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Comparison of the central and peripheral antihistamine effects of dimethindene maleate (Fenistil®) and its enantiomers

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Abstract

The H_1 histamine receptor antagonist activity and sedative effects of dimethindene maleate racemate (DIM +/−) (FENISTIL®) and the individual enantiomers (DIM + and DIM −) were monitored in parallel in a double-blind, placebo-controlled, cross-over study in 9 healthy subjects. Peripheral antihistamine activity (histamine-induced wheal and flare planimetry) and central effects (electroencephalography (EEG) and self-evaluation on a visual analogue scale (SEVS)) were measured after oral administration of a single dose of DIM +/− (4 mg), DIM + (2 mg), DIM − (2 mg) and placebo.

DIM +/−, DIM + and DIM − induced decreased SEVS scores. EEG pattern modifications indicative of a sedative effect appeared comparable for DIM +/− and DIM −, especially 2 h after drug intake, whereas DIM + exhibited spectral differences more marked at 5.5 h. Moreover, DIM +/− and DIM − significantly inhibited the cutaneous reaction to histamine, whereas DIM + activity was not different from that of placebo, demonstrating that the peripheral antihistamine activity of DIM +/− resided mainly in the DIM- enantiomer.

Introduction

Dimethindene maleate racemate (DIM +/−), the active substance of FENISTIL®, is a potent and selective H_1 histamine receptor antagonist [1, 2]. However, occasional sedation was observed with DIM +/−, as has been recognized for most antihistaminic drugs since they were introduced into the therapeutic arsenal [3].

Previous studies *in vitro* and in animals have shown that the activity of DIM − and DIM + for H_1 histamine receptors was highly stereoselective and that the antihistamine activity laid mainly in the DIM-enantiomer [4–6]. By means of quantitative analysis of the scalp electroencephalography (EEG) in man, degrees of sedation can be characterized and measured for various drugs including antihistamines [7, 8]. Indeed, quantitative EEG can be used to identify, compare and classify drugs which affect the central nervous system, and one can relate EEG findings to other measured effects. The EEG signal is most commonly quantified in fixed frequency bands, using power spectral density analysis.

In this report we wished to establish whether sedation could be correlated to H_1 antagonism alone. Therefore, we monitored in parallel the inhibition of histamine-induced wheal and flare cutaneous reaction and the central effects derived from the racemic form DIM +/− and from its individual enantiomers DIM + and DIM − using

objective measurements in healthy human volunteers.

Materials and methods

Subjects

Nine healthy male volunteers aged 20–35 years were included in the study.

Study design

Randomized, double-blind, placebo-controlled, cross-over (minimum 5 days washout). Single oral doses of 4 mg DIM +/−, 2 mg DIM +, 2 mg DIM − or vehicle alone (4 ml) presented in identically looking and tasting solutions were given at random by the investigator on days 1, 8, 15, 21.

Cutaneous reaction to histamine

Each volunteer received 2 pricks on each forearm (control and histamine-coated PHAZET™ pricks, or saline and histamine (10 mg/ml) solution pricks). Ten minutes thereafter, the areas of the wheal and flare were transferred to transparencies and analyzed by computerized planimetry.

SEVS

Each volunteer was asked to record his subjective feeling on a 100 mm line, scoring full alertness to marked sedation from left to right, respectively.

Quantified EEG

Each recording lasted 5 min with the volunteer laying at rest, eyes closed, with no check on wakefulness. The EEG signal was recorded at 4 points: right and left rolando-parietal and parieto-occipital. The signal was treated using the Nicolet MED 80 system. A program isolated 6 frequency bands: delta (0.7–3 Hz), theta (3–8 Hz), alpha 1 (8–10 Hz), alpha 2 (10–13 Hz), beta 1 (13–18 Hz) and beta 2 (18–40 Hz). For each anterior and posterior area and for each frequency band, the absolute and relative power values, as well as the principal frequency and variability index were also calculated.

Study schedule

Cutaneous reactivity and SEVS were examined 2 and 5.5 h after each dosing of DIM +/−, DIM +, DIM − and placebo on day 1, 8, 15, 21. EEG recordings were performed at day-7 (prior to entry) and on days 1, 8, 15, 21, immediately before, then 2 and 5.5 h after drug intake.

Statistical analysis

For the skin reactivity, the sizes of the wheals and erythemas after treatment were evaluated by a 2 factor variance analysis followed by a multiple protected "*t*" Student test. For the EEG, absolute powers and main frequency were compared by a 2 factor variance analysis with protected "*t*" (volunteers, treatments) for each electrode group and each frequency band. For the study of relative values, Friedman two way analysis and Wilcoxon *t* test were used.

Results

Peripheral effects

Table 1 presents the results comparing two methods of histamine induced cutaneous reaction. Using either method, DIM +/− and DIM − inhibited the reaction both 2 and 5.5 h after intake.
This inhibition was statistically significant at 5.5 h using the PHAZET™ test (27% and 43%, for DIM +/− and DIM −, respectively) and at both 2 and 5.5 h using the histamine solution prick test.
A comparable inhibition was observed at both times for DIM +/− and DIM − (37% versus 34% at 2 h; 47% versus 41% at 5.5 h, respectively). In contrast, DIM + yielded an activity comparable to that of placebo.

Central effects

On the SEVS, a tendency pointing to a moderate decrease of alertness was observed for DIM +/−, and to a lesser extent, for DIM − and DIM + 2 h after intake. At 5.5 h, this tendency was mainly observed for DIM + (data not shown).
Figure 1A and 1B shows some results of EEG recorded 2 and 5.5 h after drug administration, respectively. Studying relative powers in the posterior regions at 2 h, all three compounds showed a tendency to increase the delta- and, even more so

Table 1
Effect of Dimethindene racemate and enantiomers on histamine-induced cutaneous reactions: comparison of two methods.

Treatment	Histamine		Phazet test		Histamine prick test (10 mg/ml)			
	Lag after drug intake: 2 h		5.5 h		2 h		5.5 h	
	Mean[a]	% change	Mean[a]	% change	Mean[a]	% change	Mean[a]	% change
Placebo	1051 ± 230	–	1268 ± 179	–	972 ± 155	–	965 ± 159	–
Racemate (DIM +/−)	782 ± 129	−26	924 ± 170*	−27	614 ± 170*	−37	510 ± 85**	−47
Isomer (+) (DIM +)	1423 ± 276	+35	1025 ± 236	−19	918 ± 181	−6	923 ± 175	−4
Isomer (−) (DIM −)	819 ± 192	−22	720 ± 159***	−43	642 ± 172*	−34	491 ± 111**	−41

[a] For each patient and each compound, the results at each time are expressed as means of percent difference versus the control value (placebo).
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ versus placebo.

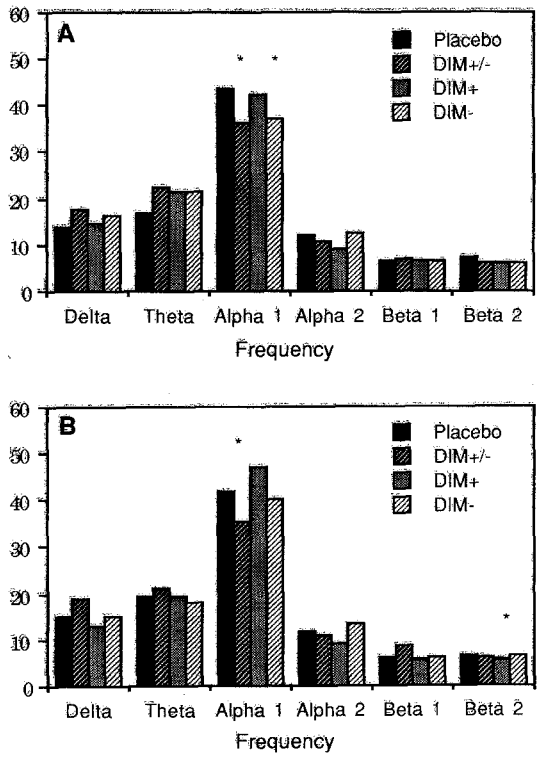

Figure 1
Relative power variation by frequency band in the posterior regions, measured at 2 h (A) and at 5.5 h (B) after intake of DIM +/− (4 mg), DIM + (2 mg) and DIM − (2 mg) compared to placebo.

the theta band. A significant decrease ($p < 0.05$) in the alpha 1 band was observed for DIM +/− and DIM −. At 5.5 h, the most reactive compound was DIM +/−, which increased delta, theta and beta 1 bands, and significantly decreased alpha 1. In contrast, DIM + increased alpha 1 and decreased significantly ($p < 0.05$) the beta 2 band. Finally, DIM − did not show any particular tendency at this time.

Discussion

Peripheral H_1 blocking effects of DIM +/−, the active principle of Fenistil®, could be demonstrated at a clinical dose of 4 mg. In histamine-induced cutaneous reactions, the inhibitory activity of DIM +/− was comparable to that of enantiomer DIM −. In contrast, compared to placebo, DIM + exerted no significant inhibition of the wheal and flare reaction. These results confirmed in man the differential activity of the DIM + and DIM − enantiomers previously reported for *in vitro* and animal investigations [4–6].
With respect to the central effects, analysis of other antihistaminic agents had shown the usefulness of EEG in monitoring sedative action and its correlation with subjective measurements [7–10]. In comparison to placebo, DIM +/− induced EEG pattern modifications in agreement with the decreased SEVS scores, pointing to a sedative effect more pronounced at 2 than at 5.5 h after intake. Whereas

comparable spectral changes were observed with DIM− at 2 h, no residual effect remained at 5.5 h. In contrast, DIM+ induced EEG pattern modifications different from DIM+/− and DIM−.
Our results also showed that not only the latter compounds, but also DIM+ exhibited EEG patterns suggesting a sedative effect. Finally, it appeared that DIM− had the lowest ratio of central to peripheral effects, especially 5.5 h after intake.

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