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Cutaneous antihistaminic action of cetirizine and dose-related EEG concomitants of sedation in man

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Abstract

The cutaneous antihistaminic action (prick test; 1:100, 1:200 and 1:1000) and neuropsychological and electroencephalographic (EEG) concomitants of sedation following the histamine H_1 receptor antagonist cetirizine (10- and 20-mg acute oral doses) and chlorpheniramine, 4 mg, were investigated in a cross-over, placebo-controlled study in healthy male volunteers (age 23–29 years). With an average C_{max} of cetirizine of 697.0 ng/ml (10 mg) and 1000.2 ng/ml (20 mg), the diameter of histamine-induced skin weals was reduced by 24.0–74.9% depending on histamine concentration and with no dose dependence for cetirizine. Placebo and chlorpheniramine were ineffective. Behavioral or neuropsychological signs of sedation were never observed. An increase of the 6.5–14.5 Hz EEG power, with anterior scalp preponderance, was observed after chlorpheniramine or cetirizine 20 mg. This effect of cetirizine was accounted for by a substantial increase of power in the 6.5–8.0 Hz frequency subsegment and is regarded, for these experimental conditions, as an established early EEG indication of mild sedation (vigilance 'stage A'). No EEG effects were observed after placebo or cetirizine at the 10 mg dose. The existence of some histaminergic (H_1) specificity of the mechanisms modulating vigilance and of a threshold dose of cetirizine for sedative action is suggested.

Keywords: Ceritizine; Chlorpheniramine; EEG (electroencephalogram), quantitative; Oral administration, acute; (Healthy volunteer); Plasma concentration, drug; Neuropsychological status

1. Introduction

Sedation is a major side effect during treatment with traditional antihistamine compounds (Clarke and Nicholson, 1978; Nicholson and Stone, 1982; Nicholson, 1983; Roth et al., 1987; Gaillard et al., 1988). This effect is conceivably accounted for, at least in part, by drug-dependent interference with the histamine H_1 receptor/neurotransmitter system of the brain (Nicholson, 1983), in agreement with the suggested role of this system in the physiological modulation of vigilance during wakefulness (Roth et al., 1987; Quach et al., 1979; Schwartz et al., 1982; Nicholson, 1983; Wada et al., 1985, 1991). In this regard, dissimilarities among antihistamine compounds are suggested to result from differences in transport across the blood-brain interface or to depend on the affinity with, or occupancy of histamine H_1 brain receptors (Snowman and Snyder, 1990). Cetirizine has a negatively charged carboxyl group, resulting in diminished passage across the blood-brain interface, and binds selectively to histamine H_1 receptors also at high concentrations (Snowman and Snyder, 1990), therefore qualifying as a suitable test compound in experimental studies. Its sedative side-effects are however questioned (Gengo et al., 1987; Seidel et al., 1987; Ramaekers et al., 1992), with discrepancies among study results that may depend on dose or reflect differences in the sensitivity of neuropsychological, electrophysiological and psychomotor methods used to assess drowsiness.

Computer-assisted quantitative methods for the analysis of the electroencephalogram (EEG) have been systematically applied to study in man the dynamics of action on the

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brain of compounds used in the treatment of psychiatric conditions (Fink, 1969, 1978; Itil, 1974; Saletu, 1976; Herrmann, 1982). These methods appear suitable for application in this context because of the peculiar sensitivity in the assessment of drug-related modifications in vigilance (Ruth, 1961; Matousek and Petersen, 1979; Matejcek, 1982; Ulrich and Frick, 1986). The purpose of this study was to compare the peripheral antihistamine action of ceritizine with the neuropsychological and quantitative EEG concomitants of sedation in a placebo-controlled study on healthy volunteers. Chlorpheniramine served as standard drug.

2. Materials and methods

2.1. Subjects and experimental procedures

Eight healthy male volunteers ranging in age from 23 to 29 years (mean: 24.9 ± 2.1 years) and in body weight from 66 to 75 kg (mean: 69.6 ± 4.6 kg) were recruited from a population of undergraduate university students. Subjects with a history or clinical evidence of relevant neurological or systemic diseases, allergies, or long-term use/abuse of drugs were excluded. All subjects were acquainted with the laboratory setting, experimental design, and recording procedures. Their screening electroencephalographic recordings were within normal limits for the age range and the physiological 'alpha' rhythm was evident on visual inspection for at least 60% of the recording time in standard resting (eyes closed) conditions. The study was given approval by the Ethical Committee of the University Medical School. All subjects signed an informed consent and agreed to avoid neuroactive compounds (including alcohol) in the 72-h period preceding each of four experimental sessions, during which they were given an acute oral dose of cetirizine (10 mg or 20 mg), chlorpheniramine (4 mg) or matching placebo. Administration was double blind in a cross-over balanced design in which each subject served as his own control. Sessions were run at weekly intervals to allow a proper wash-out, and started at 11.00 a.m. for all subjects, after a normal night's sleep and 2 h after a standardized 'continental' breakfast. The subjects were allowed water during the experimental session, while other beverages and food were not allowed. They were sitting comfortably in an air-conditioned, sound-shielded room and were allowed to read or study between recordings but not to drowse. TV monitoring was continuous during the experimental session. Experimental setting, drug administration and data acquisition were consistent with the Helsinki Declaration on biomedical research involving human subjects and the suggested guidelines for quantitative EEG studies in human neuropharmacology (Herrmann, 1982; Dumermuth et al., 1987).

2.2. Cetirizine pharmacokinetics

Venous plasma samples were collected at baseline and 1, 2, 3, 4, and 6 h after administration of cetirizine, chlorpheniramine or placebo. Plasma was extracted by centrifugation (2000 × 3 min) and the concentration of cetirizine HCl was assessed by gas liquid chromatography (nuclear proton detector) in splitless-mode after extraction with chloroform and buffering at pH 10. UCBJO28 was the internal standard. A linear coefficient of regression of 0.994 with a 9.8% coefficient of variability was obtained when calibrating on standard samples within the 40–800 ng concentration range. The lower concentration detectable with this analytical method is 20 ng/ml, with 85% estimated recovery.

2.3. Cutaneous reactivity

The subjects' cutaneous reactivity was tested by means of the prick test on the volar surface of the forearm, using 1 : 100, 1 : 200 and 1 : 1000 histamine solutions and a 4 cm distance between locations on the skin at the different concentrations. The test was performed bilaterally at each concentration of histamine and after each EEG recording at baseline or after drug administration. The skin response was quantified as the maximum diameter of skin weals.

2.4. Blood pressure, heart rate and performance in the neuropsychological tests

Heart rate and systolic and diastolic blood pressure (automatic OMEGA 1400 non-invasive system) were continuously monitored during each pre- and post-drug EEG recording. The volunteers were interviewed before baseline determination in order to verify the fulfillment of the protocol requirements concerning sleep and food or drug consumption. Following each pre- or post-drug EEG recording the subjects were requested to report informally about possible subjective symptoms; a formal Abramson Symptom Questionnaire reduced to 40 items was also administered and the volunteers were requested to report substantial changes from baseline conditions (Fink et al., 1975). The possible occurrence of drug-induced modifications in the subjects' attention or memory was verified by administering after each EEG recording a series of standardized neuropsychological tests, namely the Short-term Retention Test for sequences of letters (Peterson and Peterson, 1960), the Backward Digit Span Test (Wechsler, 1955), and the Immediate Retention Test for sequences of colors (after De Renzi and Nichelli, 1975). Volunteers returned to the laboratory 24 h after drug administration to report on after-effects observed in the 12-h period following the end of the session. The statistical significance of the post-drug variations in heart rate, blood pressure, and task performance was verified by paired t-test.

2.5. Quantitative EEG

Platinum dermal Grass electrodes were positioned according to the 10-20 International System (Fp1; F3; C3; 01; F7; T3; T5; Fp2; F4; C4; 02; F8; T4; T6) and were not removed during the experimental session. Common average reference EEG recordings (at baseline and 1, 2, 3, 4 and 6 h after drug/placebo administration) were in 3-min segments, under resting conditions with eyes closed. Analog data acquisition was through 0.3–50.0 Hz bandwidth filters combined with a 50.0 Hz line frequency rejection filter, after amplifier calibration by means of a standard sine wave signal generated electronically. The background EEG signal was processed off-line by power spectral analysis in consecutive 2-s epochs, after acquisition through multiplexed ADC processing (sequential equidistant sampling; amplitude resolution: 12 bit). Sampling was at 128 sample/s per channel. Artefacts were detected visually, and the corresponding epochs on all channels were excluded from further analyses with about 10–15% of epochs being rejected. The following EEG parameters were computed for each EEG recording and electrode on the 0.5–32.0 Hz frequency interval, with a 0.5-Hz resolution: total power in the 0.5–32.0 Hz interval; relative power values in the 0.5–6.0 Hz, 6.5–14.0 Hz (extended 'alpha' range), and 14.5–32.0 Hz adjacent bandwidths; relative power in adjacent 2-Hz subsegments of the 6.5–14.0 bandwidth (i.e.: 6.5–8.0 Hz; 8.5–10.0 Hz; 10.5–12.0 Hz; and 12.5–14.0 Hz). The frequency limits of the extended 'alpha' range were defined based on the cut-offs between the 'alpha' peak and the lower and upper frequency components of the power spectrum. The hypothesis of no difference between pre- and post-drug EEG measurements was verified by paired t-test computed on each EEG parameter for each post-drug recording and electrode. The existence of a correlation between the post-drug EEG changes and plasma concentrations of cetirizine was tested by computing the Kendall's coefficient of correlation for ranked data (Siegel, 1956).

For each recording before or after drug administration and each EEG parameter, a map of scalp distribution was obtained by transposing the electrode set-up on a bidimensional plan according to a 64×64 matrix. The resulting distortion of the electrodes' relative positions was compensated for. Triplets of adjacent electrodes were automatically selected and a power value was attributed to each point of the matrix inside each triangle by interpolating linearly from the values at the triangle vertices. The power values at each point were displayed in pseudocolors and bidimensional maps were produced according to procedures developed in this laboratory. The statistical comparison across subjects and between pre- and post-drug recordings was performed for each spectral parameter by paired t-test, computed for the data relative to each electrode at different pre- and post-drug controls and was then extrapolated to each point within the matrix. A global analysis of variance across subjects and over time (pre- and post-drug controls) was also performed.

3. Results

3.1. Subjects' compliance with the protocol requirements and experimental procedures

The requirements concerning drug consumption, food, sleep, etc., were satisfied by all volunteers, and adequate data collection was possible for each of the selected variables. The diameter of the histamine-induced skin weals in baseline conditions prior to drug administration did not differ among experimental sessions (analysis of variance (ANOVA)). Consistent with the protocol requirements, the relative power values of the EEG 'alpha' rhythm in baseline conditions before placebo, cetirizine (10 mg and 20 mg), and chlorpheniramine did not differ from each other ($48.9 \pm 8.53\%$, $46.2 \pm 7.49\%$, $51.12 \pm 9.04\%$, and $47.9 \pm 8.88\%$ of the EEG total power respectively; mean and standard deviation across subjects; right occipital electrode location).

3.2. Pharmacokinetics of cetirizine

The peak plasma concentration of cetirizine occurred in all subjects at 1 h after drug administration regardless of dose (Fig. 1). The mean C_{max} was 697.0 ng/ml and 1000.2 ng/ml at the 10 mg and 20 mg doses, with a variability across subjects of 2.72 and 2.23% respectively. The mean area under the concentration curve (AUC) and estimated half-life were 5153.7 ng/ml · h and 6.48 h respectively for the 10-mg dose, and 6427.4 ng/ml · h and 4.75 h for the 20-mg dose. C_{max}, half-life, AUC, total clearance and volume of distribution of cetirizine differed significantly between doses (Table 1).

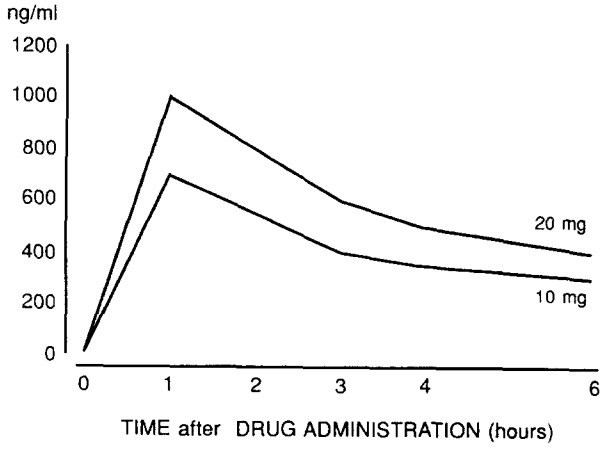


Fig. 1. Plasma concentration of cetirizine after oral administration at 10-mg and 20-mg doses.

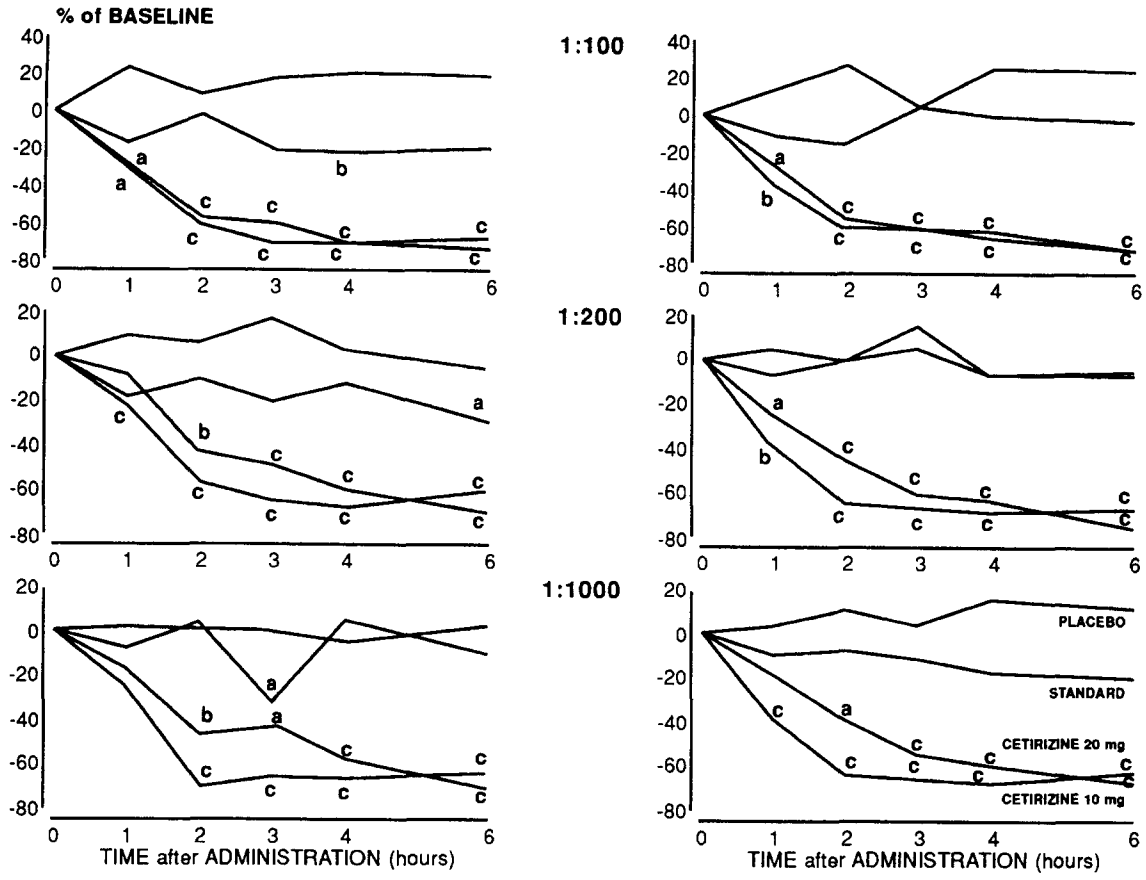


Fig. 2. Post-drug changes in the subjects' cutaneous reactivity to histamine (expressed as diameter of skin weals) at the 1 : 100, 1 : 200, and 1 : 1000 concentrations (right and left forearms). Post-drug changes are expressed as percent variations from baseline in order to reduce individual variability. Baseline determinations did not differ across sessions (analysis of variance (ANOVA); F values smaller than 1.99); post-drug changes were significant in the ANOVA when data for cetirizine and placebo were compared (F values ranging from 21.45 to 43.97 depending on histamine concentration; $P < 0.00001$) but not when chlorpheniramine and placebo were compared (F values ranging from 0.03 to 3.34, not significant). Statistical significance for the pre- versus post-drug comparison (paired t-test; two-tailed) is indicated as follows: [a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$.

3.3. Cutaneous reactivity to histamine

The subjects' skin reactivity, expressed as the diameter of the skin weals, was markedly attenuated after administration of cetirizine, without significant differences between doses. This effect was evident from the first hour after drug administration at the 1 : 100 histamine concentration and from the second hour at the 1 : 200 and 1 : 1000 histamine concentrations. The reduction of the skin weal diameter was symmetrical, though with occasional differences between sides (Fig. 2). The effect of chlorpheniramine on skin reactivity was minimal and transient; placebo proved ineffective on this parameter (Fig. 2).

3.4. Blood pressure, heart rate and performance in the neuropsychological tests

The post-drug variations in blood pressure, heart rate and performance in the neuropsychological tests administered according to the study protocol were neither relevant nor systematic across subjects after administration of placebo, chlorpheniramine or cetirizine at either dose (Ta-

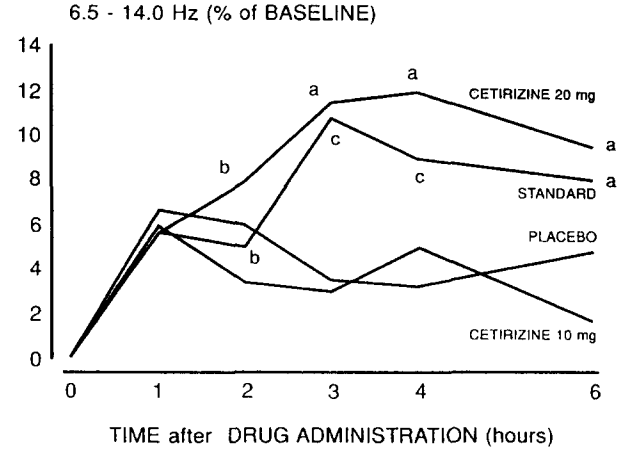


Fig. 3. Effects on the quantitative EEG (6.5–14.0 Hz relative power) of single oral doses of cetirizine, 10 and 20 mg, chlorpheniramine, 4 mg (standard), and matching placebo. Mean percent variations from baseline for eight healthy volunteers. Statistical significance in the pre- versus post-drug comparison (paired t-test; two-tailed) is indicated as follows: [a] $P < 0.05$; [b] $P < 0.02$; [c] $P < 0.01$. Post-drug changes after placebo or cetirizine, 10 mg, were less than approximately 6.0% of baseline values, therefore providing an approximate estimate of spontaneous variability over time and across subjects. Electrode: C4.

Table 1
Pharmacokinetic parameters of cetirizine 10 mg and 20 mg after acute oral administration

	10 mg	20 mg
C_{max} [ng/ml]	697.0	1000.2
	[19.0]	[22.8]
		$t = 28.894$, $P < 0.00001$ vs. 10 mg
Half-life [h]	6.480	4.757
	[0.589]	[0.615]
		$t = 5.723$, $P < 0.0001$ vs. 10 mg
Area under the curve	5153.7	6427.4
AUC [ng/ml·h]	[432.4]	[481.8]
		$t = 5.565$, $P < 0.0001$ vs. 10 mg
Total clearance	0.0020	0.0031
[dose/AUC]	[0.00017]	[0.00024]
		$t = 10.579$, $P < 0.00001$ vs. 10 mg
Volume of distribution	0.0181	0.0215
[dose/concentration]	[0.0004]	[0.00013]
		$t = 22.865$, $P < 0.00001$ vs. 10 mg

Mean across subjects, standard deviation and t-test between doses.

ble 2). Substantial changes in the subjects' alertness were not detected by the investigators upon observation of their behavior or on conventional visual inspection of the EEG recordings. The volunteers occasionally reported subjective symptoms, with post-drug timing of these reports that was neither consistent across subjects nor related to drug or dose.

3.5. Quantitative EEG

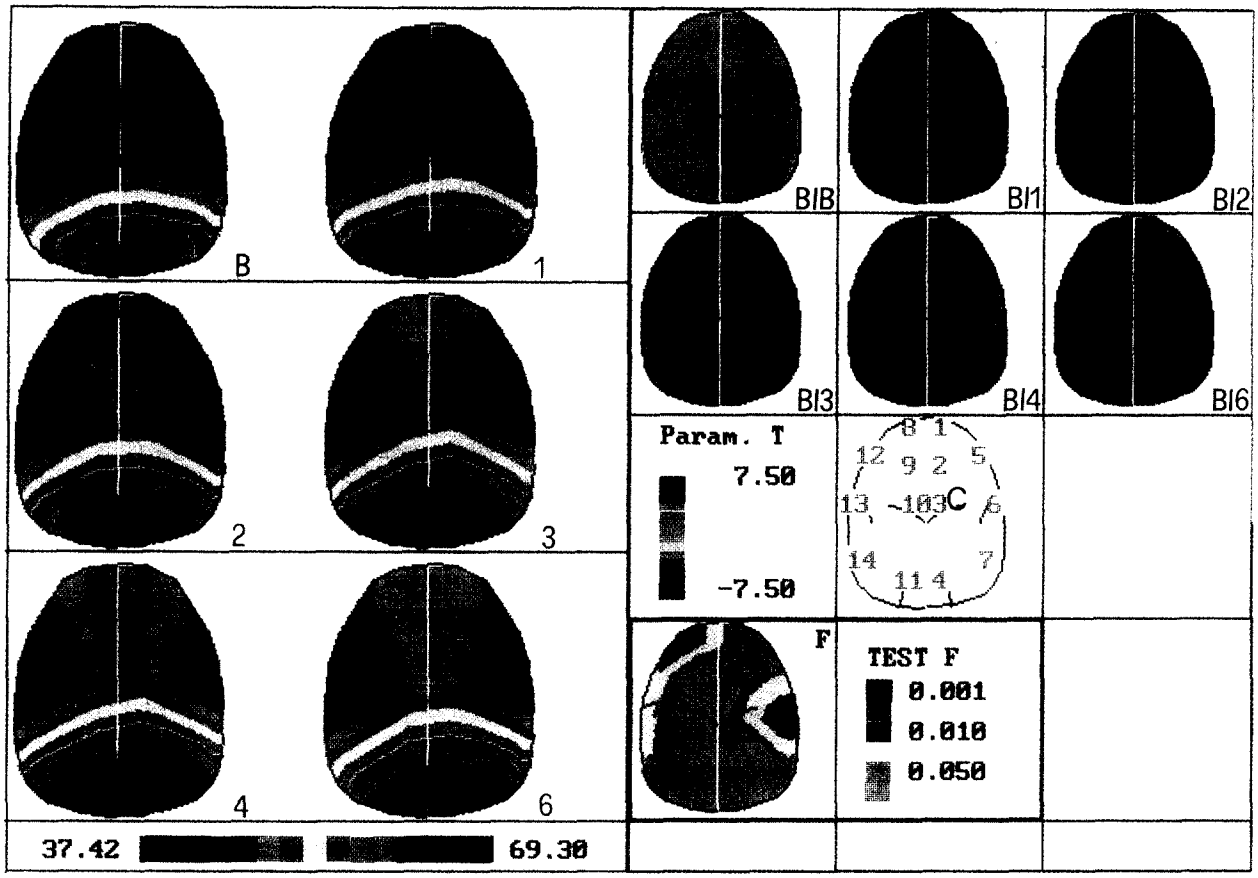
A systematic increase of power in the 6.5–14.5 Hz bandwidth was observed after administration of chlorpheniramine or cetirizine at the 20-mg dose, in the absence of significant shifts of the peak or average frequency of 'alpha' rhythm. The time course after administration, extent of variation and maximum effect (3–4 h post-drug, with 1-h approximate delay from plasma concentration T_{max}) were comparable between compounds. Cetirizine did no differ from placebo at the 10-mg dose (Fig. 3; Table 3). The post-cetirizine (20 mg) increase of power in the extended (6.5–14.0 Hz) 'alpha' range was accounted for by the substantial increase of relative power in the 6.5–8.0 Hz subsegment (i.e. in the low-frequency slope of 'alpha' peak), in the absence of systematic changes in the other subsegments of the 6.5–14.0 Hz frequency interval (Table 3).

The effect of cetirizine on the 6.5–14.0 Hz or 6.5–8.0

Table 2
Percent variations from baseline in the volunteers' performance in the neuropsychological tests

		Time after drug administration [h]				
		1	2	3	4	6
Short-term Retention Test						
Placebo		−2.02	−5.41	1.92	9.30	6.12
		[16.24]	[9.67]	[7.93]	[14.36]	[13.33]
Cetirizine	10 mg	4.88	7.88	8.24	7.66	10.62
		[28.14]	[19.58]	[13.61]	[19.93]	[14.87]
	20 mg	2.13	2.70	2.84	2.14	10.29
		[22.86]	[9.72]	[18.61]	[9.29]	[17.30]
Chlorpheniramine		7.30	8.49	11.74	8.26	9.80
		[11.86]	[13.13]	[15.04]	[12.04]	[14.52]
Backward Digit Span Test						
Placebo		−20.89	−8.69	−3.98	0.41	−8.10
		[17.96] [b]	[15.92]	[11.57]	[14.08]	[13.24]
Cetirizine	10 mg	3.16	4.50	−0.31	7.34	−8.06
		[25.15]	[30.50]	[27.09]	[19.38]	[18.47]
	20 mg	−5.98	1.11	−1.18	2.95	2.60
		[20.84]	[15.75]	[15.17]	[20.72]	[14.32]
Chlorpheniramine		−3.44	0.79	−0.99	−6.55	−4.33
		[18.20]	[12.17]	[15.67]	[35.57]	[38.95]
Immediate Retention Test						
Placebo		−6.58	9.54	4.78	15.58	15.59
		[16.73]	[44.04]	[23.93]	[21.46]	[35.83]
Cetirizine	10 mg	−3.48	7.54	8.49	7.05	11.35
		[12.99]	[20.53]	[14.41]	[12.06]	[20.90]
	20 mg	−4.44	6.65	18.23	1.12	−2.33
		[32.75]	[18.88]	[21.60] [a]	[29.61]	[28.37]
Chlorpheniramine		−4.03	−2.54	9.53	2.91	−4.03
		[20.95]	[13.96]	[17.94]	[14.15]	[31.38]

Mean across subjects and standard deviation; statistical significance for the comparison versus baseline (paired t-test) is indicated. Baseline versus post-drug paired t-test: [a] $P < 0.05$; [b] $P < 0.001$ (two-tail).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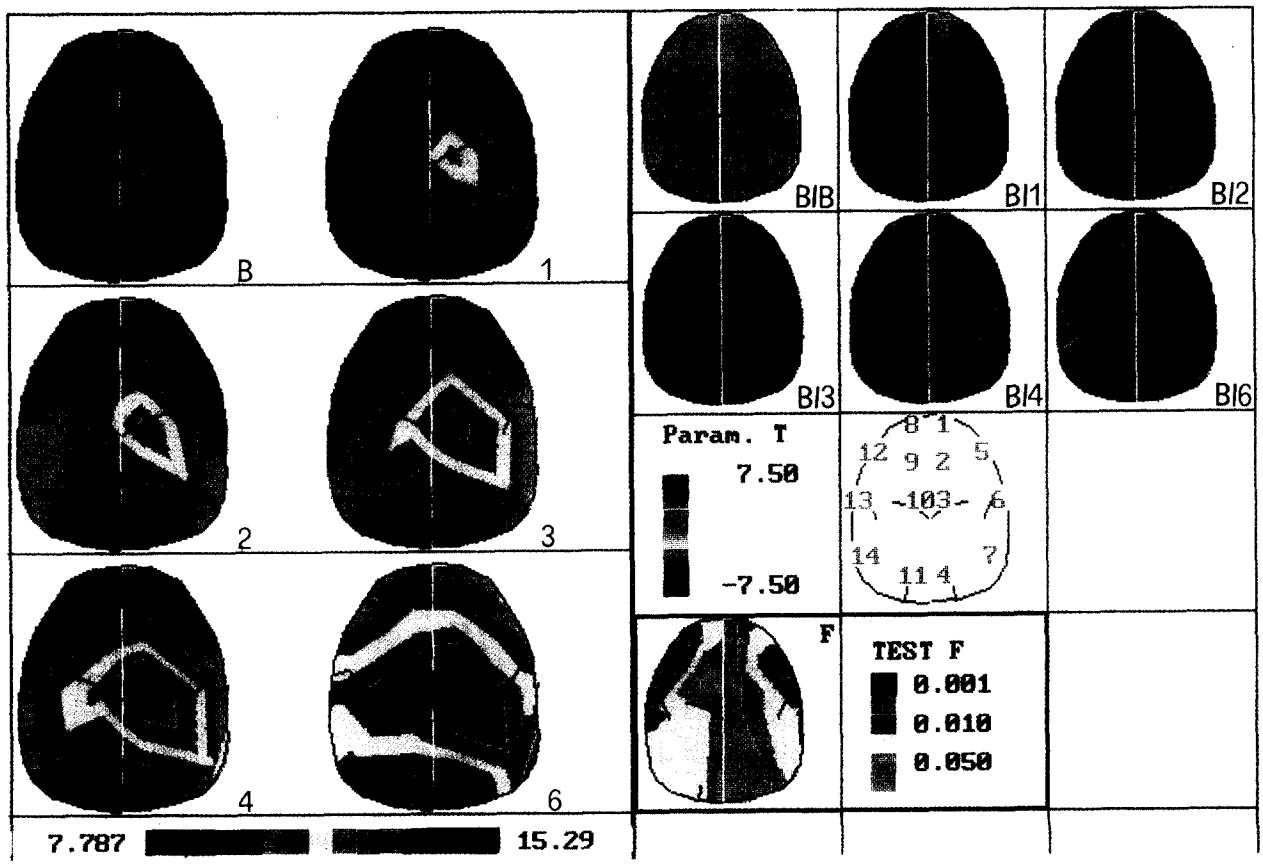
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Table 3
Effects on quantitative EEG (relative power) of single oral doses of cetirizine (10 and 20 mg), chlorpheniramine (4 mg), and matching placebo

		Time after drug administration [h]				
		1	2	3	4	6
Placebo						
	0.5–6.5 Hz	−2.02	−5.41	0.92	−3.30	−2.12
		[16.24]	[9.67]	[7.93]	[14.36]	[13.33]
	6.5–12.0 Hz	6.53	6.05	3.13	2.91	4.93
		[13.55]	[11.62]	[7.11]	[6.13]	[6.89]
	12.5–32.0 Hz	−2.89	−8.69	−3.98	4.41	−8.10
		[17.96]	[15.92]	[11.57]	[14.08]	[13.24]
Cetirizine	10 mg					
	0.5–6.5 Hz	−0.70	−5.29	0.52	0.58	−7.14
		[10.47]	[14.29]	[20.55]	[16.00]	[14.75]
	6.5–14.0 Hz	5.96	3.31	2.97	4.86	1.10
		[7.05]	[10.35]	[9.79]	[12.28]	[8.84]
	14.5–32.0 Hz	5.47	15.13	9.44	6.16	8.38
		[12.66]	[19.66]	[19.55]	[8.71]	[15.50]
Cetirizine	20 mg					
	0.5–6.5 Hz	0.91	−3.38	−6.34	−5.68	−2.72
		[7.64]	[10.88]	[8.86]	[9.12]	[9.97]
	6.5–14.0 Hz	5.45	7.89	11.55	12.42	9.15
		[8.12]	[6.26] [b]	[10.57] [a]	[11.71] [a]	[9.28] [a]
	14.5–32.0 Hz	−4.43	−4.84	1.68	−4.73	−11.98
		[6.13]	[7.31]	[18.16]	[9.62]	[12.14] [a]
	6.5–8.0 Hz	8.75	12.36	12.19	12.74	25.26
		[12.36]	[11.75] [b]	[14.55] [a]	[14.27] [a]	[19.05] [c]
	8.5–10.0 Hz	0.97	0.55	4.84	13.59	11.40
		[17.54]	[13.28]	16.62	[25.03]	[19.84]
	10.5–12.0 Hz	4.22	4.66	8.42	14.49	5.56
		[26.91]	[19.49]	[19.46]	[17.45]	[13.35]
	12.5–14.0 Hz	8.92	−1.81	7.02	5.77	1.26
		[26.33]	[15.50]	[21.28]	[33.54]	[25.66]
Chlorpheniramine						
	0.5–6.5 Hz	4.89	5.05	−5.05	−2.72	2.68
		[10.89]	[9.16]	[16.64]	[14.39]	[11.72]
	6.5–14.0 Hz	5.68	4.84	10.79	9.03	7.96
		[7.05]	[4.12] [b]	[7.01] [c]	[6.82] [c]	[7.84] [a]
	14.5–32.0 Hz	−4.86	3.51	−0.82	−5.45	7.67
		[5.73] [a]	[9.59]	[18.24]	[13.91]	[9.09]

Mean percent variations from baseline in eight healthy volunteers and standard deviation. Statistical significance for the comparison versus baseline (paired t-test) is indicated. Baseline versus post drug, paired t-test: [a] $P < 0.05$; [b] $P < 0.02$: [c] $P < 0.01$ (two-tail).

Hz power was apparent on most explored scalp areas at the pre- versus post-drug comparison by t-test. A preponderance of anterior (frontal and temporal) scalp areas could be inferred based on power distribution and on the results of the ANOVA done across subjects and over time. The post-drug changes occurring in central areas were somewhat greater but less consistent across subjects than in frontal and temporal areas (Fig. 4).

Changes in the relative power of the other frequency segments of the spectrum (or subsegments of the extended 'alpha' activity) were unsystematic across subjects and over time, with a distribution counterbalancing the drug-in-

Fig. 4. Topographic distribution of cetirizine-related increase of EEG power in the 6.5–14.0 Hz (as in Fig. 3) (upper portion of figure) and 6.5–8.0 Hz (lower portion of figure) frequency intervals. For each frequency interval – *Left:* scalp distribution of EEG power in baseline [B] and 1, 2, 3, 4, and 6 h after administration of cetirizine at the 20-mg dose, expressed in pseudocolors according to the scale at the bottom left. Note changes from green to yellow in anterior areas (6.5–14.0 Hz) and from green to yellow and red in central areas (6.5–8.0 Hz), expressing increased power for these EEG parameters. *Right, top:* paired t-test between baseline (B) and post-drug determinations (1, 2, 3, 4, and 6 h); statistical significance is indicated by pseudocolors according to the scale shown and the comparison across baseline determinations (B/B) is reported. *Right, bottom:* overall ANOVA of pre- and post-drug EEG values. The electrode distribution is indicated.

Table 4
Correlation between cetirizine plasma concentration and percent variations from baseline in the power on 6.5–14.0 Hz and 6.5–8.0 Hz EEG frequency bandwidths after administration at the 20 mg dose

Electrode		6.5–14.0 Hz	6.5–8.0 Hz
Right	frontopolar	0.446	0.020
	frontal	1.479	0.520
	central	1.459	−0.171
	occipital	2.016 [a]	−0.359
	anterior temporal	0.614	0.121
	middle temporal	−0.345	0.644
	posterior temporal	1.670	0.653
Left	frontopolar	−0.249	0.215
	frontal	1.325	0.273
	central	0.652	−0.462
	occipital	0.537	−0.379
	anterior temporal	0.739	0.004
	middle temporal	0.444	0.123
	posterior temporal	2.710 [a]	0.545

Kendall's coefficient of correlation for ranked data; z-scores and statistical probability. [a] $P < 0.05$.

duced, systematic modifications of relative power in the 6.5–14.0 Hz or 6.5–8.0 Hz frequency bands (Table 3).

The post-cetirizine increase of power in the 6.5–14.0 Hz and 6.5–8.0 Hz frequency intervals did not correlate with the drug plasma concentration (Table 4).

4. Discussion

In accordance with previous reports (Gengo et al., 1987), the kinetics of cetirizine proved dose-related. The suppression of the skin reaction to histamine, in contrast, was virtually superimposable at the 10-mg and 20-mg doses as to latency from administration, duration and extent of variation from baseline. A ceiling effect in the occupancy of histamine H_1 peripheral receptors is conceivable in this respect (Gengo et al., 1987; Muller et al., 1988; Snowman and Snyder, 1990; Snyman et al., 1992). The limited and transient reduction of skin reactivity to histamine that was observed after chlorpheniramine is consistent with the reported potency of action of this compound compared to cetirizine (Snyman et al., 1992).

No drug-induced changes in the neuropsychological status were detected after administration of cetirizine, in agreement with previous reports on the lack of behavioral effects at comparable doses (Gengo et al., 1987; Seidel et al., 1987), or after chlorpheniramine. It was also consistent with previous observations (Pechandre et al., 1988) that cetirizine proved ineffective on the quantitative waking EEG when administered at the 10-mg dose. The EEG change after administration of cetirizine at the 20-mg dose (notably increase of power in the 6.5–14.0 Hz frequency bandwidth, equivalent in adults to the extended 'alpha' rhythm of the EEG, and on its 6.5–8.0 Hz subsegment), and the preponderance of this effect on anterior scalp areas (in contrast with posterior predominance in physiological awake conditions) are regarded as early indicators of vigilance shifting from relaxed wakefulness toward mild sedation in acute experimental conditions (Bente, 1979; Matejcek, 1982; Ott et al., 1982; Streitberg et al., 1987). The definition of 'stage A' was proposed based on the characteristics of the EEG pattern and is applied to describe this stage of vigilance as opposed to 'stage B' (with peculiar disintegration of rhythmic 'alpha' into lower and higher frequency components) (Lindsley, 1960; Bente, 1979). Some histaminergic specificity of the systems modulating vigilance and the neural generators of the EEG and concurring to define the 'stage A' pattern of vigilance is conceivable. Though non-specific with respect to the drug administered and the underlying mechanisms of action, the EEG actually reflects modulation of cortical and thalamocortical processing through cholinergic and noradrenergic systems (McCormick, 1989; Steriade et al., 1990) and from diffuse histaminergic projection from the magnocellular posterior ventral hypothalamus (Pollard and Schwartz, 1987). The EEG is peculiarly sensitive to changes occurring in this transitional segment of the vigilance continuum ranging from alert wakefulness to sleep, at extents of variation that are otherwise undetectable by e.g. conventional neuropsychological testing. This sensitivity may account both for dissimilarities among results of studies based on EEG or behavioral estimates of sedation (Gengo et al., 1987; Seidel et al., 1987; Ramaekers et al., 1992), as well as for the identification in the present study of drug-related EEG changes in the absence of sizeable modifications of the subjects' neuropsychological status. This discrepancy neither implies, nor allows, the exclusion of possible sedative side-effects on operant behavioral patterns under controlled experimental conditions (e.g. psychomotor performance) or in everyday activities. It suggests, instead, a transport of cetirizine across the blood-brain interface, though at doses higher than those exhibiting a peripheral antihistaminic action and eligible for therapeutic indication, with a higher than 10-mg estimated threshold dose for sedative action in conditions comparable to those devised for this study.

The lack of a definite correlation between the post-drug EEG changes and the cetirizine plasma concentration may favour the hypothesis of a transfer from plasma to the CNS via mechanisms partly independent of concentration in the peripheral compartments. It, however, remains undefined whether the observed dose-related EEG effect of cetirizine depends on a threshold for drug transport across the blood-brain interface or reflects dose-related binding and/or a pharmacological action at histamine H_1 receptors (Snowman and Snyder, 1990) or homeostatic phenomena related to CNS histaminergic activity (Pollard and Schwartz, 1987). In view of the comparable EEG modifications that were observed after chlorpheniramine and cetirizine, possible drug effects on vigilance and on the EEG through non-H_1 histaminergic (Roth et al., 1987;

Quach et al., 1979; Schwartz et al., 1982; Nicholson, 1983) or non-histaminergic (Steriade et al., 1990) mechanisms cannot be excluded based on the selectivity of cetirizine for H_1 brain receptors, and further studies in this regard are advisable.

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