

Oral Vasoconstrictors in Perennial Non-Allergic Rhinitis

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Nasal airway resistance and nasal symptoms were evaluated in patients with perennial non-allergic rhinitis before and after vasoconstrictory drugs and placebo taken orally. The patients were partly selected; those suffering mainly from nasal obstruction being tested. Phenylpropanolamine (PPA) in a dose of 100 mg in a sustained-release preparation clearly decreased the nasal airway resistance measured rhinomanometrically. PPA in a dose of 50 mg and combined with an antihistamine had no obvious decongesting effect. Placebo and dihydroergotamine (DHE) in a dose of 5 mg did not decrease the nasal airway resistance. PPA (100 mg) and the combined preparation containing PPA in the lower dose (50 mg) taken twice a day in a cross-over, double-blind study significantly reduced nasal obstruction, secretion, and sneezing compared with placebo. Side effects of PPA are discussed.

Key words: dihydroergotamine; nasal airway resistance; nasal symptoms; perennial non-allergic rhinitis; phenylpropanolamine.

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CLINICAL ASPECTS

To patients with perennial non-allergic rhinitis (vasomotor rhinitis) suffering mainly from nasal obstruction, vasoconstrictory drugs are usually prescribed. The present study concerns the effects and side effects of two vasoconstrictory drugs, phenylpropanolamine (PPA) and dihydroergotamine (DHE), given as tablets to such patients. The effects on the nose were investigated, both objectively with rhinomanometry and subjectively with daily symptom scores. PPA, in a sustained release preparation of 100 mg, was compared both with a combined preparation of 50 mg PPA and an antihistamine and with placebo. In the rhinomanometric test, where the patients were measured every 10 min for over 3 h, PPA clearly decreased the nasal airway resistance. The combined preparation had no obvious decongesting effect. Placebo had no effect. In the symptom study, both PPA and the combined preparation reduced the nasal obstruction, secretion, and number of sneezing attacks compared with the effects of placebo. As for side effects, two patients out of 19 reported daily micturition disturbances after PPA. Blood pressure and pulse frequency were not changed by PPA. Hypertension after PPA is, however, reported in other studies. A 5 mg dose of DHE, a substance known to constrict nasal blood vessels in cats, produced no rhinomanometric improvement.

The causes of perennial non-allergic rhinitis (vasomotor rhinitis) are mainly unknown. Therefore drugs with different actions have been tried in efforts to reduce the symptoms. Although many patients with this disease are well helped by topical steroids (6, 9, 14), such a treatment is usually not first recommended. Especially among those patients who mainly

suffer from nasal obstruction, it is tempting first to try vasoconstrictory drugs.

Only few investigations concerning the effects of orally taken vasoconstrictory drugs on perennial non-allergic rhinitis are published. Benson (2) measured the maximum nasal inspiratory flow following pseudoephedrine treatment and found an increase. Laage-Hellman et

al. (12) and Renvall & Lindqvist (16) evaluated the effects of phenylpropanolamine with symptom scores and in that way showed an improvement.

The present study concerns the effects of vasoconstrictory tablets both on nasal airway resistance and on symptoms in patients with perennial non-allergic rhinitis. A selection of patients was made; those especially suffering from nasal obstruction were chosen for the study.

The tested vasoconstrictory drugs were phenylpropanolamine (PPA) and dihydroergotamine (DHE). PPA is often used in patients with nasal obstruction. PPA was also investigated in combination with the antihistamine brompheniramine (BPA). DHE in low dosages has a vasoconstrictory effect especially on veins (13, 15). In the human nasal mucosa, where sinusoids are numerous, DHE therefore could be an effective decongesting agent.

MATERIAL AND METHODS

Nasal airway resistance was measured in 20 patients. Ten of the subjects (5 women and 5 men, aged 16–64, average 38 years) were investigated before and after an oral dose of 100 mg PPA (Monydrin®, AB Draco*), 50 mg PPA and 12 mg BPA in combination (Lunerin®, AB Draco*), and placebo. The active drugs were given in sustained-release preparations. The other 10 patients (5 women and 5 men, aged 19–36, average 28 years) were rhinomanometrically tested before and after an oral dose of 5 mg DHE (Orstanorm®, Sandoz). For evaluation of symptoms, most of the patients used, were among those who entered the rhinomanometric study. Nineteen patients (8 women and 11 men, aged 16–64, average 33 years) took sustained-release tablets containing either 100 mg PPA, the combined preparation of 50 mg PPA and 12 mg BPA, or placebo twice a day in a double-blind, randomized way with cross-over technique during 10 days for each preparation. None of the patients had taken any medication for at least 2 weeks before the rhinomanometric

and symptomatic studies. For more than 6 months all of the patients had suffered mainly from nasal obstruction and also, but in less degree, from watery secretion and sneezing. The clinical history, skin sensitivity to prick testing and for some patients, RAST, revealed no relevant allergens as causes of the symptoms.

The nasal airway resistance was recorded with anterior rhinomanometry during spontaneous respiration X-Y-wise on an oscilloscope. The nasal airway resistance of the separate cavities and the total nose was calculated according to Broms et al. (5). The resistance was for statistical reasons expressed as an angle v_2 , and only v_2 of the total nose was used for the comparisons. The corresponding clinically relevant parameter is a resistance value R_2 ($R_2 = 5 \times \tan v_2$ for the total nose). Before the rhinomanometric recordings the patients rested sitting for about 50 min in the testing room. Rhinomanometry was then performed every 10 min for 200 min with the subject recumbent or sitting as shown in the Figures. The preparation in question was taken 75 min after the first recording. Every 30 min, beginning at min 20, the arterial blood pressure and pulse frequency were recorded.

In the other part of the study the symptoms were recorded by the patients on a diary card twice a day. The degree of intensity of nasal obstruction, secretion, and tiredness was recorded on an arbitrary scale from 0 to 3. Sneezing was recorded on a similar scale according to the daily number of sneezing attacks. The patients were also asked to write down side effects.

STATISTICS

Differences in v_2 were analyzed with paired comparisons and Student's *t*-test. Differences in mean daily score for each symptom between the three preparations were similarly analyzed. The significances used were: $P \leq 0.05$ (*), $P \leq 0.01$ (**), and $P \leq 0.001$ (***).

RESULTS

Figs. 1–3 show the nasal airway resistances as mean $v_2 \pm \text{SE}$ of mean before and after

* A subsidiary to AB Astra, Sweden.

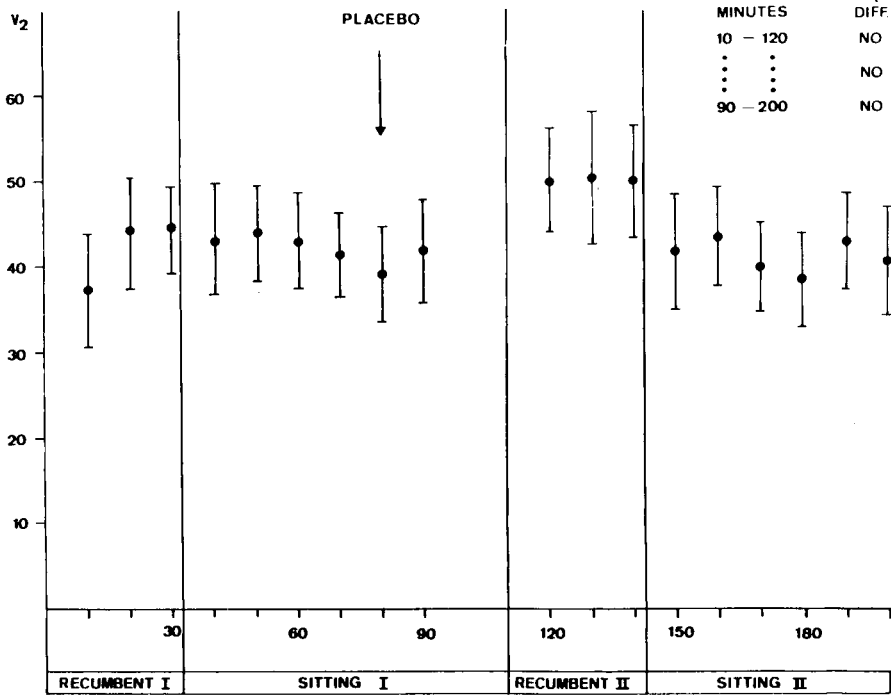


Fig. 1. Mean $\pm$ SEM of nasal airway resistance expressed as v_2 in degrees versus time in minutes for 10 patients with perennial non-allergic rhinitis. The positions of the patients are marked beneath the time scale. At min 75 a placebo tablet was taken.

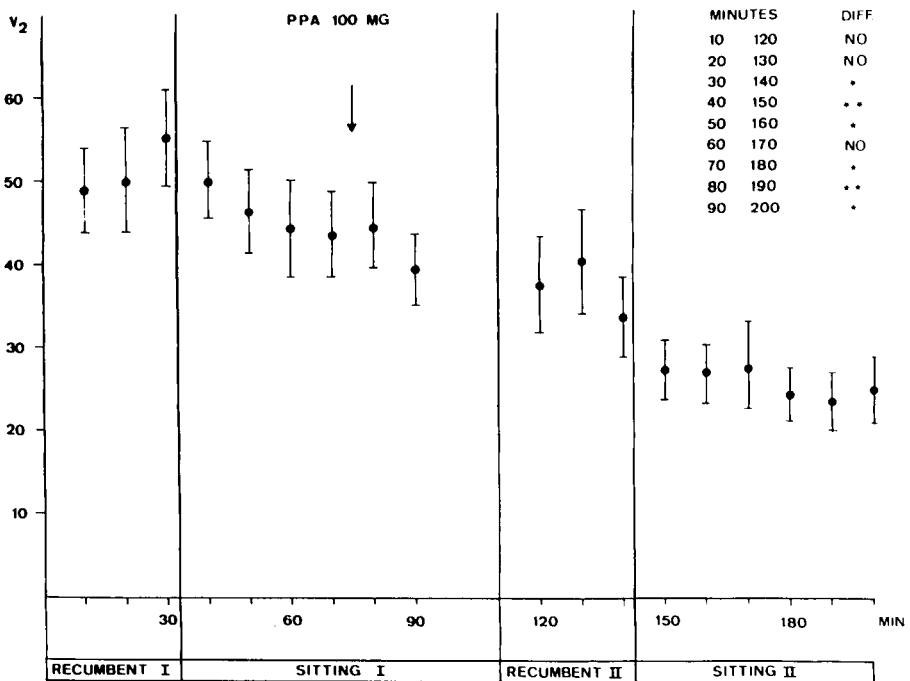


Fig. 2. Mean $v_2 \pm$ SEM versus time for the same 10 patients as in Fig. 1 before and after intake of 100 mg phenylpropanolamine (PPA) in sustained-release preparation.

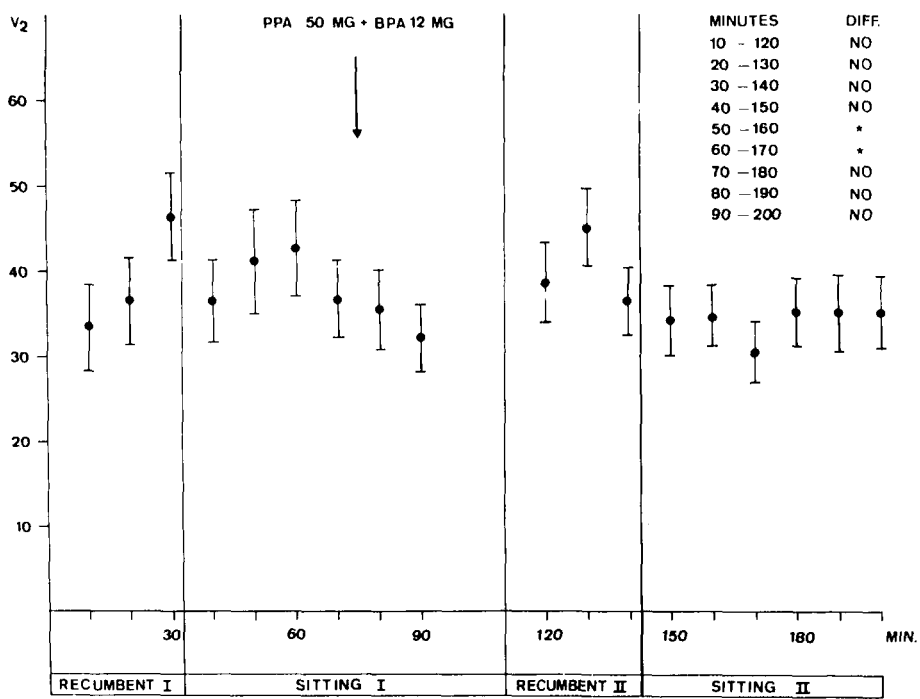


Fig. 3. Mean $v_2 \pm \text{SEM}$ versus time for the same 10 patients as in Figs. 1 and 2 before and after intake of a tablet containing 50 mg phenylpropanolamine (PPA) and 12 mg brompheniramine (BPA).

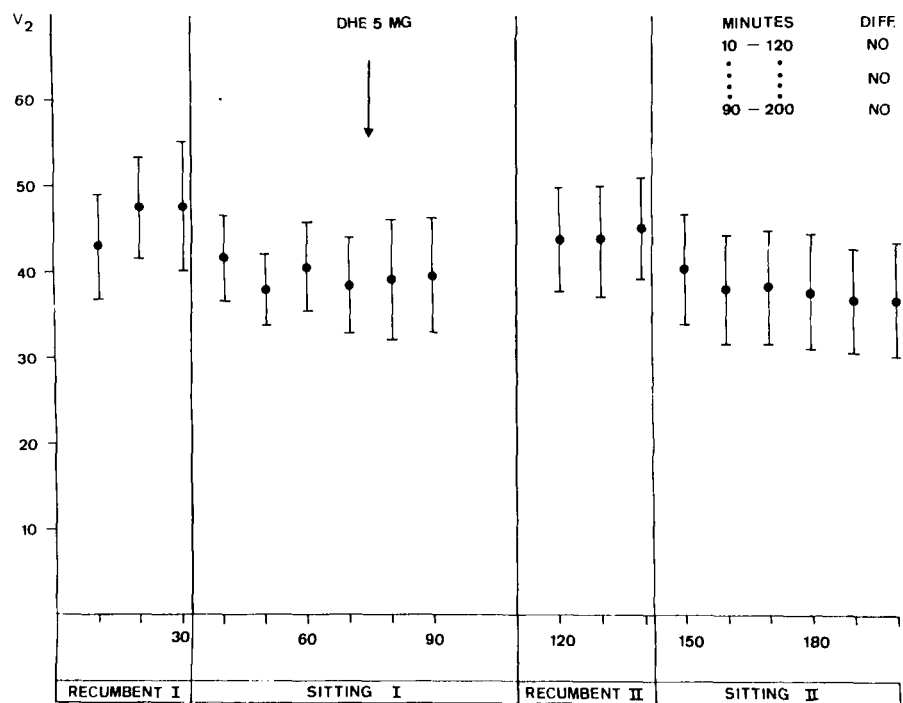


Fig. 4. Mean $v_2 \pm \text{SEM}$ versus time for 10 patients before and after intake of 5 mg dihydroergotamine (DHE) orally.

Table 1

Effects of placebo, 100 mg phenylpropanolamine (PPA), or 50 mg phenylpropanolamine (PPA) combined with 12 mg brompheniramine (BPA) in tablets taken twice a day on nasal symptoms in 19 patients with perennial non-allergic rhinitis

Preparation	Obstruction	Secretion	Sneezing	Tiredness
Mean daily symptom score				
Placebo, $n = 19$	1.34	1.29	0.74	1.21
PPA 100 mg, $n = 19$	0.97	0.98	0.55	1.26
PPA 50 mg + BPA 12 mg $n = 19$	0.78	0.67	0.31	1.27
Difference in score				
Placebo - PPA 100 mg	*	*	*	no
Placebo - PPA 50 mg + BPA 12 mg	**	***	***	no
PPA 100 mg - PPA 50 mg + BPA 12 mg	no	no	*	no

placebo, PPA, and the combined preparation, respectively. Although the three figures are based on the same 10 patients, the mean values at the same time before the intake of the preparation differed rather much. Significant differences in v_2 occurred at min 10, 20 and 40 between the PPA test and the test with the combined preparation (*), and at min 10 between the PPA test and placebo (**).

The comparisons are mainly based on differences in nasal airway resistance for corresponding positions and test occasions before and after intake of the preparation. Such differences, when they occurred, are marked in the respective Figures. From 1 h after intake of the PPA dose, the nasal airway resistance was usually significantly reduced. During a corresponding time after the combined preparation, the resistance was usually not reduced. Placebo had no effect.

During the test with DHE no differences were found either between v_2 -values from recumbent and sitting position, or between v_2 -values before and after intake of the drug (Fig. 4).

The arterial blood pressure and the pulse frequency showed no differences for any of the

preparations, either between recumbent and sitting position, or between before and after the preparation was taken. For instance, the mean values $\pm$ SD of the systolic and diastolic pressure and of the pulse frequency before and after PPA were the following: Recumbent I 121 ± 15 mmHg, 77 ± 6 mmHg, and 68 ± 10 , at Sitting I 122 ± 14 , 80 ± 6 , and 69 ± 11 , at Recumbent II 122 ± 13 , 78 ± 5 , and 66 ± 9 , and at Sitting II 126 ± 18 , 78 ± 4 , and 66 ± 9 , respectively.

Table 1 summarizes the symptom scores of the 19 patients who got placebo, PPA, and the combined preparation, together with the differences in scores. Seventeen of the patients reported side effects. When placebo was taken seven patients suffered from headache compared with two when taking PPA and one when taking the combined preparation. Two male patients, 60 and 64 years old, had micturition difficulties nearly every day they took PPA. One of them also had such problems when taking the combined preparation, but there were no problems with placebo. No differences in the patients' sleeping ability were noted between the three preparations.

DISCUSSION

Objective methods to study nose function have been rather difficult to apply. A useful method to test the nasal secretory capacity was only recently published by Borum (4). Methods to record changes of mucosal blood flow have many sources of error and have only seldom had a practical application (11). Volume changes of the mucosa, mainly due to changes in the tone of the capacitance blood vessels (13), have long been evaluated with rhinomanometry. This method has had at least two important drawbacks which have reduced the usefulness. First, nasal airway resistance varies due to reflexes and to emotions. Second, the usual ways of presenting the results have made statistical comparisons difficult. Resistances given at a certain airflow or a certain transnasal pressure difference have e.g. made comparison between low and high resistances almost impossible.

As the main symptom of the patients in the present study was nasal obstruction only rhinomanometry was used of the above-mentioned objective methods. Efforts were made to reduce the "spontaneous" variation of the nasal airway resistance. The patients rested in the test room for almost 1 h before the measurements began. Moreover, the resistance was recorded every 10 min for more than 3 h. In an attempt to demonstrate as much vasoconstrictory effect of the drugs as possible, the patients were also tested in recumbent position, in which the blood vessels are most probably more dilated than when sitting. Finally, the statistical evaluation was considerably facilitated by expressing the nasal airway resistance as angles in a polar coordinate system (5).

PPA in a dose of 100 mg in the sustained-release preparation had a clear decongesting effect on the nasal mucosa lasting from about 1 h after intake of the drug to the final measurement 1 h later. As a matter of course, the nasal effects depend on the rate of resorption and concentration in plasma of the drug, and thus the conclusions drawn are valid only for the used sustained-release preparation. In the combined preparation, the 50 mg PPA existed in a similar release preparation, which is why com-

parisons between the two different doses of PPA can be made. In the lower dose and during the time measured, PPA had no clear decongesting effect. It is possible that a measurable effect can be found later, as the maximum plasma concentration after PPA in the present sustained-release preparation in normal subjects is reached first 4 to 5 h after intake of the tablets (3).

When comparing the objective results with the subjective symptoms, some aspects are worth mentioning. Two of the 19 patients in the symptom study reported micturition disturbances after 100 mg PPA. This is a well-known side effect in elderly men. Thus, the dose of PPA necessary to objectively decongest the nasal mucosa in some patients also might evoke unwanted side effects. Although not shown in this study, it must be pointed out that micturition problems after α -adrenoceptor stimulants also occur among children (8, 17) even if it occurs much less frequently than in elderly men. Such a side effect reduces the usefulness of α -stimulants.

Blood pressure and pulse frequency were not changed by the drugs in the present study. There are many reports regarding hypertension after PPA, not only in single cases but also in controlled studies (10). The responsible PPA dose evoking hypertension has in these reports most often been 85 mg. The reason why an increased blood pressure was not observed in the present study is certainly due to the used sustained-release preparation. None the less, the number of hypertension reports calls for caution when prescribing α -adrenoceptor stimulants.

The symptom study with PPA, PPA in combination with an antihistamine, and placebo showed that both 100 mg PPA and the combination significantly reduced the three nasal symptoms. Renvall & Lindqvist (16), who compared the effects of placebo, 50 mg PPA, and 100 mg PPA, found that 100 mg was the dose necessary to reduce the nasal symptoms. According to Laage-Hellman et al. (12) 50 mg PPA was sufficient. The sustained release mechanism in the tablets of the latter study was not identical to that in the tablets used by us or by Renvall &

Lindqvist. Comparisons are therefore difficult to make. The present clinical study found no significant differences in effect on nasal obstruction between 100 mg PPA and the combination containing 50 mg PPA. This could be a sign of a synergism between PPA and the antihistamine. Aschan (1) could demonstrate synergism between PPA and an antihistamine with rhinomanometry. The design of the present rhinomanometric study does not allow a statement about the existence of such a synergism.

The symptoms of nasal secretion and sneezing were reduced by PPA. Is this due to a reduced blood flow around nasal glands, are reflexes less often activated when the nasal mucosa is decongested, or are there other explanations? Although such effects of decongesting drugs are somewhat surprising, they have been found in other similar investigations (12, 16) and also regarding sneezing in the common cold (7).

The conclusion of the present study and a literature review is that PPA in an oral preparation is not ideal as a nose decongestant. Side effects can occur when doses necessary for objective decongestion are given. It is natural with this background to try to find other drugs with good nasal decongestant effects. DHE in doses lower than those giving α -adrenoceptor blockade seemed to be a suitable drug. It constricts nasal blood vessels in cats, and the effect on the capacitance vessels is relatively more pronounced than that on the resistance vessels compared with corresponding effects of noradrenaline (13). DHE orally has previously been tried against nasal obstruction. Voegeli (18) reported that DHE with a starting dose of 5–7.5 mg orally had a very good effect in five out of 30 patients with perennial non-allergic rhinitis. It was not stated whether this investigation was performed as a double-blind trial, nor has a more detailed report of the results been found since. The conclusions of the present study of DHE are not encouraging.

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