Effect-time-relation of the H₁-receptor antagonist dimethindene maleate following intravenous injection

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Abstract

We have investigated the time-course of the weal and flare inhibiting activity of dimethindene maleate in man and compared the resulting effect-kinetic data with those from pharmacokinetic investigations. The study was carried out in a double blind, placebo controlled cross-over design with randomly assigned healthy volunteers. Dimethindene maleate (4 mg) was intravenously injected, followed by intracutaneous histamine provocations (-1, 2, 5, 14, 17, 20, 23, 26, and 29 h). The two cross-over periods were separated by a wash-out phase of 17 h. Flare and weal areas were documented 5, 10, 20, and 30 min after provocation with histamine. A strong inhibition of the development of flares and weals was observed and was more pronounced in flares than in weals. With regard to the time course of the inhibiting effect, its maxima both for flares and weals were observed at a provocation time of 2 h. The mean residence time of the inhibiting effect was calculated to be ca. 13 h for flares and ca. 15 h for weals. These values are nearly 2–3 times as high as the mean residence time of 6 h calculated from blood level data. Blood- and effect-levels are thus non-linearly related.

Introduction

Dimethindene maleate, an H₁-receptor – antagonist of high potency has been shown to possess H₁-receptor affinity in receptor binding as well as in classical functional experiments with various tissues, organs and animals [1–3]. The IC₅₀ was calculated to be 6.0 nM. The pA₂-values for various tissues were evaluated using Schild’s method to be 8.39 (guinea pig trachea), 8.62 (guinea pig atria), 9.05 (guinea pig ileum) and 9.12 (rabbit aorta). It was shown that the receptor clearance rate is low under in vitro conditions [4]. Following i.v. injections of 4 mg dimethindene maleate, maximal mean plasma levels of 42 ± 18.8 ng/ml were measured. The AUC₀–∞ was calculated to be 140.7 ± 39.2 and 150.6 ± 44.4 ng·h/ml in two separate trials. The elimination half-life was estimated following the two compartment model to be 4.89 ± 3.13 and 6.22 ± 2.75 h [5], confirming former results from urine analyses.

Based on this information it seemed worthwhile to investigate the time course of the inhibiting activity of dimethindene maleate in man and to compare the resulting effect-kinetic data with those from pharmacokinetic investigations.

Materials, methods and subjects

Purchasable ampoules containing 4 mg dimethindene maleate in isotonic solution (Fenistil®) were supplied by Zyma GmbH, München. Isotonic sodium chloride solution was used as placebo and purchased from Fresenius, Bad Homburg.
Aqueous histamine solution (0.01%) was supplied by Tropon-Werke, Cologne.

The study was carried out in a double blind, placebo controlled crossover design. The subjects were randomly assigned to the two treatment sequences. Intracutaneous histamine injections were applied from -1 to 29 h with increments of 3 h. During the sleep period (00.00–07.00 p.m.) no histamine injection was administered. Weal and flare reactions were measured as areas 5, 10, 20, and 30 min following the histamine injections and transformed into areas under the curve $\text{AUC}_{0.05-.30[\text{min}]}$ using the trapezoidal rule.

The medication with dimethindene maleate (4 mg) or placebo (equivalent volume of sodium chloride solution) was provided at time point 0 h. The overall $\text{AUC}_{0-.30[\text{h}]}$ was calculated following logarithmic transformation from the differences between $\text{AUC}_{0.05-.30[\text{min}]}$ under placebo and real treatment conditions, from the last challenge until 4:00 p.m. On day 3 the wash-out phase followed. The schedule was repeated after cross over in an identical manner. The weal and flare reactions were provoked by intracutaneous injections of 0.05 ml of aqueous histamine solution ($10^{-4}\%$) into the subjects back, left and right from the vertical median, as is usual in allergological diagnostics. The inducibility of weal and flare reactions was validated by a pretrial with repeated injections.

Cross-over analysis done both on the level of original weal and flare areas and the derived $\text{AUC}_{0.05-.30[\text{min}]}$ -values did not give any indication for potential carry-over and period effects. These effects are therefore neglected in order to simplify the data analysis by simple pooling of the results from the two treatment periods. The values from both treatment conditions, placebo and real, were summarized to an individual response value by taking differences. These differences between the $\text{AUC}_{0.05-.30[\text{min}]}$ values after placebo and real treatment ($\text{AUC}_p-\text{AUC}_r$) were calculated after logarithmic transformation.

Mean residence times were calculated according to Klotz [6]. $\text{AUMC}$ is defined as the area under the first moment curve.

$$\text{MRT} = \frac{\text{AUMC}_{0-.30[\text{h}]} - \text{AUC}_{0-.30[\text{h}]}}{\text{AUC}_{0-.30[\text{h}]}}.$$  

The main aim of the study was to evaluate the time-dependence of the effect of dimethindene maleate on the sensitivity to histamine injections. Despite this explorative character of the study, the data were subjected to a statistical analysis ($t$-test) for effect differences under the hypothesis $H_0$: $\mu_1 = \mu_2$. The criterion used for the analysis was the placebo or real specific area under the curve $\text{AUC}_{0-.30[\text{h}]}$, which was calculated from the $\text{AUC}_{0.05-.30[\text{min}]}$ -values after logarithmic transformation and baseline adjustment by subtraction of values obtained at time 0 h using the trapezoidal rule.

Eight healthy male volunteers aged between 23 and 38 years, with a body weight between 79 and 98 kg and a height between 176 and 194 cm, took part in the study. The health status was reviewed by a general medical examination including the subjects’ history, vital functions and laboratory status. The volunteers were informed about the aim and the potential risk and signed a consent form. The declaration of Helsinki and its extensions and the German Drug Act were fully considered.

**Results**

Medians and means (in brackets) of sequential weal $\text{AUC}_{0.05-.30[\text{min}]}$-values vary for weals after placebo treatment between 1357 and 2184 (1353 and 2446) mm²-min and 1482 and 1945 (1459 and 2921) mm²-min referring to sequence 1 (PR) and 2 (RP) respectively. Following real treatment the values are in the range from 984 to 1949 (921 and 2108) mm²-min and from 899 to 1381 (910 and 1596) mm²-min for both treatment sequences. Corresponding flare $\text{AUC}_{0.05-.30[\text{min}]}$-values following placebo treatment are in the range between 11441 and 17826 (10840 and 17710) mm²-min and 18029 and 34302 (22280 and 32767) mm²-min for the sequences 1 and 2 respectively. Following real treatment the range of $\text{AUC}_{0.05-.30[\text{min}]}$-values for the two sequences was 1789 and 26665 (1920 and 25060) mm²-min and 11 724 and 22 223 (11 240 and 24820) mm²-min.

The differences (placebo-real) of the logarithmic $\text{AUC}_{0.05-.30[\text{min}]}$ -values following pooling are characterized by medians (means) between $-0.069 (-0.029)$ and 0.247 (0.335) for weals and $-0.101 (0.091)$ and 0.513 (0.630) for flares.

The overall $\text{AUC}_{0-.30[\text{h}]}$ indicating the inhibiting effect was calculated to be 9.5 for flares and 3.5 for weals (median). Treatment specific $\text{AUC}_{0-.30[\text{h}]}$-values differ significantly ($p < 0.001$; $t$-test). Values level to 1.06 (placebo) and -12.01 (real) for flares.