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# DOSE-RESPONSE STUDY OF THE NASAL DECONGESTANT AND CARDIOVASCULAR EFFECTS OF PSEUDOEPHEDRINE

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**1** The effects of different doses of orally administered pseudoephedrine on nasal airway resistance (NAR) were studied in a group of eighteen healthy subjects using double-blind conditions with drugs administered in a series of cross-over experiments according to a Latin-square design.

**2** Challenge with 1% histamine diphosphate to one nostril 1 h after administration of the drugs produced increases in NAR.

**3** The effects of pre-treatment with both placebo and increasing doses of pseudoephedrine on this histamine-induced increase in NAR were examined. Pseudoephedrine 60 mg, 120 mg and 180 mg significantly ($P<0.05$) reduced the effect of histamine on NAR compared with the placebo, and the protective effects of these doses did not differ significantly from each other. Pseudoephedrine 15 mg and 30 mg did not differ from placebo in their effects on NAR.

**4** Small, but statistically significant increases in pulse and systolic blood pressure occurred after pseudoephedrine 120 mg and 180 mg, but not after pseudoephedrine 60 mg, 30 mg or 15 mg. No significant effects were produced by any of the doses of pseudoephedrine with regard to diastolic blood pressure. Similarly no dose of pseudoephedrine altered mood or produced any excess of unwanted effects compared with placebo.

**5** We conclude that pseudoephedrine 60 mg is the optimal single adult dose since this achieves maximal nasal decongestion without cardiovascular or other unwanted effects.

## Introduction

L (+)-pseudoephedrine is primarily an α-adrenoceptor stimulant with action similar to D (−)-ephedrine, but it has the advantage that it exhibits less vasopressor action (Drew, Knight, Hughes & Bush, 1978) and causes less cerebral stimulation (Bye, Dewsbury & Peck, 1974). The vasoconstrictor effects of pseudoephedrine reduce nasal blood flow, and thus it is widely used as a nasal decongestant for the symptomatic relief of rhinitis (Benson, 1971; Empey, Bye, Hodder & Hughes, 1975).

The purpose of the present study was to determine the minimum dose of pseudoephedrine which produced maximal nasal decongestion, and to compare this with its cardiovascular effects. In order to avoid problems with varying baselines we have studied normal subjects and induced nasal congestion by histamine challenge. This method has proved effective in earlier studies (McLean, Mathews, Solomon, Brayton & Ciarkowski, 1977) and we have used our own, previously described technique to measure nasal airway resistance (Britton, Empey, John, McDonnell & Hughes, 1978). We have also examined the effects of varying doses of pseudoephedrine on pulse, systolic blood pressure and mood.

### *Subjects*

Eighteen normal volunteers (age 19–33 years) were studied on six occasions 1 week apart. The volunteers all gave their informed consent, and were suffering from no significant medical conditions, and had no nasal obstruction or deformity.

### *Drugs*

Identical tablets were made up as follows:
pseudoephedrine hydrochloride 15 mg;
pseudoephedrine hydrochloride 60 mg;
lactose placebo;
these were then allocated so that on each occasion each subject took three tablets in appropriate combinations and thus received one of the following: placebo alone, pseudoephedrine 15 mg, 30 mg, 60 mg, 120 mg or 180 mg. A balanced, double-blind,

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randomized design was used with each subject receiving all the preparations according to a series of three Latin squares.

Sterile histamine was prepared as 1% histamine diphosphate dissolved in normal saline in sealed ampoules. A Rogers Crystal Spray (Riddell Products Limited) was used to deliver histamine to the left nostril as an aerosol. Each challenge consisted of three activations of the hand pump which delivered approximately 0.025 ml of solution. The spray was directed medially, centrally and laterally in succession to obtain even distribution over the nasal mucosa.

*Equipment*

Nasal airway resistance (NAR) was determined by our own technique of passive anterior rhinometry (Britton *et al.*, 1978). The exact method is described in our earlier paper. An infant's tracheostomy tube is used to make an airtight seal in the external nares, and a low flow of air is passed briefly into the nostril. The back pressure which develops is plotted against flow rate on an X-Y recorder and the nasal resistance obtained from the slope of the line. The equipment used was NART ® (P. K. Morgan Limited, 10 Manor Road, Chatham, Kent, ME4 6AL).

Blood pressure was recorded using a mercury sphygmomanometer, and radial pulse was counted over 30 s.

A symptom score card system was used to record the occurrence of adverse reactions, and subjective effects were investigated using eighteen visual analogue scales (Lader & Norris, 1969).

*Study design*

Volunteers attended the laboratory on six mornings at weekly intervals. They starved from midnight, and after a 15 min rest period, blood pressure and pulse readings were taken followed by baseline measurements of nasal airway resistance (NAR) taking five readings from each nostril. A symptom score card was completed, and then the allocated drug taken with a glass of water.

One hour later pulse and blood pressure were again recorded, and five measurements of NAR were made from each nostril before and exactly 2 min after histamine challenge of the left nostril only. NAR was again measured 10 min, 30 min, and 75 min after challenge; pulse and blood pressure were recorded 140 min after the drugs had been given. Following the last recording of nasal resistance three drops of ephedrine 0.5% BP, were instilled into the left nostril and 5 min later NAR was again measured in both nostrils. Another symptom score card was completed by each subject at the end of the morning and again approximately 9 h after taking the drug. The following day each subject was asked to assess whether their sleep was improved, unchanged or worse than usual.

*Statistical methods*

The significance level was taken as 5% throughout. Duncan's Multiple Range Test was used, where indicated, in all cases to examine differences between the six drugs more closely.

*1. NAR data;* In our previous study logarithmic transformation of NAR data was required (Britton *et al.*, 1978). Examination of the data from this study again suggested that logarithmic transformation be applied in order to stabilize the variance. The means of the logarithms of the individual replicates (usually 5) for each nostril at each time were used in all subsequent NAR analyses. Out of a total of 1,512 occasions when NAR was measured five replicates were available except on 14 occasions when only four replicates were obtained; the missing readings were extimated by their appropriate averages. An overall 4-way analysis of variance was performed allowing differences between subjects, drugs, nostrils, time and their interaction to be examined simultaneously. This analysis was performed both including and excluding the ephedrine data. Significant interactions were detected for 'nostril by time' and 'treatment by time', but not for 'nostril by treatment'. Regardless of whether the interaction between drugs, time and nostrils were significant or not, separate analyses of variance were made at each time for each nostril to examine any drug differences.

*2. Pulse, systolic blood pressure and diastolic blood pressure data;* A three-way analysis of variance was performed for each of these variables, allowing differences between subjects, drugs, and times and their interactions to be examined simultaneously. In each analysis a significant interaction of drug with time was found, indicating a different pattern of response for each drug at the three times considered. Separate two-way analyses of variance were therefore performed at each time, allowing differences between the five doses of drug and placebo to be examined for each variable.

*3. Subjective effects;* The raw scores were analysed at each time using a Latin square analysis of variance. Scores for mental sedation, physical sedation and tranquillization were calculated and similarly analysed.

*4. Side effects;* The responses were tabulated.

All subjects completed all occasions with the exception of two individuals, one of whom developed anxiety and sinus tachycardia following 180 mg pseudoephedrine and was therefore excluded from taking 120 mg pseudoephedrine on the next occasion, and the other who became ill with acute bronchitis at the end of the study and missed the 30 mg occasion.

**Table 1** Nasal airway resistance (kPa $l^{-1}$ $s^{-1}$) for 18 subjects; geometric means $n=10$ for L and R, means not differing at the 5% level have a common underlining. Pseudoephrine 30 mg and 120 mg, L and R nostrils—the means shown include the estimates of the missing readings because $n=17$ for these doses.

| *Pseudoephedrine* | *Placebo* | *15 mg* | *30 mg* | *60 mg* | *120 mg* | *180 mg* | *Differences* |
|---|---|---|---|---|---|---|---|
| *Control* | | | | | | | |
| L | 0.401 | 0.452 | 0.672 | 0.366 | 0.429 | 0.301 | None |
| R | 0.291 | 0.301 | 0.323 | 0.292 | 0.378 | 0.247 | None |
| *Drug + 1h* | | | | | | | |
| L | 0.571 | 0.513 | 0.713 | 0.283 | 0.330 | 0.344 | Ps.30 Plac. Ps.15 Ps.180 Ps.120 Ps.60 |
| R | 0.338 | 0.371 | 0.224 | 0.302 | 0.195 | 0.232 | None |
| *Challenge + 2 min* | | | | | | | |
| L | 2.546 | 2.521 | 2.108 | 0.863 | 0.891 | 0.761 | Plac. Ps.15 Ps.30 Ps.120 Ps.60 Ps.180 |
| R | 0.604 | 0.604 | 0.823 | 0.435 | 0.265 | 0.355 | Ps.30 Ps.15 Plac. Ps.60 Ps.180 Ps.120 |
| *Challenge + 10 min* | | | | | | | |
| L | 3.286 | 3.237 | 1.960 | 0.794 | 1.119 | 1.332 | Plac. Ps.15 Ps.30 Ps.180 Ps.120 Ps.60 |
| R | 0.779 | 0.467 | 0.412 | 0.275 | 0.275 | 0.217 | Plac. Ps.15 Ps.30 Ps.60 Ps.120 Ps.180 |
| *Challenge + 30min* | | | | | | | |
| L | 1.875 | 1.608 | 1.313 | 1.049 | 1.073 | 0.686 | None |
| R | 0.513 | 0.275 | 0.326 | 0.181 | 0.327 | 0.242 | Plac. Ps.120 Ps.30 Ps.15 Ps.180 Ps.60 |
| *Challenge + 75min* | | | | | | | |
| L | 1.322 | 1.231 | 1.045 | 0.540 | 0.674 | 0.420 | Plac. Ps.15 Ps.30 Ps.120 Ps.60 Ps.180 |
| R | 0.436 | 0.270 | 0.454 | 0.218 | 0.213 | 0.173 | None |
| *Ephedrine + 5min* | | | | | | | |
| L | 0.612 | 0.791 | 0.841 | 0.395 | 0.445 | 0.324 | None |
| R | 0.406 | 0.259 | 0.476 | 0.196 | 0.205 | 0.160 | None |

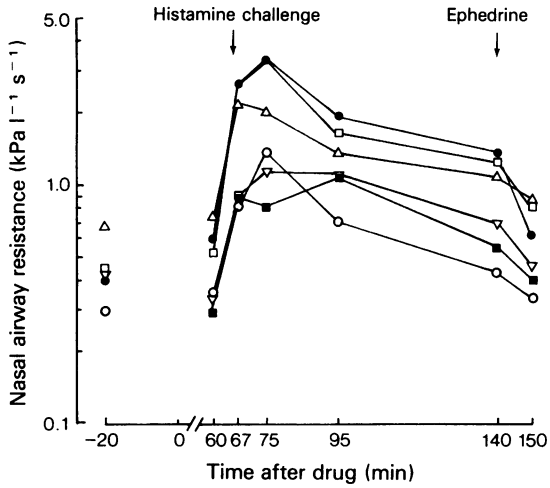


**Figure 1** Geometric mean nasal airway resistance of challenged (left) nostrils plotted against time after taking drug. Results for eighteen subjects in each case except for pseudoephedrine 30 mg and 120 mg when $n = 17$. ● = placebo, □ = pseudoephedrine (PS) 15 mg, △ = PS 30 mg, ■ = 60 mg, ▽ = PS 120 mg and ○ = PS 180 mg.

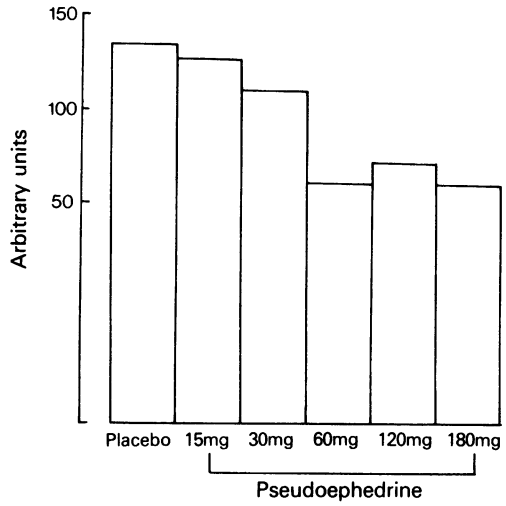


**Figure 3** Areas under the curves shown in Figure 1 between the time of histamine challenge and the time of ephedrine administration expressed in arbitrary units on a logarithmic scale for placebo and each dose of pseudoephedrine.

## Results

The results for NAR in each nostril are shown in Table 1, and Figures 1 and 2. The baseline readings for NAR did not differ between any of the groups. There were no important differences between the groups prior to histamine challenge, although on the occasion when pseudoephedrine 30 mg was given, the group had a higher NAR on the left side compared with the occasions when pseudoephedrine 60 mg, 120 mg and 180 mg were given. No active drug group differed from placebo and the difference between the drug groups probably occurred by chance. Two minutes after challenge to the left nostril, the drugs formed two significantly different groups when the NAR data from the left nostril was considered. One group exhibited a higher rise in nasal resistance and included placebo, pseudoephedrine 15 mg and 30 mg, and the other showed some protection against the effects of histamine challenge, and included pseudoephedrine 60 mg, 120 mg and 180 mg. These differences were largly maintained throughout the study period and the details can be seen in Table 1. NAR fell in the left nostril following instillation of ephedrine, but there were no drug differences with regard to this effect. The values of NAR on each side following ephedrine did not differ significantly from the pre-challenge values.

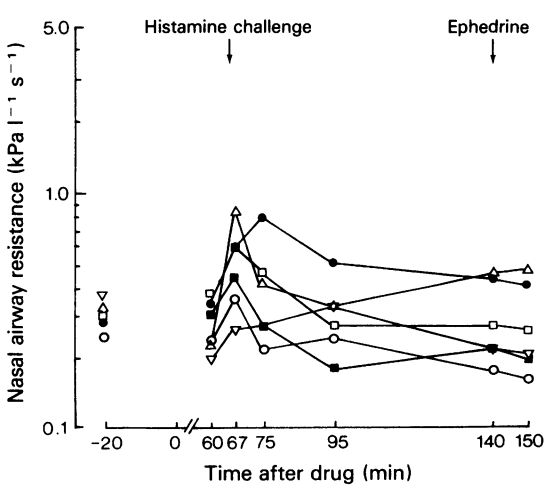


**Figure 2** Geometric mean nasal airway resistance of unchallenged (right) nostrils plotted against time after taking drug. Number of subjects equals eighteen except for pseudoephedrine 30 mg and 120mg where $n = 17$. ● = placebo, □ = pseudoephedrine (PS) 15 mg, △ = PS 30 mg, ■ = PS 60 mg, ▽ = PS 120 mg and ○ = PS 180 mg.

To obtain an estimate of overall effect of the different doses of pseudoephedrine the areas under the curves following histamine challenge and prior to ephedrine instillation have been calculated and are displayed on a histogram with a logarithmic scale in Figure 3.

The results for pulse and blood pressure are shown in Table 2. At no time did pseudoephedrine 60 mg differ from placebo and none of the doses had any effect at any time on diastolic blood pressure.

Analyses performed on the subjective line data revealed significant differences, pre-drug on three

**Table 2** Pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), $n=18$ unless otherwise shown. Means not differing at the 5% level have a common underlining.

| *Pseudoephedrine* | *Placebo* | *15 mg* | *30 mg* | *60 mg* | *120 mg* | *180 mg* | *Differences* |
|---|---|---|---|---|---|---|---|
| *Control* | | | | | | | |
| Pulse (beats/min) | 70.0 ± 2.7 | 70.3 ± 2.8 | 71.9 ± 2.0 ($n=17$) | 68.3 ± 3.5 | 69.6 ± 2.5 ($n=17$) | 68.4 ± 2.9 | None |
| SBP (mmHg) | 110.8 ± 2.5 | 110.6 ± 2.2 | 110.6 ± 2.3 ($n=17$) | 110.8 ± 2.3 | 109.7 ± 2.4 ($n=17$) | 107.8 ± 2.1 | None |
| DBP (mmHg) | 67.5 ± 2.2 | 69.4 ± 1.9 | 67.1 ± 1.8 ($n=17$) | 68.1 ± 1.9 | 67.1 ± 2.1 ($n=17$) | 65.8 ± 1.5 | None |
| *Drug + 1h* | | | | | | | |
| Pulse (beats/min) | 66.3 ± 2.7 | 68.4 ± 3.1 | 68.3 ± 2.7 ($n=17$) | 67.8 ± 2.8 | 72.1 ± 3.0 ($n=17$) | 72.2 ± 2.5 | Ps.180 Ps.120 Ps.15 Ps.30 Ps.60 Plac |
| SBP (mmHg) | 108.1 ± 2.6 | 107.6 ± 2.6 | 108.8 ± 2.2 ($n=17$) | 111.3 ± 2.6 | 114.1 ± 2.2 ($n=17$) | 117.5 ± 2.4 | Ps.180 Ps.120 Ps.60 Ps.30 Plac Ps.15 |
| DBP (mmHg) | 65.6 ± 1.9 | 65.8 ± 1.7 | 66.2 ± 1.7 ($n=17$) | 67.4 ± 1.9 | 70.1 ± 1.6 ($n=17$) | 68.9 ± 1.7 | None |
| *Drug + 140min* | | | | | | | |
| Pulse (beats/min) | 68.1 ± 3.0 | 69.4 ± 2.7 | 69.4 ± 3.0 ($n=17$) | 72.0 ± 3.1 | 76.1 ± 3.8 ($n=17$) | 77.6 ± 3.2 | Ps.180 Ps.120 Ps.60 Ps.15 Ps.30 Plac |
| SBP (mmHg) | 108.6 ± 2.3 | 108.2 ± 2.2 | 109.7 ± 2.5 ($n=17$) | 109.7 ± 2.4 | 111.4 ± 1.9 ($n=17$) | 115.1 ± 2.3 | Ps.180 Ps.120 Ps.60 Ps.30 Plac Ps.15 |
| DBP (mmHg) | 66.4 ± 1.5 | 65.7 ± 1.7 | 66.2 ± 1.9 ($n=17$) | 66.4 ± 1.5 | 66.4 ± 1.5 ($n=17$) | 67.2 ± 1.9 | None |

**Table 3** Subjective effects: Significant drug differences from analyses of raw data

| | |
|---|---|
| | *Pre-drug* |
| Lethargic/energetic: | Ps.180 Ps.120 Ps.60 Plac Ps.30 Ps.15 |
| Happy/sad: | Ps.15 Ps.30 Plac Ps.60 Ps.120 Ps.180 |
| Antagonistic/amicable: | Ps.180 Ps.120 Plac Ps.15 Ps.60 Ps.30 |
| | *9 h post-drug* |
| Antagonistic/amicable: | Ps.30 Ps.120 Ps.180 Plac Ps.15 Ps.60 |

Means from raw scores have been ranked in ascending order. Absolute values of the ratings have been omitted for clarity. The treatments underlined by a common bar do not differ significantly ($P > 0.05$). Treatments not under lined by a common bar are significantly different ($P < 0.05$).

**Table 4** Side effects: numbers of subjects reporting each side effect are given.

*i) Side effects reported 2.5h post-drug*

| | *Pseudoephedrine (mg)* | | | | | |
|---|---|---|---|---|---|---|
| | *Plac* | *15* | *30* | *60* | *120* | *180* |
| Sweating | 1 | 1 | + | 1 | 1 | 2 |
| Anxiety | – | – | – | – | – | – |
| Appetite better | 1 | 1 | 1 | 1 | 1 | – |
| Palpitations | 1 | – | – | 1 | – | 2 |
| Nausea | – | – | – | – | – | – |
| Dry mouth | 3 | 2 | 1 | 1 | – | 1 |
| Appetite worse | – | – | – | 2 | 1 | – |
| Difficult vision | – | – | – | – | – | – |
| Breathlessness | – | – | – | 1 | 1 | – |
| Headache | 2 | 5 | 2 | 1 | 2 | 1 |
| Difficulty passing urine | – | – | – | – | – | – |
| Dizziness | – | – | 1 | – | – | 1 |
| Tremor | – | – | – | – | – | – |
| Number with ⩾ 1 side effect | 5 | 6 | 2 | 6 | 4 | 5 |
| Number with no side effects | 13 | 12 | 15 | 12 | 13 | 13 |
| *ii) Side effects reported 9h post-drug* | | | | | | |
| Sweating | 1 | 1 | – | 1 | 1 | – |
| Anxiety | – | – | – | – | – | 1 |
| Appetite better | – | – | – | 1 | – | 1 |
| Palpitations | 1 | – | – | 1 | – | 2 |
| Nausea | – | – | – | – | – | 3 |
| Dry mouth | 1 | 2 | 1 | 2 | 2 | 3 |
| Appetite worse | – | 1 | – | 2 | – | 3 |
| Difficult vision | – | – | – | – | – | – |
| Breathlessness | – | – | – | – | – | – |
| Headache | 4 | 4 | 1 | 3 | 2 | 2 |
| Difficulty passing urine | – | – | – | – | – | 1 |
| Dizziness | – | 1 | – | – | 1 | 1 |
| Tremor | – | – | – | – | – | – |
| Number with ⩾ 1 side effect | 4 | 5 | 1 | 6 | 3 | 9 |
| Number with no side effects | 14 | 12 | 14 | 11 | 13 | 9 |
| Next day-sleep improved | 2 | – | – | 2 | 1 | 1 |
| Next day-sleep worse | 1 | – | 1 | – | – | 3 |

scales and nine hours post-drug on one scale; details are shown in Table 3. Clearly there are no important drug effects at any dose with regard to these variables.

Unwanted effects are tabulated in Table 4. There is no difference in the incidence and nature of these effects between the pseudoephedrine preparations and the placebo.

## Discussion

To assess the effects of any drug in relieving a pathological condition, it is generally desirable to study patients suffering from that condition. In the case of allergic or vasomotor rhinitis, however, it is hard to perform serial comparative studies because of the great spontaneous day-to-day variation which occurs in symptoms and nasal patency. Nasal decongestants cannot easily be studied in normal subjects because the decrease in nasal resistance which is possible when the subject already has almost fully patent nasal passages is too small to be easily detected. We have therefore chosen to use normal subjects in order to obtain a stable baseline, but to induce nasal congestion in a standardized way using histamine. This choice is supported by the fact that histamine is an important mediator in the production of the symptoms of allergic rhinitis (Stone, Merril & Meneely, 1955), and that the nasal response to histamine is the same in both subjects who have allergic rhinitis and those who do not (McLean *et al.*, 1977).

The anterior rhinometric method for measuring nasal airway resistance is probably the best compromise between accuracy and patient acceptability, and it has proved to be a useful technique (Britton *et al.*, 1978). It has the added advantage of allowing both nostrils to be studied separately; if total nasal resistance is required this can be simply calculated by summing the reciprocals of the values for each nostril obtained separately, the resultant value equalling the reciprocal of the total nasal resistance. We have not done this in our study because the measurements were performed sequentially rather than simultaneously, but it is clear from inspection of Figures 1 and 2 that total nasal resistance rose following histamine challenge. We were careful to perform our studies at the same time of the day in each patient in order to minimize any effect which cyclical changes in nasal resistance might have produced. The time course of such cycles appears to be over 2 to 3 h, so these would not have affected the results we obtained in the first 10 or even 30 min following histamine challenge, (Dallimore & Eccles, 1977); also, the magnitude of cyclical changes in NAR is much less than that produced by 1% histamine (Eccles, 1978).

Our results clearly show that 15 mg and 30 mg pseudoephedrine produced no protection against the effects of histamine challenge. Pseudoephedrine 60 mg, 120 mg and 180 mg, all produced statistically significant protection against the effects of histamine challenge, and there was little difference between these three doses. Of the doses of pseudoephedrine which we have investigated, it appears that 60 mg is the lowest one which will achieve maximal nasal decongestion. It is always hard to extrapolate results obtained in the laboratory to a clinical situation, but in this instance we feel that it is justified. The study was performed in humans, the effects of the drugs were examined in the relevant organ (nasal mucosa) and the pathological changes were induced by a naturally occurring mediator of the inflammatory response (histamine).

With regard to effects on the cardiovascular system the two higher doses of pseudoephedrine, 120 mg and 180 mg produced statistically significant increases in pulse and systolic blood pressure, but these were clinically unimportant; the changes were quantitatively considerably less than would occur with emotion or mild exercise. None of the doses we used produced any significant changes in diastolic blood pressure. In addition, no subjective effects on mood, or unwanted effects were identified following any dose of pseudoephedrine up to 180 mg.

We conclude that a single dose of 60 mg pseudoephedrine is the optimal one to produce maximal nasal decongestant effects without cardiovascular effects in healthy subjects. Earlier work has indicated that 60 mg of pseudoephedrine three times per day is appropriate to maintain effective blood levels through the day (Bye, Hill, Hughes and Peck, 1974), this should be the recommended dose regime for the control of symptoms of allergic and vasomotor rhinitis in adult patients.

We are grateful to Dr A.W. Peck for his advice on many aspects of this study. Requests for reprints should be addressed to Dr D.T.D. Hughes, The Wellcome Research Laboratories, Langley Court, Beckenham, Kent, BR3 3BS.

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