

Effect of short term hormone replacement in the treatment of obstructive sleep apnoea in postmenopausal women

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Abstract

Background - Women appear to be increasingly susceptible to snoring and sleep disordered breathing after the menopause. This observation, coupled with the considerable sex difference in sleep apnoea, may be explained on the basis of a protective effect of female hormones. This study was carried out to determine whether hormone replacement therapy has a role in the management of obstructive sleep apnoea in postmenopausal women.

Methods - The effect of short term (mean (SE) 50 (3) days) hormone replacement therapy with either oestrogen alone or in combination with progesterone on sleep disordered breathing was investigated in 15 postmenopausal women with moderate obstructive sleep apnoea. The effect of treatment on the ventilatory response to hypoxia and hypercapnia was assessed in 10 patients.

Results - There was no reduction in the clinical severity of obstructive sleep apnoea after hormone treatment despite an increase in the serum oestrogen level from 172 (23) to 322 (33) pmol/l. There was a small but clinically insignificant reduction in the apnoea/hypopnoea index during REM sleep from 58 (6) to 47 (7). There was no difference in response between the oestrogen only group and the oestrogen plus progesterone group. Hypercapnic ventilatory responsiveness did not change with hormone treatment, but an increase in hypoxic ventilatory responsiveness was observed.

Conclusions - These data indicate that short term hormone replacement is unlikely to have an effective role in the clinical management of postmenopausal women with obstructive sleep apnoea. The observed reduction in the apnoea/hypopnoea index during REM sleep, however, suggests that longer term treatment, or the use of higher doses, may have an effect.

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these phenomena. Female sex hormones may protect against the development of sleep disordered breathing, whilst androgens may promote the disorder. The increased prevalence of sleep apnoea in postmenopausal women may therefore be related to the decline in oestrogen and progesterone levels after the menopause. In support of this, progestin and oestrogen have been shown to reduce mild sleep disordered breathing in healthy postmenopausal women.² A previous case report described a considerable improvement with combined hormone treatment in a postmenopausal woman with obstructive sleep apnoea.³

The aim of this study was to determine whether short term hormone replacement in clinically conventional doses reduces more severe obstructive sleep apnoea in postmenopausal women. We also measured ventilatory responses to hypoxia and hypercapnia in a subgroup of patients to investigate the effects of oestrogen and progesterone on chemosensitivity, since this could be an explanation for a reduction in sleep disordered breathing.

Methods

Fifteen consecutive postmenopausal women who presented to our Sleep Disorders Centre with obstructive sleep apnoea were studied. All subjects gave informed consent to the study which was approved by the ethics committee of our institution. They had a mean (SE) age of 60 (1) years, mean body mass index of 32.2 (1.5) kg/m², mean neck circumference of 37 (1) cm, mean waist size of 103 (4) cm, and mean hip size of 112 (3) cm. Menopause was defined as the absence of menstrual periods for more than six months, and was confirmed by the presence of low oestrogen levels and elevated luteinising hormone and follicle stimulating hormone levels.

Subjects underwent baseline nocturnal polysomnographic recording and ventilatory response tests (in a subgroup), and were subsequently commenced on hormone replacement therapy. These studies were repeated after 50 (3) days of treatment. Hormone replacement therapy consisted of oestrogen alone in those patients who had previously undergone hysterectomy (n=6), and oestrogen plus progesterone in the rest (n=9). Oestrogen treatment consisted of conjugated equine oestrogens (0.625 mg/day), oestradiol valerate (1 mg/day), or transdermal oestradiol (8 mg/week). Progesterone was administered as medroxyprogesterone acetate (2.5-10 mg/day).

Standard nocturnal polysomnography was

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Sleep disordered breathing is less common in women than men until after the menopause.¹ The reason for this sex difference, and the increased prevalence of sleep disordered breathing in postmenopausal women, is unknown, but hormonal factors may explain

performed as previously described by our laboratory.⁴ Calculated respiratory variables were the apnoea/hypopnoea index (number of apnoeas and hypopnoeas per hour of sleep), apnoea duration, and minimal oxygen saturation during apnoeas. Obstructive sleep apnoea was defined as an apnoea/hypopnoea index > 5. Apnoeas were defined as cessation of airflow for at least 10 seconds. Hypopnoea was defined as a reduction in amplitude of airflow or thoracoabdominal wall movement of greater than 50% of baseline for more than 10 seconds, associated with desaturation or arousal. These events were defined as obstructive if they occurred in association with continued diaphragm EMG activity and thoracoabdominal wall movement. Central events were defined as those accompanied by absence of diaphragm EMG activity and thoracoabdominal wall movement.

Hypoxic and hypercapnic ventilatory response tests were performed in 10 patients using previously described techniques.^{5,6} Hypoxic ventilatory response tests were performed at two end tidal carbon dioxide tensions – that is, resting end tidal CO₂ (PETCO_{2a}) and an end tidal CO₂ tension approximately 5 mm Hg higher (PETCO_{2b}). The relation between breath by breath ventilation and arterial oxygen saturation (Sao₂) was calculated by linear regression for both PETCO₂ values. The slope of these regression lines was then plotted against the PETCO₂ value at which the test was performed. Hypoxic ventilatory response was expressed by the formula described by Slutsky *et al.*^{7,8}

$$\text{hypoxic sensitivity} = d\dot{V}/d\text{Sao}_2 = k_1 \cdot \text{PCO}_2 + k_2$$

where k_1 represents the slope of the slopes of ventilation (\dot{V}) *v* Sao₂ at the PCO₂ at which hypoxia was induced, and k_2 is the *y* intercept. This formula expresses a differential change in response for a given differential change in stimulus, and allows comparisons between individuals with different PCO₂ levels and within individuals for different levels of PCO₂.⁸ The results of hypoxic ventilatory response testing are presented as k_1 and k_2 values.

DATA ANALYSIS

All data are presented as mean (SE). The ventilatory response data were analysed using linear

regression by plotting ventilation against Sao₂ or PETCO₂ levels. Paired *t* tests were used to compare sleep and ventilatory response data before and after hormone replacement. Unpaired *t* tests were used to compare the oestrogen only group with the oestrogen plus progesterone group. A *p* value < 0.05 was considered significant. Correlation coefficients were measured by linear regression.

Results

Most patients had moderate obstructive sleep apnoea with an apnoea/hypopnoea index of 43 (9) (range 6–106) and minimum oxyhaemoglobin saturation (minSao₂) of 79 (3)% (range 93–54). The baseline apnoea/hypopnoea index showed a significant correlation with neck size ($r=0.54$, $p<0.05$), waist size ($r=0.71$, $p<0.005$), and waist/hip ratio ($r=0.74$, $p<0.005$). Hormone replacement was generally well tolerated with minimal side effects, all of which were gynaecological in nature. Subjective response to treatment was poor. Only three patients reported a reduction in snoring and witnessed apnoeas (according to their partner). One patient reported a significant improvement in daytime hypersomnolence but objectively there was worsening of obstructive sleep apnoea.

The results are summarised in the table. There was a significant increase in serum oestrogen levels in patients receiving hormone replacement therapy, but in one patient the oestrogen level fell following hormone replacement. There was no change in BMI. Total sleep time, sleep architecture, length of apnoeas, and body position were not significantly different during the two sleep studies. Although there were no significant changes in

Summary of results

	Before treatment	After treatment	<i>p</i>
Serum oestrogen (pmol/l)	172 (23)	322 (33)	< 0.005
BMI (kg/m ²)	32.2 (1.5)	32.4 (1.4)	NS
Total sleep time (min)	350 (20)	355 (19)	NS
REM (%)	15.3 (1.9)	17.4 (1.9)	NS
Non-REM (%)	84.7 (1.9)	82.6 (1.9)	NS
AHI	43 (9)	40 (10)	NS
AHI (REM sleep)	58 (6)	47 (7)	< 0.05
MinSao ₂ (%)	79 (3)	75 (4)	NS
HVR: k_1 (l/min/%Sao ₂ /Pco ₂)	0.05 (0.02)	0.13 (0.04)	< 0.05
k_2 (l/min/%Sao ₂)	-1.3 (0.6)	-4.2 (1.3)	< 0.05
PETCO _{2a} (mm Hg)	39.8 (1.4)	38.0 (0.8)	NS
PETCO _{2b} (mm Hg)	44.4 (1.5)	43.0 (0.6)	NS
HCVR (l/min/mm Hg)	1.7 (0.3)	1.8 (0.2)	NS

BMI = body mass index; AHI = apnoea/hypopnoea index; REM = rapid eye movement; MinSao₂ = minimum oxyhaemoglobin saturation; HVR = hypoxic ventilatory response; PETCO₂ = end tidal carbon dioxide tension; HCVR = hypercapnic ventilatory response. Values are mean (SE).

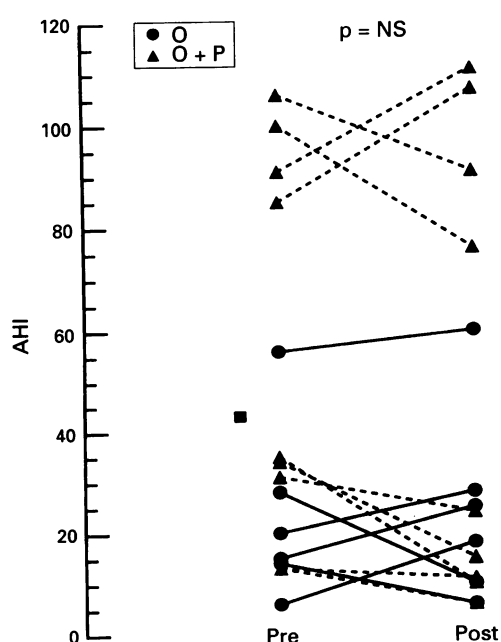


Figure 1 Overall apnoea/hypopnoea indices (AHI) for individual patients before (pre) and after (post) hormone replacement with either oestrogen alone (O, solid circles) or oestrogen + progesterone (O + P, solid triangles). Solid squares indicate means.

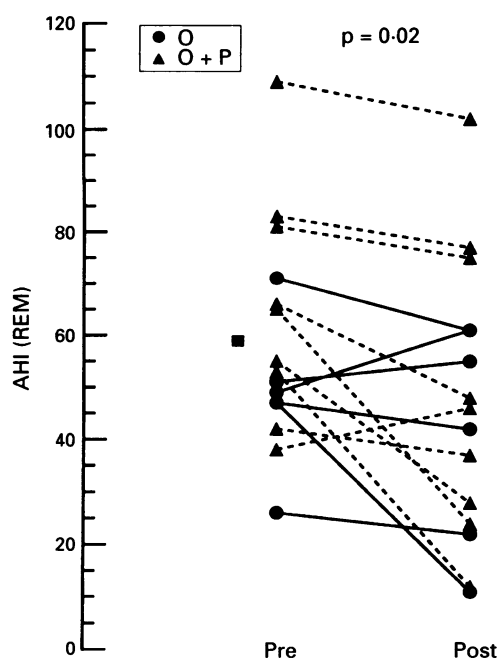


Figure 2 Apnoea/hypopnoea indices (AHI) during rapid eye movement (REM) sleep for individual patients before (pre) and after (post) hormone replacement with either oestrogen alone (O, solid circles) or oestrogen + progesterone (O + P, solid triangles). Solid squares indicate means.

overall apnoea/hypopnoea index and minSaO_2 , there was a significant reduction in the apnoea/hypopnoea index during REM sleep from a mean of 58 to 47 ($p < 0.05$) (figs 1 and 2). There was no difference in the percentage of REM sleep between the two studies (15.3% v 17.4%).

Ventilatory response results are presented in the table. There was no change in the hypercapnic ventilatory response with hormone treatment. The results of hypoxic ventilatory response tests could not be analysed in three patients because of incomplete data due to technical problems. In the remaining seven subjects there was a significant increase in hypoxic ventilatory response expressed as k_1 and k_2 . The PETCO_2 levels at which the hypoxic ventilatory response tests were performed tended to be lower in the tests performed after hormone replacement, but this did not reach statistical significance. Again, there was no difference in response between the oestrogen only and oestrogen plus progesterone groups.

Discussion

Our data indicate that short term hormone replacement therapy with either oestrogen alone or in combination with progesterone had no clinically significant effect on sleep disordered breathing in postmenopausal women with moderate obstructive sleep apnoea, despite a significant increase in serum oestrogen levels into the normal premenopausal range. These data do not support the idea that sleep disordered breathing in postmenopausal women is simply due to low levels of oestrogen and progesterone.

The recognition of a male preponderance in

the prevalence of sleep apnoea, and an increasing prevalence in women after the menopause, has led to speculation that hormonal factors may influence the pathogenesis of sleep apnoea. A number of studies have suggested that androgens may adversely affect sleep disordered breathing in both men and women.^{9,10} However, androgen blockade does not reduce sleep apnoea in men with moderate to severe sleep apnoea.¹¹ The low prevalence of sleep apnoea in premenopausal women and the increasing frequency after menopause has stimulated interest in the effect of female sex hormones on sleep and breathing. Pickett *et al*¹² investigated respiration during sleep in nine healthy postmenopausal women after one week of treatment with combined oestrogen and progesterone or placebo. Mild sleep apnoea was observed in patients receiving placebo (apnoea/hypopnoea index 15 (4)), which decreased following treatment with oestrogen and progesterone to 3 (1). Despite these changes no difference in sleep architecture or arousals, and only minimal decreases in mean apnoea/hypopnoea duration, were observed between medication and placebo. Because of the impressive decrease in the apnoea/hypopnoea index after combined hormone treatment reported in that study, and a case report of the effectiveness of combined treatment in more severe sleep apnoea,³ we proceeded to examine the effect of conventional dose oestrogen and progesterone replacement in postmenopausal patients presenting with moderate to severe forms of sleep apnoea. Our negative findings strongly suggest that conventional hormone replacement therapy is not a treatment alternative for postmenopausal women with sleep apnoea.

A number of factors may explain the discrepancy between the results of our study and those of the previous reports. Most patients in our study were obese and this, rather than changes in hormone levels, is likely to be the dominant factor in producing apnoea. The subjects studied by Pickett *et al*¹² were all of normal weight with no reported history of sleep apnoea. High, non-conventional doses of oestrogen and progesterone were used in their study (medroxyprogesterone acetate 20 mg three times daily and conjugated equine oestrogens, Premarin, 1.25 mg twice daily), and these are likely to be associated with significant side effects precluding their clinical use. Our study was open and not placebo controlled, so it is possible that a therapeutic effect of hormone replacement may have been obscured by a "first night effect" leading to reduced apnoea severity at baseline. We feel this is unlikely as patients had similar sleep architecture in both studies.

We did note a small but clinically insignificant reduction in the apnoea/hypopnoea index during REM sleep, despite no change in the absolute amount of REM sleep. There were also some individuals with a clinically significant fall in the apnoea/hypopnoea index but this did not correlate with the increment in serum oestrogen level following treatment. It is possible, therefore, that some individuals may well have a therapeutic response to oestrogen and progesterone, but in general the effect

of hormone replacement on sleep apnoea was disappointing.

Sex hormones influence ventilatory control which, in turn, may affect sleep apnoea. Progesterone is known to stimulate ventilation and increase chemosensitivity during the luteal phase of the menstrual cycle,¹² in pregnancy,¹³ and in normal men.^{14,15} Progesterone can improve ventilation in patients with alveolar hypoventilation,¹⁶ but its effects on the degree of sleep apnoea in men¹⁷ are relatively minor. Goodman *et al*¹⁸ found that the ventilatory stimulation induced by progesterone was prolonged in the presence of oestrogen. Maximum stimulation of ventilation by progesterone has been shown to occur after seven days, with initial effects at 48 hours.¹⁹ Surprisingly, we were unable to show a significant change in the hypercapnic ventilatory response in our patients after 50 (3) days of treatment, even in those receiving progesterone. It is likely that this relates to the lower doses used in our study compared with previous studies. In contrast, the hypoxic ventilatory response did increase. Despite a tendency for PETCO₂ levels to be lower after hormone replacement, there was a significant increase in the slope of sensitivity *v* PCO₂ (k_v) indicating a larger interactive component with carbon dioxide. The significance of this finding in the absence of any major change in apnoea is uncertain. It is possible, however, that this change in hypoxic responsiveness might relate to the improved apnoea in REM. Although there are conflicting data from animal and human studies, at least one study suggests that the hypoxic reflex system plays a relatively more important part in REM sleep.²⁰

In summary, our data indicate that short term hormone replacement therapy in conventional doses does not significantly reduce the clinical severity of obstructive sleep apnoea in postmenopausal women. It is possible that higher doses or longer treatment may influence sleep apnoea in some individuals but, in general, sleep disordered breathing does not appear to be related simply to low levels of oestrogen and progesterone.

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