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The hypnotic effects of an antihistamine: promethazine

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Twelve volunteer poor sleepers of mean age 59 years took placebo on one night, promethazine 20 mg on one night and promethazine 40 mg on one night, in a double-blind balanced order study. Sleep in the EEG laboratory was increased by nearly 1 h after either dose of promethazine, and sleep interruptions were reduced. Slow-wave sleep was unaffected, but the larger dose reduced the percentage of sleep spent as REM sleep. Sleep was improved subjectively by both doses of promethazine which appears to be an effective hypnotic.

Keywords promethazine sleep REM sleep hypnotic antihistamine

Introduction

It has been widely accepted that when patients take promethazine for its antihistamine properties they frequently feel drowsy, and Hindmarch & Parrott (1978) reported that, compared with placebo, promethazine 25 mg taken at bedtime caused subjectively quicker sleep onset and subjectively improved sleep quality. However, the anti-depressant drug trazodone is an example of another drug that will cause sleep quality to be subjectively improved, yet it does not increase the duration of sleep (Montgomery *et al.*, 1983), as do the established hypnotic drugs. Many hypnotic drugs are the subject of dependence and abuse, whereas the reputation of phenothiazine drugs, including promethazine, is of low potential for dependence and abuse. This last factor provides one justification for the non-prescription sale of promethazine in the United Kingdom as an hypnotic drug (Sominex: Beecham Proprietaries). It was therefore of interest to determine whether in the sleep laboratory promethazine would be found not merely to improve sleep subjectively but to increase its duration and make sleep less broken by objective measurement.

Methods

Twelve volunteers, selected because they believed themselves to be poor sleepers, nine women and three men, aged 45–70 (mean 59 years), took part in the study. They had taken no CNS drugs in the preceding 6 weeks, they agreed to abstain from alcohol and other CNS drugs for the week before and throughout the study. They 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 4 nights spread over 2 weeks, coming at intervals of 4 days. The first night was for adaptation and placebo was taken. On the other three nights, each subject received one of three matching medications: placebo, promethazine 20 mg, promethazine 40 mg, according to a double-blind, balanced order design.

On each night the electroencephalogram (EEG), eye movements, and submental muscle tone were recorded. Lights-out was at about 22.30 h and 8.25 h were recorded each night. Eventually all sleep records were coded, mixed

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in order and categorised 'blind' for the different stages of sleep and wakefulness. The code was then broken and the data analysed.

Each subject, on every morning after sleeping in the laboratory, about 20 min after rising, completed visual analogue 100 mm scales to make a subjective rating of the quality of the night's sleep (worst possible—best ever) and of how alert and vigilant he or she felt (marvellously alert and energetic—awfully sleepy and lacklustre).

Analysis of variance with nights as the repeated measure and, where appropriate, subsequent *t*-tests for paired observations, were generally used in the statistical evaluation, where the pair-differences were normally distributed. Sleep onset latency data were first normalised by converting the raw values into natural logarithms. The Friedman non-parametric analysis of variance was employed for the REM latency data. All *P* values quoted are for two-tailed level of significance.

Results

Table 1 shows the principal findings as means for the twelve subjects. Both doses of promethazine led to a significant increase by nearly an hour in the total duration of sleep, mainly by increasing the amount of Stage 2 sleep. All subjects on all nights slept for at least 4 h and both dosages of promethazine significantly reduced the number of awakenings from sleep in the course of accumulating the first 4 h of sleep. Slow-wave sleep (stages 3 + 4) was not affected by promethazine. The percentage of total sleep spent as REM sleep was significantly reduced by the 40 mg dose of promethazine. Significance did not emerge from the REM latency data, using the non-parametric analysis of variance. The preliminary analysis of variance for the sleep latency data did not approach significance. Comparisons between the effects of the 20 mg and the 40 mg dosage did not reveal any significant differences.

The subjective ratings of sleep quality showed an increase from a mean of 45.8 mm on placebo to 63.5 mm on promethazine 20 mg ($t = 2.82$, df = 11, $P < 0.02$) and to 65.3 mm in the case of promethazine 40 mg ($t = 2.76$, df = 11, $P < 0.02$). The preliminary analysis of variance for subjective morning vigilance ratings did not approach significance.

Discussion

The results confirm that promethazine, in as small a dose as 20 mg, is not only an effective hypnotic by subjective criteria, but also by objective criteria, and the findings suggest a direct effect on the brain rather than, for example any effect via reduced nasal congestion. The increase of sleep duration and the reduction in the brokenness of sleep caused by promethazine parallel what is found in middle-aged poor sleepers after, for example, nitrazepam 5 mg or chlormezanone 400 mg (Adam & Oswald, 1982), lormetazepam 1 mg (Adam & Oswald, 1984), loprazolam 1 mg or triazolam 0.5 mg (Adam *et al.*, 1984), and it is of interest that since 1985 promethazine has been marketed in the United Kingdom as a non-prescription hypnotic. The

Table 1 Means ± s.d. for the 12 subjects when on each treatment.

	Placebo	*Promethazine 20 mg*	*Significance*	*Promethazine 40 mg*	*Significance*
Total sleep (min)	401.0 ± 58.6	458.9 ± 16.0	$P < 0.01$	452.7 ± 44.9	$P < 0.05$
Total stage 1 (min)	36.3 ± 23.6	41.2 ± 19.4	NS	37.8 ± 18.0	NS
Total stage 2 (min)	217.2 ± 42.8	257.9 ± 38.5	$P < 0.01$	258.9 ± 49.8	$P < 0.05$
Total stages 3 + 4 (min)	62.9 ± 36.3	74.7 ± 31.2	NS	79.2 ± 53.4	NS
Total REM sleep (min)	84.5 ± 28.0	85.1 ± 23.4	NS	76.8 ± 23.0	NS
REM %	21.0 ± 5.9	18.5 ± 5.0	NS	16.9 ± 4.8	$P < 0.01$
Number of awakenings in first 4 h accumulated sleep	3.8 ± 2.1	2.1 ± 0.8	$P < 0.05$	2.2 ± 1.9	$P < 0.05$

Significance refers to within-subject comparisons and placebo-20 mg or placebo-40 mg differences

present study was, however, limited to the effects of single dosages only, whereas in the other studies cited, assessment was made of any tolerance during 3 weeks of regular intake and of any later withdrawal effects.

The larger dose of 40 mg reduced the proportion of sleep spent as REM sleep, but precise pharmacological mechanisms cannot be inferred. A few drugs have been found to increase per cent REM sleep, including the α-adrenoceptor blocking agent, thymoxamine, given intravenously (Oswald *et al.*, 1975) or physostigmine given intravenously (Sitaram *et al.*, 1977). On the other hand a wide variety of drugs reduce per cent REM sleep, including amphetamines, barbiturates, scopolamine, monoamine oxidase inhibitors, clomipramine and desipramine (Oswald, 1973). The reduction we found is consistent with the report by Risberg *et al.* (1975) that promethazine in 50–200 mg dosage reduced per cent REM sleep. The latter authors had used 10 young men aged under 30 years as volunteers and found no effect on sleep duration. They correctly remarked that it is difficult to improve the sleep of those who already sleep well and that a study in insomniacs would probably give a different answer, as has now proved to be the case.

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