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# Vascular effects of phenylpropanolamine on human nasal mucosa

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SUMMARY

*The duration of the decongestant effect of phenylpropanolamine 2.5% as nose drops as well as the effect of the drug on nasal mucosal blood flow was studied in man. The nasal patency was significantly improved for up to three hours in patients with nasal congestion, while no effect on nasal mucosal blood flow was achieved. These results were discussed in relation to other more long-lasting nose-drops with blood flow-reducing effects.*

## INTRODUCTION

Phenylpropanolamine (PPA) is widely used as a peroral decongestant, alone or in combinations with antihistamins. Clinical experience has confirmed that topically administered PPA as 1-5% aqueous solution is well tolerated (Stockton et al., 1931; Solo, 1941). However, its effectiveness, when locally applied in various concentrations, was only recently demonstrated (Bende et al., 1984).

Topical nose drops have been claimed to be prompt in their onset of action, but objective documentation on their duration of action is sparsely seen in the literature. The effect of nasal decongestants is mainly due to their effect on the blood content in the mucosa, but also to some degree on the mucosal oedema. These factors influence the nasal airway resistance (NAR), objectively reflected by means of rhinomanometry. However, nasal decongestants might also have effect on the blood flow on the nasal mucosa, which is regulated independently of blood content (Paulsson et al., 1985). With the recently presented $^{133}Xe$ wash-out method (Bende et al., 1983) changes in nasal mucosal blood flow could be determined. Previous studies have shown considerable differences in effect of topical decongestants on nasal blood flow (Andersson and Bende, 1984).

The purpose of the present study was to evaluate the decongestive effect of PPA during a 5-hour period and to test the hypothesis that nasal decongestion could be achieved without influencing nasal mucosal blood flow.

## MATERIAL AND METHODS

### *Nasal airway measurement*

Otherwise healthy subjects were selected to this study if they were congested due

to mucosal engorgement on the basis of mucosal reactivity, i.e. greater than 20% decongestion, in a physical exercise test. Thus, eleven patients (5 men, 6 women, age 16–35 years) were included. Nasal airway resistance (NAR) was measured bilaterally in the sitting position by anterior rhinomanometry. Results were evaluated according to the method described by Broms et al. (1982) and total NAR, expressed as an angle $v_2$, was used for statistical calculations. Increasing values of $v_2$ denoted as increasing NAR.

NAR was measured at rest several times during one hour until steady base line values were achieved. After application of drug, three drops (about 0.1 ml) of 2.5% PPA into each cavity, NAR was recorded at intervals for up to 320 min. Thereafter a physical exercise test was performed using an ergometer bicycle. To achieve a physiological decongestion a heart rate above 120 per min was demanded. Rhinomanometry was performed within two min after the exercise.

*Nasal blood flow measurement*

The blood flow in nasal mucosa was determined in five patients with nasal congestion (2 men, 3 women, mean age 29 years), 30 min after application of three drops of 2.5% PPA, by means of the $^{133}$Xe-wash-out method (Bende et al., 1983). Thus, 0.1 ml $^{133}$Xe in a saline solution containing 1–10 MBq was injected into the mucosa of the inferior turbinate. Elimination of the isotope was followed with a scintillation detector. Blood flow was calculated from initial slope of the first five minutes of the wash-out curve.

*Statistics*

Statistical analyses were performed using two-tailed paired t-test.

RESULTS

Figure 1 shows the total NAR as mean $v_2 \pm$ SEM before and after PPA and the exercise test, respectively. There is a statistically significant decongestant effect of PPA lasting for up to three hours. The exact onset of action cannot be calcu-

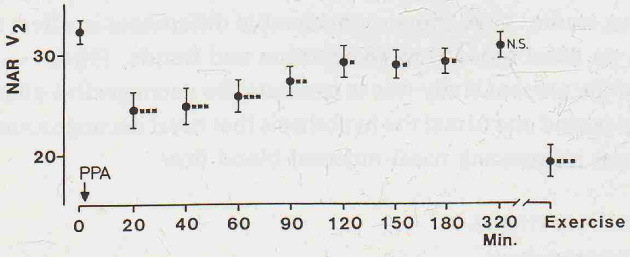


Figure 1. Nasal airway resistance expressed, as $v_2$, in rest, after topical application of PPA and after exercise.

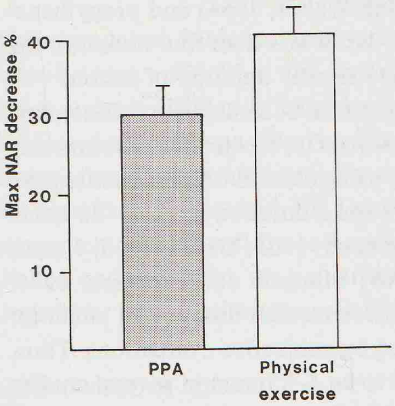


Figure 2.
The maximum decrease of nasal airway resistance obtained by PPA or exercise in 11 subjects.

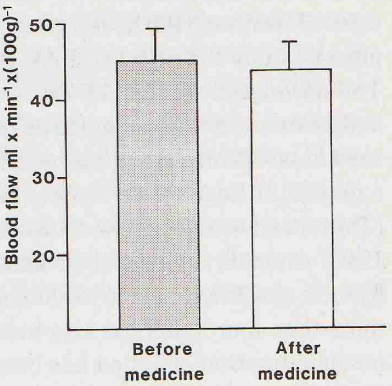


Figure 3.
Nasal mucosal blood flow ($ml \cdot min^{-1} \cdot (100\ g)^{-1}$) before and after topical application of PPA.

lated from this study, since no examination was done within the first 20 min. The maximum decrease of total NAR, expressed as per cent changes from zero-time values, obtained by medication or physical exercise is presented in Figure 2. Decongestion immediately after exercise is statistically superior to nose drops ($p < 0.01$).

$v_2$-values of the left and right cavities were neither statistically different at start, 38.9 and 47.0 respectively, nor at any time after nose drops or exercise. Calculating the absolute value of the per cent flow difference according to the formula

$$\left| \frac{v_{2\text{sin}} - v_{2\text{dx}}}{v_{2\text{total}}} \right|$$

a significant decrease in asymmetry of the NAR between cavities could be registered during 90 min after nose drops as well as immediately after physical exercise.

Throughout test-period, none of the individuals experienced untoward effects or were found to have an increased NAR by 20% or more above their initial values. As shown in Figure 3, PPA was found to have no significant effect on mucosal blood flow. The 95 per cent confidence interval of blood flow before and after PPA were found to be 37.3, 53.3 and 37.5, 50.9 $ml \cdot min^{-1} \cdot (100\ g)^{-1}$, respectively.

## DISCUSSION

The duration of effect of topical nasal decongestants, such as phenylephrine (Green, 1966; Harris, 1967; Connell, 1969; Knothe and Rietschel, 1976), ephe-

drine (Aschan and Drettner, 1964; Thulin and Walter, 1964) and propylhexedrine (Hamilton, 1982), has been reported to be of less than four hours. In the present study the effect of PPA seems to have similar duration of action.

The decongestive effect of imidazoline-compounds, such as naphazoline, oxy- and xylometazoline, seems to be more longlasting. Oxymetazoline, a commonly used nasal decongestant, has been reported by using objective techniques to have a maximum decongestive effect for 5–6 hours and a duration up to 10–12 hours (Thulin and Walter, 1964; Slodki and Montgomery, 1965; Green, 1966; Harris, 1967; Connell, 1969; Cohen and Duffy, 1969; Murgolo and Bickham, 1974; Knothe and Rietschel, 1976; Döderlein, 1980). A median duration of effect for more than four hours has also been supported by subjective evaluations. Thus, median duration of action has been reported to be 4–8 hours in several studies (Falkenberg, 1963; Hladik, 1963; Miller, 1964; Cunningham, 1965; Eyck and Schleuning, 1966; Aikman et al., 1975) and 8–12 hours in one study (Haines, 1966).

In previous studies it was found that the blood flow in the human nasal mucosa was regulated by alpha$_2$-adrenoceptors (Andersson and Bende, 1983) and that oxymetazoline, a selective alpha$_2$-adrenoceptor agonist, in clinical doses induced a marked decrease of this blood flow (Bende, 1983). On the other hand, Andersson and Bende (1983) and the present study show that nasal decongestants of phenylamine types, preferentially alpha$_1$-adrenoceptor agonists, are not influencing mucosal blood flow. It is tempting to correlate an ischaemic state to the longlasting decongestive effect of the imidazoline-compounds. Topical nasal decongestants are most commonly used in acute infectious rhinitis and are very effective to improve nasal patency. It has also been found that in an acute rhinitis the nasal mucosal blood flow is increased and that oxymetazoline reduced the blood flow to the same level as in healthy subjects (Bende, 1983). It is plausible to suggest that a reduced blood flow might not be of value in the treatment of an acute infectious rhinitis.

After excessive use of topical nasal decongestants a rebound phenomenom has been reported in several studies. Different criterias have been used to define this rebound phenomenon, e.g. greater that 5 square mm or 50 ml/s increase above initial values (Connell, 1969; Döderlein, 1980). Owing to variability in individual measurements of NAR (Cole et al., 1980), we have chosen to define an increase of NAR greater than 20% to be outside the variation of our method and thus adherent to the drug. Using this criteria we have in this study found no obvious secondary engorgement within a reasonable time-period as compared to the duration of drug effect. Further studies after long-term treatment is in progress.

Thus, it seems that topically administered PPA is as effective decongestant as other available nose-drops, has a reasonable duration of action, and the advantage, compared to the imidazoline derivatives, not to influence nasal mucosal blood flow.

ZUSAMMENFASSUNG

Wir behandelten Patienten mit Nasentropfen, die eine 2,5%-ige Phenylpropanolamin-Lösung enthielten, und untersuchten das Mittel im Bezug auf die Dauer seines abschwellenden Effektes sowie seiner Einwirkung auf die Durchblutung der Nasenschleimhaut. Die Nasenatmung von Patienten mit infolge Schleimhautanschwellung behinderter Nasenatmung wurde für die Dauer von drei Stunden signifikant verbessert. Die Durchblutung der Nasenschleimhaut wurde dagegen nicht beeinflusst. Diese Resultate wurden mit Behandlungsresultaten verglichen und diskutiert, die bei Anwendung von Nasentropfen mit längerer Wirkingsdauer und durchblutungs-reduzierendem Effekt erzielt wurden.

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