Rapid communication

Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome

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Abstract
Background—Patients with the sleep apnoea/hypopnoea syndrome (SAHS) report improved sleepiness, cognitive function, and psychological well being after continuous positive airway pressure (CPAP) therapy, and it is for these daytime features that CPAP is usually given. However, few randomised or controlled studies exist on the effects of CPAP on daytime function.
Methods—A prospective, randomised, single blind, placebo controlled, crossover trial of daytime function after CPAP was conducted in 23 patients with SAHS, all with ≥15 apnoeas+hypopnoeas/hour and ≥2 symptoms of SAHS. All patients spent four weeks on CPAP therapy and four weeks on oral placebo treatment, following randomisation to treatment order. With ethics committee approval, patients were told the placebo tablet might improve upper airway function. Average effective CPAP use was monitored using hidden time clocks. Assessments of objective and subjective sleepiness, symptoms, cognitive performance, and psychological well being were performed on the last day of each treatment and compared.
Results—Objective sleepiness measured by sleep onset latency on the multiple sleep latency test improved with CPAP (mean difference from placebo +2.4 min, 95% CI 0.8 to 4.0; p<0.001) as did subjective sleepiness on the Epworth scale (mean difference –6, 95% CI –3 to –9; p = 0.001). Symptom total score also fell with CPAP (mean difference –1.6, 95% CI –2.2 to –1.0; p<0.001). No determinants of these changes with active treatment were identified, and no significant enhancements to cognitive function or psychosocial well being were found in this small sample.
Conclusions—These findings provide further evidence for clinically significant benefits to daytime function from CPAP.
(*Thorax* 1998;**53**:341–345)

Keywords: sleep apnoea/hypopnoea syndrome; continuous positive airway pressure; sleepiness; psychomotor performance; affective disorders

Excessive daytime sleepiness, cognitive deficits, and impaired psychosocial function[1–5] are major features of the sleep apnoea/hypopnoea syndrome (SAHS), and provide the greatest incentive to seek treatment. The current treatment of choice is continuous positive airway pressure (CPAP) but the evidence for the efficacy of CPAP has recently been challenged by Wright *et al*[6] who concluded from a systematic review of the benefits of CPAP in SAHS that "the results . . . do not . . . provide sufficiently robust evidence for the effectiveness of continuous positive airway pressure".

Randomised controlled trials of daytime function after intervention with CPAP are few.[7 8] In one recent report of 32 patients with a wide range of severity of SAHS[7] we observed significant enhancements for objective and subjective sleepiness, cognitive function, psychological well being, and functional status following CPAP therapy. A smaller study in 16 patients with mild SAHS[8] showed no changes in sleepiness but improved symptoms, cognitive performance, and psychosocial well being with CPAP.

We report here a further prospective, randomised, placebo controlled study designed to control for placebo and learning effects, and conducted in a sample of symptomatic patients with moderate and severe SAHS. The trial tested the hypothesis that sleepiness, cognitive performance, and psychological well being would improve with CPAP, and sought possible determinants of such improvements.

Methods

STUDY PROTOCOL
A prospective series of 23 patients with SAHS completed the single blind, placebo controlled, crossover study of daytime function on CPAP following the previously reported assessment protocol.[7] Entry criteria included ≥15 apnoeas + hypopnoeas per hour slept on polysomnography, scored by our usual methods,[1 9] in

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Table 1   Daytime function assessments

Sleepiness	Multiple sleep latency test (MSLT)
	Epworth sleepiness scale
	UWIST mood adjective checklist (UMACL)
Symptoms	8-item questionnaire
	(snoring, nocturnal choking, morning headache, morning confusion, nocturnal awakenings, daytime napping, evening napping, sleepiness whilst driving)
Cognitive performance	30 minute SteerClear
	TrailMaking B
	WAIS-R performance IQ (Block Design and Digit Symbol Substitution)
	National Adult Reading Test (NART)
	Rapid Visual Information Processing (RVIP)
	8-choice reaction time
	Paced Auditory Serial Addition Test (PASAT: 2 second presentation rate)
	Verbal Fluency
	Benton Visual Retention Test (BVRT)
Psychological well being	Hospital Anxiety and Depression Scale (HADS)
	General Health Questionnaire-28 (GHQ-28)
	Nottingham Health Profile (NHP) part 2

conjunction with two or more of eight symptoms of SAHS (table 1).[2] Patients with lung disease, neurological disorders, and coexisting sleep disorders or who lived more than 50 miles from the Scottish National Sleep Centre were excluded.

Patients spent four weeks on CPAP (Sullivan APD-1 units, ResCare Ltd, Abingdon, UK) and four weeks on an oral placebo tablet (Glaxo, UK) in random order. The trial was conducted and analysed on an "intention to treat" basis with the randomisation slot of one unavoidable patient withdrawal (due to myocardial infarction during the CPAP limb) filled with the next available recruit. With the permission of the local ethics subcommittee patients were told that the placebo treatment, prescribed as two tablets per night, might improve upper airway function. Patients were advised to use CPAP as long as possible each night, had access to telephone advice and nursing support, and were contacted two weeks into the CPAP treatment limb to manage any problems or side effects, so optimising compliance.

Before starting treatment patients underwent baseline evaluation on all daytime function tests except the multiple sleep latency test (MSLT) (table 1) in order to reduce subsequent learning effects, and were educated in the mechanisms of action of CPAP therapy and placebo. All attended for overnight CPAP titration to establish an optimum pressure to reduce hypopnoeas and arousals. During the CPAP treatment period objective CPAP use was monitored with two hidden time clocks, one logging total duration that units were switched on and the second that CPAP was delivered effectively to the nasal mask,[10] allowing average use rates to be calculated. All measurements in table 1 were repeated on the last day of each treatment period. At the final assessment subjects were asked to rate which treatment they preferred.

ANALYSIS OF DATA

The measurements obtained at assessments during placebo and CPAP treatment periods were compared with alpha significance set at p values of <0.05. Analyses were conducted using repeated measures analysis of variance for continuous normally distributed variables, paired Wilcoxon tests for ordinal and non-normally distributed data, and McNemar tests for dichotomous variables. Treatment preference was assessed by binomial test. The analysis of variance included treatment type as a within subject factor and treatment order as a between subjects factor. Significant treatment order effects were managed as recommended[11] by performing unpaired comparisons of first treatment assessments only to evaluate treatment effects.

Determinants of treatment effect were sought by entering effective CPAP use and polysomnographic variables (apnoea/hypopnoea index (AHI), microarousal index, 4% desaturation index, and minimum oxygen saturation, each normalised by log transformation) as covariates

Table 2   Mean (SD) treatment effects on daytime function

	Direction of improvement	*Baseline*	*Placebo*	*CPAP*	Treatment difference (CPAP—placebo)		
					Mean	*(95% CI)*	*p value*
Sleepiness							
Mean sleep onset latency (min)	+	Not performed	6.8 (4.3)	9.2 (3.9)	+2.4	(0.8 to 4.0)	<0.001
Epworth sleepiness score*	−	12.0 (4)	12 (4)	6 (3)	−6	(−3 to −9)	0.001
UMACL Energetic arousal	+	21 (5)	21 (4)	22 (5)	+1	(−1 to 4)	NS
Symptoms							
Symptom total†	−	5.1 (1.5)	3.8 (1.3)	2.2 (1.6)	−1.6	(−2.2 to −1.0)	<0.001
Cognitive performance							
SteerClear (obstacles hit)†	−	100 (63)	71 (40)	63 (27)	−8	(−21 to 5)	NS
TrailMaking B (s)†	−	84 (41)	68 (32)	69 (32)	+1	(−7 to 9)	NS
Digit symbol substitution	+	48 (12)	52 (14)	52 (13)	0	(−2 to 2)	NS
Block design	+	29 (11)	31 (8)	33 (9)	+1	(−1 to 3)	NS
Performance IQ decrement	−	6 (12)	4 (11)	3 (11)	−1	(−3 to 2)	NS
RVIP (correct)	+	28 (10)	35 (13)	34 (15)	−1	(−4 to 2)	NS
8-choice reaction time (ms)	−	346 (57)	325 (38)	327 (46)	+2	(−8 to 12)	NS
2 second PASAT	+	31 (8)	35 (11)	37 (11)	+2	(0 to 5)	NS
Verbal fluency (total)	+	39 (12)	42 (11)	41 (12)	−1	(−4 to 2)	NS
BVRT (correct)†	+	7.3 (2.3)	7.7 (1.7)	7.7 (1.5)	+0.1	(−0.5 to 0.7)	NS
Psychological well being							
HADS anxiety†	−	8.3 (4.4)	7.0 (4.5)	7.0 (3.6)	0.0	(−1.4 to 1.4)	NS
HADS depression†	−	5.7 (4.4)	4.3 (3.8)	3.9 (3.4)	−0.5	(−1.8 to 0.8)	NS
GHQ-28†	−	6.6 (6.5)	3.7 (6.1)	5.0 (5.8)	+1.3	(−1.5 to 4.1)	NS
NHP Pt 2†	−	8.0 (5.0)	6.3 (5.7)	5.8 (5.4)	−0.5	(−2.5 to 1.5)	NS

NS = non-significant; UMACL = UWIST mood adjective checklist; RVIP = rapid visual information processing; PASAT = paced auditory serial addition test; BVRT = Benton visual retention test; HADS = Hospital anxiety and depression scale; GHQ-28 = General health questionnaire-28; NHP = Nottingham health profile.
*First assessments compared.[11]
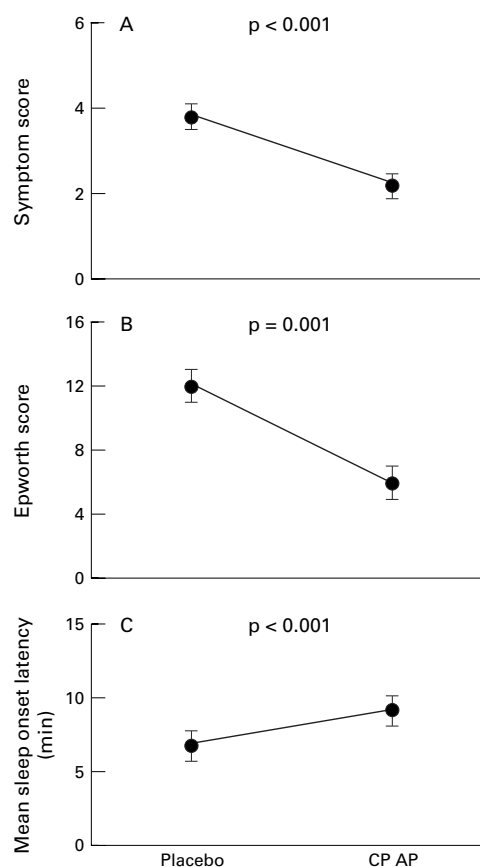†Mann-Whitney test.

Figure 1 Significant improvements in (A) symptom total score, (B) subjective sleepiness (Epworth score), and (C) objective sleepiness (MSLT) showing mean (SE) values on placebo and CPAP.

in significant analyses of variance. All analyses were conducted using SPSS/PC+.

Results

The mean (SD) age of the 23 patients (two women) was 47 (12) years, with a mean body mass index of 30 (7) kg per m² at baseline. Clinical polysomnography yielded an average AHI of 43 (37) per hour slept, 50 (36) micro-arousals per hour slept, 21 (30) 4% O_2 desaturations per hour slept, and mean minimum oxygen saturation of 77 (13)%.

Thirteen patients were randomised to commence with the placebo treatment and 10 with CPAP therapy. During the CPAP limb, CPAP
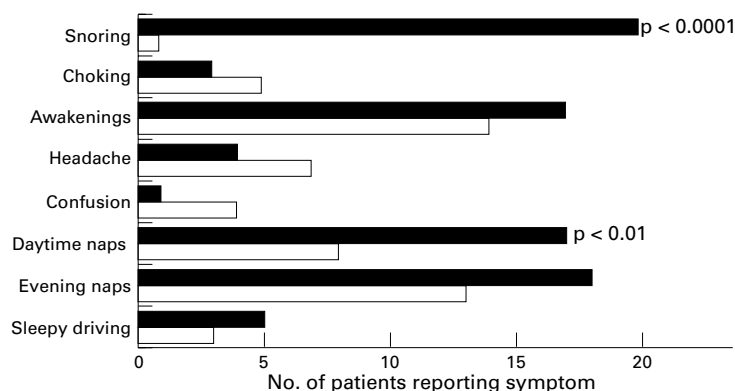

Figure 2 Frequencies of patients reporting individual symptoms on placebo (solid bars) and CPAP (open bars). Significant treatment differences in symptoms are labelled; unlabelled differences are not significant.

units were switched on for an average 3.2 (1.9) hours per night and used effectively for 2.8 (2.0) hours per night. The patient sample available for analysis was reduced to 22 for each of SteerClear and eight-choice reaction time tasks (due to computer malfunction), paced auditory serial addition test (due to a patient's stammer), and Epworth scale (due to the late addition of this measure).

TREATMENT ORDER AND LEARNING EFFECTS

A significant effect of treatment order was demonstrated for Epworth sleepiness score alone, necessitating in this variable a secondary analysis of treatment effect.[11] Significant treatment × treatment order interactions, representing learning effects from first to second treatment assessment, were demonstrated for sleep onset latency on the multiple sleep latency test (MSLT), and scores for Steer-Clear, rapid visual information processing (RVIP), two second paced auditory serial addition test (PASAT), and Benton visual retention test (BVRT). These learning effects were controlled by randomised treatment order.

TREATMENT EFFECTS

Mean sleep onset latency from the multiple sleep latency test (MSLT) was significantly higher on CPAP (mean (SD) 9.2 (3.9)) by an average 2.4 min (95% CI 0.8 to 4.0 min; p<0.001) compared with placebo values, reflecting improved objective daytime sleepiness (table 2, fig 1C) approaching the range characterised as normal.[12] Subjective sleepiness (Epworth scale (fig 1B)) was also reduced by six points (95% CI –3 to –9; p = 0.001) with CPAP, the mean placebo rating (12 (4)) falling within the pathological range and average CPAP score (6 (3)) within normal limits.[3] The total symptom score fell by a mean 1.6 (95% CI –2.2 to –1.0; p<0.001) on CPAP compared with placebo (fig 1A) with two of the eight individual items (snoring and daytime napping) showing significant improvements (p<0.01; fig 2). Twelve of the 23 patients preferred CPAP treatment, this proportion remaining non-significant (p>0.9). No changes in cognitive performance or psychosocial function with active CPAP treatment were found.

ANALYSES OF COVARIANCE

No significant covariates for these significant treatment effects were found amongst the putative determinants of effective CPAP use and polysomnographic severity variables.

Discussion

These 23 patients with moderate and severe SAHS showed improvements in objective sleepiness and symptoms after CPAP similar in scale to those documented in our report in patients with a wide range of severity of SAHS.[7] In addition, self ratings using the Epworth scale showed a substantial reduction in subjective sleepiness with CPAP, similar in scale to that seen in uncontrolled studies of CPAP treatment.[3] The changes in objective and

subjective sleepiness observed are not only statistically but clinically significant, and are as large or larger than those in a placebo controlled study of stimulant therapy in narcolepsy which used similar measures of daytime function.[13] Through randomisation of treatment order and the inclusion of a placebo limb, this trial offers controls for the effects of learning and the expectation of treatment benefit by patients. We believe that this further randomised controlled trial provides some of the evidence needed to rebut the conclusion of Wright *et al*[6] of lack of convincing evidence for the efficacy of CPAP.

The crossover study design employed allowed the scale of combined learning and placebo effects to be estimated by the differences between baseline and placebo scores (table 2), which demonstrate large and wide ranging improvements in both objective and subjective measurements. Despite test familiarisation at the baseline assessment, significant learning effects between the subsequent treatment assessments, evaluated as treatment × treatment order interactions, were also common. These observations accent the need, highlighted by Wright,[6] for controlled studies of treatment intervention.

Both Wright *et al*[6] and an Australian systematic review[14] questioned the use of an oral placebo in a previous study.[7] This was selected, as in this trial, for scientific reasons, as subtherapeutic (sham) CPAP might induce hypoxaemia[15] and because the lesser force of reduced CPAP is perceptible, thus unblinding a crossover trial. Our oral placebo was represented to the patients as a treatment which might improve upper airway function, and 12 of 23 patients preferred placebo, suggesting that some believed its efficacy. Our previous study[7] was also criticised for lack of a washout period[6] but no measurements were made for 28 days after crossover of treatments, while the effects of CPAP last as little as 24 hours.[16] The low severity of SAHS in our patients was also questioned[14] and is addressed by this study which included only patients with moderate or severe SAHS.

The substantial improvement in subjective sleepiness reported with CPAP contrasted with a smaller magnitude of change in objective measurements of sleep onset latency. Small or non-significant increases in sleep onset latency following CPAP have also been observed previously by ourselves[7 8] and others[4 16] in patients with SAHS. The contrast between subjective and objective sleepiness outcomes highlights unresolved methodological difficulties in repeated measures of sleepiness. A proportion of this discrepancy may arise from the learning effect for mean sleep onset latency demonstrated in this trial, in which onset latencies shortened by an average of two minutes on second testing, independent of treatment type.

No enhancements to cognitive function or psychosocial well being were documented in the 23 patients. It is likely that the relatively small sample size and limited statistical power of this trial will have contributed to this result,

particularly in cognitive variables which show high variability between treatments.

As in previous studies,[7 8 10 16] covert monitoring revealed low objective CPAP use rates, despite proactive efforts to minimise side effects. Although disappointing, such low use rates are a feature of prospective "intention to treat" trials which do not exclude self-selecting "CPAP refusers". Compliance with tablet and inhaler therapy in other chronic conditions is of the same order.[17 18] CPAP is an obtrusive therapy and this probably contributes to relatively low use rates, and also to some patient's preference for placebo tablets.

This study contained 18 outcome measurements, included because of lack of evidence indicating which domains of function improve after CPAP, but raising the possibility of type 1 statistical errors. Although this cannot be discounted, the number of significant differences observed between CPAP and placebo, their consistent direction showing better function with CPAP as hypothesised, and their cross-validation from previous studies in independent samples,[7 8] strengthen the reliability of these findings.

This randomised controlled crossover study shows that patients with SAHS, with an AHI of ≥ 15 per hour slept, benefit from CPAP treatment, and provides objective and controlled substantiation of patients' reports of functional improvements with CPAP.[19]

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