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Sedation and histamine H_1-receptor antagonism: studies in man with the enantiomers of chlorpheniramine and dimethindene

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1 The effects of 10 mg (+)- and (−)-chlorpheniramine and 5 mg (+)- and (−)-dimethindene on daytime sleep latencies, digit symbol substitution and subjective assessments of mood and well-being were studied in 6 healthy young adult humans. Each subject also took 5 mg triprolidine hydrochloride as an active control and two placebos.

2 Daytime sleep latencies were reduced with triprolidine, (+)-chlorpheniramine and (−)-dimethindene, and subjects also reported that they felt more sleepy after (+)-chlorpheniramine and (−)-dimethindene. Performance on digit symbol substitution was impaired with (+)-chlorpheniramine.

3 Changes in measures with (−)-chlorpheniramine and (+)-dimethindene were not different from changes with placebo.

4 In the present study, changes in measures of drowsiness and performance were limited to the enantiomers with high affinity for the histamine H_1-receptor. These findings strongly suggest that sedation can arise from H_1-receptor antagonism alone, and provide further support for the belief that the histaminergic system is concerned with the regulation of alertness in man.

Keywords: Antihistamines; H_1-receptor antagonists; chlorpheniramine; dimethindene; stereoselective effects; sedation in man

Introduction

It is well recognized that many antihistamines lead to drowsiness and impaired performance (Nicholson, 1983; 1987) and, although not demonstrated conclusively, it is believed that such effects are due to antagonism of central histamine H_1-receptors (Quach *et al.*, 1979; Schwartz *et al.*, 1982; Nicholson *et al.*, 1985). Studies in healthy man have shown, however, that the peripheral antihistaminic and central sedative effects of such drugs may be poorly correlated and the question arises whether central depressant effects are related to other pharmacological activity (Peck *et al.*, 1975; Levander *et al.*, 1985). Many antihistamines are not specific H_1-receptor antagonists, and modulation of the activity of neurotransmitters other than histamine could be involved in the sedative effects of a particular drug.

It is in this context that we have carried out the present study in man on the central effects of the enantiomers of two well-established antihistamines, chlorpheniramine and dimethindene, as drowsiness and sedation are reported commonly with each of these drugs. However, the affinities of the isomers for the H_1-receptor indicate a high degree of stereoselectivity (Chang *et al.*, 1979; Borchard *et al.*, 1985), and so studies with the enantiomers may help to resolve whether sedation is related specifically to the steric configuration and is due to H_1-receptor antagonism alone.

Methods

Six healthy volunteers (four females and two males) who were not taking any other medication gave informed consent to participate in the study. The protocol was approved by the RAF Institute of Aviation Medicine Ethics Committee. The subjects were aged between 19 and 28 (mean 23.7) years, and weighed between 50.0 and 95.5 (mean 70.2) kg. They abstained from alcohol and beverages containing caffeine from 18 h 00 min on the evening preceding and on the day of an experiment, and retired at their usual bedtime on the night before an experiment. Subjects ate a light breakfast before arriving at the laboratory. Test sessions commenced at 08 h 30 min, 10 h 00 min, 11 h 00 min and 12 h 30 min, with drug ingestion between the first and second sessions at 09 h 30 min. Each subject took, on separate occasions, 10 mg (+)- and (−)-chlorpheniramine maleate, 5 mg (+)- and (−)-dimethindene maleate, 5 mg triprolidine hydrochloride as an active control, and two placebos. All medication was identical in appearance and the study was double blind. Treatments were arranged in a pseudo-random order balanced for linear sequence, with a placebo among the first and last three drug ingestions, and at least four days separated each assessment.

Each test session was identical. Performance was measured by digit symbol substitution (Nicholson & Stone, 1986), and subjects were trained in this task to achieve a consistent level of performance before the study began. Mood, well-being and alertness were assessed subjectively by use of a series of 12 visual analogue scales (Nicholson & Stone, 1986) and the Stanford Sleepiness Scale (SSS) (Hoddes *et al.*, 1973). After these assessments, sleep latency was measured. Two channels of electroencephalographic (EEG) activity (C_4-A_1 and O_1-A_2) and bilateral electro-oculographic (EOG) activity were recorded with silver-silver chloride electrodes on a Nihon Kohden 4300 Series EEG machine. The paper speed was 10 mm s^{-1} and 70% amplitude frequency response was 0.16 to 35 Hz for the EEG and 1.6 to 15 Hz for the EOG. Subjects lay in bed in individual rooms which were light-proofed, sound-attenuated and temperature-controlled (18 ± 3°C). They were instructed to lie in bed quietly and to try to fall asleep. Each test was ended after the onset of stage 1 (drowsy) sleep or after 20 min if the sleep onset criterion was not met. The latency to stage 1 sleep was determined independently by two analysts, and differences were resolved.

Materials

Racemic chlorpheniramine maleate (Smith, Kline & French) and racemic dimethindene maleate (Zyma) were converted into the free base forms. Samples of (+)- and (−)-chlorpheniramine maleate ($[\alpha]^{24}_D$ + 23.2° and −23.9°, *circa* 1% in

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water, respectively) and (+)- and (−)-dimethindene maleate ($[\alpha]^{24}_D$ + 197.8° and −206.6°, *circa* 1% in methanol, respectively) were obtained by resolution of racemic chlorpheniramine base with D- and L-ditoluoyltartaric acids, and racemic dimethindene base with D- and L-tartaric acids. In each case fractional crystallization was continued until specific rotations of diastereoisomeric salts showed relatively little change on further crystallization.

The products were checked for purity. C, H and N analyses were within 0.4% of the required values, and high performance liquid chromatography (h.p.l.c.) examination (on a Cyclobond I column) gave purities >99%. M.p.'s were 113–115°C and 112–114°C respectively for (+)- and (−)-chlorpheniramine maleate, and 127–129°C for each enantiomer of dimethindene maleate. Additional evidence of optical purity was obtained by chiral h.p.l.c. or ^{1}H n.m.r. methods (Mercer, 1989). The pure enantiomeric drug was triturated with lactose, and capsules were filled with 150 mg of the triturate (or pure lactose for the placebo) to provide doses of 10 mg chlorpheniramine maleate and 5 mg dimethindene maleate. Capsules, each containing two 2.5 mg tablets of triprolidine hydrochloride (Wellcome), were used as the active control.

Measurement of pharmacological activity in vitro

H_1-receptor antagonism was assayed *in vitro* against histamine-induced contraction of guinea-pig ileum. Guinea-pigs of either sex weighing between 400–700 g were used. Immediately after an animal was killed, the terminal ileum was removed, washed and mounted in a 15 ml bath containing magnesium-free Tyrode solution gassed with 95% O_2/5% CO_2 and maintained at 30°C. The tissue was loaded with 0.5 g and contractions in response to histamine were detected by a force transducer and displayed on a potentiometric recorder. Cumulative histamine dose-response curves were obtained prior to and following 8 min incubations with three different concentrations of the antagonist (7–10 observations), and pA_2 values were determined by Schild analysis. The slopes of the Schild plots are indicated in Table 3, and were not significantly different from unity within 95% limits.

The affinities of the enantiomers of chlorpheniramine maleate and dimethindene maleate and of triprolidine hydrochloride for types of central receptor were also determined. Binding assays for radiolabelled prazosin (α_1-adrenoceptors), UK-14304 (5-bromo-6-[2-imidazolin-2-ylamino]-quinoxaline bitartrate) (α_2-adrenoceptors), dihydroalprenolol (β-adrenoceptors), 5-hydroxytryptamine (5-HT) (5-HT_1-receptors), ketanserin (5-HT_2-receptors), 3-quinuclidinyl benzilate (QNB) (muscarinic receptors) and flunitrazepam (benzodiazepine receptors) were conducted on bovine frontal cortex, and for radiolabelled spiperone (dopamine D_2-receptors) on bovine striatum. Assays were also carried out with standard agents. Details of the methods are given in Table 1. Apparent K_i values were calculated from IC_{50} values by the Cheng-Prusoff equation (Cheng & Prusoff, 1973).

Measurement of pharmacological activity in vivo

H_1-receptor antagonism of the enantiomers of dimethindene was assessed *in vivo* against histamine-induced bronchoconstriction in the anaesthetized guinea-pig (Brown *et al.*, 1986). Increasing doses of antagonist were given intravenously and dose-ratios for the displacement of histamine dose-response curves were obtained. The dose of antagonist giving a (dose-ratio − 1) = 10 was determined from a Schild plot.

Statistical analysis of performance, subjective assessment and sleep latency data

Visual analogue scales of mood and well-being were assigned ranks for each subject separately and the principal components of the correlation matrix of the ranks for 12 measures were calculated. Two components were derived and, after varimax rotation, these were identified as measures of sleepiness and feelings associated with mood. Digit symbol substitution scores, SSS ratings and the components derived from the visual analogue scales were investigated by analysis of variance. Sleep latencies were censored at 20 min and so an iterative extension to a standard analysis of variance procedure was used to investigate this measure. Digit symbol substitution scores were screened for possible effects of sequence by analysis of covariance on dummy variables (John & Quenouille, 1977) and if an order effect was found it was used to correct the data.

The assumptions of analysis of variance, homogeneity of variance, normality and additivity, were studied by considering transformations of the raw measures using the maximum likelihood method of Box & Cox (1964). The residuals from an analysis of variance, applied to the data by use of the selected transformation, were then examined after the method of Anscombe (1961) and, if appropriate, this transformation was applied. All of the transformations were logarithmic and so random variation and treatment effects were proportional rather than additive. Back-transformed means are presented for the subjective assessment and sleep latency data.

After analysis of variance, the effects of the drugs on differences between measures before ingestion (08 h 30 min) and those after ingestion (10 h 00 min, 11 h 00 min and 12 h 30 min) were investigated. Two planned comparisons, using the mean differences for six subjects, were made between the two placebos and between the active control (triprolidine 5 mg) and the mean of the two placebos. Each of the remaining drugs was compared with the mean of the two placebos and each enantiomer was compared with its respective isomer by the multiple comparison method of Dunnett (1964). The test of

Table 1 Details of ligand binding assays

Receptor *Bovine frontal cortex:*	*Radioligand*	(nM)	*Non-specific binding defined by* (μM)		*Buffer*	*Incubation time* (min)	*Temp* (°C)
α_1	[^{3}H]-prazosin	0.2	Phentolamine	10.0	50 mM Tris (pH 7.6)	30	25
α_2	[^{3}H]-UK-14304	0.5	Phentolamine	10.0	50 mM Tris (pH 7.6)	30	25
β	[^{3}H]-dihydroalprenolol	2.0	Propranolol	1.0	50 mM Tris (pH 7.6) + 10 mM Mg^{2+}	30	25
5-HT_1	[^{3}H]-5-HT	2.0	5-HT	10.0	50 mM Tris (pH 7.4) + 4 mM Ca^{2+}	30	25
5-HT_2	[^{3}H]-ketanserin	1.0	Spiperone	1.0	50 mM Tris (pH 7.6)	30	25
Muscarinic	[^{3}H]-QNB	0.1	Atropine	1.0	Krebs-50 mM Tris (pH 7.6)	60	25
Benzodiazepine	[^{3}H]-flunitrazepam	0.5	Diazepam	10.0	50 mM Tris (pH 7.6)	60	5
Bovine striatum:							
D_2	[^{3}H]-spiperone	0.2	Butaclamol	1.0	50 mM Tris (pH 7.6)	30	25

References to methods: α_1-adrenoceptor, Greengrass & Bremner (1979); α_2-adrenoceptor, Loftus *et al.* (1984); β-adrenoceptor, Williams *et al.* (1976); 5-HT_1 receptor, Peroutka & Snyder (1979); 5-HT_2 receptor, Leyson *et al.* (1982); muscarinic receptor, Yamamura & Snyder (1974); benzodiazepine receptor, Chiu *et al.* (1982); D_2-dopamine receptor, Leyson *et al.* (1978).

each of these hypotheses was made with a specified size *a posteriori*, and so no account was taken of the composite F test for differences between treatments. The different components of the error term, which applied to each group of comparisons, were tested for homogeneity by Bartlett's test.

Results

The results of the performance measures, sleep latency tests and subjective assessments are shown in Table 2 and Figure 1. With 5 mg triprolidine there was a greater reduction compared with placebo in the latency to stage 1 (drowsy) sleep at 11 h 00 min ($P < 0.01$). Changes in subjective assessments and digit symbol substitution scores were not different from changes with placebo.

Changes in measures with (−)-chlorpheniramine were not different from changes with placebo. With (+)-chlorpheniramine the reduction in sleep latency at 11 h 00 min was more marked than with the (−)-isomer ($P < 0.01$) and with placebo ($P < 0.05$). Increased subjective sleepiness was greater at 11 h 00 min and 12 h 30 min with (+)-chlorpheniramine than with the (−)-isomer (visual analogue scales $P < 0.05$; SSS $P < 0.01$) and with placebo (12 h 30 min, visual analogue scales $P < 0.05$; 11 h 00 min and 12 h 30 min, SSS $P < 0.05$). Impairment of digit symbol substitution was greater at 11 h 00 min and 12 h 30 min with (+)-chlorpheniramine than with the (−)-isomer ($P < 0.05$).

Changes in measures with (+)-dimethindene were not different from those with placebo. With (−)-dimethindene there was a more marked reduction in sleep latency at 11 h 00 min than with the (+)-isomer and with placebo ($P < 0.05$). Subjects reported a greater increase in sleepiness at 12 h 30 min with (−)-dimethindene than with the (+)-isomer ($P < 0.05$). Changes in performance with (−)-dimethindene did not differ from changes with the (+)-isomer or with placebo.

Pharmacological activity in vitro

H_1-receptor antagonist activities of the enantiomers of chlorpheniramine and dimethindene against histamine-induced contraction of the guinea-pig ileum are shown in Table 3. Stereoselectivity ratios were greater than 50 for each pair of enantiomers, with (+)-chlorpheniramine and (−)-dimethindene showing greater potency than their respective isomers. There was some depression of the maximum response with the higher concentrations of (+)-chlorpheniramine (64% at a dose-ratio of 4.5), (−)-chlorpheniramine (30% at a dose-ratio of 3.2) and (−)-dimethindene (31% at a dose-ratio of 5.2), but not with (+)-dimethindene (6% at a dose-ratio of 8.1).

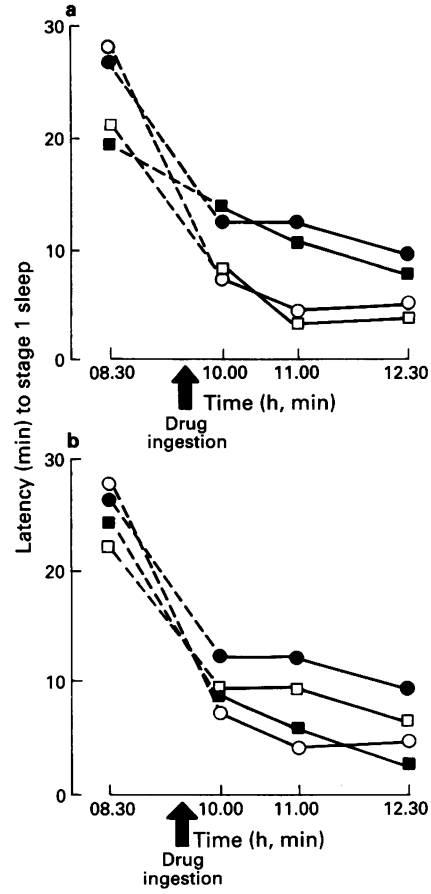

Figure 1 Effect of drugs on sleep latencies (means for 6 subjects). (a) There was a greater reduction in sleep latency from 08 h 30 min to 11 h 00 min with triprolidine (○, $P < 0.01$) and with (+)-chlorpheniramine (□, $P < 0.05$) compared with placebo (●), and with (+)-chlorpheniramine (□) compared with the (−) isomer (■, $P < 0.01$). (b) There was a greater reduction in sleep latency from 08 h 30 min to 11 h 00 min with triprolidine (○, $P < 0.01$) and with (−)-dimethindene (■, $P < 0.05$) compared with placebo (●), and with (−)-dimethindene (■) compared with the (+)-isomer (□, $P < 0.05$).

The results of the radioligand binding assays are shown in Table 4. Standard agents showed nanomolar affinity for their

Table 2 Sleep latencies, subjective sleepiness and performance 1.0 h (08 h 30 min) before and 0.5, 1.5, and 3.0 h (10 h 00 min, 11 h 00 min and 12 h 30 min) after drug ingestion

Measure	*Time* (h)	*Placebo*	*Triprolidine* (mg) 5	*Chlorpheniramine* (mg) (+)10	(−)10	*Dimethindene* (mg) (+)5	(−)5
Sleep latency (min)	0830	26.5	27.5	20.6	19.5	21.9	23 8
	1000	12.6	7.6	7.7	13.1	8.3	8.1
	1100	12.2	3.5[b]	3.3[a, d]	10.5	8.8	3.8[a, c]
	1230	9.0	4.4	3.5	7.2	5.6	2.8
Digit symbol substitution	0830	248.1	224.5	245.7	245.0	249.8	248.8
(number of substitutions)	1000	244.2	239.2	246.0	244.7	250.8	242.8
	1100	242.3	236.2	228.8[c]	245.5	246.3	236.8
	1230	243.6	236.0	232.0[c]	248.3	246.0	241.8
Subjective sleepiness:							
Visual analogue scales	0830	−0.38	−0.16	−0.31	−0.37	−0.42	−0.20
(arbitrary units)	1000	−0.37	−0.06	−0.09	−0.15	−0.34	−0.23
from −1.32 (wide awake)	1100	0.03	0.67	0.98[c]	−0.07	0.19	0.59
to 3.60 (extremely sleepy)	1230	−0.36	0.17	1.12[a, c]	−0.21	0.25	0.74
Standford sleepiness scale	0830	2.51	2.35	2.35	2.69	2.69	2.16
(arbitrary units)	1000	2.44	2.52	2.52	2.52	2.66	2.50
from 1.00 (wide awake)	1100	2.68	3.34	3.79[a, d]	2.69	2.84	2.89
to 7.00 (extremely sleepy)	1230	2.58	2.99	3.97[a, d]	2.52	2.63	3.28[c]

Values are back transformed means for 6 subjects.
Comparisons of differences from before ingestion with placebo: [a]$P < 0.05$; [b]$P < 0.01$.
Comparisons of differences from before ingestion between enantiomers: [c]$P < 0.05$; [d]$P < 0.01$.

Table 3 H_1-histamine receptor antagonist affinities of the enantiomers of chlorpheniramine and dimethindene against histamine-induced contraction of the guinea-pig ileum

Drug	n	pA_2 (95% confidence interval)	*Slope*	*Published* pA_2 values
(+)-Chlorpheniramine	7	9.02 (8.89–9.15)	1.42 ± 0.47	9.30[a]
(−)-Chlorpheniramine	9	7.11 (6.95–7.26)	0.97 ± 0.44	7.84[a]
(+)-Dimethindene	8	7.86 (7.71–8.07)	0.74 ± 0.19	7.80[b]
(−)-Dimethindene	10	9.54 (9.31–9.83)	0.73 ± 0.33	9.10[b]

pA_2 and slope values determined by Schild analysis. Dose-ratios were: 1.17–5.17 for (+)-chlorpheniramine, 1.61–3.80 for (−)-chlorpheniramine, 1.66–9.67 for (+)-dimethindene, and 1.33–5.83 for (−)-dimethindene.

[a] Van den Brink & Lien (1977).

[b] Borchard *et al.* (1985).

respective receptors. (+)-Chlorpheniramine showed similar affinity to (−)-chlorpheniramine for α_1-, β-, 5-HT_1-, muscarinic, D_2- and benzodiazepine receptors, and was less active with respect to α_2- and 5-HT_2-receptors. (−)-Dimethindene was more potent than (+)-dimethindene at 5-HT_2-, muscarinic and D_2-receptors. Triprolidine showed higher affinity for α_1- and 5-HT_2-receptors than for the other receptors. However, with respect to all drugs and all receptors examined, inhibitory concentrations were in the micromolar range.

Pharmacological activity in vivo

(−)-Dimethindene at doses of 0.001, 0.003 and 0.01 μmol kg^{-1} produced dose-related inhibition of histamine-induced increases in airway pressure. Dose-ratios (mean ± s.e.mean, $n = 5$) were 2.9 ± 0.8, 12.0 ± 6.2 and 46.7 ± 26.6, respectively. The dose giving a (dose-ratio − 1) = 10 was 0.003 μmol kg^{-1}. (+)-Dimethindene at doses of 0.01, 0.1, 1.0 and 10.0 μmol kg^{-1} gave dose-ratios of 1.6 ± 0.2, 2·3 ± 0.5, 5·0 ± 1.1 and 21.7 ± 3.9, respectively ($n = 4$ or 5). The dose required to give a (dose-ratio − 1) = 10 was 4.5 μmol kg^{-1}.

Discussion

There is much evidence to suggest that histamine is involved in the control of arousal. Histaminergic pathways originating from the reticular formation project diffusely to the cerebral cortex in a similar way to monoaminergic pathways concerned with alertness (Garbarg *et al.*, 1980; Pollard & Schwartz, 1987). Further, administration of histamine or drugs which enhance histaminergic transmission leads to desynchronization of the EEG and wakefulness (Wolf & Monnier, 1973; Monti *et al.*, 1986; Lin *et al.*, 1988), and histamine may also modulate the activity of medullary neurones (Jones *et al.*, 1983; Bradley *et al.*, 1984). Circadian rhythms in the level of histamine have been found in various regions of the brain (Friedman & Walker, 1968; Orr & Quay, 1975), and the rate of formation of histamine is elevated in rodents during the period of darkness when spontaneous activity is maximal (Schwartz *et al.*, 1976).

Nevertheless, it is possible that pharmacological activity other than H_1 antagonism may give rise to sedation with antihistamines, and the drugs used in the present study, in particular chlorpheniramine, are not specific H_1-receptor antagonists. Chlorpheniramine also modulates the activity of monoamine transmitters, with evidence both *in vitro* and *in vivo* of moderate to marked inhibition of 5-HT, noradrenaline and dopamine uptake compared with drugs, such as tricyclic antidepressants, which have recognised effects on reuptake mechanisms (Carlsson & Lindqvist, 1969; Farnebo *et al.*, 1970; Fuxe *et al.*, 1970; Horn *et al.*, 1971; Lidbrink *et al.*, 1971; Symchowicz *et al.*, 1971; Korduba *et al.*, 1973; Young *et al.*, 1988).

With respect to the other receptors examined, the binding data indicate that interactions of chlorpheniramine and dimethindene occur only at relatively high concentrations. Previous studies have also shown that chlorpheniramine has much lower affinity for peripheral α-adrenoceptors and muscarinic sites than for H_1-receptors (O'Neill & Patil, 1975; Van den Brink & Lien, 1977), and that (+)-chlorpheniramine is similarly less potent at central muscarinic sites (Kubo *et al.*, 1987). Published studies on dimethindene are limited, though the racemic compound has less potent anticholinoceptor than antihistamine receptor activity, both centrally and peripherally, and does not antagonize cardiovascular effects of noradrenaline, adrenaline and acetylcholine in the dog. However, doses of dimethindene which inhibit histamine-induced gastro-intestinal motility also reduce the response to 5-HT (Barrett *et al.*, 1961; Kubo *et al.*, 1987).

In the present study, changes in measures of drowsiness and performance with (−)-chlorpheniramine and (+)-dimethindene, the enantiomers with low affinity for the H_1-receptor, were not different from those with placebo. This would indicate, too, that any other pharmacological activity of these antihistamines is unlikely to be a significant factor in their sedative action, unless such activity is also related to steric configuration. The binding data suggest that this is unlikely. (+)-Chlorpheniramine showed either similar affinity to the

Table 4 Inhibition of radioligand binding at central receptors by the enantiomers of chlorpheniramine and dimethindene, and by triprolidine

Receptor	*Standard agent*	K_i(nM)	Triprolidine	K_i(μM) Chlorpheniramine (+)	Chlorpheniramine (−)	Dimethindene (+)	Dimethindene (−)
α_1	Prazosin	0.15	1.6	2.6	2.7	0.33	0.55
α_2	Phentolamine	3.1	>10.0	>10.0	>10.0	>10.0	>10.0
β	Propranolol	4.1	>10.0	>10.0	>10.0	>10.0	>10.0
5-HT_1	5-HT	1.1	>10.0	>10.0	>10.0	2.8	>10.0
5-HT_2	Ketanserin	1.8	3.3	>10.0	1.9	>10.0	2.2
Muscarinic	Atropine	0.87	>10.0	>10.0	>10.0	>10.0	0.93
Benzodiazepine	Flunitrazepam	2.2	>10.0	>10.0	>10.0	>10.0	>10.0
D_2	Butaclamol	3.3	>10.0	>10.0	>10.0	2.7	0.3

Each value represents the mean of two experiments performed in duplicate, using 5–6 concentrations for each compound.

(−)-isomer, or was less active, at various central receptors, and although (−)-dimethindene was more potent than (+)-dimethindene at 5-HT_2-, muscarinic and dopamine D_2-receptors, inhibitory concentrations were in the micromolar range. It has also been reported previously that the enantiomers of chlorpheniramine have similar affinities for cholinoceptors and adrenoceptors (O'Neill & Patil, 1975; Van den Brink & Lien, 1977). Further, though comparative studies of modulation of 5-HT and noradrenaline activity have not been carried out, it is known that inhibition of dopamine uptake with chlorpheniramine is not stereoselective (Symchowicz *et al.*, 1971).

Although enantiomers share the same physico-chemical properties and should, therefore, be absorbed and penetrate the central nervous system with equal ease, stereoselectivity may lead to pharmacokinetic differences due to differences in protein binding or metabolism (Williams & Lee, 1985; Drayer, 1986; Lam, 1988). Studies have shown that (+)-chlorpheniramine is metabolised more rapidly than the (−)-isomer in rat and rabbit liver microsomes, but not in those of the mouse. Further, when the enantiomers were given as the pseudoracemate, differences in metabolism were potentiated in rabbit, but not rat, microsomes (Thompson & Shioshita, 1981).

Clearly, there are species differences in chlorpheniramine metabolism, and enantiomeric interaction may occur when the isomers are administered together. Studies in man have demonstrated higher serum levels and slower elimination of (+)-chlorpheniramine following both simultaneous and separate administration of the isomers (Miyazaki & Abuki, 1976; Fujiwara *et al.*, 1989). However, it is unlikely that such differences would explain entirely the differential effects of the isomers of chlorpheniramine observed in the present study in which higher doses were used. Further, there is no evidence that the metabolism of dimethindene is influenced by steric configuration.

Previous studies in the cat have indicated that electroencephalographic effects of (−)- and (±)-chlorpheniramine are not related to their ability to antagonize histamine (Faingold & Berry, 1972). However, this does not appear to be the case in man. Sedation with both chlorpheniramine and dimethindene was limited to the enantiomers with high affinity for the histamine H_1-receptor. While (−)-chlorpheniramine and (+)-dimethindene were without effect on the measures tested, (+)-chlorpheniramine and (−)-dimethindene increased the tendency to fall asleep, and subjects reported that they felt more sleepy. (+)-Chlorpheniramine also impaired performance, with lower scores on the digit symbol substitution test.

(+)-Chlorpheniramine is 30–200 times more potent than the (−)-isomer in antagonizing histamine-induced contraction of the guinea-pig ileum (Roth & Govier, 1958; Van den Brink & Lien, 1977), and is approximately 100 times more potent *in vivo* against histamine-induced lethality in guinea-pigs (Roth & Govier, 1958). Marked differences between the activity of the enantiomers have also been observed in rabbit aorta (O'Neill & Patil, 1975). Similarly, there is also evidence for stereoselective antagonism of H_1-receptors in the central nervous system. (+)-Chlorpheniramine inhibits [^{3}H]-mepyramine binding to brain membranes to a greater (up to 240 times) extent than the (−)-isomer in a number of species, including man (Hill *et al.*, 1978; Tran *et al.*, 1978; Chang *et al.*, 1979; Quach *et al.*, 1980). It is of interest that there are no marked species differences in stereoselectivity ratios, even though the ability of chlorpheniramine to displace the labelled ligand varies (Chang *et al.*, 1979).

Dimethindene is a potent H_1 antihistamine, with activity similar to or greater than that of (+)-chlorpheniramine in a number of tests of histamine receptor function (Barrett *et al.*, 1961) and in receptor binding studies (Tran *et al.*, 1978; Kubo *et al.*, 1987). Its stereoselectivity with respect to H_1 sites is less well documented, but (−)-dimethindene is between 20 and 100 times more potent than the (+)-isomer in blocking the response to histamine receptor activation in various guinea-pig tissue preparations (Borchard *et al.*, 1985). In the present study, the stereoselectivity ratio on guinea-pig ileum was greater than 50, and (−)-dimethindene was a more potent inhibitor of histamine-induced bronchoconstriction than the (−)-isomer.

These studies in man with enantiomers of chlorpheniramine and dimethindene strongly suggest that sedation can arise from H_1 antagonism alone. Drugs such as terfenadine, astemizole, loratadine and mequitazine which are either non-sedating or non-sedating at certain therapeutic doses (Clarke & Nicholson, 1978; Nicholson, 1982; Nicholson & Stone, 1982; 1983; Bradley & Nicholson, 1987) usually exhibit poor penetration of the central nervous system, and in some cases possibly lower affinity for central H_1-receptors than for peripheral sites (Quach *et al.*, 1980; Barnett *et al.*, 1984; Ahn & Barnett, 1986; McQuade *et al.*, 1990). The stereoselective activity of two potent antihistamines shown in the present study in man provides further support to the belief that the histaminergic system is concerned with the regulation of alertness.

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