and 19 failed to complete the two succeeding months. Only 11 of the remaining 43 women were lost during the second phase: 37 (54% of the original 68) completed six months, and 32 (47%) the full seven study months. Of the 37 partial finishers, 10 were taking a (combined) oral contraceptive, and of the 32 finishers, nine.

A follow-up letter was sent to each study drop-out requesting details of the reason(s) for leaving but only five replied and no further attempts were made to contact the remaining women.

Symptom scores

The nine individual symptoms (plus 'other' menstrual symptoms) which the women had been requested to grade in severity were divided for the analysis into three groups according to type:

- 'Emotional' (depression, irritability, tiredness)
- 'Somatic' (headache, breast discomfort, swollen abdomen, swollen hands/feet)
- 'Menstrual' (stomach cramps, backache, other)

The scores for each woman in each study cycle during the seven days before menstruation commenced were totalled for each symptom type. The possible score ranges were thus 0–63 for 'emotional' and 'menstrual' type symptoms and 0–84 for 'somatic' type symptoms. Adjustment was then made for the general level of symptom reporting during each cycle by subtracting a baseline score calculated from the days between the end of menstruation and ovulation; the latter was assumed to occur 14 days before the end of the cycle. The mean length of the baseline period was 7.8 days and each woman's individual baseline score was standardized, where necessary, to a seven-day period (to correspond to the length of the premenstrual phase). Thus, for example, an adjusted score of 3.5 implies that there was a mean symptom score increase of 0.5 per day during the premenstrual phase in comparison with the baseline period.

In order to compare the scores for each symptom type during the drug months with those during the placebo months of the study, the scores for each phase were averaged over each woman. Thus, each woman had, for each symptom type, three scores: that for the initial month; an average for the drug months; and an average for the placebo months of the study. These average scores are henceforth referred to simply as 'adjusted scores'.

The analysis was performed first with the finishers only, and then including the five non-finishers who had defaulted only during the final study month. The missing seven-month values were calculated from the average of the five- and six-month scores.

Statistical analysis

The adjusted symptom scores were approximately normally distributed. Standard methods of analysis for a two-period crossover trial were used to test for treatment, trial phase, and treatment by phase effects[21] with Student's t-tests, paired (within women) where a mean difference is specified and grouped (between women) otherwise. Data are given as means (± standard errors) for the finishers only, unless otherwise stated. No significant phase or treatment by phase effects were found and so the results for these tests are not given. Nevertheless, because of the unbalanced nature of the study (the ratio of the patient numbers completing the trial in the two study groups was 18:14) and its relatively low power, a possible phase effect was taken into account in the analysis.

Results

Initial month

The symptom patterns for each part of the cycle for the initial month, averaged over the 37 women finishing at least six study months, are displayed in Table 1. The adjusted premenstrual symptom scores, which are all statistically significantly different from zero at $P<0.01$, are also shown on Table 1. Thus, the women entering the study showed notable cycle variability with respect to the symptoms being recorded. The 32 women completing the full seven study months presented with noticeably higher premenstrual symptom levels than did the 11 completing four to six study months (Table 2).

Trial phases one and two

Table 3 displays the adjusted premenstrual symptom scores averaged over each phase of the trial for both trial groups for each symptom type. Table 4 displays the adjusted premenstrual

Table 1. Initial month: mean symptom scores for each part of the cycle, standardized to a typical 28 days, with adjusted premenstrual scores.

Symptom type	Mean score (±SE) ($n = 37$) Menstrual Days 1–7	Baseline Days 8–14	Days 15–21	Premenstrual Days 22–28	Adjusted premenstrual[a]	99% confidence limits of adjusted premenstrual score
Emotional	11.11 (±1.33)	4.80 (±1.15)	6.04 (±1.29)	14.66 (±1.70)	9.87 (±1.85)	5.10–14.64
Somatic	11.81 (±1.23)	2.07 (±0.59)	3.61 (±0.67)	15.03 (±1.67)	12.96 (±1.88)	8.11–17.81
Menstrual	5.26 (±0.72)	0.47 (±0.21)	1.00 (±0.25)	2.14 (±0.60)	1.66 (±0.62)	0.06– 3.26
Total	28.18 (±2.32)	7.34 (±1.67)	10.65 (±1.86)	31.82 (±3.07)	24.48 (±3.53)	15.37–33.59

[a]Premenstrual scores minus baseline scores.

Table 2. Initial month: mean adjusted premenstrual symptom scores for women finishing the full seven study months and those completing at least four study months.

Symptom type	Mean adjusted premenstrual score (±SE) Finishers ($n = 32$)	Non-finishers ($n = 11$)
Emotional	10.94 (±1.81)	5.73 (±3.95)
Somatic	14.40 (±1.84)	6.81 (±3.19)[a]
Menstrual	1.73 (±0.66)	0.75 (±0.85)
Total	27.06 (±3.22)	13.29 (±7.37)

[a]$P = 0.06$.

Table 3. Mean adjusted premenstrual symptom scores by trial phase and trial group for each symptom type for the 32 finishers.

Trial group and symptom type	Mean adjusted premenstrual score (±SE) Phase 1	Phase 2	Mean difference (±SE)[a]
Group A ($n = 18$)	*drug*	*placebo*	
Emotional	3.39 (±1.38)	7.40 (±2.08)	4.01 (±2.02)[b]
Somatic	8.26 (±1.68)	7.49 (±1.25)	–0.77 (±1.78)
Menstrual	0.95 (±0.50)	1.65 (±0.65)	0.70 (±0.46)
Total	12.60 (±2.22)	16.54 (±2.48)	3.94 (±2.82)
Group B ($n = 14$)	*placebo*	*drug*	
Emotional	6.61 (±1.32)	4.68 (±1.07)	1.93 (±1.70)
Somatic	10.87 (±1.80)	9.23 (±1.91)	1.65 (±2.28)
Menstrual	1.18 (±0.48)	1.40 (±0.89)	–0.21 (±0.91)
Total	18.67 (±3.00)	15.30 (±3.36)	2.93 (±4.33)

[a]Placebo score minus drug score; [b]$P = 0.06$.

scores averaged over drug and placebo months. It is only on emotional type symptoms that pyridoxine had any statistically significant effect: for the finishers the mean (±standard error) difference between placebo and drug scores was 3.10 (±1.35), $P<0.05$ (adjusted for phase effect = 2.97 (±1.37), $P<0.05$); for the finishers and non-finishers the mean difference was 2.76 (±1.21), $P<0.05$ (adjusted for phase effect = 2.72 (±1.23), $P<0.05$).

Month by month figures for the finishing group are given in Figure 1.

Oral contraceptive users

There was a non-significant tendency for the women taking oral contraceptives to have higher adjusted premenstrual symptom scores, most notably emotional type symptoms, during both placebo and drug months. For example, for the 32 women who completed the study those taking an oral contraceptive had an adjusted emotional type symptom score of 8.06 (±3.66) during the placebo months, while those taking no oral contraceptives had a level of 6.66 (±1.14). Similarly, during the drug months the adjusted levels of emotional type symptoms were 5.58 (±1.26) and 3.32 (±1.14), for those taking and those not taking an oral contraceptive respectively. However, the relative improvement in emotional type symptoms on pyridoxine was similar in the two groups. Table 5 displays the adjusted drug and placebo scores averaged over oral contraceptive users and non-users and the differences adjusted for a possible phase effect.

Nature of the placebo response

When placebo was administered first (group B), the level of all symptom scores decreased significantly from the initial to the fourth month of the trial by an average of 57% ($P = 0.001$). Specifically, emotional type symptom scores decreased by 69% ($P<0.05$), somatic type by 52% ($P<0.05$), and menstrual type by 15% (not significant). In contrast, when placebo was administered second (group A) the level of all symptom scores combined increased non-significantly by an average of 37%, with emotional scores increasing by 116%, and menstrual by 145%. Somatic scores decresed by 12% (all not significant).

Table 4. Mean adjusted premenstrual symptom scores for drug and placebo months for each symptom type for the 32 finishers and differences adjusted for a possible phase effect.

Symptom type	Mean adjusted premenstrual score (±SE) ($n = 32$) Drug	Placebo	Mean difference (±SE)[a] Actual	Adjusted
Emotional	3.96 (±0.90)	7.06 (±1.29)	3.10 (±1.35)*	2.97 (±1.37)*
Somatic	8.69 (±1.24)	8.97 (±1.08)	0.29 (±1.41)	0.44 (±1.42)
Menstrual	1.14 (±0.47)	1.45 (±0.42)	0.30 (±0.47)	0.25 (±0.48)
Total	13.79 (±1.91)	17.47 (±1.89)	3.69 (±2.38)	3.66 (±2.44)

*$P<0.05$. [a]Placebo score minus drug score.

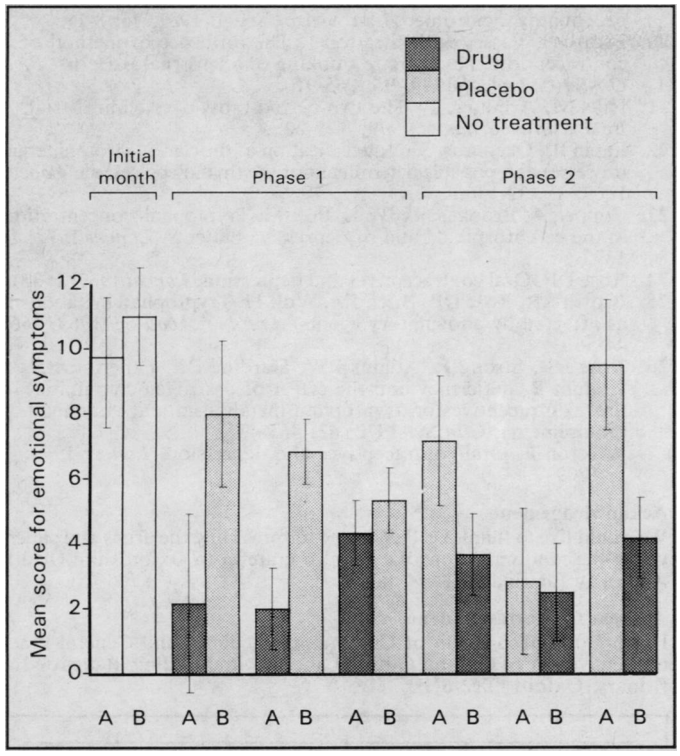

Figure 1. *Mean adjusted scores for emotional type premenstrual symptoms over the seven months of the study for the 32 finishers: 18 in group A, 14 in group B. Mean difference = 3.10 (±1.35); P<0.05.*

Discussion

The present study was complicated by a number of factors, including publicity by the media of pyridoxine neuropathy, but perhaps the main problem, especially for a trial conducted by post and telephone, was its length and complexity. This is likely to be responsible for the relatively high drop-out rate of 50%. The women completing the study presented with symptoms which were on average more severe than those of the women completing four to six months, and thus their motivation to complete the study could have been correspondingly higher. We have no symptom details of the women who completed less than four study months as unfortunately their diaries were misplaced. However, it is likely that their symptoms would have been even less severe than those of the women completing four to six months.

. No woman complained of neurological symptoms or any other adverse effects and in view of the low dose of pyridoxine administered this is not surprising. The pattern of symptoms during the initial month supports Clare's definition of the premenstrual syndrome, with symptom exacerbation in the week before menstruation being the key feature.[4]

The results strongly suggest that pyrixodine, even in a dose as low as 50 mg per day, has a statistically significant beneficial effect on emotional type symptoms (depression, irritability and tiredness) during the premenstrual period in women with the premenstrual syndrome; there was an approximate halving of these symptoms in drug months compared with placebo months.

Pyridoxine is believed to affect brain monoamine metabolism specifically by an alteration in the metabolism of tryptophan. It is suggested that depression may be a consequence of a

Table 5. Mean adjusted premenstrual symptom scores for drug and placebo months averaged over oral contraceptive users and non-users for the 32 finishers, and differences adjusted for a possible phase effect.

Contraceptive use and symptom type	Mean adjusted premenstrual score (±SE)		Mean difference, adjusted (±SE)
	Drug	Placebo	
Oral contraceptive users (n = 9)			
Emotional	5.58 (±1.26)	8.06 (±3.66)	3.81 (±4.03)
Somatic	8.59 (±2.70)	8.37 (±2.32)	0.50 (±3.34)
Menstrual	1.53 (±0.86)	2.05 (±0.94)	0.55 (±0.45)
Total	15.70 (±3.45)	18.48 (±4.68)	4.86 (±6.01)
Oral contraceptive non-users (n = 23)			
Emotional	3.32 (±1.14)	6.66 (±1.14)	3.44 (±1.40)*
Somatic	8.72 (±1.41)	9.21 (±1.23)	0.44 (±1.72)
Menstrual	0.99 (±0.57)	1.21 (±0.46)	0.25 (±0.65)
Total	13.04 (±2.32)	17.08 (±1.97)	4.12 (±2.84)

*$P<0.05$.

Table 6. Characteristics of the five previous randomized controlled trials of pyridoxine in the premenstrual syndrome.

Authors and date	Study design	Pyridoxine dose (mg)	Results
Stokes and Mendels (1972)	8–12 month double-blind multiple crossover study on 13 women treated for 18 days before and during menstruation	50	4 'improved', but only one significantly. These results were at odds with previous uncontrolled studies showing notable improvements in premenstrual syndrome mood but not somatic symptoms
Abraham and Hargrove (1980)	6-month double-blind crossover study on 25 women treated each day	500	Improved total premenstrual symptoms in 21 subjects on pyridoxine
Mattes and Martin (1982)	6-month double-blind multiple crossover study on one woman treated for 10 days prior to menstruation	50	Improved premenstrual depression and irritability in this one woman and in 2 women subsequently tested in an identical fashion
Hagen, *et al* (1985)	2-month double-blind crossover trial on 34 women treated each day	100	No beneficial effect of pyridoxine observed, with placebo being the preferred drug — this a result of a period effect
Kendall and Schnurr (1987)	3-month double-blind pair-matched study on 55 women treated continuously by pyridoxine or placebo after a 1-month baseline period	150	Beneficial effect of pyridoxine seen on autonomic and behavioural symptoms, with no effect observed on depression and anxiety

decrease in the metabolism of tryptophan to 5-hydroxytryptamine (5HT)[22,23] and that imbalances in the levels of steroid hormones may cause a relative deficiency of pyridoxine, the necessary co-factor in this pathway.[24-25] In this respect, it has been observed that about 80% of women taking oral contraceptives have abnormal tryptophan metabolism.[26] Thus, it is particularly encouraging that the effect of pyridoxine in this trial was seen only on the emotional component of the syndrome. We may postulate (as first suggested by Winston[27]) that supplementation of the diet with this vitamin overcomes the deficiency, thereby decreasing the psychological symptoms characteristic of the premenstrual syndrome.

It is interesting to compare our results with those from five previous randomized crossover trials of pyridoxine (Table 6). Two of these trials[15,16] reported an improvement in premenstrual depression; one an improvement in other symptoms;[14] and two no response.[12,13] There is no indication of any association with the dose of pyridoxine taken. These inconsistent results suggest a possible relationship between pyridoxine and a reduction in premenstrual syndrome symptoms, but the placebo effect obscures the results in two trials, and it is unclear which symptom type is improved. The present study provides further evidence for an improvement in premenstrual depression in women on pyridoxine. This would be important if confirmed by future studies since of all the reported symptoms associated with the premenstrual syndrome, depression is particularly likely to interfere with daily activities and thus reduce the quality of a woman's life.

References

1. Frank RT. The hormonal causes of premenstrual tension. *Arch Neurol Psychiatry* 1931; **26:** 1053-1057.
2. Abplanalp JM. The premenstrual syndrome: a selective review. *Womens Health* 1983; **8:** 107-123.
3. Clare AW. Psychological profiles of women complaining of premenstrual symptoms. *Curr Med Res Opin* 1977; **4** (suppl 4): 23-28.
4. Clare AW. Premenstrual syndrome. *Br J Psychiatry* 1981; **138:** 82-83.
5. Dalton K. Why don't doctors treat the premenstrual syndrome? *MIMS Magazine* 1975; **15:** 89.
6. O'Brien PMS. The premenstrual syndrome: a review. *J Reprod Med* 1985; **30:** 113-126.
7. Baumblautt MJ, Winston F. Pyridoxine and the pill. *Lancet* 1970; **1:** 832-833.
8. Adams PW, Rose DP, Folkard J, *et al.* Effect of pyridoxine hydrochloride (vitamin B_6) upon depression associated with oral contraception. *Lancet* 1973; **1:** 897-904.
9. Biskind MS, Biskind GR. Effect of vitamin B complex deficiency on inactivation of estrone in liver. *Endocrinology* 1942; **31:** 109-114.
10. Chakmakjian ZH. A critical assessment of therapy for the premenstrual tension syndrome. *J Reprod Med* 1983; **28:** 532-538.
11. Kerr GD. The management of the premenstrual syndrome. *Curr Med Res Opin* 1977; **4** (Suppl 4): 29-34.
12. Stokes J, Mendels J. Pyridoxine and premenstrual tension. *Lancet* 1972; **1:** 1177-1178.
13. Hagen I, Nesheim B-I, Tuntland T. No effect of vitamin B_6 against premenstrual tension: a controlled clinical study. *Acta Obstet Gynecol Scand* 1985; **64:** 667-670.
14. Kendall KE, Schnurr PP. The effect of vitamin B_6 supplementation on premenstrual symptoms. *Obstet Gynecol* 1987; **70:** 145-149.
15. Abraham GE, Hargrove JT. Effect of vitamin B_6 on premenstrual symptomatology in women with premenstrual tension syndrome: a double blind crossover study. *Infertility* 1980; **3:** 155-165.
16. Mattes JA, Martin D. Pyridoxine in premenstrual depression. *Hum Nutr Appl Nutr* 1982: **36A:** 131-133.
17. Schaumberg H, Kaplan J, Windebank A, *et al.* Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. *N Engl J Med* 1983: **309:** 445-448.
18. Parry GJ, Bredesen DE. Sensory neuropathy with low-dose pyridoxine. *Neurology* 1985; **35:** 1466-1468.
19. Dalton K, Dalton MJT. Characteristics of pyridoxine overdose neuropathy syndrome. *Acta Neurol Scand* 1987; **76:** 8-11.
20. Brown S, Vessey MP, Stratton I. The influence of method of contraception and cigarette smoking on menstrual patterns. *Br J Obstet Gynaecol* 1989; **95:** 905-910.
21. Hills M, Armitage P. The two-period cross-over clinical trial. *Br J Clin Pharmacol* 1979; **8:** 7-20.
22. Lapin IP, Oxenkrug GF. Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect. *Lancet* 1969; **1:** 132-136.
23. Coppen A, Brooksbank BWL, Peet M. Tryptophan concentration in the cerebrospinal fluid of depressive patients. *Lancet* 1972; **1:** 1393.
24. Rose DP. Oral contraceptives and depression. *Lancet* 1969; **2:** 321.
25. Brown RR, Rose DP, Price JM, Wolf H. Tryptophan metabolism as affected by anovulatory agents. *Ann NY Acad Sci* 1969; **166:** 44-56.
26. Rose DP, Strong R, Adams PW, Harding PE. Experimental vitamin B_6 deficiency and the effect of oestrogen-containing oral contraceptives on tryptophan metabolism and vitamin B_6 requirements. *Clin Sci* 1972; **42:** 465-477.
27. Winston F. Oral contraceptives and depression. *Lancet* 1969; **1:** 1209.

Acknowledgements

We would like to thank Dr B. Winsley for providing the drugs and supervising the randomization. We are also grateful to Oxfordshire Health Authority for financial assistance.

Address for correspondence

Helen Doll, Department of Community Medicine and General Practice, University of Oxford, Gibson Laboratories Building, Radcliffe Infirmary, Oxford OX2 6HE.