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A Comparison of Antihistaminic and Sedative Effects of Some H_1-receptor Antagonists*

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All H_1-receptor antagonists cause drowsiness, some compounds more than others. In treating allergic diseases the sedation is an undesirable side effect, whereas it may be beneficial when antihistamines are used to alleviate itching in atopic dermatitis or other pruritic diseases. It would thus be of value for the clinician to have a "therapeutic index" showing the relation between peripheral histamine-antagonistic and central sedative effects for the antihistamine compounds. In the present investigation such relations were studied in three antihistamines.

METHODS

In a pilot study 20 mg hydroxyzine (Atarax, UCB), 3 mg clemastine (Tavegyl, Sandoz) and 3 mg azatadine (not registered in Sweden, Schering Corp.) were found to suppress histamine responses about 30% when measured 5 h after drug intake. These approximately equivalent doses and placebo were then studied in 24 healthy volunteers by a double-blind, cross-over design. Inhibition of itch and flare reactions induced by intradermally injected histamine was measured. Concurrently we analyzed central sedation by a set of computerized neuropsychological tests, such as finger tapping, reaction time and trailmaking, and by analog ratings of alertness, concentration, tiredness, sleepiness, tenseness and discomfort. Registrations were made for 5½ h after intake of single oral doses.

RESULTS AND DISCUSSION

Hydroxyzine, 20 mg, had a stronger antihistamine effect than clemastine 3 mg and azatadine 3 mg but a less sedative effect than the other two drugs. There was no significant difference between clemastine and azatadine regarding histamine antagonism but a tendency that clemastine caused more sedation than the other two drugs. A score reflecting the balance between antihistamine and CNS effects was computed and was found to be 1.39 for hydroxyzine, 0.27 for clemastine, and 0.62 for azatadine. High values indicate a pronounced peripheral and a moderate central effect. Hydroxyzine was superior to clemastine ($p<0.001$) and azatadine ($p<0.01$), whereas clemastine and azatadine did not differ significantly.

Histamine antagonism and sedation were found to be independent in a correlational analysis. This observation suggests that it should be possible to synthesize antihistamines without sedative effects.

There was an individual sensitivity to the peripheral antihistamine effects, i.e. a pronounced effect of one drug predicted a marked effect of the other two drugs. For the central effects the situation was more complicated. There was a high correlation between hydroxyzine and clemastine, implying that an individual who becomes drowsy after hydroxyzine probably will develop drowsiness also after clemastine. On the other hand there was no individual correlation between azatadine and the other two drugs. Transferred to the clinical situation this implies that if a patient experiences marked sedation

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after hydroxyzine, a shift to clemastine is not indicated since the effects of hydroxyzine and clemastine are intercorrelated both peripherally and centrally. A shift to azatadine treatment is more logical, since there is 50% chance that the sedation for this drug is less pronounced than for hydroxyzine, relative to an unchanged peripheral efficiency.

This investigation of peripheral histamine antagonism vs. central sedation using computerized neuropsychological tests, incicates that hydroxyzine has a relatively higher antihistamine and a lower sedative effect than clemastine and azatadine. However, the data must be interpreted with caution since they are based on single-dose kinetics. Further studies should include both the single and the continuous dose situations and should be extended to other antihistamines, in particular to the more recent compounds claimed to have no sedative action.

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