currently in use there is a case for minimising the dose of progestogen to reduce the chances of thromboembolism.

We thank Sir Richard Doll for advice on the analyses. We also thank the Committee on Safety of Medicines, which kindly allowed us the use of its data, but the opinions expressed in the paper are entirely our own. We are grateful to Mr S Cardy for extensive help over the provision of the records. We thank the organisations that provided sales figures.

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(Accepted 2 April 1980)

Progesterone, fluid, and electrolytes in premenstrual syndrome

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Summary and conclusions

Changes in mood, plasma progesterone concentration, urinary volume, sodium excretion, sodium:potassium ratio, and body weight during the menstrual cycle were determined in 18 women with premenstrual syndrome and 10 symptomless (control group) women. Plasma progesterone concentration was higher in the women with symptoms during the postovulatory phase of the cycle, and the peak progesterone concentration appeared earlier. The changes in progesterone concentration were accompanied by a natriuresis and diuresis that fell towards preovulatory values in the premenstrual phase. Sodium retention was not confined to any definite period. Mood symptoms occurred after the changes in progesterone and electrolyte concentrations.

Progesterone deficiency is probably not the cause of premenstrual syndrome. Thus treatment with progesterone is probably illogical unless a deficiency is detected. Treatment should be aimed at preventing the natriuretic effect of progesterone in the postovulatory phase and the sodium-retaining and water-retaining effects of aldosterone in the premenstrual phase.

Introduction

The aetiology of the premenstrual syndrome remains undetermined. It has been attributed¹ to vitamin deficiency, hypoglycaemia, antidiuretic hormone, "menotoxin," the renin-angiotensin system, aldosterone, prolactin, and imbalance of ovarian hormones. There is little evidence for any of these hypotheses. A

recent study has shown that a mechanism including aldosterone is unlikely.² Studies on prolactin concentrations have given inconsistent findings,³ and many of the other theories have been inadequately investigated. The theory of progesterone deficiency has been popular for some time,⁴ though the evidence is conflicting. Some studies⁵⁻⁶ have shown lower concentrations of progesterone in patients with the syndrome, while others⁷ have shown lower concentrations in only 30% of patients. Moreover, symptoms appeared to precede the hormonal change. Gillman⁸ produced symptoms by administering progesterone, and many of the "progestagenic complications" associated with oral contraceptives are similar to premenstrual syndrome. We report here the relation between changes in progesterone concentration, fluid and electrolytes, body weight, and mood.

Subjects and methods

We studied the cycles in 28 women (18 with premenstrual syndrome and 10 who were symptomless—the control group). Changes in mood, 24-hour urinary volume, total sodium, sodium:potassium ratio, and plasma progesterone concentration were measured in each of four phases of the cycles. Basal body temperature was measured to determine the time of ovulation. Body weight was measured daily.

Change in mood—Visual analogue scales were used for the following characteristic symptoms: tension, anxiety, bloatedness, sadness, depression, aggression, libido, and lethargy. Volunteers marked the 100-mm line every day according to their mood, and the total for all moods was calculated. The difference between the preovulatory phase mean and premenstrual phase mean gave the premenstrual mood index. Thus a single figure was obtained to reflect these symptoms in each cycle. All subjects had already been defined, symptomatic subjects having a consistently positive premenstrual mood index.

Progesterone concentrations were measured by radioimmunoassay, antiserum raised in rabbits being used against an 11-conjugate coupled to rabbit serum albumin after being extracted with hexane.⁹ Standards were assayed in triplicate and samples in duplicate. Replicate assays on commercial control serum (Ortho diagnostic controls III) gave a mean value of $6.29 \pm \text{SD } 0.736 \text{ nmol/l}$ ($1.8 \pm 0.2 \text{ ng/ml}$) with a coefficient of variation of 11.69% between assays and 9.06% within assays. Blood samples were taken on days 4, 12, 18, and 24 of each cycle.

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Urine collections were made in the 24 hours before the visits to the clinic at which the blood samples were taken. Urinary volume was recorded. Sodium and potassium concentrations were measured photometrically. Twenty-four-hour urinary sodium and the sodium:potassium ratio were calculated.

Body weight was measured daily by the patients and controls first thing every morning and after voiding.

Results in the group with symptoms were compared with those in the control group using the Mann-Whitney test, and Spearman's correlation coefficient was used for assessing correlation between various indices.

Results

Serum progesterone concentration—The mean ($\pm$ SE) serum progesterone concentration in the women with premenstrual syndrome was significantly higher than that in the control group during the postovulatory phase (table, $p < 0.025$). When the values were plotted

index (premenstrual mood score minus preovulatory mood score) in the women with symptoms was 62.13 ± 13.0 and in the control group -14.0 ± 12.0 . The index showed a negative correlation with the change in urinary sodium:potassium ratio ($r = -0.3886$, $p < 0.005$) throughout the cycle. There was a positive correlation between the index and the postovulatory serum progesterone concentration ($r = 0.4267$, $p < 0.05$). Although the changes in fluid and electrolytes appeared consistent, they could not be confirmed statistically because of the wide range of values and the relatively small number of subjects. Although there was a small increase in mean body weight in both groups, there was no consistent gain or loss in weight in either group.

Discussion

Postovulatory natriuresis, diuresis, and increase in the sodium:potassium ratio seemed to follow the secretion of progesterone. Progesterone acts as a natriuretic agent through its inhibition of aldosterone at the renal distal tubule.¹⁰ The changes appeared

Changes in indices in 18 women with premenstrual syndrome (symptomatic group) and in 10 asymptomatic women (control group) throughout menstrual cycle. Results given as means $\pm$ SE

Index	Group	Phase of cycle			
		Menstrual	Preovulatory	Postovulatory	Premenstrual
24-hour urinary sodium (mmol)	Symptomatic	116.5 $\pm$ 12.9	106.4 $\pm$ 11.4	151.0 $\pm$ 15.6	128.0 $\pm$ 16.0
	Control	144.5 $\pm$ 19.3	128.6 $\pm$ 21.4	143.2 $\pm$ 20.1	137.8 $\pm$ 12.6
Sodium:potassium ratio	Symptomatic	2.4 $\pm$ 0.5	2.2 $\pm$ 0.2	2.7 $\pm$ 0.3	2.1 $\pm$ 0.3
	Control	2.7 $\pm$ 0.3	2.2 $\pm$ 0.4	2.9 $\pm$ 0.6	2.0 $\pm$ 0.3
24-hour urinary volume (ml)	Symptomatic	1299 $\pm$ 29	1193 $\pm$ 122	1569 $\pm$ 159	1358 $\pm$ 130
	Control	1313 $\pm$ 144	1342 $\pm$ 157	1542 $\pm$ 136	1613 $\pm$ 197
Body weight (kg)	Symptomatic	63.3 $\pm$ 3.4	63.6 $\pm$ 3.2	63.9 $\pm$ 3.2	64.1 $\pm$ 3.3
	Control	60.0 $\pm$ 4.0	59.5 $\pm$ 4.0	59.7 $\pm$ 4.1	60.2 $\pm$ 3.9
Serum progesterone (nmol/l)	Symptomatic	2.3 $\pm$ 0.5	2.4 $\pm$ 0.5	22.4 $\pm$ 4.0*	30.2 $\pm$ 4.7
	Control	1.8 $\pm$ 0.4	1.7 $\pm$ 0.4	8.7 $\pm$ 3.8*	32.4 $\pm$ 9.5

*Difference between means significant at $p < 0.025$.

Conversion: SI to traditional units—Sodium: 1 mmol $\approx$ 1 mEq. Serum progesterone: 1 nmol/l $\approx$ 0.32 ng/ml.

in relation to the time of menstruation, the peak concentration occurred about three days earlier and had a higher mean value in the group with symptoms (figure) than in controls. This was not accounted for by anovulation or cycle length. This change appeared to coincide with the changes in fluid and electrolytes and to precede changes in mood.

Mean serum progesterone concentrations in 18 women with premenstrual syndrome (symptomatic group) and in 10 asymptomatic women (control group).

Conversion: SI to traditional units—Serum progesterone: 1 nmol/l $\approx$ 0.32 ng/ml.

Changes in fluid and electrolytes—The mean ($\pm$ SE) 24-hour urinary sodium excretion in the group with symptoms was lowest during the preovulatory phase (106.4 ± 11.4 mmol (mEq)/24 h) and highest during the postovulatory phase (151.0 ± 15.6 mmol (mEq)/24 h). The results were similar in the control group, though the changes were not as large (128.6 ± 21.4 mmol (mEq)/24 h and 143.2 ± 20.1 mmol (mEq)/24 h respectively). The excretion rate fell towards preovulatory values during the premenstrual phase in both groups (table).

Twenty-four-hour urinary volume—The variation in mean 24-hour urinary volume and sodium:potassium ratio closely resembled that in sodium excretion, suggesting a natriuresis and diuresis that followed secretion of progesterone. Thus, there was a tendency towards sodium and water retention in the premenstrual phase.

Premenstrual mood index—The mean ($\pm$ SE) premenstrual mood

greater in the women with symptoms of premenstrual syndrome, but only those at the higher concentrations of progesterone were confirmed statistically.

Secretion of progesterone after ovulation normally occurs before an increase in plasma aldosterone concentration. The earlier secretion in the group with symptoms is probably unopposed by aldosterone, which would account for the higher natriuresis in this group. Plasma aldosterone concentrations have been reported to be the same in women with and without premenstrual symptoms.² The flat phase of progesterone secretion in the presence of rising aldosterone concentrations may be related to the sodium-retaining phase.

Water retention in the premenstrual phase is not so important a factor in the premenstrual syndrome as has been suggested, and the postovulatory natriuresis followed by a return to original values is probably more important. This may explain inconsistencies among published reports. Increased concentrations of exchangeable sodium have been shown in affective disorders—for example, in depression.¹¹ Cyclical variation in electrolytes and fluid state of the neurones may be related to the swing in mood found in this syndrome.

This study is not conclusive, since the changes in fluid and electrolytes were not confirmed statistically. A separate study, in which daily samples were taken for progesterone and urinary electrolyte estimation, would be required to establish the importance of these changes more firmly.

Several conclusions, however, emerge from our study. We have shown that the assumption that progesterone deficiency is the causative agent in the syndrome is probably wrong; hence treatment with progesterone is illogical in the absence of evidence of progesterone deficiency. This conclusion has recently been supported by a double-blind cross-over study in which progesterone was shown to be no more effective than placebo.¹²

Progesterone secretion seemed to be more directly related to the production of symptoms. This may in turn be related to alterations in electrolytes and fluid. The return to baseline

values in the premenstrual phase may result in symptoms of water retention. Treatment should, therefore, be aimed at preventing both the natriuretic effect of progesterone in the postovulatory phase and the sodium-retaining and water-retaining effects of aldosterone in the premenstrual phase.

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(Accepted 15 February 1980)

SHORT REPORTS

Neutropenia during allopurinol treatment in total therapeutic starvation

Allopurinol, a xanthine oxidase inhibitor, has been recommended to prevent the development of hyperuricaemia during total therapeutic starvation.¹ Leucopenia and even fatal agranulocytosis have occasionally been noted in patients treated with allopurinol for gout,² while neutropenia occurs quite often during prolonged fasting, although its exact causation remains obscure. We report here three patients who developed neutropenia during therapeutic starvation when allopurinol was prescribed to prevent hyperuricaemia.

Case reports

We studied three obese patients, all of whom underwent prolonged total therapeutic starvation resulting in pronounced, progressive weight reduction. During the fast all received supplements of potassium (as Slow K), allopurinol (300 mg/day), folic acid, and vitamins A, B, C, and D (as Multivite). One patient (case 1) also received oral iron treatment. Throughout the period of starvation all patients maintained normal serum vitamin B₁₂ and iron concentrations.

Case 1—A 23-year-old woman weighing 134 kg underwent a three-month fast. Before starting the fast her white blood cell count was normal ($6.8 \times 10^9/l$) but fell as low as $3.5 \times 10^9/l$ (neutrophil count of $1.7 \times 10^9/l$) when allopurinol was started. On refeeding the patient continued to receive allopurinol for a further month and a minimal neutropenia persisted ($2.4 \times 10^9/l$). When allopurinol was withdrawn the neutrophil count returned to normal. Sternal marrow biopsy performed during the fast showed normal maturation of the granulopoietic series but rather scanty numbers of polymorphs and precursors.

Case 2—A 20-year-old man weighing 113 kg had a white cell count of $8.3 \times 10^9/l$ before fasting. Neutropenia (neutrophils $1.7 \times 10^9/l$, total white cell count $3.6 \times 10^9/l$) developed after 34 days' starvation. Allopurinol was withdrawn and the white cell and neutrophil counts returned to normal (white blood cell count $5.8 \times 10^9/l$) after three weeks.

Case 3—A 19-year-old man weighing 130 kg had a white blood cell count of $8.5 \times 10^9/l$ before therapeutic starvation started. After four weeks of total fasting and treatment with allopurinol he developed leucopenia ($3.9 \times 10^9/l$), which persisted until the end of the fast. The lowest neutrophil count recorded was $1.3 \times 10^9/l$. Allopurinol was continued for nine days of refeeding, during which time the neutropenia persisted. Thereafter the drug was withdrawn and his neutrophil count returned to normal after two days.

Comment

Neutropenia has often been observed during total therapeutic starvation and is known to occur in starving patients who have never received allopurinol. Hypotheses to explain its appearance during fasting have included the effects of protein deficiency on marrow activity^{3,4} and intravascular redistribution of the neutrophils.⁴ Some

dispute exists about whether neutropenia may be caused in starving patients by folate deficiency, but clearly this could not have been a factor in our patients, all of whom received regular folate supplements.

The evidence of our present study suggests that allopurinol was either an initiating or an aggravating factor in the neutropenia we observed. In particular, the persistence of neutropenia after the fast was broken points strongly to this drug as the cause of the phenomenon. In view of the very low neutrophil counts recorded in the patients whom we studied, we suggest that the white blood cell and neutrophil count should be estimated regularly in fasting patients receiving allopurinol.

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(Accepted 28 January 1980)

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Lorazepam withdrawal seizures

Reports of seizures after benzodiazepine withdrawal have been appearing since 1961,¹ yet despite recent publicity² it is not widely appreciated that withdrawal seizures can occur with these drugs. Seizures after lorazepam withdrawal have not been reported; prescription of lorazepam is increasing, and it is now fourth in the benzodiazepine-prescribing league. For these reasons I report the following cases.

Case reports

Case 1—A 22-year-old woman had no history of seizures or brain damage. She had been taking at least 7.5 mg of lorazepam daily for four years because of anxiety. She decided to stop taking lorazepam, and one day