handwashing studies show that chlorhexidine hand cleanser is an easy, practical method of removing such organisms from the hands of staff, and these findings agree with those of Lowbury *et al*[10] who studied alcoholic solutions for the preoperative disinfection of surgeon's hands.

The reduction in klebsiella colonisation or infection of newly-admitted patients that coincided with increased staff handwashing, and which was sustained over two-years, provides perhaps the most convincing evidence that hands are a major, but correctable, route of transmission for *Klebsiella* spp.

Transmission of klebsiellae from hands explains several epidemiological features of klebsiella infection we have previously observed in this ward. It explains how the serotypes contaminating food may be transmitted from the bowel of a colonised patient to clinical lesions in others, and why food types relate to patient-isolates on this ward as a whole while individual patients do not always acquire the strain that they have themselves ingested. Furthermore, such a route of transmission would contribute, via cross-infection, to the "clusters" of clinical infection and colonisation with the same serotype that we observed between 1969 and 1973. Hands may also be an important route of transmission in types of hospital-acquired klebsiella infection of obscure epidemiology, such as the spread of gentamicin-resistant klebsiella strains.

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Requests for reprints should be sent to Dr M W Casewell.

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Effect of oestrogen on the sleep, mood, and anxiety of menopausal women

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Summary

A double-blind controlled study of the effect of piperazine oestrone sulphate on sleep, depression, anxiety, and hot flushes was performed in 34 perimenopausal women. Half of the patients were given six weeks' placebo followed by eight weeks' oestrogen, and half remained on placebo throughout. Sleep was recorded electrophysiologically every week, and mood and anxiety were rated daily by means of visual analogue scales. Hot flushes were counted daily. Observer rating scales of anxiety and depression were completed at intervals.

During the first month of active treatment the amount of intervening wakefulness in the first six hours of sleep decreased significantly more in the oestrone group than in those on placebo. Between the baseline period and the second treatment month the oestrone group showed a significantly greater decrease in the total amount of intervening wakefulness and in the frequency of awakenings. Their total amount of rapid eye movement sleep increased. Mood and anxiety improved and the number of hot flushes decreased to a similar degree in both groups.

Although oestrogen did reduce the number of episodes of wakefulness in perimenopausal women complaining of insomnia, its effects on their psychological symptoms were little different to those of placebo.

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Introduction

The perimenopausal period has long been considered to be a time of increased morbidity, and various epidemiological surveys[1-3] have shown that complaints of hot flushes, insomnia, depression, and anxiety are especially common at this time. The symptoms may be due to hormonal changes, but it is also possible that the psychological symptoms might be due to fear of aging or to the social changes of middle age. Jaszman[1] and Ballinger[4] have inferred that insomnia is due to hormonal changes, since their surveys have shown that the incidence of the complaint rises as oestrogen levels fall in the perimenopausal period. Other possible causes are aging, anxiety, and depression, all of which are associated with sleep disturbance.[5-7]

Hormone replacement therapy has been used to treat menopausal symptoms since 1896 but remains controversial. McKinlay and McKinlay[8] reviewed the many studies of hormone replacement therapy but found that results were conflicting and that studies lacked consistency in defining the menopause, the symptoms associated with it, and the age group to be studied.

We therefore carried out a double-blind controlled study of the effect of oestrogen therapy on sleep, mood, anxiety, and hot flushes in perimenopausal women.

Patients and methods

Patients were referred by local general practitioners. All were aged 45-55 and had had amenorrhoea for at least three months and symptoms of insomnia, depression, anxiety, and hot flushes. They received no other medication, had no contraindications to oestrogen therapy, and were asked to abstain from alcohol for the duration of the study.

Each patient was studied for 14 weeks, and throughout this time they attended the sleep laboratory in pairs on one night each week for electrophysiological recording of sleep. In the first six weeks all patients received a placebo. In the remaining eight weeks one of each pair received piperazine oestrone sulphate in a dose of 1·5 mg twice

daily while the other remained on placebo. All patients were warned that the pills they received might be blanks.

The first two nights spent in the sleep laboratory were for adaptation purposes only, and the next four were for baseline recordings. The subsequent four nights were in the first treatment month and the final four in the second treatment month. Ultimately the sleep records were scored blind according to standard criteria.[9]

Each day throughout the study patients rated their mood and anxiety, using 100-mm visual analogue scales, and they noted the number of hot flushes they experienced. Hamilton observer rating scales of anxiety[10] and depression[11] were completed at the beginning and end of the baseline placebo period, at the end of the first treatment month, and at the end of the second treatment month.

Statistics—Intragroup changes in the different periods of the experiment were compared by t tests for paired observations. The changes between the baseline period and first treatment month and between the baseline and second treatment month were also examined for each group, and the magnitude of change in the two groups was then compared using Student's t test. A one-tailed test was used for intervening wakefulness and frequency of arousals, which we had predicted would decrease with oestrogen treatment, and a two-tailed test in all other cases.

Results

Thirty-four patients completed the study. Eight others had started but failed to complete the study, seven dropping out in the first week, and one in the eighth week because of urinary tract infection. The mean age was 49·7 years in the oestrogen group (n = 17) and 48·5 years in the placebo group (n = 17). The two groups were comparable in terms of menstrual age.

SLEEP DURATION

The duration of sleep increased in both groups. In the oestrogen group mean sleep duration (±SE) increased from a baseline value of 423·2±8·2 minutes to 442·2±7·7 minutes in the first treatment month ($t = 3·305$; $P < 0·01$) and rose to 446·5±7·2 minutes in the second treatment month ($t = 2·939$; $P < 0·01$). In the placebo group the increase from the baseline duration of 418·2±7·2 minutes to 424·3±8·2 minutes in the first treatment month was not significant, but the increase from the baseline value to 429·4±7·2 minutes in the second treatment month was significant ($t = 2·735$; $P < 0·02$). The difference between the two groups was not significant.

INTERVENING WAKEFULNESS

A measure of the brokenness of sleep is provided by the amount of time awake that intervenes between periods of sleep. Comparing the baseline period and the first treatment month, the oestrone group showed a decrease in the amount of intervening wakefulness during the whole of sleep of 14·4±5·1 minutes, and the placebo group showed a decrease of 4·7±4·5 minutes. The difference between the two groups was just short of significance ($t = 1·454$). In the second treatment month the oestrone group had 15·8±5·8 minutes less intervening wakefulness than in the baseline period and the placebo group 2·1±2·2 minutes less. The difference between the two groups was significant ($t = 2·176$; $P < 0·025$).

The oestrone-treated group also woke less often. In the second treatment month they showed a decrease in the number of arousals from sleep to wakefulness of 0·9±0·4 compared with the baseline period, whereas the placebo group showed a small mean increase of 0·1±0·4. The difference between the two groups was significant ($t = 1·717$; $P < 0·05$).

The results were also analysed in terms of the first six hours of accumulated sleep to keep the sleep duration constant among subjects and nights. The mean cumulative intervening wakefulness in the first six hours of sleep in oestrone and placebo groups is shown in fig 1. The mean value during the baseline period was higher in those who later received oestrone, but not significantly so ($t = 1·140$; NS). Between the baseline period and first treatment month the oestrone group showed a decrease in intervening wakefulness of 17·2±6·6 minutes and the placebo group a decrease of 2·6±4·6 minutes ($t = 1·816$; $P < 0·05$). When the baseline value was compared with that in the second month of treatment the oestrone group showed a decrease of 18·0±7·3 minutes and the placebo group a decrease of only 1·0±2·4 minutes, the difference between the two groups again being significant ($t = 2·205$; $P < 0·025$).

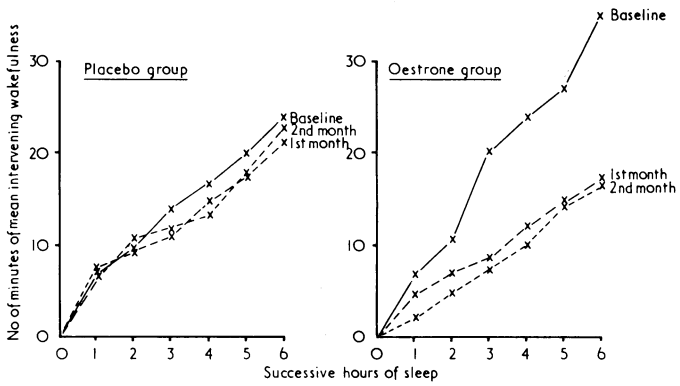

FIG 1—Mean cumulative wakefulness intervening during accumulation of first six hours of sleep in oestrone and placebo groups in baseline period, first treatment month, and second treatment month.

The number of arousals to wakefulness in the first six hours of sleep in the two groups is shown in fig 2. The oestrone group showed a decrease in the number of awakenings of 1·1±0·5 between the baseline and second treatment months, while the placebo group showed an increase of 0·2±0·3. The difference between the two groups was significant ($t = 2·260$; $P < 0·025$).

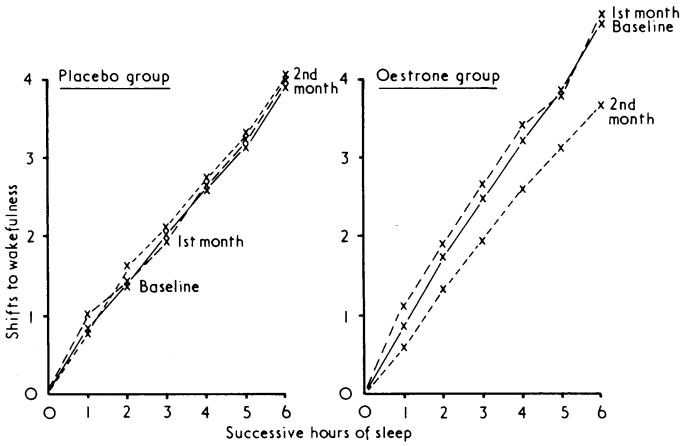

FIG 2—Cumulative mean number of awakenings in first six hours of sleep in oestrone and placebo groups in baseline period, first treatment month, and second treatment month.

SLEEP STAGES

The total amount of rapid eye movement (REM) sleep in the oestrone group increased throughout the study. Between the baseline month and first treatment month the difference between the groups was not significant, but between the baseline and second treatment months the oestrone group showed an increase in REM sleep of 13·3±4·7 minutes and the placebo group of 2·3±2·0 minutes: the difference between the groups was significant ($t = 2·184$; $P < 0·05$). There was no increase in REM sleep in the first six hours of sleep in either group.

No significant changes in stage 1, stage 2, or slow-wave sleep were observed.

MOOD

Both oestrone and placebo groups showed an improvement in mood throughout the study, as shown by Hamilton rating scales and visual analogue scales. The mean Hamilton depression score of the oestrone group was 16·3±1·9 at the start of the study, 7·9±1·2 at the end of the baseline period, 7·3±1·3 at the end of the first treatment month, and

5·9±1·8 at the end of the second treatment month. Over the same period the scores of the placebo group fell from 18·2±2·0 to 10·1±1·5, to 6·2±1·3, and finally to 4·5±0·7.

In both groups the difference in values between the start and end of the baseline period was significant (oestrone group: $t=4·465$, $P<0·001$; placebo group: $t=6·125$; $P<0·001$). In the placebo group there was a significant decrease from the end of the baseline period to the end of the first treatment month ($t=2·810$; $P<0·02$) and to the end of the second treatment month ($t=3·301$; $P<0·01$), but in the oestrone group these changes did not reach significance ($t=0·997$ and 1·552). There were no significant differences between the two groups.

ANXIETY

Both oestrone and placebo groups showed a steady improvement in anxiety as measured by Hamilton anxiety rating scales and visual analogue scales throughout the study. The Hamilton anxiety score of the oestrone group fell from 17·2±1·8 at the start of the study to 9·7±1·3 at the end of the baseline period, 7·7±1·2 at the end of the first treatment month, and 5·6±1·4 at the end of the second treatment month. The scores of the placebo group fell from 20·1±2·1 to 11·4±1·3, to 6·5±1·1, and to 5·4±0·7 at the end of the study.

In both groups the difference in values between the start of the study and the end of the baseline period was significant (oestrone group: $t=5·455$, $P<0·001$; placebo group: $t=5·605$, $P<0·001$). The decrease from the end of the baseline period to the end of the first treatment month was significant for the placebo group ($t=4·363$; $P<0·001$) but not for the oestrone group ($t=1·748$), and the decrease from the end of the baseline period to the end of the study was significant in both groups (oestrone group: $t=3·422$, $P<0·01$; placebo group: $t=4·348$, $P<0·001$). There were no significant differences between the two groups.

HOT FLUSHES

The mean hot flush count of both groups fell steadily throughout the study, from a mean of 14·4±4·4 per week at the outset to 8·5±3·3 in the 14th week in the placebo group and from 13·3±3·6 to 5·9±2·2 in the case of the oestrone group. There were no significant differences between the two groups.

Discussion

We have shown that oestrogen treatment diminishes the number and duration of episodes of wakefulness that interrupt sleep in perimenopausal women complaining of insomnia. The patients treated with oestrogen also showed an increase in the duration of sleep, but this did not reach significance when oestrone and placebo groups were compared. The increase in REM sleep shown by the oestrogen group in the second treatment month was probably due to the increase in sleep duration, since no changes in REM sleep were found in the first six hours of sleep, and it is known that REM periods become more frequent and prolonged towards the end of the night.

We have previously reported a highly positive correlation between nocturnal plasma oestrogen and free plasma tryptophan concentrations in perimenopausal women,[12] and Aylward[13] has reported that oestrogen treatment increases free plasma tryptophan concentrations in perimenopausal women. Free plasma tryptophan is the precursor of the cerebral neurotransmitter serotonin, and Jouvet[14] has proposed that serotonin depletion by pharmacological means leads to insomnia. Falling oestrogen levels at the time of the menopause may lead to a fall in free plasma tryptophan concentrations, which is reversed by oestrogen therapy, and the effect of oestrogen in sleep may be mediated through changes in plasma tryptophan influencing cerebral serotonin metabolism.

We found that depression, anxiety, and hot flushes in these perimenopausal women responded strongly to placebo. Donovan[15] reported that in 95% of cases menopausal symptoms could be relieved by history-taking alone, while an injection of saline relieved symptoms in the remainder. Pratt and Thomas[16] also observed a pronounced placebo effect in their blind controlled study and found no significant difference between oestrogen and placebo in relieving either physical or psychological symptoms.

Subjective rating methods for measuring such factors as mood are less precise and less suitable for studying small groups than the objective, electrophysiological measures. This may have contributed to our failure to find that oestrogen was significantly more effective than placebo in relieving depression and anxiety in menopausal women. Our findings contrasted with those of Aylward,[13] who found in a double-blind study using the same dose and type of oestrogen that we used that oestrogen did relieve depression. His patients, however, had undergone oophorectomy and may therefore have differed from women who have experienced a physiological menopause, since the postmenopausal ovary secretes androgenic hormones.[17,18] Utian[19] and George *et al*[20] also carried out controlled studies of the effect of conjugated equine oestrogens on the psychological symptoms of women who had undergone oophorectomy. Utian reported that oestrogen had a mental tonic effect, but George, who used a smaller dose of oestrogen, found that oestrogen was not significantly more effective than placebo in relieving psychological symptoms and suggested that the mental tonic effect might be dose-related.

We found a marked placebo effect on hot flushes, similar to that described by Coope *et al*[21] and Pratt and Thomas,[16] and it was not possible to predict on the basis of changes in hot flush count or severity which patients were receiving oestrogen therapy.

In conclusion, whereas we found only placebo effects on depression, anxiety, and hot flushes, oestrogen treatment produced an objective decrease in the brokenness of sleep in perimenopausal women complaining of insomnia.

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