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Acute Effects of Hydroxyzine on Nocturnal Sleep and Sleep Tendency the Following Day: a C-EEG Study

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The acute hypnotic effects of hydroxyzine 25 mg and 50 mg nocte, were examined in six male and six female volunteers. Continuous electrophysiological measures (C-EEG) were taken to assess both nocturnal sleep and sleep tendency the following day. Both doses produced significant reductions in sleep onset latency and decreases in waking during sleep; reciprocal increases in sleep duration were also seen. Female subjects demonstrated a greater hypnotic response, including a dose-dependent decrease in sleep onset latency. Increases in sleep duration following both doses were significant for the female group alone. C-EEG measures of increased drowsiness the following day failed to achieve significance; although the largest effects on daytime sleepiness, including dose-dependent increases, were again seen with the female subject group and corresponded with subjective ratings. These results demonstrate the hypnotic efficacy of hydroxyzine, whilst failing to detect significant C-EEG hangover effects. However, variability in response to antihistamines, registered here as differences between the sexes, requires further consideration.

KEY WORDS—Hydroxyzine, sleep, hypnotic efficacy, hangover effects, sex differences.

INTRODUCTION

Following the detection of aminergic histamine blocking activity (Bovet and Staub, 1937) a wide variety of compounds have been synthesized (Goodman *et al.*, 1980). Sedation is a most common side-effect of antihistamine administration (White and Rumbold, 1988 Martindale, 1989); particularly for H1 blockers used in the control of allergic reactions and motion sickness; whilst H2 blockers generally exhibit less CNS penetration and less sedative side-effects when used in the control of gastric hypersecretion.

The sedative properties of H1 antagonists have led to their incorporation in many non-prescription preparations to aid sleep. Older compounds enter the CNS more readily and may be associated with greater sedative effects than newer compounds, which are supposed not to enter so readily, although their presence has been reported (Goodman *et al.*, 1980; White and Rumbold, 1988).

However, marked individual variation exists in sensitivity to the sedative effects of antihistamines (Clarke and Nicholson, 1978; Hindmarch and Bhatti, 1987), which may contribute to the lack of consistency for sedative effects reported in the literature.

Subjective effects on nocturnal sleep were investigated by Hindmarch and Parrott (1978) with five antihistamines, each given to a group of 10 subjects. Neither mebhydrolin nor clemastine produced significant effects. Ketotifen improved perceived sleep onset and quality, whilst promethazine additionally impaired perceived awakening. In contrast, chlorpheniramine improved perceived onset but not quality, whilst waking function the next day was significantly impaired. Adam and Oswald (1986a) also reported a significant increase in perceived sleep duration following promethazine; although Nicholson *et al.* (1985) observed a subjective sleep improvement with the H2 blocker ranitidine which was not seen with objective sleep measures.

Sleep laboratory studies have been few. Nicholson *et al.* (1985) investigated H1 blockers and reported a reduction in the number of awakenings with mequitazine, a reduction in REM with tripolidine but no effect for mepyramine given to six volunteers. They found an increase in slow-wave sleep (SWS) with cimetidine, but no effect for ranitidine amongst the H2 blockers. Solomon *et al.*

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(1989) also failed to find significant effects on SWS for the H1 blocker mepyramine, although an increased trend was apparent in their six volunteers.

Bassano and Caille (1979) reported a REM reduction with dexchlorpheniramine but did not see this effect with mequitazine when given to 12 healthy subjects for 7 days. However, their review cites common reductions in sleep latency to stage 2 for methapyrilene, hydroxyzine and diphenhydramine; but increases in REM latency for methapyrilene, promethazine and trimeprazine.

Two studies by Adam and Oswald (1986a,b) investigated the effects of H1 antihistamines on 12 poor sleepers. Whilst temelastine failed to produce significant effects, consistent with poor CNS penetration; promethazine significantly increased sleep duration including stage 2, with a reduction in awakenings, and reduction in REM% for the higher 40 mg) dose. They cite Risberg *et al.* (1975), who failed to find significant sleep duration effects with 50–200 mg promethazine given to normal sleepers; suggesting that it is difficult to improve sleep in 'good sleepers'. Adam and Oswald (1986a) alone indicate a significant increase in objectively measured sleep; standing against the claim by Roehrs *et al.* (1984) that antihistamines may not be effective hypnotics, failing to increase sleep duration although sleep latency may be reduced.

The present investigation was undertaken to evaluate the hypnotic potential of the H1 antihistamine hydroxyzine. This compound has been used as an anxiolytic and anti-stress agent with known significant subjective sedative effects (De Brabander and Deberdt, 1990). Effects on sleep have indicated a dose-related increase in subjective sleep duration (Brown *et al.*, 1974), although objective increases have yet to be established. Similarly, the sedative hangover potential on waking activity the following day, common to several benzodiazepine hypnotics (Alford and Hindmarch, 1992), requires investigation. The results of electrophysiological monitoring (C-EEG) are included here, with a summary of subjective measures, whilst a detailed psychometric evaluation will be presented separately (Alford *et al.*, 1991c).

MATERIALS AND METHODS

Subjects

The volunteer sample comprised six females and six males (mean age 33·8 years; range 18–44 years), who were run in two single-sex groups. All subjects were in normal physical health, having no history of cardiovascular, gastric, renal, hepatic or psychiatric disorder. Those receiving concurrent medication or other medical treatment (excluding the contraceptive pill), and those liable to become pregnant, or who were pregnant, were excluded from the study. Transport was provided for subjects, who were not permitted alcohol or caffeine containing foodstuffs and beverages on study days or the preceding 24 hours. Volunteers gave their informed consent in writing and the experimental protocol, written in accordance with the Declaration of Helsinki (Rome and Tokyo amendments), was approved by an independent Ethical Committee.

Treatments

Hydroxyzine 25 mg and hydroxyzine 50 mg were compared to placebo. All treatments were administered orally 1·5 hours before bedtime.

Experimental design and schedule

Subjects acted as their own controls in a double-blind crossover design; treatments were given according to a predetermined code based on Latin squares, and with subjects randomly assigned to a treatment number. A washout period of 1 week was observed between the start of each treatment.

Each treatment block lasted 24 hours, beginning with a light meal at 19.00 hours after arrival at the study centre. Electrodes were then attached to subjects and ambulatory monitoring commenced prior to a baseline psychometric test battery. This was followed by medication ($t0$), then a shorter version of the test battery (t_{+1}), and bedtime at 1·5 hours after treatment administration to allow for absorption (Gengo *et al.*, 1987). Subjects were awakened after an 8 hour nocturnal sleep period and completed a sleep questionnaire. Following breakfast and change of electrode placements to the daytime recording montage, a test battery was undertaken at $t_{+10{\cdot}5}$ hours. Subjects remained at the study centre where they had lunch, before completing a final test battery at 21 hours post-treatment. Electrodes were then removed before subjects returned home at the end of the study period.

A complete 24 hours attendance preceded the first treatment block, being run as a 'blind' (placebo) treatment, to provide familiarization with study procedure and a sleep adaptation period (Agnew, *et al.*, 1966). The use of Medilog ambulatory elec-

trophysiological monitors enabled two groups of six to be run, with bedrooms shared by subject pairs at the study centre.

Assessments

Continuous electrophysiological monitoring (C-EEG). Electrophysiological measures were taken using four-channel Oxford 'Medilog' ambulatory recorders providing a non-invasive technique for continuous electrophysiological measurement. For nocturnal sleep three channels of activity were recorded including EEG (C_z–A_1); EOG (FP_2–A_1); and submental bipolar electrode placements for EMG; to provide data compatible with the criteria of Rechtschaffen and Kales (1968).

For daytime recording the EMG channel was replaced with an occipital channel (O_z–A_2), providing specific information for the determination of sleep/wake status (Carskadon *et al.*, 1986). The fourth channel recorded time/event information. In addition to EEG the montage provided eye movement (EOG) activity and muscle artefact (EMG) information for the polygraphic determination of sleep/wake status. C-EEG recording is continuous, across both night and day periods.

The utility of portable recorders for assessing sleep has been demonstrated by Sewitch and Kupfer (1985). Previous research from our centre has demonstrated the further utility of the technique for assessing daytime sedation with antihistamines and for the evaluation of nocturnal sleep (Alford *et al.*, 1989; Rombaut *et al.*, 1989).

Each record was analysed visually, replaying the tape through the Oxford PMD12 replay monitor, with a 16 second epoch window. When required individual epochs were examined in detail. For the daytime analysis a note was made of the time and duration of alpha and theta activity synonymous with drowsiness. Sleep status was similarly evaluated using Rechtschaffen and Kales EEG criteria for each 16 second epoch. Two scorers were used to evaluate data, each scoring all data for a given subject.

Subjective assessments. Line analogue rating scales (LARS) were used to measure subjective feelings of 'tiredness', 'drowsiness' and 'alertness' with the mean score providing a measure of perceived sedation. The Leeds Sleep Evaluation Questionnaire (LSEQ) is similarly based on 10 cm line analogue scales recording subjective ratings for each of getting to sleep (GTS), sleep quality (QOS), ease of awakening from sleep (AFS) and perceived hangover following waking (BFW).

Statistical analysis. Analysis of variance procedures (ANOVA) were used to assess overall significance ($p<0{\cdot}05$) between subjects, sex and treatments. Where significant effects were obtained with ANOVA, differences between treatment means were contrasted using two-tailed 95 per cent confidence intervals (Kirk, 1968; Gardner and Altman, 1986; Bulpitt, 1987).

Electrophysiological data are frequently skewed (Oswald, 1980) and benefit from transformation to improve normality prior to parametric analyses. Consequently the results from the C-EEG analyses, for both nocturnal sleep and waking activity, were first assessed for skew using the dimensionless third moment and standard normal deviate (Snedecor and Cochran, 1967) with a technique adapted from Dunlap and Duffy (1974). Assessments were made for the raw data, and following a sequence of square root, log and reciprocal transformations (Winer, 1962, 1971; Kirk, 1968). The output was evaluated in sequence, starting with the raw data, to determine the minimum transformation yielding an approximation to normality. These data were then selected for statistical evaluation; although the means for the raw data and associated confidence intervals are presented in Tables 1–5.

RESULTS

Nocturnal sleep parameters reflecting overall sleep integrity and duration are presented in Table 1. These include measures of sleep latency, movement, waking and sleep duration. The frequency and duration of individual sleep stages are given in Table 2. Where significant, the response to treatments by sex are given in Table 3.

Measures of daytime sleepiness are given in Table 4, with a selected summary including statistical comparison of males and females given in Table 5.

Nocturnal sleep

Significant treatment effects were observed for sleep onset latencies to stage 1 (SOL1; $F = 18{\cdot}10$, $p < 0{\cdot}0001$) and stage 2 (SOL2; $F = 14{\cdot}63$; $p < 0{\cdot}0001$); and for the related sleep duration measures of total sleep time (TST; $F = 7{\cdot}05$; $p < 0{\cdot}0048$), sleep period time (SPT; $F = 7{\cdot}18$; $p < 0{\cdot}0045$) and sleep efficiency (SE%, $F = 4{\cdot}60$, $p < 0{\cdot}023$).

Table 1. Nocturnal sleep parameters—latencies, overall durations and integrity: untransformed means (95 per cent. confidence intervals)

Measure	Transform	Placebo	Hydroxyzine 25 mg	Hydroxyzine 50 mg
SOL1	Log	16·55	7·15*	7·30*
		(2·83)	(2·71)	(2·71)
SOL2	Log	22·55	12·28*	11·72*
		(3·61)	(3·46)	(3·46)
REML	Sqrt	129·73	113·36	105·08
		(16·1)	(16·1)	(15·41)
FMT	Log	9·91	10·50	10·00
		(2·10)	(2·01)	(2·01)
DuMT	Log	6·80	5·41	4·78
		(2·04)	(1·96)	(1·96)
FW	Log	6·45	5·00	3·33*
		(1·37)	(1·37)	(1·31)
DuW	Sqrt	24·36	14·45*	14·62*
		(4·46)	(4·46)	(4·27)
DuFW	Sqrt	11·82	8·19	8·88
		(4·46)	(4·46)	(4·27)
TIB	None	466·55	475·46	470·42
		(10·32)	(10·32)	(9·88)
SPT	None	432·18	455·59*	449·82
		(9·71)	(9·71)	(9·30)
TST	None	417·20	441·71*	439·50
		(11·43)	(11·43)	(10·95)
SE%	None	89·49	92·94	93·43
		(2·21)	(2·21)	(2·11)

SOL1, SOL2: sleep onset latencies (min) to stages 1 and 2; REML: latency (min) to stage REM; FMT: frequency of movement time (movement time = at least half an epoch obscured by movement artefact); DuMT: duration (min) of movement time; FW: frequency of waking; DuW: duration (min) of waking during sleep; DuFW: duration (min) of final waking after sleep until getting up; TIB: time in bed (min); SPT: sleep period time (min) = TIB − DuFW − SOL2; TST: total sleep time (min) = SPT − DuW; SE%: sleep efficiency = TST/TIB × 100.
Transformations: None: untransformed; recip: reciprocal; Sqrt: square root.
* Placebo vs $p < (0{\cdot}05)$ (95 per cent. confidence intervals).

Treatment effects were also seen for the frequency (FW; $F = 4{\cdot}81$; $p < 0{\cdot}020$) and duration of waking within sleep (DUW; $F = 4{\cdot}74$; $p < 0{\cdot}021$), including the stage percentage for waking (STPW; $F = 5{\cdot}78$; $p < 0{\cdot}010$). However, frequency and duration measures for other stages were not significant.

Although sex-by-drug interactions were not significant, some significant sex differences were apparent. These included sleep onset latencies SOL1 ($F = 8{\cdot}28$; $p < 0{\cdot}0074$), and SOL2 ($F = 10{\cdot}05$; $p < 0{\cdot}0036$). Sleep stage frequencies for stage 1 (F1; $F = 4{\cdot}26$; $p < 0{\cdot}048$), stage 2 (F2; $F = 10{\cdot}71$; $p < 0{\cdot}0028$) and REM (FREM; $F = 5{\cdot}11$; $p < 0{\cdot}032$).

Contrasts between means for the individual treatments indicated significant reductions in SOL1 and SOL2 after both 25 mg and 50 mg doses of hydroxyzine in comparison to placebo. Stage 1 latencies were approximately halved from 16 to 7 minutes, as were stage 2 latencies from 22 to 12 minutes, for both hydroxyzine doses in contrast to placebo. Dose-dependent decreases in REM latency (REML) of about 16 and 25 minutes were seen following hydroxyzine, but failed to achieve significance.

Movement scores were non-significant and remained stable across treatments with the exception of movement time duration (DuMT), where a dose-dependent trend for reduced movement time occurred. Similarly, a reduction in waking frequency achieved significance for the higher dose of hydroxyzine, whilst decreases in waking duration were similar and achieved significance following both 25 mg and 50 mg hydroxyzine.

Increases in sleep period time (SPT) and total

Table 2. Nocturnal sleep parameters—sleep stages: frequencies, durations and percentages: untransformed means (95 per cent. confidence intervals)

Measure	Transform	Placebo	Hydroxyzine 25 mg	Hydroxyzine 50 mg
F1	Sqrt	8·46	9·09	6·00
		(2·64)	(2·64)	(2·53)
Du1	Log	17·75	15·83	11·76
		(5·70)	(5·70)	(5·46)
Du2	None	216·36	233·09	227·48
		(24·95)	(24·95)	(23·89)
Du3	None	36·26	35·70	42·78
		(9·23)	(9·23)	(8·83)
Du4	None	65·00	61·76	68·55
		(12·71)	(12·71)	(12·17)
FREM	Recip	5·27	5·73	5·92
		(1·30)	(1·30)	(1·24)
DuREM	Sqrt	90·03	97·76	96·71
		(10·74)	(10·74)	(10·28)
STPTh	Recip	0·94	0·45	1·00
		(0·68)	(0·68)	(0·66)
STP1	Log	4·12	3·47	2·61
		(1·30)	(1·30)	(1·25)
STP2	None	50·03	51·15	50·59
		(5·42)	(5·42)	(5·19)
STP3	None	8·41	7·87	9·53
		(2·05)	(2·05)	(1·96)
STP4	None	15·06	13·56	15·26
		(2·97)	(2·97)	(2·85)
STPREM	Sqrt	20·79	21·44	21·50
		(2·30)	(2·30)	(2·21)
STPW	Sqrt	5·64	3·18*	3·27*
		(1·03)	(1·03)	(0·98)

F: frequency scores; Du: duration (min) scores; STP: stage percentages = Du/Sleep period time × 100 for sleep stages 1–4, REM and waking. Transformations: None: untransformed; Recip: reciprocal; Sqrt: square root.
* Placebo vs $p < (0·05)$ (95 per cent. confidence intervals).

sleep time (TST) of about 20 minutes reflected the reductions in sleep onset latency and waking duration for both hydroxyzine doses. However, the increases for the lower dose alone achieved significance in contrast to placebo, being slightly greater than those seen with the higher dose. Sleep efficiency scores demonstrated dose-dependent improvements of approximately 3 and 4 per cent following hydroxyzine over the placebo value of 89·5 per cent.

The response of individual sleep stages, excluding waking, failed to achieve significance (Table 2). However, a dose-related decrease in stage 1 duration (Du1) of about 2 and 6 minutes was contrasted with increased scores for stages 2 and REM, which were consistent across both doses.

Slow-wave sleep (stages 3 and 4) showed little change, although a slight increase in stage 3 (Du3) was observed following the higher dose (50 mg). The results for stage durations were mirrored in the stage percentage scores (STP1–4) including waking (STPW), where significant reductions occurred after hydroxyzine; although sleep stage frequencies were relatively unaffected.

Contrasts between the sexes indicated significantly greater frequencies for sleep stages 1 and 2 for females, and a significant reduction in latency to stage 2 for combined treatments when contrasted with males. The contribution of female and male subject groups to treatment effects was evaluated for variables where significant ANOVA effects occurred. Significant contrasts (Table 3) revealed the shortest sleep latencies for females. Although significant reductions in SOL1 were apparent for both sexes, a dose-related reduction was apparent for the females alone with sleep onset latency reduc-

Table 3. Nocturnal Sleep Parameters—Comparison of Male and Female Subject Groups : Untransformed means (95 per cent. Confidence Intervals)

Measure	Transform	Placebo	Hydroxyzine 25 mg	Hydroxyzine 50 mg
SOL1	Log			
Females		14·67	6·13*	4·77*
		(3·85)	(3·85)	(3·85)
Males		18·80	8·17*	9·83*
		(4·22)	(4·22)	(3·85)
SOL2	Log			
Females		22·00	10·21*	7·93*
		(4·91)	(4·91)	(4·91)
Males		23·20	14·33	15·50
		(5·38)	(5·38)	(4·91)
FW	Log			
Females		7·83	6·17	3·00*
		(1·85)	(1·85)	(1·85)
Males		4·80	3·60	3·67
		(2·03)	(2·03)	(1·85)
SPT	None			
Females		423·50	458·58*	451·57*
		(13·15)	(13·15)	(13·15)
Males		442·60	452·00	448·07
		(14·41)	(14·41)	(13·15)
TST	None			
Females		404·17	442·53*	440·07*
		(15·48)	(15·48)	(15·48)
Males		432·84	440·72	438·93
		(16·96)	(16·96)	(15·48)
SE%	None			
Females		87·83	92·62	94·02*
		(2·99)	(2·99)	(2·99)
Males		91·48	93·32	92·85
		(3·27)	(3·27)	(2·99)

SOL1, SOL2: sleep onset latency (min) to stages 1 and 2; FW: frequency of waking; SPT: sleep period time (min) = Time in bed (TIB)—Duration of final waking—SOL2; TST: total sleep time (min) = SPT—DuW; SE%: sleep efficiency = TST/TIB × 100. * Placebo vs $p < (0{\cdot}05)$ (95% confidence intervals.).

ing from approximately 15 to 5 minutes with hydroxyzine 50 mg. Similarly, stage 2 latency was significantly reduced for females alone, who again demonstrated a dose-dependent decrease with hydroxyzine, latencies dropping by about a half and two-thirds for the two doses in contrast to placebo.

This greater response of the female subject group was apparent for other measures. The reduction in waking frequency following 50 mg hydroxyzine was significant for females alone, as were the increases in TST and SPT for both doses. Sleep efficiency increases just failed to achieve significance for the 25 mg dose but achieved significance with the higher dose; increases for either the male subject group, or sexes combined, failing to achieve significance. The reduction in waking failed to achieve significance for either group when analysed separately, although the lowest levels were again seen in females for whom the reduction in STPW approached significance.

Daytime sleepiness

Significant treatment effects were not seen with the daytime measures for any of the individual scoring categories (QWP–DREM), and only the total drowsiness scores (DRTOT; $F = 3{\cdot}94$; $p < 0{\cdot}035$) were significant for the combined scoring categor-

Table 4. C-EEG measures of daytime sleepiness (s) : untransformed means (95 per cent. confidence intervals)

Measure	Transform	Placebo	Hydroxyzine 25 mg	Hydroxyzine 50 mg
QWP	Sqrt	2364·0	3120·0	2871·5
		(748·6)	(781·9)	(748·6)
QW	Log	2236·0	2011·6	2342·0
		(436·8)	(456·2)	(436·8)
WIA	Sqrt	445·0	530·2	522·0
		(184·5)	(192·7)	(184·5)
WA	Log	265·0	378·5	628·8
		(231·0)	(241·2)	(231·0)
ITh	Sqrt	318·0	636·0	664·0
		(239·3)	(249·9)	(239·3)
D1	Log	182·0	375·3	334·0
		(180·9)	(188·9)	(180·9)
D2	Recip	550·0	672·0	736·0
		(485·3)	(506·8)	(485·3)
D3	Log	62·0	109·1	86·0
		(94·1)	(98·3)	(94·1)
D4	Recip	6·0	196·4	20·0
		(222·9)	(232·8)	(222·9)
DREM	Recip	68·0	0·0	12·0
		(77·1)	(80·6)	(77·1)
SWS	Recip	68·0	305·5	106·0
		(283·0)	(295·7)	(283·0)
TST2	Recip	618·0	977·5	842·0
		(631·1)	(659·3)	(631·1)
TST1	Log	800·0	1352·7	1176·0
		(732·5)	(765·0)	(732·5)
QWTOT	Log	4600·0	5131·6	5213·5
		(960·6)	(1003·2)	(960·6)
WTOT	Sqrt	5310·0	6040·4	6364·3
		(1011·7)	(1056·7)	(1011·7)
ThTOT	Sqrt	1118·0	1988·7	1840·0
		(728·1)	(760·5)	(728·1)
DRTOT	Sqrt	1028·0	1544·7	1814·8
		(417·0)	(435·5)	(417·0)
SEDTOT	Sqrt	1828·0	2897·5	2990·8
		(773·8)	(808·2)	(773·8)

Duration scores (s) for daytime C-EEG recording.
Waking categories: QWP: quiet waking plus = waking activity with some muscle activity or eye movements but excluding active waking; QW: quiet waking. *Drowsiness categories*: WIA: waking with intermittent alpha; WA: waking with continuous alpha; ITh: intermittent theta; D1: sleep stage 1 duration (continuous theta). *Sleep categories from stage 2*: D2: stage 2 duration; D3: stage 3 duration; D4: stage 4 duration; DREM: stage REM duration. *Combined scoring categories*: SWS: slow-wave sleep = stages 3 + 4; TST2: total sleep from stage 2 = D2 + D3 + D4 + DREM; TST1: total sleep from stage 1 = D1 + TST2; QWTOT: quiet waking total = QWP + QW; WTOT: waking total = QWP + QW + WIA + WA; ThTOT: theta total = ITh + D1; DRTOT: drowsiness total = WIA + WA + ITh; SEDTOT: sedation total = DRTOT + TST1.
*$p < (0{\cdot}05)$ (95 per cent. confidence intervals).

ies, although the total sedation scores (SEDTOT) approached significance ($F = 3{\cdot}22$; $p < 0{\cdot}060$).

Sex-by-drug interactions were not seen, in keeping with the results for nocturnal sleep. Significant sex differences were seen for the waking categories QWP ($F = 5{\cdot}22$; $p < 0{\cdot}030$) and WTOT ($F = 4{\cdot}43$; $p < 0{\cdot}044$); drowsiness categories WA $F = 6{\cdot}50$; $p < 0{\cdot}016$), ITh ($F = 26{\cdot}50$; $p < 0{\cdot}0001$), ThTOT ($F = 33{\cdot}62$; $p < 0{\cdot}0001$) and DRTOT ($F = 12{\cdot}48$; $p < 0{\cdot}0014$); for sleep categories D1 ($F = 14{\cdot}85$; $p < 0{\cdot}0006$), D2 ($F = 17{\cdot}71$; $p < 0{\cdot}0002$), TST2 ($F = 17{\cdot}70$; $p < 0{\cdot}0002$), TST1 ($F = 15{\cdot}39$;

Table 5. C-EEG measures of daytime sleepiness (s)—selected comparison of male and female subject groups: untransformed means (95 per cent. confidence intervals)

Measure	Transform	Placebo	Hydroxyzine 25 mg	Hydroxyzine 50 mg
ITh	Sqrt			
Females		496·0	902·0	1184·0*
		(338·4)	(338·4)	(338·4)
Males		140·0	316·8	144·0
		(338·4)	(370·7)	(338·4)
DRTOT	Sqrt			
Females		1520·0	2220·0*	2638·0*
		(589·8)	(589·4)	(589·8)
Males		536·0	734·4	991·5
		(589·8)	(646·1)	(589·8)
SEDTOT	Sqrt			
Females		3004·0*	3992·0*	4974·0*
		(1094·5)	(1094·5)	(1094·5)
Males		652·0	1584·0	1007·5
		(1094·5)	(1198·9)	(1094·5)

Duration scores (s) for daytime C-EEG recording.
ITh: intermittent theta; DRTOT: drowsiness total = waking alpha + intermittent theta; SEDTOT: sedation total = drowsiness total + total sleep from stage 1.
*Males vs females $p < (0{\cdot}05)$ (95 per cent. confidence intervals).

$p < 0{\cdot}0005$), and for combined drowsiness and sleep SEDTOT ($F = 26{\cdot}34; p < 0{\cdot}0001$).

Treatment means for the combined sexes are given in Table 4. Apart from the waking category (QW) some increases in scores were seen with both the 25 mg and 50 mg doses of hydroxyzine for all the individual scoring categories except REM duration (DREM), and for all the combined scoring categories. However, these increases were either small, or the confidence intervals relatively large, so that significant treatment contrasts were not obtained. Only the increase in DRTOT approached significance following the higher dose of hydroxyzine.

Mean contrasts between sexes for combined treatments revealed significantly higher scores with females for categories where significant sex differences were obtained with ANOVA, apart from QWP and WA where scores approached significance. However, treatment contrasts for separate male and female subject groups failed to achieve significance; although with females increases approaching significance may be seen for ITh, DRTOT and SEDTOT (Table 5). The statistical comparison between sexes included in this table reveals significantly higher scores for females which increase with the inclusion of further drowsiness/sleep categories from ITh to SEDTOT.

DISCUSSION

Nocturnal sleep

The significant reductions in sleep onset latency (SOL1, SOL2) with hydroxyzine demonstrate the hypnotic potency of this compound when taken 1·5 hours before bedtime. That sleep onset latencies were halved in these normal subjects serves to emphasize the considerable pro-hypnotic effects for both 25 mg and 50 mg doses of hydroxyzine.

The reductions in waking frequency and duration during sleep (FW, DuW, STPW), combined with the reciprocal increase in sleep duration (SPT, TST), reflect the consolidated nature of the resulting sleep over the 8 hour recording period.

The lack of significant treatment effects for all other sleep stages is of interest, as other sedatives and hypnotics can produce marked changes in sleep structure (Kay *et al.*, 1976). These results also contrast with previous research evaluating the effects of H1 antihistamines on sleep. Decreases in REM duration and increased REM latency, were seen to accompany reduced sleep latency and increased sleep duration (Risberg *et al.*, 1975; Bassano and Caille, 1979; Nicholson *et al.*, 1985; Adam and Oswold, 1986a).

The slight increase in SPT and TST for the lower dose over the higher dose of hydroxyzine reflects

the increase in time-in-bed (TIB) of approximately 1 per cent, recorded with Medilogs for the lower dose. The resulting increases in sleep efficiency (TST/TIB%) are dose-related, and do not indicate a grater hypnotic effect for the lower dose.

Analysis by sex revealed significantly shorter sleep onset latencies for female subjects; whilst analysis of treatment effects by sex indicated a greater response to hydroxyzine for female subjects, including more marked and dose-dependent decreases in sleep onset latencies to stages 1 and 2.

The significant increases in SPT and TST for female subjects alone further demonstrated their greater sensitivity to hydroxyzine-induced hypnotic effects; as did their greater relative increase in sleep efficiency which achieved significance with the higher dose.

Trends approaching significance with female subjects included a reduction in waking percentages (STPW) for both doses, and increase in sleep efficiency (SE%) following the lower dose. However, placebo sleep durations were lower, which may have facilitated the drug-related improvements seen in this group.

Daytime sleepiness

The lack of significant treatment effects with ANOVA for all daytime C-EEG measures except combined drowsiness scores (DRTOT), combined with a lack of significant means contrasts, suggests a possible lack of morning hangover effects for the subject group as a whole.

However, mean scores for all drowsiness and sleep categories, except REM duration (DREM), increased following hydroxyzine administration. The failure to achieve statistical significance was due either to small changes in mean values (e.g. stages 3 and 4), implying a lack of treatment effects for those measures; or, where clear mean differences were observed, to variability in the scores resulting in wide confidence intervals (e.g. DRTOT, SEDTOT), implying marked variation between subjects in response to hydroxyzine.

The relative lack of increase in sleep stages 2, 3, 4 and REM (D2, D3, D4, SWS, DREM, TST2) indicates that profound sedation, resulting in daytime sleep, was not seen in response to hydroxzyine.

The alpha/theta drowsiness categories (WA, ITh, ThTOT, DRTOT) demonstrated the tendency for hydroxyzine to increase measures of drowsiness. Increases in the combined drowsiness score (DRTOT) from 1000 seconds with placebo to 1800 seconds with the high dose of hydroxyzine approached significance for the daytime recording period of approximately 10 hours. Drowsiness categories contributed most to the comparable increase in total sleep and drowsiness (SEDTOT) from 1800 to 3000 seconds.

Whilst daytime recording was evaluated as a single period, the limitation of the 'hangover' effect to the morning should not be precluded, in keeping with the significant subjective hangover found on waking. Sedation assessments following daytime administration of lorazepam to similar numbers of subjects have found significant effects, with 3–4-fold increases in C-EEG scores in contrast to placebo (Alford *et al.*, 1991a,b).

Variability between individuals in response to the sedative effects of antihistamines is recognized (Clarke and Nicholson, 1978; Hindmarch and Bhatti, 1987; Maibach, 1988), but has not been related to subject gender. The finding of significant sex differences with ANOVA for five of the 10 individual scoring categories for daytime sleepiness, and six of the eight combined scoring categories, was borne out by significant mean contrasts between males and females for combined treatments with all but two of these (QWP, WA). Drowsiness total was 2100 for females in contrast to 750 seconds for males; whilst SEDTOT scores were approximately 4000 and 1000 seconds, respectively.

Separate analysis of response to treatments indicated higher scores for female subjects with both placebo and hydroxyzine, achieving significance when contrasted with male scores. The increase in placebo values for 'daytime sedation' may indicate a genuine difference between the sexes; or may simply reflect sampling variation with only six subjects in each group. Sex differences in background EEG activity have been reported, including menstrual cycle variation (Creutzfeldt *et al.*, 1976; Vogel *et al.*, 1976; Kaplan *et al.*, 1990); but would not account for the differences observed here for continuous theta and other sleep stages.

This study was designed primarily to investigate the effects of hydroxyzine on a mixed-sex sample; the relatively small sample sizes for each sex group may have precluded finding significant mean contrasts for treatments; although trends approaching significance were observed with females for increases in intermittent theta (ITh), combined drowsiness as well as combined sleep and drowsiness scores (DRTOT, SEDTOT) as indicated in Table 5.

The increased response to hydroxyzine with

females, both in relation to nocturnal sleep measures and tendency for a residual hangover the next day, warrants further investigation with larger samples and an appropriately designed study. There was a significant weight difference between groups, females averaged 58 kg in comparison to 74 kg for males, which may account for the observed difference in response to hydroxyzine. Further, the sexes were run in separate groups, which may account for some overall differences in scores.

Performance measures taken prior to bedtime, in the morning and evening of the following day failed to reveal consistent impairments; either at bedtime reflecting sedative potency, or the next day indicating a hangover effect (Alford *et al.*, 1991c). Subjective measures were more comparable with C-EEG results; including significant increases in perceived sedation (LARS) following hydroxyzine 50 mg, and in both awakening from sleep (AFS) and behaviour following waking (BFW) with Leeds Sleep Evaluation Questionnaire indicating a significant waking hangover. The highest scores for perceived sedation were also seen in female subjects, reflecting C-EEG monitoring.

These results support the increased incidence of sleepiness next day found by Brown *et al.* (1974) with hydroxyzine. they also complement the subjective hangover reported by Hindmarch and Parrott (1978) for chlorpheniramine and promethazine.

In conclusion, these results demonstrate the hypnotic potency of both 25 mg and 50 mg doses of hydroxyzine assessed from 1·5 hours post-dose as decreases in sleep onset latency. Similarly, measures of sleep duration were increased and waking decreased significantly in comparison to placebo. Findings are in keeping with those reported by Adam and Oswald (1986a) for promethazine, as opposed to the more limited effects of reduced sleep latencies without increased durations of daytime naps reported by Roehrs *et al.* (1984) after diphenhydramine.

Increases in C-EEG drowsiness were recorded the following day but failed to achieve significance, contrasting with significant residual effects established for some benzodiazepine hypnotics (Ogura *et al.*, 1978; Alford and Hindmarch, 1992). Whilst sleep onset latency reductions (SOL1) were significant for male and female subject groups in response to both doses of hydroxyzine, other measures indicated that the greatest response occurred with female subjects. These included both changes in nocturnal sleep duration and waking; as well as increased daytime sleepiness the following day. C-EEG results were also comparable with subjective measures of sedation.

Although not typically used as an hypnotic, nor taken 1·5 hours before bedtime, results for the combined subject groups demonstrate the significant hypnotic efficacy of the antihistamine hydroxyzine given as acute 25 mg and 50 mg doses; with a failure to detect significant C-EEG sedative effects the following day.

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