intensive care unit. Our results confirm that it provides satisfactory sedation in patients requiring mechanical ventilation with a range of severity of illness as determined by their APACHE II scores. The degree of sedation with isoflurane was easily and rapidly controlled by changing the inspired isoflurane concentration delivered to the patient. The effective dose of isoflurane for sedating ventilated patients in the intensive care unit was confined to a narrow range (0·1-0·4% concentration), whereas the requirement for midazolam showed considerable variability between patients (0·014-0·140 mg/kg/h). Patients sedated with isoflurane were often tranquil and cooperative, whereas those sedated with midazolam were often confused and disruptive, requiring increasingly higher infusion rates that resulted in oversedation. Provided that patients were not hypovolaemic, isoflurane or midazolam sedation did not have deleterious effects on haemodynamic stability.

In conclusion, isoflurane in subanaesthetic concentrations (0·1-0·6%) provides a useful alternative technique for sedation of ventilated patients in the intensive care unit. It has many advantages over conventional intravenous sedative agents. The quality of sedation and speed of recovery from sedation are significantly better with isoflurane than midazolam. Further studies are required to assess the side effects of prolonged isoflurane sedation.

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Local hyperthermia benefits natural and experimental common colds

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Abstract

***Objective*—To determine whether inhaling fully humidified air at 43°C gave more benefit to cold sufferers than inhaling air at 30°C.**

***Design*—Randomised double blind trial.**

***Setting*—General practice and the common cold research unit.**

***Subjects*—87 Unselected patients with typical acute nasal and upper respiratory symptoms (general practice study), and 84 volunteers aged 18-50 without a history of chronic or allergic diseases.**

***Interventions*—Subjects breathed from apparatus delivering 40 litres of room air heated to 43°C or 30°C and fully humidified (relative humidity 100%) per minute.**

***End point*—Reduction in severity of disease.**

***Measurements and main results*—Patients recorded their symptoms (general practice study) and observers recorded symptoms and signs, weight of nasal secretions, isolation of virus, and antibody responses in volunteers. Patients treated for 20 minutes at 43°C had in the succeeding days roughly half the score for symptoms of those treated at 30°C. Volunteers treated for 30 minutes on three occasions when they were starting a cold showed a 43% reduction in symptoms. Treatment of volunteers for 20 minutes at the onset of the cold and for 10 minutes on succeeding days showed no difference between 43°C and 30°C.**

***Conclusions*—Nasal hyperthermia can improve the course of a common cold and also give immediate relief of symptoms.**

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Introduction

Inhaling warm, damp air is widely accepted to relieve the symptoms of colds and other acute respiratory infections, and, indeed, inhaling humidified air is part of the management of lower respiratory disease in some paediatric centres. Greater benefit, however, may be obtained by administering hot humidified air so that the temperature of the nasal mucosa is raised. Equipment to do this has undergone preliminary trials (A Beacham, J Levenstein, unpublished), which suggested that inhalations that raised the temperature of the nasal mucosa to 43°C for 20 minutes led to a rapid resolution of common colds.

Lwoff suggested that raising the mucosal temperature to 43°C for three periods of 30 minutes at intervals of two hours would block the replication of rhinoviruses and so abort common colds.[1] An apparatus to do this (the Rhinotherm) was developed in Israel, and it was claimed that 80% of subjects who used the apparatus in the early stages of a cold were better the next day.[2] The control groups in this trial were not apparently balanced with the experimental group, and the control apparatus would have been readily distinguished from the active apparatus as it

delivered only 5% of the air of the active apparatus. An effective double blind design is essential in trials that depend heavily on the patients' reports of symptoms. We investigated the use of hot humidified air with an apparatus that was easy to use and delivered 40 litres of fully saturated air at either 43°C or 30°C per minute.

Subjects and methods

The machines, which were unlabelled, were placed on a table, and the patient sat on a chair and breathed through a vented anaesthetic mask. Some machines were set at 43°C and others at 30°C; the mean temperatures of the nasal mucosa were 43°C and 33°C, respectively. Both machines gave the sensation of breathing warm, moist air. Other aspects of the administration and assessment were carefully double blinded.

General practice study—Patients came to the Adelaide Centre, Andover, in response to circulars and advertisements, and one of us (JA) took a simple history, asking particularly for any serious underlying disease, chronic or recurrent respiratory infections, respiratory allergies such as hay fever and asthma, and other allergies. Patients whom he thought had true common colds were admitted to the trial. The diagnosis was made on the basis of a short history and presence of typical symptoms, such as runny nose, stuffiness, sore throat, cough, and headache. All the subjects were adults and signed the consent section of a record form, and the full protocol of the trial was approved by Winchester ethical committee. Patients were allocated to treatment by reference to a list of random numbers and inhaled on one occasion for 20 minutes under observation. They were seen immediately after treatment by a doctor, who asked about adverse effects and recorded whether their symptoms were the same, better, or worse. They recorded the severity of their symptoms daily for the next five days on a form with a four point scale (0 to 3). These forms were returned and used for the analysis.

Volunteer study—Volunteers were recruited to the common cold unit in Salisbury, housed in isolation, and observed as previously described.[3] The experiment was approved by Harrow district ethical committee. After two days' quarantine they were inoculated twice with intranasal drops containing about 100 times the median tissue culture dose of human rhinovirus type 14. Those volunteers who developed early signs of colds—that is, who used at least four paper handkerchiefs more than their baseline rate and developed one other symptom of a cold—were entered into the trial and allocated at random to receive treatment at 43°C or 30°C. They received three treatments of 30 minutes each with one and a half hours between them. Any immediate change in symptoms was recorded as before, and thereafter their total symptom score and the weight of nasal secretions were recorded by standard methods. Nasal washings were collected each day and tested for the virus. Neutralising antibody was also measured in serum samples collected on arrival and about three weeks later.

TABLE I—*Characteristics of patients with colds randomised into general practice study for treatment with warmed air*

	Air at 43°C (n=45)	Air at 30°C (n=42)
Men	23	17
Women	22	25
History of other conditions*	11	18
Duration of symptoms before treatment (days):		
1-2	21	21
3-4	16	15
≥5	7	4
No of symptoms:		
5	1	7
4	5	17
3	16	8
2	20	7
1	3	3
Mean No of symptoms	2·6	3·4

*Such as hay fever or sinusitis.

TABLE II—*Immediate effect of 20 minutes of treatment with warmed air on symptoms as reported by volunteers (first trial)*

	Rating of stuffy nose*		
Temperature of air	Worse	Same	Better
30°C (n=39)	3	20	16 (41%)
43°C (n=45)	3	20	22 (49%)

*Similar results were seen for sore throat, cough, headache, and runny nose.

Statistical analysis—Rank two way analysis of variance[4] was used to analyse the results of each trial and was performed on a microcomputer with a program from the statistical package for personal computers (P Royston, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex). This included a facility for "blocking" data into groups according to the values of a third variable—for example, serum antibody titre or initial clinical score.

Results

GENERAL PRACTICE STUDY

Ninety six subjects were enrolled in the general practice trial, from whom 87 satisfactory records were obtained. The two groups, treated with moist air at 30°C and 43°C, were similar in size, ratio of sexes, other clinical conditions, and duration of colds, but those subsequently treated at 30°C had significantly more symptoms on presentation (table I). Immediately after treatment 22 (49%) of those given air at 43°C and 16 (41%) of those given air at 30°C reported an improvement in nasal stuffiness (table II); there were similar small differences in the response of other symptoms to the two treatments. During the subsequent days the mean symptom scores were substantially lower in the group given air at 43°C, the mean total scores being 9·3 and 25·9, respectively.

As the group given air at 30°C had had significantly more symptoms than the group given air at 43°C on admission to the trial the significance and size of the beneficial effect might have been overestimated by a simple analysis. We therefore performed a rank analysis of variance. This gave a valid statistic, although the symptom scores were not normally distributed, and we also "blocked" for the scores before treatment. The differences were highly significant (fig 1). We allowed approximately for the differences in numbers of symptoms before treatment by "correcting" the total score ($25·9\times(2·6/3·4)=19·8$), suggesting that the scores of the treated group were reduced to 47% (9·3/19·8) of those expected.

The subgroups with only nasal symptoms were analysed separately, and, though the numbers were small, the initial illnesses were comparable. The mean total scores were 12·3 after treatment with air at 30°C and 7·7 after treatment at 43°C ($p<0·05$), representing a reduction of 37%, and the differences in the mean daily scores were also significant (fig 2). We also looked at the day on which no symptoms were recorded, which was assumed to be the end of the cold. On the fourth day of observation 21 (47%) of the group given air at 43°C had a symptom score of zero, whereas only 1 (2%) of the group given air at 30°C did.

We concluded that, in spite of the imbalance of the study groups, local hyperthermia for 20 minutes had improved the course of the colds, though the effect was less than that reported earlier. On the other hand,

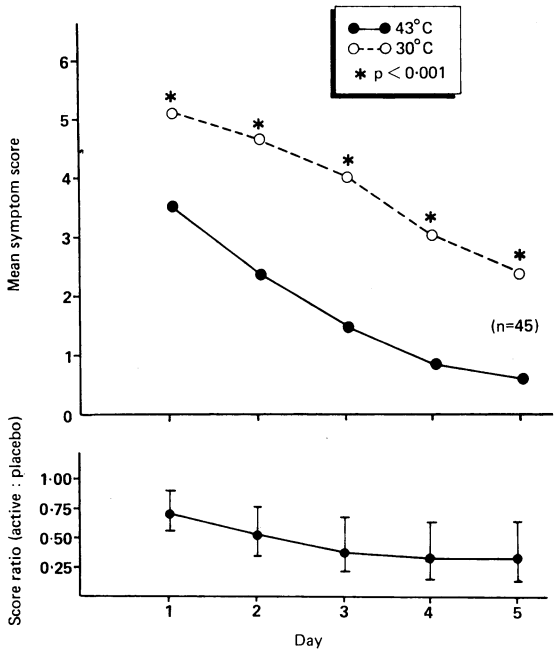

FIG 1—*Top: Mean symptom scores for patients with natural colds treated with air at 43°C or at 30°C. Mean duration of colds after treatment at 30°C was 4·9 days and at 43°C was 3·5 days. Bottom: Daily ratio of symptom scores with test based 95% confidence intervals*

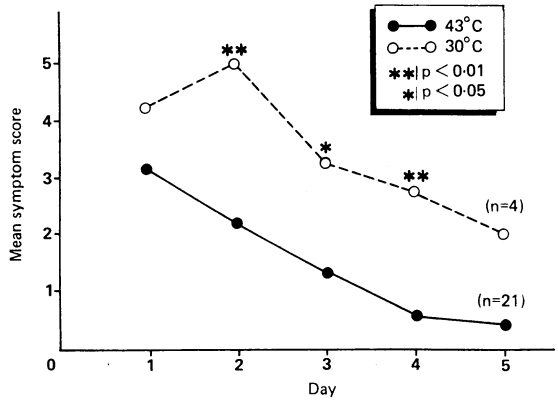

FIG 2—*Mean symptom scores for patients who had nasal symptoms only. Mean duration of symptoms after treatment at 30°C was 4·7 days and at 43°C was 3·0 days*

we had treated our subjects less intensively than prescribed by Lwoff and we had not tested whether the treatment had prevented further infection with the virus as he predicted.[1] Our volunteer study helped to resolve these problems.

VOLUNTEER STUDIES

In all, 27 of the 75 volunteers inoculated developed colds. For these volunteers there was clearly greater benefit from air at 43°C (table III). The difference in the proportions of the groups of volunteers who showed improvement was significant (61% (95% confidence interval 31% to 91%)).

Figure 3 shows the subsequent courses of the colds as indicated by mean total daily symptom scores and the mean weights of daily nasal secretions. The scores of the two groups were similar on the day of treatment and were subsequently reduced by about 20% in those treated at 43°C; likewise the weights of secretion were reduced by a maximum of 42% after two days. By simple rank analysis these differences were not significant; when "blocked" by the initial weight of nasal secretions (allowing for the fact that on entry to the trial some volunteers had worse colds than others), however, they reached significance on several days. The difference in mean total score was significant (14 *v* 24, p=0·02, one tail test) as was the difference in mean total weight of secretions (26 *v* 33, p=0·027), these reductions being 43% and 21%, respectively.

By contrast there were no differences in the proportion of volunteers shedding the virus between the two groups after treatment, although the proportion was lower, though not significantly so, on the day of treatment in the group given air at 43°C (fig 3, bottom). The frequency of antibody response (5/14 at 43°C and 7/13 at 30°C) and the mean titres in convalescence (1/3·7 *v* 1/8·0) were also not significantly different.

Some volunteers mentioned local discomfort in the first few minutes of treatment at 43°C. Although volunteers were encouraged to report freely and were examined daily, there was no indication of adverse effects from the treatment.

We wanted to establish whether shorter treatments would yield the same results, so a similar study was done with a modified scheme in which volunteers received 20 minutes of treatment on the day of diagnosis and a further 10 minutes each morning until the symptoms resolved or the trial ended. In this case no continued improvement was seen.

Discussion

The main purpose of these studies was to show impartially whether local hyperthermia benefits colds. We believe that we found evidence for this in two quite different groups of subjects and with different designs of trial. Furthermore, our subjects found the treatment acceptable and the amount of benefit was clinically important.

In our first study (general practice study) we treated naturally acquired colds, most of which had been present for over a day; in the second and third studies (volunteer studies) we treated colds that had been present for only a few hours and caused by a single type of rhinovirus. In the first study we relied on subjective self reporting (though we have evidence that this gives results similar to those obtained by a trained independent observer (S Macintyre, in preparation)). In the second and third we also used a trained doctor and an objective measure of disease—that is, weight of daily nasal secretions. All three trials had weaknesses: in the first randomisation generated groups with disease in which the prevalences of symptoms were different; in the second and third the numbers were small for practical reasons.

In spite of this the trials showed some immediate subjective benefit, and in the second study this was clearly greater with air at 43°C than 30°C. The first two studies showed a clinical advantage for those treated at 43°C, and this continued for two or three days and was confirmed by our most objective measure. The amount of benefit could not be measured exactly, but symptoms and signs were reduced by up to 40%.

TABLE III—*Immediate effect of three 30 minute episodes of treatment on symptoms as reported by volunteers (volunteer study)*

Treatment	Rating of symptoms			
	Total	Worse	Same	Better
At 30°C:				
First episode	15	2	8	5
Second episode	15	2	9	4
Third episode	14*	2	7	5
Total	44	6	24	14 (32%)
At 43°C:				
First episode	14		1	13
Second episode	14		2	12
Third episode	14			14
Total	42		3	39 (93%)

*One volunteer refused third episode of treatment.

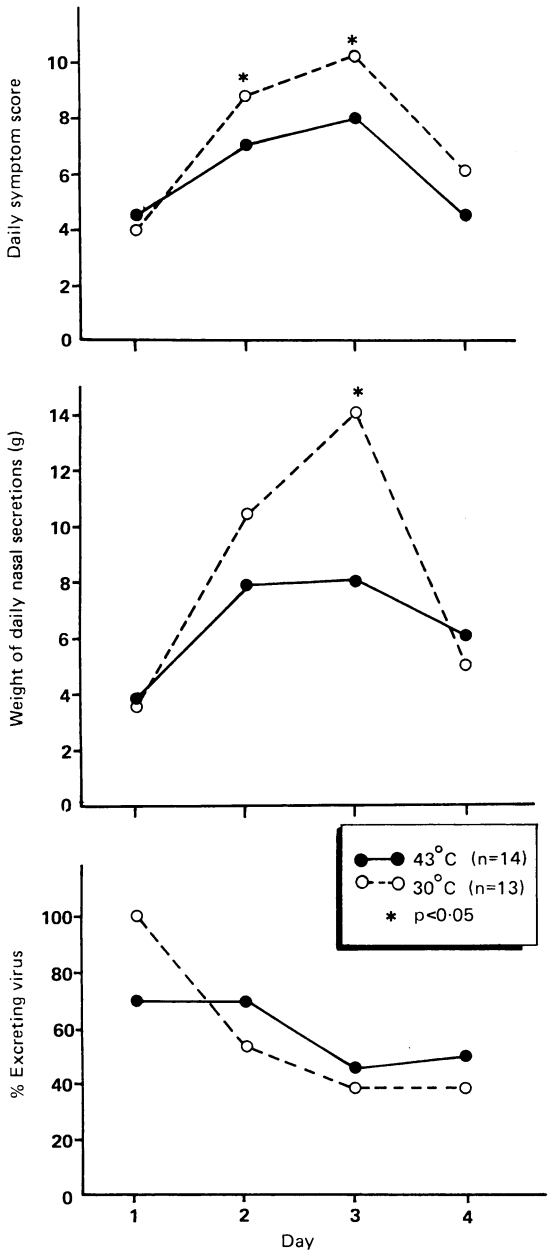

FIG 3—*Results of treating volunteers with colds induced by rhinovirus. Symptoms, scores, and weights of secretions on day 1 refer to the 24 hours in which treatment was started; results of virus isolation on day 1 are given as percentage of those volunteers who received treatment before specimens were collected*

Interestingly, a recent independent study in Israel with an improved Rhinotherm apparatus showed that two treatments of 20 minutes given to patients with natural colds reduced another objective variable, nasal airway resistance, by about a third for several days.[7] Thus, though we cannot support the claim that 80% of people with a cold recover by the day after treatment,[2] we believe that three separate satisfactory trials have now shown that colds are improved for several days after treatment and that this is clinically and statistically significant. There is also immediate relief of symptoms, which may be better if the machine is run at 43°C rather than at 30°C. In clinical practice there would probably also be a useful placebo effect, and some patients would probably start to treat a mild cold that was going to improve anyway. We therefore find plausible the results of an uncontrolled trial which showed that about 80% of subjects reported that their colds were considerably improved the day after 20 minutes of hyperthermia at 43°C (J Levenstein, unpublished data).

Several questions are still unanswered. Evidence suggests that 20 minutes of treatment at 43°C of an already developed "natural" cold is beneficial; 20 minutes given early in a mild experimental cold gave no continuing benefit but three treatments of 30 minutes did. Treatments of 10 minutes had little effect. We have no clear evidence that virus replication is halted, as proposed by Lwoff.[1] There may be a temporary effect, but this seems to disappear and presumably other biological effects are possible. Pyrexia is known to be beneficial in systemic infections, but the details of the mechanisms are obscure. As local hyperthermia at 43°C is reported to benefit hay fever[8] possibly it diminishes inflammatory processes or other reflexes or immunological responses. In laboratory models hyperthermia in vitro or in vivo turns on heat shock genes in a wide range of cells, including lymphocytes, and can alter cell behaviour—for instance, it can prevent degranulation of mast cells and induce production of interferon.[9-12] The regulation and expression of the heat shock genes is, however, complex.[13] For further clinical evaluation a plausible hypothesis of the mode of action would be valuable and more research on the biological effects of local hyperthermia is justified.

Prolonged respiratory hyperthermia has been used to raise the body core temperature after accidental and experimental immersion in cold water and has been free of unwanted effects[5] (J S Hayward, personal communication). We did not observe any adverse effects in the subjects taking part in these controlled studies or in others treated under uncontrolled conditions. Nevertheless, a watch should be kept for reactions, perhaps in the few patients who are sensitive. Also, some people may derive more immediate benefit than others. These uncontrolled observations have also suggested benefit in conditions such as asthma and chronic sinusitis so controlled studies are needed on these indications too. Lwoff (personal communication) believes that more dramatic results are obtained if air is insufflated into the nose rather than breathed in from a mask; this idea is also worth further study.

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