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COMMUNICATIONS

The effects of oral administration of (−)-menthol on nasal resistance to airflow and nasal sensation of airflow in subjects suffering from nasal congestion associated with the common cold

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Abstract—The effects of oral administration of a lozenge containing 11 mg (−)-menthol on nasal resistance to airflow (NAR) and nasal sensation of airflow in 62 subjects suffering from nasal congestion associated with naturally acquired common cold infection have been studied. NAR was measured by posterior rhinomanometry and nasal sensation of airflow by means of a visual analogue scale (VAS). The effects of the lozenge were compared with a candy placebo lozenge in a double blind randomized trial. NAR showed a significant increase ($P<0.05$) in both the menthol and placebo groups over the 2 h experiment with no difference between the groups at any time. The VAS scores showed significant changes of subjective improvement in nasal sensation of airflow ($P<0.001$) in the menthol-treated group 10 min after dosing whereas the placebo group showed no change. It is concluded that dosing with 11 mg menthol in subjects with common cold has no effect on NAR as measured by posterior rhinomanometry but causes a marked change in nasal sensation of airflow with a subjective sensation of nasal decongestion.

Lozenges containing menthol are widely used as common cold remedies for the symptomatic treatment of nasal congestion. Despite its widespread use as a nasal decongestant there is little if any published literature concerning menthol's action on nasal airway resistance (NAR) in subjects suffering from common cold symptoms. In several studies on normal healthy subjects we have investigated the effects of inhalation of menthol vapour on NAR and nasal sensation of airflow (Eccles et al 1987, 1988a). In those investigations the vapour had no effect on NAR but had marked effects on nasal sensation of airflow causing a subjective increase in the sensation of nasal airflow.

However, since menthol is normally used to treat the congested nose it was suggested that the results of our studies on normal healthy subjects might differ from those obtained from subjects with nasal congestion associated with the common cold. This suggestion was reinforced by Cohen (1987) who reported that administration of a lozenge containing 11 mg menthol to subjects with nasal congestion associated with the common cold caused a decrease in NAR which was sustained for up to 2 h.

The present investigation attempts to confirm the above report and determine if menthol has nasal decongestant action when administered orally as a lozenge to subjects suffering from nasal congestion and common cold.

Materials and methods

Volunteers (32 F, 30 M, age 22·5±0·8 mean±s.e.m. range 18–50 y), suffering from acute nasal congestion due to common cold infections of less than 72 h duration, were recruited from the staff and students of the University by poster advertisement during April to November 1988. All were free from anatomical nasal obstruction, nasal allergy or bronchopulmonary disease. None had taken any other medication apart from paracetamol in the 6 h preceding the trial. Subjects whose total nasal resistance to airflow was less than 0·3 Pa cm^{-3} s were excluded from the study, as the aim was to investigate the decongestant action of menthol.

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NAR was measured by active posterior rhinomanometry using a Mercury Electronics (Glasgow, UK) NR6 Rhinomanometer; measurements were made at a reference pressure of 75 Pa. The instrument was programmed to give the mean NAR of four consecutive breaths, and for each subject three consecutive series of breaths were used to calculate an overall mean of twelve breaths. If the coefficient of variation (CV) of the overall mean NAR for a subject was greater than 20% then the readings were repeated until the calculated CV was less than 20%. Smoking, meals and drink were forbidden during the trial.

The trial design was randomized and double blind and the subjects did not know that the aim of the study was to investigate the effects of menthol on the nose. Subjects were grouped according to whether their basal NAR was above or below 0·425 Pa cm^{-3} and then were randomly allocated to one of two groups, to receive either a candy lozenge containing 11 mg(−)-menthol or a placebo candy lozenge.

Five min after the measurement of basal NAR the subjects were given a coded lozenge.

All subjects dissolved the lozenge within 10 min. NAR was then measured at 10, 40, and 80 min after dosing.

In addition to rhinomanometry, each subject also scored at the same times nasal sensation of airflow on a 100 mm visual analogue scale (VAS) with the ends labelled; 'nose feels extremely clear' and 'nose feels extremely blocked'.

Paired and unpaired *t*-tests were used for statistical analysis of the data (Statworks, Cricket Software) and all data are expressed as mean±standard error of the mean.

Results

Of the 62 volunteers, 30 were randomly allocated to the treated group and received the menthol lozenge and 32 to the placebo group.

Nasal resistance to airflow. Subjects were separated according to the basal measurement of NAR into high NAR (>0·425 Pa cm^{-3} s) and low NAR (<0·425 Pa cm^{-3} s) groups.

The results for the 62 subjects before separation are illustrated in Fig. 1; basal NAR measurements were made 5 min before

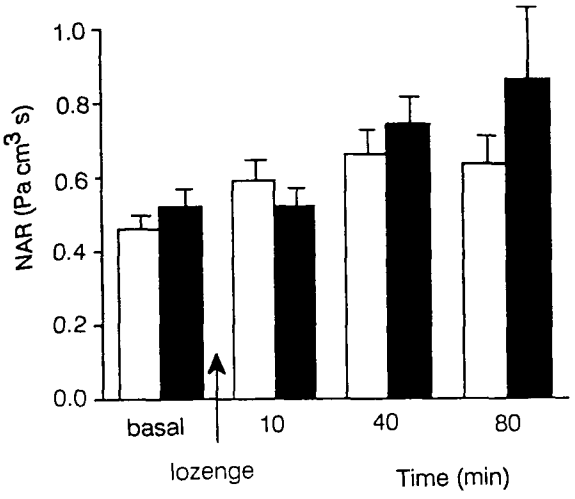

FIG. 1. The effects of administration of a lozenge containing 11 mg menthol (shaded bars, n = 30) and candy placebo (unshaded bars, n = 32) on NAR. None of the between group differences were significant ($P > 0.05$). There were significant ($P < 0.05$) increases in NAR in the placebo and treated groups from basal to 40 min. The results represent the means ± s.e.m. Basal NAR measurements were made 5 min before dosing with the lozenge and the times (10, 40, 80 min) are given as those after dosing.

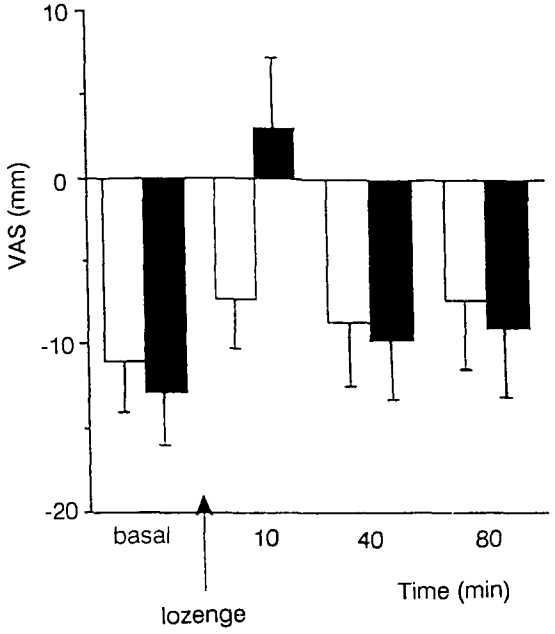

FIG. 2. The effects of administration of a lozenge containing 11 mg menthol (shaded bars) and candy placebo lozenge (unshaded bars) on visual analogue scores (VAS). The scores for VAS were measured from the midline of a 100 mm scale with 0 to −50 mm towards the side marked 'nose feels extremely blocked' and between 0 and +50 mm towards the side marked 'nose feels extremely clear'. There was a significant difference between basal and 10 min post-dosing scores in the menthol group ($P < 0.001$), and between the placebo and menthol groups at the 10 min post-dosing time ($P < 0.05$). The results represent the means ± s.e.m. (n = 30 for placebo, n = 32 for menthol group). Basal VAS scores were taken immediately before dosing with the lozenge and the times (10, 40, 80 min) are given as those after dosing.

dosing with the lozenges and the times on the histograms refer to minutes after dosing with the lozenge. Before dosing, the treatment and placebo groups were well matched for basal NAR with similar, not significantly different, mean values in each group (placebo 0·46 ± 0·03, n = 32; treatment 0·53 ± 0·05 Pa cm^{-3} s n = 30). After dosing there was no significant difference between treated and placebo groups at any time and measurements at 10 min after dosing were not significantly different from the basal NAR values. Over the course of the trial there was a significant increase ($P < 0.05$) in NAR when compared with basal NAR in both the treated and placebo groups so that at 40 min the NAR in the placebo group increased to 0·74 ± 0·12 Pa cm^{-3} s and that in the treated group increased to 0·64 ± 0·08 Pa cm^{-3} s.

Separation of subjects into high and low NAR groups did not identify any effect of menthol on NAR when placebo and treated groups were compared at all times.

Nasal sensation of airflow. In contrast to the NAR measurements, with both lozenges having similar effects on NAR and an overall trend towards increasing nasal congestion with time, the VAS scores showed a highly significant score of subjective decongestion after dosing with menthol (Fig. 2).

There was no difference between the placebo and menthol treated group under basal conditions with both groups scoring towards the side of the VAS marked 'nose feels extremely blocked' the score for the placebo being −11·0 ± 3·2 and for the treated group −12·8 ± 3·4 mm. After dosing, the menthol-treated group scores changed significantly ($P < 0.001$) to +2·9 ± 4·2. The menthol group was also significantly ($P < 0.05$) different from the placebo −7·3 ± 2·8. At 40 min after dosing there was no significant difference between the groups with respective scores of −8·6 ± 3·8 and −9·7 ± 3·4 min.

Discussion

The present results demonstrate that dosing with an 11 mg menthol lozenge has no effect on NAR in subjects suffering from nasal congestion associated with the common cold. Under similar conditions a topical sympathomimetic nasal spray would have at least halved the nasal resistance.

There was a significant increase in NAR during the course of the experiment and this trend with time is probably due to the subjects remaining relatively inactive for the 2 h test since they only moved when called for rhinomanometry. It is well documented that exercise causes a decrease in NAR (Richerson & Seebohm 1968; Dallimore & Eccles 1977) and since the subjects had probably been active before the experiment the 2 h period of relative inactivity could itself lead to an increase in NAR. A similar increase in NAR over 2 h in subjects suffering from common cold symptoms has been reported (Gronborg et al 1983) but this was explained as being caused by intranasal procedures or forced nose blowing.

It is possible that any mild decongestant action of menthol would be hidden by the increase in NAR associated with the inactivity of the experimental situation but this would mean that the decongestant action of the menthol lozenge was so small as to be of no clinical significance.

In the present investigation the dose of menthol used was 11 mg and it is possible that a higher dose would have been more effective, however, most commercially available menthol lozenges contain only 2–4 mg menthol per lozenge. Immediate subjective relief of nasal congestion was felt by the subjects on sucking the lozenge and it is this response which matters to the subject rather than any objective change in NAR.

It is difficult to explain the failure of the present study to confirm the preliminary report (Cohen 1987) that dosing with a

similar menthol lozenge caused a highly significant reduction in NAR which was sustained for 2 h. There were minor protocol differences: Cohen used posterior rhinomanometry, as did we, although he used a sample flow point of 0·5 L s^{-1} rather than a sample pressure of 75 Pa to measure NAR; he also excluded all subjects with NAR > 6·5 H_2O $L^{-1}s$. But from these variations the studies are directly comparable and the dose of menthol the same. We have previously examined the effects of menthol inhalation on NAR in normal subjects and failed to demonstrate any decongestant action (Eccles et al 1987, 1988a). As a measure of NAR, rhinomanometry is sensitive to changes in the cross sectional area of the nasal valve region and it may be that other areas of the nasal mucosa are decongested by menthol and these changes are not detected by rhinomanometry. This could explain the discrepancy between the objective measurements of NAR and the subjective scores of nasal sensation.

The marked short-term subjective effect of sucking the lozenge is clearly apparent in the VAS results but it was not sustained as at 40 min there was no difference in scores between the groups.

A subjective change in nasal sensation of airflow caused by inhalation of menthol vapour has been previously reported from experiments on normal healthy subjects (Eccles et al 1987, 1988a) and the present results indicate that normal and congested subjects respond in the same way to menthol either as vapour or orally with the mechanism of action of the drug probably being the same. As the lozenge dissolves, vapours will enter the nasal passages, via the posterior nares on swallowing and via the nostrils when the mouth is opened. It is unlikely that the drug exerts its effect on nasal sensation systemically as there would be a delayed onset of action and other menthol sensitive areas such as the surface of the eye, face and the ano-genital area (Watson et al 1978) would also be affected.

The effect of menthol on the nasal sensation of airflow is probably due to some action on nasal airflow receptors (Eccles et al 1987). These may be trigeminal thermoreceptors in the squamous epithelium of the nasal vestibule which respond to the cooling action of inspired air (Tsubone 1989). The facial skin, which is identical to the lining of the nasal vestibule, is sensitive to the drug's cooling action and this is believed to be via interaction with trigeminal thermoreceptors (Watson et al 1978).

It is unlikely that the effect of menthol on nasal sensation of airflow is due to some non-specific action of the volatile vapour, perhaps causing cooling of the nasal mucosa, as if this were so all of the eight isomers of menthol might be expected to cause the same enhancement of nasal sensation of airflow. Only (−)-menthol has been shown to enhance nasal sensation of airflow and (+)-menthol, (+)-isomenthol and (+)-neomenthol have been shown to be inactive (Eccles et al 1988a). This indicates a specific pharmacological action for (−)-menthol on nasal sensory nerve endings (Watson et al 1978; Eccles et al 1988b). As far as the drug's basic mechanism of action on nerve cell membranes is concerned, there is now evidence that it acts on thermoreceptors by interfering with calcium conductance thereby inducing depolarization and sensitization or stimulation of the receptor (Schafer et al 1986; Swandulla et al 1986).

Although we have found menthol to give only subjective relief of nasal congestion in our subjects with upper respiratory tract infection, there may be other beneficial effects associated with menthol treatment. Its inhalation into the nose has been shown to reflexly influence the activity of upper airway accessory respiratory muscles around the nose in the cat and man (Davies & Eccles 1985; Eccles et al 1989). If this action extends to other similar groups of muscles supporting the airway, then menthol may influence the patency of the upper airway during inspiratory efforts against high NAR. Such a proposed action could be important during sleep where nasal obstruction has been linked to sleep disturbances and sleep apnoea (Prowse & Allen 1988).

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