No effects on sleep of a histamine H₁-receptor antagonist: temelastine

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Twelve volunteer poor sleepers of mean age 57 years took placebo on each of 3 consecutive nights, and temelastine 100 mg on 3 consecutive nights in a double-blind balanced order study. Sleep in the EEG laboratory was unaffected by the drug.

Keywords antihistamines H₁-receptor antagonist temelastine sleep

Introduction

The older antihistamine drugs have the disadvantage of causing drowsiness by day and when, for example, promethazine 20 mg is studied in the sleep laboratory for its effects on the sleep of middle-aged poor sleepers it is found to be a potent hypnotic in that it increased sleep duration and reduces the frequency of interruptions of sleep (Adam & Oswald, 1986). Temelastine (SK&F93944) is a new selective H₁-receptor antagonist with minimal entry to the brain (Brown *et al.*, 1986). The present study was designed to investigate possible CNS effects by determining whether temelastine 100 mg would have any detectable effect on EEG measures of sleep. The dose used was that reported to be effective in treatment of allergic rhinitis (McCall *et al.*, 1985), with an action of rapid onset and duration of at least 8 h (Alexander *et al.*, 1984).

Methods

Twelve volunteers, selected because they believed themselves to be poor sleepers, nine women and three men, aged 50–69 (mean 57 years) took part. They had taken no CNS drugs in the preceding 3 months, they agreed to abstain from alcohol and other CNS drugs for 1 week before and throughout the study, and gave their informed consent. They took part with the

agreement of their family doctors, and with the approval of the Ethics Committee of the Royal Edinburgh Hospital. None suffered from nasal obstruction or allergic disorders.

Subjects attended the sleep laboratory on 3 consecutive nights and then after an interval of 4 days attended for a further 3 consecutive nights. On one group of 3 nights subjects received temelastine 100 mg, 30 min before lights-out and matching placebos on the other 3 nights, in accordance with a double-blind, balanced order design.

On each night the electroencephalogram (EEG), eye movements, and submental muscle tone were recorded. Lights-out was at 22.30 h and the recordings ended at 07.00 h, all subjects on all nights being recorded for the same length of time. Eventually all sleep records were coded, randomly mixed in the order in which they would be scored, and then scored 'blind' for the different stages of sleep and wakefulness. The code was then broken and the data analyzed.

Parametric analysis was used for the majority of measures, employing a two-way analysis of variance with two treatments and three nights as the repeated measures factors. Because only two conditions were compared, this part of the analysis of variance was equivalent to a paired *t*-test between the means of the 3 placebo nights and the means of the 3 drug nights. A significant

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F value for the night term in the analysis of variance would have alerted us to any difference in sleep across the 3 nights and a significant treatment $\times$ night interaction would have suggested a difference between the two treatments in the pattern of sleep across the 3 nights. Sleep latencies are skewed in distribution and these were analyzed by first converting to natural logarithms before parametric statistical analysis. REM sleep latency has a bimodal distribution, and these results were analyzed using the Wilcoxon signed ranks test to compare the subjects' means for the 3 placebo nights with their means for the drug nights. The Wilcoxon test was also used to analyze measures of wakefulness.

Results

A total of 30 sleep measures were investigated, without finding any indication of a drug effect, and Table 1 shows only the more important variables, as means for the 12 subjects. The

subjects averaged 10 min more sleep after temelastine, but there was no significant difference from the placebo treatment ($F = 0.91$, $df = 1, 11$, $P = 0.36$). There was no suggestion at all of any reduction of REM sleep by the drug. All subjects on all nights slept for a total of at least 4 h and Table 1 shows that awakenings and REM sleep in the first 4 h of accumulated sleep were similar on both treatments. There were no significant night effects, nor treatment $\times$ night interaction effects, which means that there was no evidence of a cumulative effect, nor of any emerging effect by the third night of drug intake.

Discussion

As age advances the brokenness of sleep tends to increase and consequently a middle-aged group such as the present provides a sensitive instrument for the investigation of any effects of a drug on sleep. Two experimental approaches can be adopted to assess whether an antihistamine drug may have sedative properties: its effects on

Table 1 Sleep after placebo and after temelastine

	Placebo	Temelastine 100mg	Significance of within-subject comparisons
Total sleep (min)	420.1 $\pm$ 38.9	429.9 $\pm$ 27.2	NS
Sleep latency (min)	28.7 (8.4 – 59.9)	28.1 (9.9 – 56.5)	NS
Total stage 1 (min)	32.9 $\pm$ 10.6	31.9 $\pm$ 8.6	NS
Total stage 2 (min)	233.8 $\pm$ 30.7	236.4 $\pm$ 25.9	NS
Total stages 3 + 4 (min)	68.9 $\pm$ 21.9	70.5 $\pm$ 24.3	NS
Total REM sleep (min)	84.4 $\pm$ 19.7	91.1 $\pm$ 15.6	NS
REM %	19.9 $\pm$ 3.7	21.1 $\pm$ 3.3	NS
REM latency	73.3 (47.0 – 143.0)	69.4 (52.7 – 83.9)	NS
Number of awakenings in first 4 h accumulated sleep	3.3 (1.0 – 8.0)	3.3 (0.0 – 9.3)	NS
Min of wakefulness in first 4 h accumulated sleep	25.0 (3.2 – 75.0)	15.3 (0.0 – 34.7)	NS
Min of REM sleep in first 4 h accumulated sleep	36.8 $\pm$ 12.1	37.9 $\pm$ 9.1	NS
Means $\pm$ s.d. (or range) for the 12 subjects on each treatment			

sleep can be measured, or its effects on daytime psychomotor functions. It is the first of these that has been adopted here by analogy with our earlier study of a conventional antihistamine, promethazine 20 mg, which we found to increase the sleep duration of a similar group of subjects by nearly 1 h (Adam & Oswald, 1986). The uniformly negative findings from the present study stand in sharp contrast, and suggest that temelastine may belong to a small group of antihistamines free of sedative effects, consistent with its negligible entry into the central nervous

system (Brown *et al.*, 1986). Whereas enhancement of sleep at night by promethazine 20 mg is paralleled by impaired daytime psychomotor function after a 25 mg dose (Hindmarch & Parrott, 1978), it may be predicted from our present negative findings that daytime psychomotor testing with temelastine 100 mg would fail to show impairment. It is noteworthy that terfenadine, a histamine H_1 -receptor antagonist, has been reported not to speed sleep onset (Roehrs *et al.*, 1984), nor to cause impairment on a daytime driving task (Betts *et al.*, 1984).

References

- Adam, K. & Oswald, I. (1986). The hypnotic effects of an antihistamine: promethazine. *Br. J. clin. Pharmac.*, **22**, 715–717.
- Alexander, F., Stote, R. M., Hurley, J. N., Allison, N. L., Tatoian, D., Familiar, R. G. & Dubb, J. W. (1984). Inhibitory activity of SK&F 93944 on histamine induced wheals. *Pharmacologist*, **26**, 222, Abstr. 492.
- Betts, T. Markman, D., Debenham, S., Mortiboy, D. & McKeivitt, T. (1984). Effects of two antihistamine drugs on actual driving performance. *Br. med. J.*, **288**, 281–282.
- Brown, E. A., Griffiths, R., Harvey, C. A. & Owen, D. A. A. (1986). Pharmacological studies with SK&F93944, a novel histamine H_1 -receptor antagonist with negligible ability to penetrate the central nervous system. *Br. J. Pharmac.*, **87**, 569–578.
- Hindmarch, I. & Parrott, A. C. (1978). A repeated dose comparison of the side effects of five antihistamines on objective assessments of psychomotor performance, central nervous system arousal and subjective appraisals of sleep and early morning behaviour. *Arzneim.-Forsch. (Drug Res.)*, **28**, 483–486.
- McCall, M. K., Nair, N., Wong, S., Townley, R. G., Lang, D. & Weiss, S. J. (1985). Double-blind controlled safety and efficacy trial of SK&F93944. *J. Allergy clin. Immunol.*, **75**, 168, Abstr. 256.
- Roehrs, T. A., Tietz, E. I., Zorick, F. J. & Roth, T. (1984). Daytime sleepiness and antihistamines. *Sleep*, **7**, 137–141.

(Received 18 March 1986,
accepted 1 August 1986)