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Effects of oral norephedrine on common cold symptoms

H. Grønborg, B. Winther, S. Brofeldt, P. Borum and N. Mygind

SUMMARY

The aim of the trial was to examine the effectiveness of an oral decongestant in common cold. Thirty subjects with naturally acquired colds got a 100 mg sustained release tablet containing norephedrine on one day and a placebo tablet on another day in double blind design. Changes in nasal patency were assessed by rhinomanometry, measurement of nasal expiratory peak flow, and a self-assessment test, and the number of sneezes and of nose blowings were recorded in a 10 hours period after medication. Rhinomanometry, but not peak flow measurements showed a significant difference ($p < 0.02$) two hours after medication, and the self-assessment of nasal blockage showed that the effect lasted for the entire 10 hours observation periode ($p < 0.01$). Nasal respiration was reestablished in half of the blocked noses. There was no effect on number of sneezes and nose blowings. In conclusion, oral norephedrine has a moderate decongestant effect, which may justify its use in adults with common colds. This symptom amelioration must be balanced against cost of therapy and risk of side effects. A prevention of otitis media and of sinusitis has not been documented in the literature.

Oral decongestants alone or in combination with antihistamines have for years been used for common cold symptoms, but the number of reports on placebo-controlled studies markedly contrasts with the immense sale of these preparations (Aschan, 1974; Roth et al., 1977; Bye et al., 1980). Norephedrine (phenylpropanolamine hydrochloride) is one of the most widely used oral decongestants. In contrast to ephedrine, it primarily exerts a sympathomimetic effect by direct stimulation of alpha-adrenoceptors. The decongestant effect in the nose is similar to that of ephedrine, but effects on the heart are less frequent (Black, 1937; Boyer, 1938; Persson et al., 1973), and because it is more hydrophilic than ephedrine, it causes less central nervous stimulation (Wilkinson and Beckett, 1968). We have therefore chosen norephedrine for the study of the efficacy of oral decongestants in naturally acquired common colds.

PATIENTS AND METHODS

Patients. We advertized for volunteers with common colds in a student magazine from 1 November 1979 to 1 February 1980. The students were included in the

Table 1. Criteria for including volunteers in the study.

1.	Sudden occurrence of sneezing, nasal discharge and blockage, or at least of two of these symptoms
2.	Nasal symptoms lasting 12–48 hours
3.	The student felt sure that he had catched a cold
4.	The investigator observed signs of a cold (nasal voice, sneezing, nose blowing) during a 10–15 minutes observation period
5.	A nose blowing of at least 0.1 ml could be provided in the observation period

trial when all the criteria, given in Table 1, were fulfilled. One third (34 of 101) of the students who responded fulfilled the criteria and were all included in the study. Four subjects were excluded as it became evident on the second day that their cold symptoms had disappeared. Of the remaining 30 students, who completed the trial, 13 were female and 17 male. The mean age was 23.0 years (range 18–32).

Treatment. In a double-blind cross-over design each student got a single dose of 100 mg norephedrine in sustained relaese form (two tablets Rinexin®) and placebo in randomized order, at the same time of the day (9 a.m.–2 p.m.) on two consecutive days. The tablets were supplied in coded vials by H. Lundbeck and Co., Copenhagen, Denmark. This was the only treatment given.

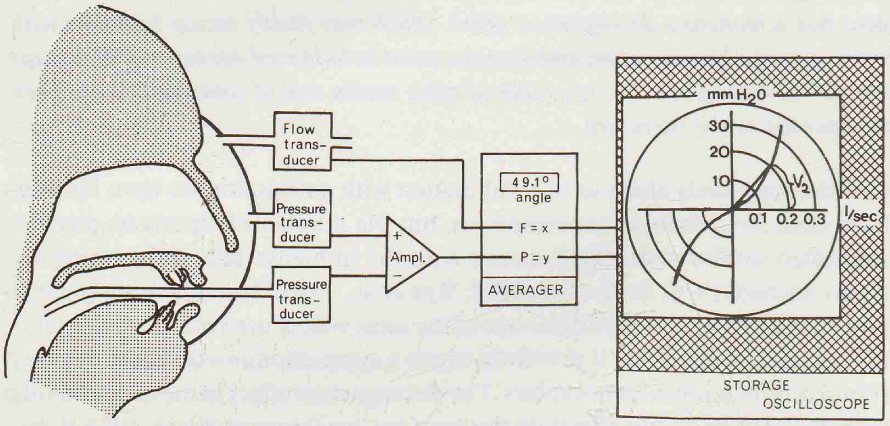

Figure 1. Measurement of nasal airway resistance. The test subject breathes into a mask that fits closely around nose and mouth. A thin rubber tube, attached to the inner of the mask, passes through the mouth into the oropharynx. The apparatus records continuously the pressure in the mask (i.e. in the front of the nostril) and in the oropharynx, as well as the airflow through the nose, inasmuch as the subject breathes through the nose with the mouth closed around the rubber tube.
The corresponding values for flow and fall in pressure through the nose are fed into a computer and a storage oscilloscope. The computer averages five full in- and expirations and on this mean curve calculates the angle v_2 (defined in the text), which is expressed in a digital display.

Rhinomanometry. Nasal airway resistance was measured by posterior rhinomanometry immediately before and two hours after medication. The set-up used is described in more detail in Figure 1. The principles are those usually employed for active posterior rhinomanometry, and the result is, according to Broms and co-workers (1979) expressed as v_2. This value follows a normal distribution more closely than the ratio between pressure difference and flow, used earlier. The v_2 value is defined as the angle between the horizontal axis and a straight line between zero and the intersection between the respiration curve and a curve, cutting the Y-axis (pressure difference) at 2 cm H_2O and the X-axis (flow) at 0.2 liter/sec (see Figure 1). When a series of consecutive respirations are displayed on the oscilloscope screen, the curves can vary slightly, so the intersection with the circle is not precisely defined, and the reading of the v_2 value depends to some degree upon the investigator's interpretation of the curve. In order to eliminate this as a potential source of bias, we have added a computer to the set-up, which digitally diplays the mean v_2 value of five consecutive respiration curves.

Nasal peak flow. Immediately after rhinomanometry, the nasal peak flow was measured by a Wright Peak Flow Minimeter equipped with a child anaesthesia mask. The volunteers were encouraged to blow as forcefully as possible through the nose with the mouth firmly closed, without consideration to contamination of the mask with nasal secretions. When relatively constant values were obtained, the median of the next three readings was used.

Self-assessment of nasal blockage. A self-assessment test for nasal blockage was performed hourly, 2–10 hours after medication (Tables 2 and 3). Alarm clocks were supplied to remind the students of this exercise.

Table 2. Self-assessment test for recording of nasal blockage. After examination of both cavities together, each cavity is assessed separately by occluding the other nostril gently but tightly with a thumb from beneath.

self-assessment	score
completely free nasal breathing	0
sensation of slight obstruction, but continuous breathing is possible at ordinary rate and depth	1
continuous nasal breathing is only possible by change of respiration rate and depth	2
continuous nasal breathing is not possible, but there is some airflow in the nose at ordinary respiration rate and depth	3
no airflow at ordinary respiration, but some air can be forced trough the nose	4
complete blockage	5

Table 3. Symptom index for nasal blockage, based upon the self-assessment scores.

self-assessment score			
both cavities together	one side	the other side	symptom index for nasal blockage
0–1	0–1	0–1	→ 1
0–1	0–1	2	→ 2
0–1	0–1	3	
0–1	2	2	→ 3
0–1	0–1	4–5	
0–1	2	3	→ 4
2	2	2	→ 5
2	2	3	→ 6
2	2	4–5	
2	2	3	→ 7
3	3	3	→ 8
3	3	4–5	→ 9
4–5	4–5	4–5	→ 10

Table 4. Results of the side effect questionnaire: "Have you had any of the following symptoms after medication and if so have they been slight, moderate or severe, as defined below?" The figures in the table refer to number of subjects.

	norephedrine			placebo		
	1*)	2**)	3***)	1*)	2**)	3***)
dissiness	2		1	2		
nausea	1				1	
headache	1	1	1	4	2	
dyspesia		1				
irritation in the nose	2	1	1	1	1	1
palpitation	2				1	
trembling	1	1		1		
fatigue		3	1		3	
mouth dryness	2	1				
cough	1	2	1	1		1
insomnia	1	2		1		
heartburn	1					
dyspnoea		1			1	

1*) Slight symptoms: Without significance for continuous mediaction.
2**) Moderate symptoms: between slight and severe.
3***) Severe symptoms: Incompatible with continuous use of the drug.

Recording of sneezes and nose blowings. The volunteers were supplied with paper handkerchieves and the number of nose blowings (or equivalent procedures) and of sneezes was continuously recorded on a score card and compiled hourly.

Side effects. A questionnaire about new symptoms was filled in in the evening. Probable norephedrine side effects as well as irrelevant symptoms were included (Table 4).

Statistical calculations. A non-parametric test (Mann-Whitney U test) was used for all comparisons.

RESULTS

Side effects. There were only few and insignificant new symptoms occurring during the treatment period, and no distinction could be made between active and placebo preparations based on side effects. The trial was therefore undertaken with a blind design.

Rhinomanometry. Two hours after medication there was an increase in nasal airway resistance following placebo treatment, while there was a slight decrease after norephedrine. The difference between the two groups was statistically significant ($p < 0.02$) (Figure 2).

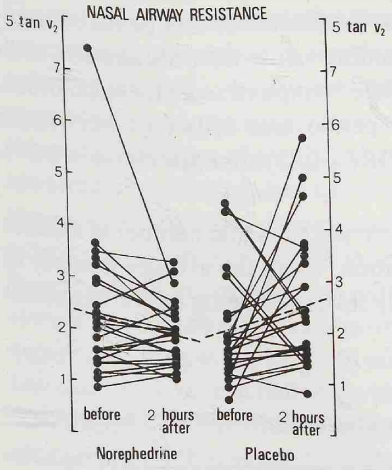

Figure 2. Nasal airway resistance before and two hours after administration of norephedrine and placebo ($p < 0.02$).

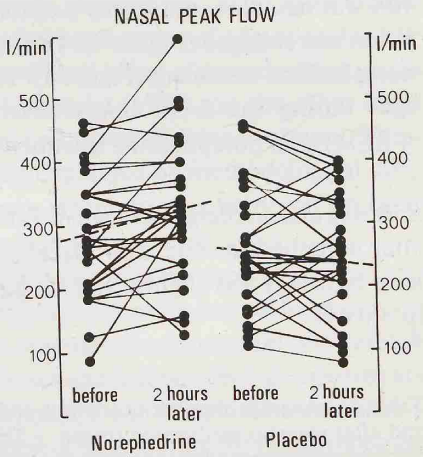

Figure 3. Nasal peak flow before and two hours after treatment with norephedrine and placebo ($p > 0.05$).

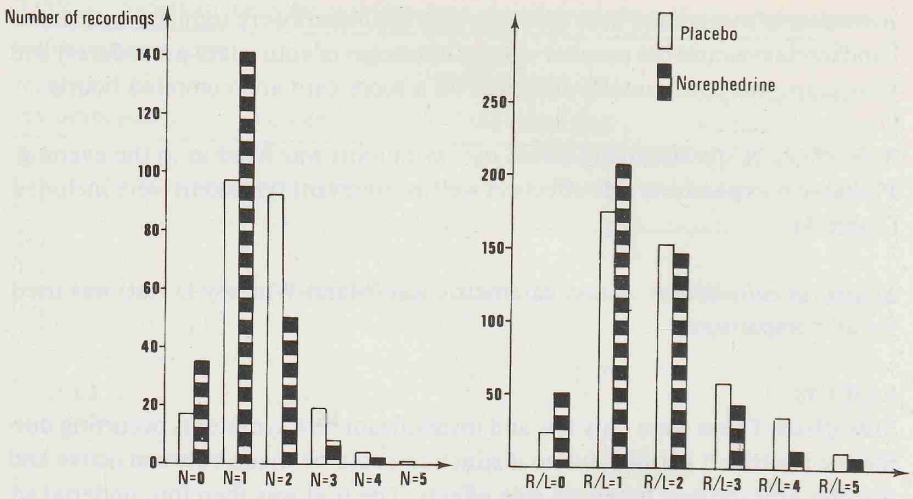

Figure 4. Individual self-assessment scores for nasal blockage in the period from 2–10 hours after mediaction (see Table 1). N=nose; R/L=right nostril/left nostril.

Nasal peak flow. The mean value for nasal peak flow, measured two hours after medication, was slightly increased after norephedrine and slightly decreased after placebo (Figure 3). The difference between active and placebo treatment was not statistically significant ($p > 0.05$).

Self-assessment of nasal blockage. In the period, 2–10 hours after placebo medication, mouth breathing was necessary in 10% of the observations and in another 40% was nasal breathing only possible, when the frequency and depth of respiration was changed (Figure 4). The corresponding values were 5% and 20% after norephedrine treatment (Figure 4). The average "symptom score for nasal blockage" during the 2–10 hours observation period was 3.10 (± 0.38) (mean $\pm$ SEM) after norephedrine treatment and 4.28 (± 0.43) after placebo ($p < 0.01$).

Sneezing and discharge. As seen in Table 5, there was the same number of sneezes after norephedrine and after placebo medication, while the average number of nose blowings was slightly and insignificantly lower following active treatment ($p > 0.05$).

Table 5. Average number of sneezes and of nose blowings per hour after norephedrine and after placebo medication (mean $\pm$ SEM).

	norephedrine	placebo
sneezes	0.37 (± 0.11)	0.36 (± 0.08)
nose blowings	1.22 (± 0.16)	1.50 (± 0.25)

DISCUSSION

Somewhat unexpectedly the nasal airway resistance increased after placebo medication and was almost unchanged after norephedrine treatment. These findings may be caused by irritation from the intranasal procedures (rhinoscopy, forceful nose blowings), by environmental factors, or perhaps by diurnal variation of nasal patency. Although such data have not been reported, there is a marked diurnal variation of nasal secretory activity (Mygind and Thomsen, 1976).

Anyhow there was a significant difference in nasal patency after norephedrine as compared to placebo, when measured by rhinomanometry, but nasal peak flow measurements were unable to unveil any differences. Taylor and co-workers (1973) have found nasal peak flow measurements of value for evaluating the result of nasal allergen provocation, but our results suggest that the sensitivity of this test is too low for disclosing a moderate drug effect on nasal patency. In addition, forceful nose blowings in a peak flow meter are unpleasant and unphysiological.

The self-assesment test for nasal blockage, on the other hand, was accepted by the patients, and its sensitivity was sufficient for showing a significant difference between norephedrine and placebo throughout the 10 hours observation period. This simple test seems suitable for clinical trials and also for examination of candidates for septoplastic surgery. In the research laboratory it cannot replace rhinomanometry, as it is not able to detect airflow changes in a patent nose, and as there is a considerable variation in how different subjects correlate the self-assesment score to the rhinomanometric result.

Theoretically, vasoconstrictors may aggravate rhinorrhoea, as in vitro studies have shown stimulation of airway glands after application of adrenoceptor agonists (Nadel, 1981). We did not find any significant effect of norephedrine on the amount of nasal discharge. Renvall and Lindquist (1979), on the other hand, showed a reduction of nasal discharge from oral vasocontrictor treatment. These apparently conflicting data can probably be explained by methodological differences in trial design. Improvement of one symptom may come off on other symptoms, when patients fill in score cards in the evening.

Norephedrine in combination with antihistamine is often used to combat cold symptoms, but the effectiveness on sneezing and discharge has not been fully documented (West et al., 1975). In our study, oral norephedrine could only reestablish nasal breathing in half of the blocked noses and had no effect on sneezing and discharge. In a proportion of patients with colds, it will therefore be necessary to change to the more potent topical application of ipratropium for rhinorrhoea and xylomethazoline or oxymethazoline for blockage (Borum et al., 1981).

It can therefore be argued that it is more simple and equally safe to start the treatment with these sprays, when short-term therapy is intended. In addition, reports

are accumulating about transient CNS disturbances (children) and urinary retention (elderly men) after high dose oral vasoconstrictor therapy, as used in our trial (2–3 mg/kg/day) (Kane and Green, 1966; Wharton, 1970; Meistrup-Larsen et al., 1978; Widerlöw, 1979.

It is an advantage of oral decongestants over nasal sprays that they can be used for prolonged periods without risk of rhinitis medicamentosa. Treatment of perennial rhinitis appears therefore to be a main indication for their use. Theoretically, it is also an advantage of the oral preparations that they reach the middle ear and paranasal sinuses, and they are widely used for prevention and treatment of otitis and sinusitis. This practice is more based on pathophysiological arguments than on controlled trials. While the reports on efficacy of oral decongestants in secretory otitis media are contradictory (Miller, 1970; Jackson, 1971; Olson et al., 1978; Saunte and Johansson, 1978), they are mostly negative for acute otitis media (Rubenstein et al., 1965; Kjellman et al., 1978; Chilton and Skipper, 1979; Randall and Hendley, 1979) and sinusitis (Aust et al., 1979).

In conclusion, a moderate decongestant effect of oral norephedrine can be of some value for common cold sufferers, but it is not proven that this therapy can prevent otitis and sinusitis or ameliorate the symptoms of these complications.

ZUSAMMENFASSUNG

Die Untersuchung hat beabsichtigt die Wirkung von Norephedrin per os auf die Anschwellung der Nasenschleimhaut beim gewöhnlichen Schnupfen zu bestimmen. Dreissig erkältete Personen bekamen in einem zweitätigen dobbelt-blind durchgeführten Versuch am einen Tage eine Norephedrintablette mit protrahierter Wirkung, am anderen eine Plazebotatblette. Änderungen der Nasendurchgängigkeit wurden mittels Rhinomanometrie und Messung der maximalen Durchströmung während der Expiration bestimmt. Ausserdem wurden die Patienten aufgefordert selbst die Durchgängigkeit der Nase zu beurteilen. Ferner wurden in einem Zeitraum von 10 Stunden nach Einnahme der Tabletten die Anzahl von Niesern und die Häufigkeit mit der sich die Versuchspersonen die Nase putzten registriert. Im Gegensatz zur Messung der maximalen Expiration erwies die Rhinomanometrie zwei Stunden nach der Tabletteneinnahme eine signifikante Verbesserung ($p < 0.02$). Ferner zeigte die subjektieve Beurteiling eine Verbesserung, welche die ganze Observationszeit von 10 Stunden anhielt. Die Nasenatmung wurde bei der Hälfte der völlig verlegten Nasen wiederhergestellt. Niesen und Nasenputzen waren dagegen unbeeinflusst.

Als Schlussfolgerung muss festgestellt werden, dass Norephedrin eine mässige abschwellende Wirkung besitzt, die ihre Anwendung bei Erwachsenen rechtfertigen kann. Der symptomatische Effekt muss aber den Kosten und eventuellen Nebenwirkungen gegenübergestellt werden. Eine präventive Wirkung auf Mittelohr – oder Nebenhöhlenentzündung ist in der Literatur nicht nachgewiesen worden.

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H. Grønborg, M.D.
Otopathological Laboratory
University ENT-Department
Rigshospitalet
Blegdamsvej 9
DK-2100 Copenhagen
Denmark