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Comparison of pseudoephedrine and triprolidine, alone and in combination in preventing nasal congestion in subjects with allergic rhinitis using nasal histamine challenge

D. W. EMPEY[1], M. F. FROSOLONO[2]. D. T. D. HUGHES[1] & J. G. PERKINS[2]
[1]Clinical Research Division, The Wellcome Research Laboratories, Beckenham, Kent BR3 3BS and Pulmonary Research Unit, The London Hospital, Whitechapel, London E1 1BB and [2]Department of Clinical Research, Burroughs Wellcome Co., Research Tringle Park, North Carolina, United States of America

The abilities of triprolidine 2.5 mg and pseudoephedrine 60 mg, alone and in combination, to protect against an increase in nasal airway resistance (NAR) after histamine challenge were determined in eighteen individuals with grass pollen allergy. The study was conducted outside the pollen season using a double-blind, placebo controlled crossover design. The prior administration of pseudoephedrine 60 mg and triprolidine 2.5 mg alone or in combination was superior to placebo in reducing the increase in NAR after challenge with 1.0% histamine. However, such NAR measurements did not differentiate between pseudoephedrine 60 mg and triprolidine 2.5 mg administered alone or in combination. Challenge with 0.1% histamine failed to discriminate between any of the test medications.

Keywords pseudoephedrine triprolidine nasal congestion histamine allergic rhinitis

Introduction

The value of histamine challenge in demonstrating the clinical activity of pseudoephedrine and triprolidine as separate therapeutic entities has previously been demonstrated (Britton *et al.*, 1978). Both drugs reduced the increase in nasal airway resistance (NAR) elicited by histamine sprayed onto the nasal mucosa. The combined effect of pseudoephedrine and triprolidine was not explored, and the present study was carried out to see if the combination might be more effective than either of its constituents alone in reducing the rise in NAR after nasal histamine challenge.

Methods

Subjects

Eighteen healthy volunteers (aged 19–38 years) with a history of grass pollen induced rhinitis and positive prick skin tests were selected. The study was performed during the winter months. The individuals all gave their informed consent and had no nasal obstruction or deformity.

Drugs

Test agents were administered in the form of identical tablets manufactured by Burroughs Wellcome Co. and contained the following constituents:

either (a) triprolidine HCl 2.5 mg and pseudoephedrine HCl 60 mg
or (b) triprolidine HCl 2.5 mg
or (c) pseudoephedrine HCl 60 mg
or (d) placebo.

Nasal airway resistance (NAR) measurement and histamine challenge

The method used to measure NAR was that previously described in this journal (Britton *et al.*, 1978). In the present study only two concentrations of histamine (namely 0.1 and 1.0%) were sprayed into the test nostril. Ephedrine (0.5% solution) was administered locally at the end of each test period.

Study design

Volunteers were studied on four separate occasions at least 1 week apart. They had discontinued any topical or systemic decongestants, sympathomimetics or antihistamines during the preceding 48 h. Most were not receiving therapy at this time of year in any case. On arrival they were interviewed and NAR measured. Any subject with coryza or a basal NAR greater than 2.0 kPa^{-1} s had the trial of any drug deferred. Baseline measurements of NAR, pulse and blood pressure were recorded 20 min before drug administration. Subjects then received one of the test treatments. Single tablets of these were given and tests carried out on four occasions at least 1 week apart. A balanced double-blind randomised design was used, each volunteer receiving all the preparations according to a Latin-square design.

When the geometric means of NAR for the challenged nostril as a function of time were plotted, there were small differences between the values at −20 and +60 min (both before the 0.1% histamine challenge) and also between those at +60 and +120 min.

After completion of the baseline phase, the volunteers entered the treatment phase. Tablets were taken at time 0. The respective measurements and histamine challenges were performed at the following times in relation to time 0: histamine challenge — 0.1% solution +65 min; 1.0% solution +125 min; NAR — +60, 67, 75, 95, 120, 127, 135, 155, 180 and 190 min; pulse — +60, 120, 195 min; blood pressure — +195 min; 0.5% ephedrine drops — +185 min. In addition to the above measurements, the volunteer's opinion as to whether an active drug was received was solicited at 100 and 195 min after time 0. Possible responses were: 'yes', 'no' or 'don't know'. The subjects were asked to report any adverse reactions occurring throughout the study or on the morning of the next day.

Statistical analysis

The arithmetic mean of five determinations was used in the statistical analyses as the measurement of NAR at each time point. As before (Britton *et al.*, 1978; Empey *et al.*, 1980), logarithmic transformations of the means was performed before final analysis of data. The differences in prechallenge (i.e. at +60 and +120 min) NAR values were incorporated in the statistical model to independently assess the effects of the 0.1% and 1.0% histamine challenges.

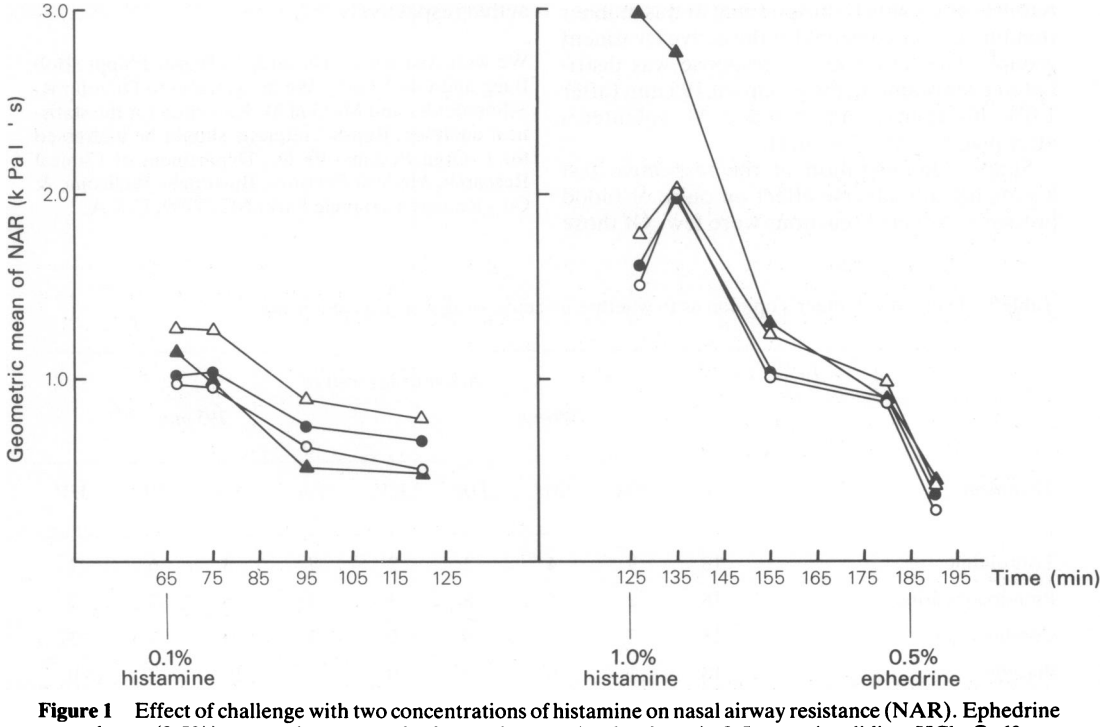

Figure 1 Effect of challenge with two concentrations of histamine on nasal airway resistance (NAR). Ephedrine nose drops (0.5%) were given at end of experiment. ▲ placebo, △ 2.5 mg triprolidine HCl, ● 60 mg pseudoephedrine HCl and ○ combination.

Results

Because of the differences in prechallenge NAR values (i.e. at 60 and 120 min) the results were incorporated in a statistical model which adjusted for volunteer, sequence, and period effects, and revised NARs obtained. These more accurately reflect the response(s) elicited by the histamine and are depicted in Figure 1. Challenge by 0.1% histamine failed to discriminate between the four treatments. By contrast, challenge with 1.0% histamine segregated the plot for placebo from those of the other three groups which were virtually superimposable. The differences observed at 127 min were statistically significant.

The subjective assessments of whether an individual received an active drug are shown in Table 1. Overall, the combination was responsible for the most positive responses (9 and 7 after 0.1 and 1.0% histamine, respectively). Triprolidine elicited more 'yes' answers than pseudoephedrine: 7 and 5 compared to 2 and 3 after 0.1 and 1.0% histamine respectively. Volunteers who responded 'no' to the query were divided fairly evenly among the treatment groups after challenge with 0.1% histamine. The more concentrated histamine solution resulted in 10 'no's' from the placebo group, or an increase of 4 volunteers. By contrast, the number of volunteers responding in this manner remained fairly constant for the active treatment groups. The 'don't know' response was distributed evenly among the groups at 195 min (after 1.0% histamine) but included 11 volunteers after placebo (at +100 min).

Single administration of the respective test agents had no adverse effect on pulse or blood pressure. Adverse reactions were few. Of those directly enquired about, only anxiety was elicited by the administration of the combination but not by the single agents or placebo. Dizziness was noted by a single volunteer after administration of the combination, 60 mg pseudoephedrine and 2.5 mg triprolidine. Any other adverse reactions were mild. There were relatively few instances of individual volunteered information and, as before, they were mild in nature. The only adverse reaction of this type observed by more than one volunteer was drowsiness. Four volunteers complained of drowsiness after receiving the combination, while two experienced the reaction after the placebo. Sleep was unaffected by all treatments.

Discussion

The present study confirmed the previous report of the efficacy of tripolidine and pseudoephedrine in protecting against rises in NAR produced by histamine challenge. It failed to demonstrate any advantage of the combination over either agent alone on the NAR measurements but our subjective results showed that more volunteers perceived triprolidine as active, compared with pseudoephedrine, and the combination and placebo were perceived as the most and least active respectively.

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Table 1 Data on volunteer's opinion as to whether an active drug was received or not.

		Active drug received							
		100 min				*195 min*			
Treatment	n	*'Yes'*	*'No'*	*DK*	*MV*	*'Yes'*	*'No'*	*DK*	*MV*
Triprolidine	18	9	4	3	2	7	3	6	2
Pseudoephedrine	18	2	5	8	3	3	5	7	3
Combination	18	7	3	8	0	5	3	7	3
Placebo	18	1	6	11	0	1	10	7	0

DK = 'don't know'
MV = Missing value

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