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Original article

Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study

Background: In a recent study, we showed that intranasal capsaicin spray gives a significant and long-term reduction of symptoms in nonallergic noninfectious perennial rhinitis patients. However, in daily practice, the studied application regimen proved to be impractical because of the large number of visits required in a short period of time. In the present study, we conducted a double-blind double-dummy parallel groups trial to determine whether a more practical capsaicin application schedule is equally effective.
Methods: Thirty patients were randomized into two different treatment regimens: one group received capsaicin five times on the first day at 1-h intervals. This was followed by a placebo dummy once every second or third day for a total of five treatments 2 weeks after the capsaicin application (group A). The other group (B) received the placebo dummy five times on the first day followed by capsaicin once every second or third day for a total of five treatments 2 weeks after the placebo application.
Results: The visual analogue scale scores for overall nasal symptoms, rhinorrhea and nasal blockage showed significant decrease after the start of treatment in both groups, with a significantly steeper decrease in group A. A significant reduction in cold dry air dose responsiveness was also found up to 9 months after therapy in both groups, reflecting a decrease in nasal hyperreactivity. No significant changes in safety data (smell, blood pressure, heart rate) were found.
Conclusions: We conclude that intranasal capsaicin seems safe to use and that five treatments of capsaicin on a single day is at least as effective as five treatments of capsaicin in 2 weeks.

J. B. Van Rijswijk[1], E. L. Boeke[1], J. M. Keizer[1], P. G. H. Mulder[2], H. M. Blom[3], W. J. Fokkens[1]

[1]Department of Otorhinolaryngology, Erasmus Medical Centre, Rotterdam, The Netherlands; [2]Department of Epidemiology & Biostatistics, Erasmus Medical Centre, Rotterdam, The Netherlands; [3]Department of Otorhinolaryngology and Head & Neck Surgery, The Red Cross Hospital and The Juliana Children Hospital, The Hague, The Netherlands

Key words: capsaicin; nasal hyperreactivity; nasal provocation test; rhinitis vasomotor; treatment.

J. B. van Rijswijk
Outpatient Department of Otorhinolaryngology
Erasmus MC
Room D-127
Dr. Molewaterplein 40
3015 GD Rotterdam
The Netherlands

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Perennial rhinitis is a common disorder causing significant morbidity. Chronic rhinitis can be due to common factors such as mechanical obstruction, allergy or less common factors such as xylometazoline abuse or cystic fibrosis. But there are several types of chronic rhinitis of which the pathophysiology is not yet fully elucidated. Syndromes of chronic rhinitis with an unknown aetiology include nonallergic noninfectious perennial rhinitis, formerly referred to by us as NANIPER. In accordance with the 'World Health Organization Initiative, Allergic Rhinitis and its Impact on Asthma' (1), henceforth we will be using the term idiopathic rhinitis (IR) to describe this pathology. IR, formerly also called vasomotor rhinitis, is a diagnosis of exclusion and is given to patients who suffer from perennial nasal congestion, rhinorrhea and/or sneezing with no identifiable aetiology. IR is unrelated to allergy, infection, structural lesions, polyposis and other systemic diseases (2). Patients with nonallergic rhinitis with eosinophilia syndrome (NARES) form another subgroup of IR patients. They have significant mucosal eosinophilia [a nasal smear with more than 25% eosinophils (3)] and respond well to nasal corticosteroids (4). In previous studies, we found hardly any patients with NARES in our IR patient groups, probably because we only selected IR patients in whom no therapeutic effect had been achieved with nasal corticosteroids (5, 6).

The population incidence of IR is estimated at 2–4% (1). The impact on the quality of life of patients suffering from chronic rhinitis is significant, a fact that is often underestimated and neglected (7). In many patients, treatment with anti-histamines, nasal steroids or even nasal surgery is not beneficial (2).

The pathophysiology of IR is largely unknown. Several hypotheses have been put forward. Inflammatory cells

Abbreviations: CGRP, calcitonin-gene-related-peptide; CI, confidence interval; DRC, daily record chart; IR, idiopathic rhinitis; MCA, minimal cross-sectional area; MMCA, mean of the minimal cross-sectional area; NANIPER, nonallergic noninfectious perennial rhinitis; NARES, nonallergic rhinitis with eosinophilia syndrome; PNIF, peak nasal inspiratory flow; SD, standard deviation; SP, substance-P; TMMCA, sum of right and left MMCA; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analogue scale.

appear to play a minor part in the vast majority of patients (5, 6). It is assumed that neurogenic mechanisms play an important role (8). Neuropeptides (CGRP, SP, etc.) are released from peptidergic neurons in the nasal mucosa after activation by unspecific stimuli, and can be responsible for the symptoms of IR (9–11). Several studies have been published showing a therapeutic effect in IR patients for repeated topical applications of capsaicin (12–15). Capsaicin, the pungent agent in hot pepper, is known for its degeneration/desensitization effect on peptidergic sensory C-fibres, possibly explaining its therapeutic effect (16, 17).

In a recent paper, we showed that repeated administration of capsaicin in a double-blind placebo-controlled trial led to a significant and long-term reduction of symptoms (15). That study showed that intranasal capsaicin application once every second or third day for a total of 7 days has a significant, long-lasting beneficial effect compared with placebo. However, in daily practice, the studied application regimen proves to be unpractical for both patient and physician because of the large number of visits required in a short period of time.

The purpose of the present study was to conduct a double-blind double-dummy parallel groups trial to determine whether a more practical capsaicin application schedule is equally effective. Furthermore, we collected more safety data (blood pressure, heart rate) and paid specific attention to nasal capsaicin sensitivity, mucosal sensibility and olfactory function before and after therapy.

Material and methods

Subjects

Patients were admitted to the study if they had a history of nasal complaints such as nasal obstruction, sneezing and/or rhinorrhea for a period of over 1 year, which could not be attributed to allergic, nasal or paranasal infection, anatomical disorders affecting nasal function, pregnancy or lactation and/or systemic disorders (Table 1). They had to have used a nasal corticosteroid spray for at least 6 weeks without any beneficial effect on their nasal symptoms. They were nonsmokers not using medication affecting nasal function. All patients underwent nasendoscopy and patients with nasal polyps were excluded.

Patients with a diagnosis of IR scored their nasal complaints for a period of 2 weeks using a daily record chart (DRC) (Table 2). They were included in the study if periods of either clear nasal discharge and/or sneezing, and/or congestion persisted for an average of at least 1 h a day for at least 5 days during a period of 14 days (18). Thirty patients participated under conditions of informed consent (male/female: 14/16); mean age was 36 years (16–65 years). Procedures were approved by the local Medical Ethics Committee.

Study design

This study was performed in a double-blind randomized fashion. Patients were randomized 1 : 1 either for group A or for group B. For this purpose, a computer generated randomization list was prepared in blocks of eight randomly permuted allocations. On the basis of this list the double-blind medication was prepared by the local pharmacist. Patients in group A were first treated with capsaicin five times on a single day at 1-h intervals. After 2 weeks, they received a total of five treatments with dummy placebo once every second or third day. Patients of group B first received dummy placebo five times on a single day at 1-h intervals. This was followed 2 weeks later by a total of five treatments with capsaicin once every second or third day. The dummy placebos serve to ensure blindness of the study. The study design is shown in Fig. 1.

Each application of capsaicin or placebo was preceded by three applications of xylometzoline-hydrochloride 0.1% [Otrivin® nebulisator (1 mg/ml Zyma, Breda, Holland)] in each nostril for decongestion. The nasal mucosa was then anaesthetized by three applications (10 mg/puff) of lidocaine base [100 mg/ml, Xylocaine® 10% spray (Astra, Rijswijk, Holland)] in each nostril. To ensure good anaesthesia a pause of 15 min was introduced. The lips, columella and philtrum were covered with a petrolatum/lanolin/glycerine salve. The capsaicin solution (0.1 mmol/l) consisted of 30.3 mg pelargonic acid vanillylamide dissolved in 3 ml alcohol

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Age between 16 and 65 years
Negative Phadiatop (Pharmacia, Uppsala, Sweden)
Symptoms for more than 1 year
Periods of nasal discharge, sneezing and congestion for an average of at least 1 h per day for at least 5 days during a period of 14 days
No beneficial effect of nasal corticosteroid spray (for a period of at least 6 weeks)
Exclusion criteria
Use of systemic or inhaled corticosteroids in the previous month
Use of inhaled sodium cromoglycate or nedocromil sodium in the previous month
Use of astemizole in the previous month
Inability of the patient to stop taking medication affecting nasal function
A serious and/or unstable disease
Smoking (in the previous 6 months)
Nasal surgery in the previous 6 weeks
Nasal polyps or a history of nasal polyps
Significant anatomical abnormalities affecting nasal function
Nasal or paranasal sinus infection (abnormal sinus X-ray)
Pregnancy or lactation

Table 2. Design of the daily record chart for defining nasal symptoms in IR patients

Possible scores on the daily record chart	
Nasal blockage (not being able to breathe freely through the nose)	0 = absent 1 = between 0 and 1 h per half day 2 = between 1 and 2 h per half day 3 = more than 2 h per half day
Clear nasal discharge (runny nose)	
Sneezing	0 = absent
Coughing	1 = less than five periods per half day 2 = between 5 and 10 periods per half day 3 = more than 10 periods per half day
Green/yellow mucus production	0 = absent 1 = present

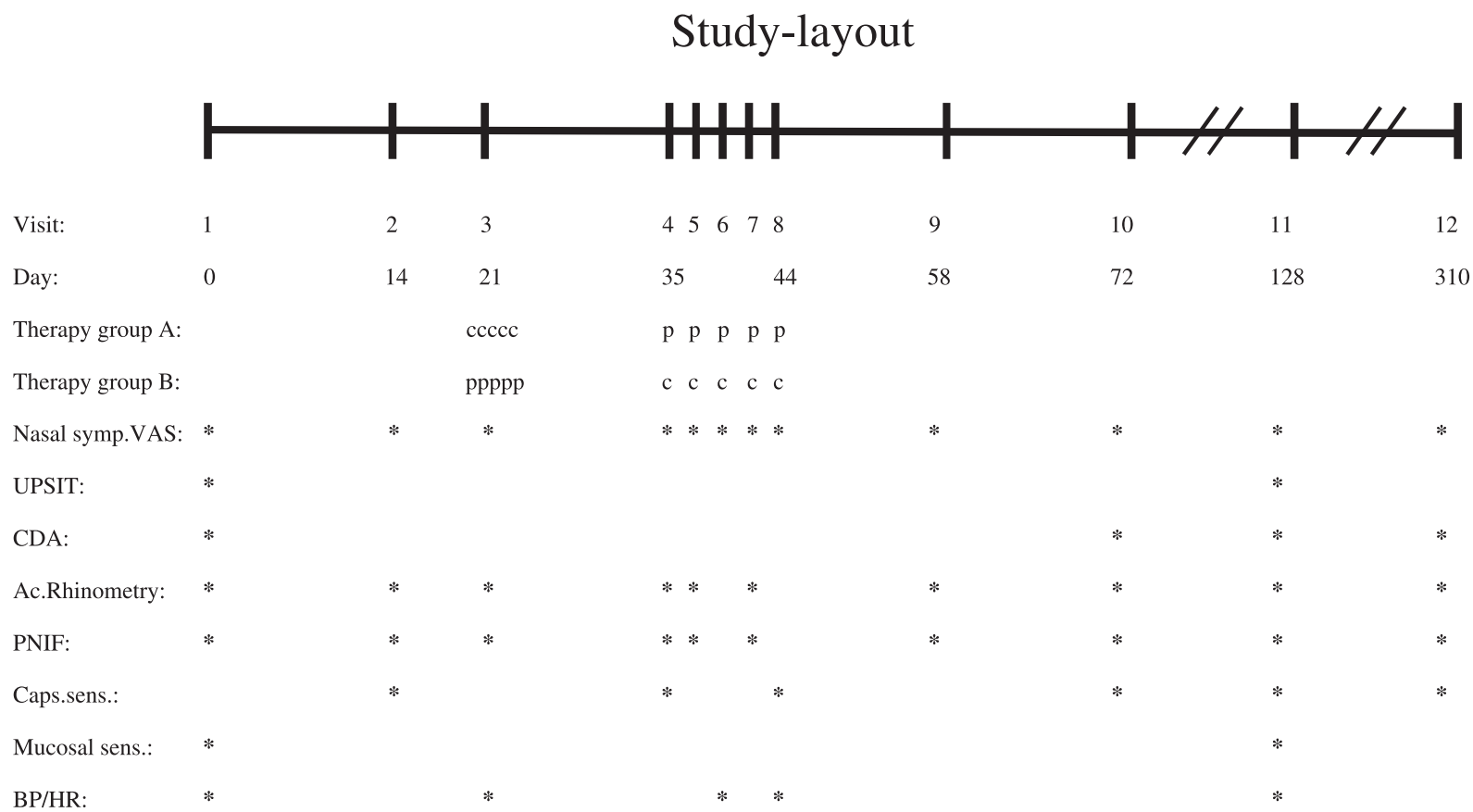


Figure 1. Study-layout. c: Capsaicin application. At visit 3, five times at intervals of 1 hour in group A; at visits 4–9, once every visit in group B. p: Placebo application. At visit 3, five times at intervals of 1 hour in group B; at visits 4–9, once every visit in group A. BP, blood pressure; HR, heart rate.

(96%) and diluted in 1 l NaCl solution (0.9%). As placebo, we used the capsaicin solvent only. During provocation, 0.27 ml of solution (three applications) was sprayed into each nostril with a metered nasal spray (0.09 ml per actuation, coefficient of variation 4%).

At every visit, the subjects rated the following four nasal symptoms during the last 3 days on four separate visual analogue scales (VAS) (0–10 cm, 0 cm represented an absence of symptoms and 10 cm represented highest intensity of symptoms): overall nasal symptoms, rhinorrhea, nasal obstruction and sneezing. DRC scoring was continued during administration with capsaicin and placebo until 4 weeks after the last treatment and 1 week before every follow-up visit thereafter.

Olfactory function

Olfactory function was measured before and after treatment using the University of Pennsylvania Smell Identification Test (UPSIT) (19).

Cold dry air provocation/nasal reactivity

Nasal reactivity (nasal patency, mucus production and sneezing) was measured using standardized cold dry air provocation (CDA) before and after therapy. The dose steps for cold dry air were 12.5, 25, 50, 100, 200 and 400 l, comprising of a first step of 12.5 l/min and other steps of 25 l/min at, respectively, 1, 1, 2, 4, 8 and 16 min. The –10°C air leaving the respiratory heat exchanger (Jaeger GmbH, Wurzburg, Germany) had a relative humidity of $< 10\%$ and entered the nasal cavity by means of a specially designed nose cap (Respricare, The Hague, The Netherlands). As soon as a threshold dose resulting in 40% reduction of nasal patency and/or 0.5 g mucus production (cut-off lines) was reached, the provocation series was stopped (20).

Nasal patency: acoustic rhinometry and PNIF

Nasal patency was studied before, during and after therapy. The acoustic rhinometer Rhin2100 (RhinoMetrics, Denmark) was used to measure the first two minimal cross-sectional areas (MCA1 and MCA2) using contoured nose-adaptors. To reduce variability, three replicate measurements were done and the mean of these measurements (MMCA1 and MMCA2) was used for further analysis.

Nasal patency was also studied on the basis of peak nasal inspiratory flow (PNIF) before, during and after therapy. On each occasion, three replicate PNIF measurements were done and the best one was used for further comparison/statistics.

Capsaicin sensitivity

Capsaicin sensitivity was measured before, during and after therapy by spraying capsaicin solution and placebo into both nostrils in a random order and asking the patient to point out which of the applications caused a pungent sensation (to discriminate the capsaicin solution from the placebo). Starting at 10^{-8} M, the capsaicin concentration was increased multiplicatively each time by the cubic root of 10, until the patient correctly distinguished the capsaicin solution from placebo three times in a row. This concentration indicated capsaicin sensitivity.

Mucosal sensibility

To study mucosal sensibility before and after therapy we touched the patients' nasal mucosa in a random order with a cotton wool stick (testing epicritic sensibility) and a thin metal rod (testing protopathic sensibility) and asked them to rate this sensation on a VAS (0–10 cm, 0 cm represented an absence of sensation and 10 cm represented highest intensity of sensation). This was done before and after therapy.

Blood pressure/heart rate

During several visits before, during and after therapy, blood pressure and heart rate were measured in a sitting position by standard sphygmomanometry.

Statistical analysis

Total nasal symptom VAS score was the primary outcome variable. No formal power calculation underlies this sample size.

Nasal symptom VAS data (10 repeated measurements under treatment) were analysed using repeated measures analysis of variance after log transformation with the baseline measurement as covariate. Exponential time trends, differences in time trends and, if no significant differences were found, constant differences in mean level between the two treatment groups were tested.

The various DRC symptom scores are defined in Table 2. DRC symptom scores were aggregated in six periods by averaging the daily scores per period per patient. The following six periods were distinguished: a baseline period of 3 weeks (period 0), period 1 (weeks 4 and 5 after baseline), period 2 (weeks 7 and 8), period 3 (week 10), period 4 (week 17) and period 5 (week 41). These aggregated data were analysed using repeated measures analysis of variance with the baseline average as covariate, the period as a within-patient factor (with five levels) and treatment as a between-patient factor with two levels. The interaction between period and treatment was also tested. The residuals were assumed to have a Gaussian spatial covariance structure accounting for differences in time between the repeated measurements.

UPSIT data were analysed using analysis of covariance with the baseline measurement as covariate for between-group differences. Within-group changes from baseline were tested using the paired *t*-test.

CDA data were analysed after $\log_2$ transformation using repeated measures analysis of variance with the baseline measurement as covariate. By this transformation, effects are expressed in doubling dose units.

Mucosal sensibility VAS data and capsaicin sensitivity data were analysed using nonparametric tests: the Wilcoxon signed rank test for within group changes and the Mann–Whitney *U*-tests for differences between the two groups. For capsaicin sensitivity the paired Wilcoxon test was applied after log transformation.

Acoustic rhinometry, PNIF, heart rate, systolic and diastolic blood pressure were analysed using repeated measures analysis of variance with the baseline measurement as covariate. For acoustic rhinometry, the sum of right and left for MMCA1 (TMMCA1) and MMCA2 (TMMCA2) was taken. Linear time trends were tested, as well as differences in time trends between the two treatment groups.

For differences in heart rate, and in systolic and diastolic blood pressure between the two treatment groups, differences between the visits and the interaction between these factors were tested. The null hypothesis is that the mean outcome variable does not change in time and is the same for both groups.

For all tests the significance level was set at 0.05. If appropriate, 95% confidence intervals (CI) of between-groups differences in treatment effect are presented.

Results

The application of Xylocaine® 10% spray in the nasal airway was immediately followed by a painful sensation that was described by all subjects as most unpleasant.

Patients did not complain of irritation of nose and lips during or after capsaicin/placebo application. We feel this study was effectively blinded for both patients and investigator.

Pre-treatment baseline data for patient characteristics and for efficacy variables per group are shown in Table 3 for both groups.

Symptoms

Visual analogue scale. The improvement of the median for VAS 'overall nasal symptoms' for both groups is shown in Fig. 2. In both groups a significant improvement of overall nasal symptoms was observed (also described later). Note the improvement started within 2 weeks after start of the treatment with capsaicin (visit IV for group A and visit VIII/IX for group B).

In group A, the VAS score for 'overall nasal symptoms' decreased significantly by 3.2% per week after the start of treatment and in group B by 1.3%, the difference in time trend being significant (95% CI: 0.4–3.5% points; $P = 0.016$). The VAS score for 'rhinorrhea' decreased significantly after the start of treatment by 3.7% per week in group A and by 2.6% in group B, the difference in time trend not being significant ($P = 0.26$). However, there was a constant difference in VAS level: group B scored on average 2.1 times higher than group A (95% CI: 1.4–3.2; $P = 0.0014$). The VAS score for 'obstruction' decreased significantly after the start of treatment by 3.2% per week in group A and by 1.8% in group B, the difference in time trend being significant (95% CI: 0.01–2.9% points; $P = 0.0484$). The VAS score for 'sneezing' decreased after the start of treatment by 2.8% per week in group A and by 1.3% in group B, the difference in time trend not being significant (95% CI: –0.2 to 3.3% points; $P = 0.0916$). Also no significant constant difference in VAS level was seen between the two groups (95% CI for group B to A ratio: 0.8–3.6; $P = 0.17$). For all nasal symptoms, the within-group VAS score decrease was significant in groups A and B (all P-values smaller than 0.04).

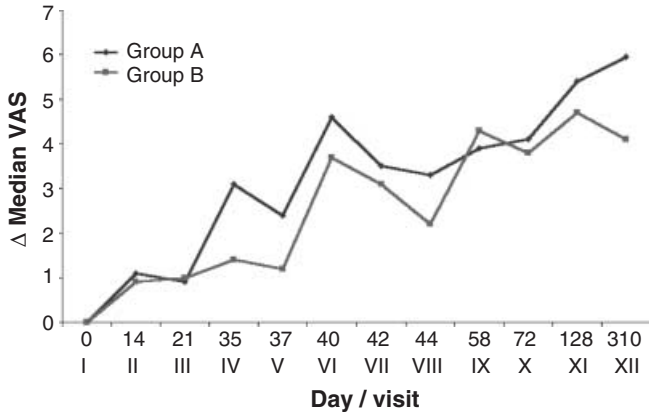


Figure 2. Improvement in median VAS for 'overall nasal symptoms'. Patients in group A were first treated with capsaicin five times on a single day at intervals of 1 h (visit 3). After 2 weeks, they received a total of five treatments with placebo once every second or third day (visits 4–8). Patients of group B first received placebo five times on a single day at intervals of 1 h (visit 3). This was followed two weeks later by a total of five treatments with capsaicin once every second or third day (visits 4–8). On every visit, they rated their 'overall nasal symptoms' on a visual analogue scale (0–10 cm). The change in median VAS score from visit 1 is shown. In both groups a significant improvement of overall nasal symptoms was observed. Note the improvement started within 2 weeks after start of the treatment with capsaicin (visit IV for group A and visit VIII/IX for group B).

Table 3. Baseline data

	Group A	Group B
Number of patients (male patients)	15 (6)	15 (8)
Age* (years)	33 (17–54)	37 (16–65)
VAS		
Overall nasal symptoms*	6.4 (2.5–9.5)	8.2 (2.8–9.7)
Rhinorrhea*	4.3 (0.1–9.1)	5.2 (0.2–9.6)
Obstruction*	6.7 (0.8–9.7)	7.2 (4.7–9.9)
Sneezing*	1.8 (0.1–7.9)	3.5 (0.0–9.7)
Epicritic sensibility*	2.5 (0.1–6.5)	4.6 (0.1–9.7)
Protopathic sensibility*	1.9 (0.3–6.5)	4.1 (0.3–9.8)
TMMCA 1† (cm^2)	1.3 (0.30)	1.0 (0.19)
TMMCA 2† (cm^2)	1.3 (0.39)	1.0 (0.40)
PNIF† (l)	172 (66)	147 (71)
CDA threshold dose* (l)	50 (12.5–200)	25 (12.5–400)
Capsaicin sensitivity* (M)	1.0×10^{-6} (4.6×10^{-8} to 4.6×10^{-6})	1.0×10^{-6} (4.6×10^{-8} to 2.2×10^{-6})

* Median (range).
† Mean (standard deviation).

Daily record chart. For rhinorrhea, a significant mean difference was found of 0.34 scale units (95% CI: 0.01–0.67; $P = 0.0424$) in favour of group A. A significant time effect was also found ($P = 0.0002$), showing a decrease in DRC score from baseline. There was no evidence of a time by group interaction ($P = 0.76$).

No significant difference between the groups was found for nasal blockage (95% CI: –0.38 to 0.30 scale units; $P = 0.81$). A significant time effect was found ($P = 0.0095$), showing a decrease in DRC score from baseline. There was no evidence of a time by group interaction ($P = 0.24$).

For all other DRC scores, no significant effects of time or treatment were found.

Smell

UPSIT. The mean UPSIT score at visit 2 was 30 for group A (SD = 7.5) and 29 for group B (SD = 4.9). At visit 11, the mean score was 32 for group A (SD = 4.6) and 29 for group B (SD = 7.6). No significant changes were found in either group ($P = 0.052$ for group A and $P = 0.67$ for group B). Also between the two groups no significant difference (B – A) in level was found (95% CI: –6.2 to 0.3; $P = 0.082$).

CDA hyperreactivity

Cold dry air provocation. The median of the threshold dose for cold dry air provocation for both groups is shown in Fig. 3. In each group, there was a significant change from baseline (visit 1) at posttreatment visits 10, 11 and 12 (all *P*-values smaller than 0.0001). There was no significant treatment by visit interaction ($P = 0.89$). Also no significant constant difference in level between the two groups (B – A) was found (95% CI: –1.6 to 0.3 doubling dose units; $P = 0.20$).

Nasal patency

Acoustic rhinometry. The TMMCA1 increased significantly over time for group A and almost significantly for group B: by 0.014 cm^2/week ($P = 0.0027$) for group A and by 0.009 cm^2/week ($P = 0.0596$) for group B. The difference (B – A) in time trend was not significant (95% CI: –0.018 to 0.007 cm^2/week; $P = 0.42$). Also no significant constant difference in level between the two groups (B – A) was found (95% CI: –0.06 to 0.07 cm^2; $P = 0.86$).

The TMMCA2 had no significant linear time trend in either treatment group ($P = 0.78$ for group A and $P = 0.87$ for group B). The difference in time trend (B – A) was not significant (95% CI: –0.018 to 0.017 cm^2/week; $P = 0.94$). Also no significant constant difference in level between the two groups (B – A) was found (95% CI: –0.05 to 0.13 cm^2; $P = 0.34$).

Peak nasal inspiratory flow. The time trend decreased by 0.12 l/s per week in group A ($P = 0.69$) and increased by 0.30 l/s per week in group B ($P = 0.30$). The time trend in either treatment group was not significant, nor was the difference (B – A) in time trend between the two treatment groups (95% CI: –0.39 to 1.21; $P = 0.31$). Also no significant constant difference in level between the two groups (B – A) was found (95% CI: –65 to 3 l/s; $P = 0.0732$).

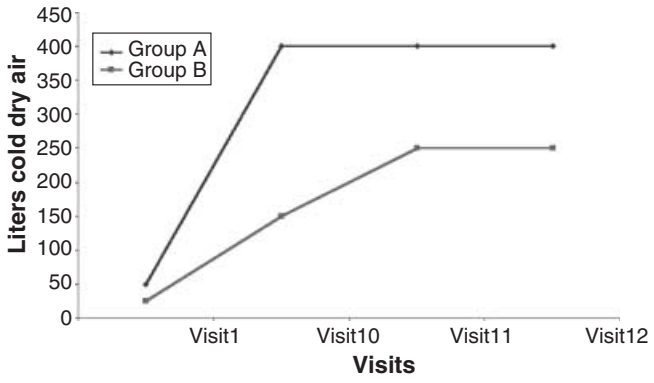


Figure 3. Median threshold dose for cold dry air. Patients in group A were first treated with capsaicin five times on a single day at intervals of 1 h (visit 3). After 2 weeks they received a total of five treatments with placebo once every second or third day (visits 4–8). Patients from group B first received placebo five times on a single day at intervals of 1 h (visit 3). This was followed 2 weeks later by five treatments with capsaicin once every second or third day (visits 4–8). Nasal reactivity was measured using standardized cold dry air provocation before (visit 1) and after (visits 10–12) therapy. The median threshold dose for cold dry air is shown.

Sensitivity/sensibility nasal mucosa

Capsaicin sensitivity. No significant differences were found (in either group) between capsaicin sensitivity concentrations during and after therapy compared with the capsaicin sensitivity concentration before therapy ($P > 0.42$). In addition, no significant differences between the two groups were found for all visits ($P > 0.09$).

Mucosal sensibility

No significant changes from baseline were found in either treatment group for either epicritic ($P = 0.44$ for group A and $P = 0.055$ for group B) and protopathic sensibility ($P = 0.57$ for group A and $P = 0.064$ for group B). No significant difference was found between the two therapy groups ($P = 0.51$ for epicritic and $P = 0.39$ for protopathic sensibility).

Safety

Blood pressure/heart rate. For heart rate, systolic and diastolic blood pressure, no significant effects of visit and group were found.

Discussion

In a recent double-blind placebo controlled study, we showed that repetitive capsaicin administration for a total of seven applications in 14 days gives a significant and long-term reduction of symptoms (15). The present study attempted to find a capsaicin application regimen that was more practical for both patient and doctor and at least equally effective as the previous one.

From our results, we can conclude that capsaicin treatment five times on a single day at intervals of 1 h (group A) is at least as effective as capsaicin treatment once every second or third day for a total of five treatments (group B). Some study parameters like the VAS scores for 'overall nasal symptoms', rhinorrhea and obstruction and the DRC score for rhinorrhea show even a significant better treatment effect for capsaicin treatment on a single day (group A).

A possible explanation for this is that, although the cumulative capsaicin dose was the same for both treatment groups, the concentration of capsaicin at the level of the nasal mucosa can reach much higher values for a longer period in the group that is treated five times in 1 day than in the group treated over a period of 5 days because of the wash-out effect in the latter group. This seems to be in agreement with the hypothesis that capsaicin leads to a selective degeneration/desensitization of peptidergic neurons in the nasal mucosa because higher concentrations of capsaicin for one longer time period can cause more degeneration/desensitization and reduce the opportunities for repair of these neurons than would be the case with five interrupted shorter periods. More effective degenerating/desensitising could mean that fewer neuropeptides will be released locally after irritating stimuli like cold dry air (anti-dromic effect). Also less sensory neural central stimulation might take place after irritating stimuli giving less central protective neural reflex mechanisms like secretion, extravasation and vasodilatation (ortho-dromic effect).

This provides an attractive explanation for the significant therapeutic capsaicin effect and the decrease in nasal hyperreactivity for cold dry air provocation.

Patients repeatedly treated with intranasal capsaicin solution are found to have reduced symptoms of pain and burning sensation with each successive capsaicin application as a sign of capsaicin desensitization (21). We had hoped to demonstrate, with our novel capsaicin sensitivity method, a decrease in capsaicin sensitivity after therapy as a result of the postulated capsaicin desensitization. However, this was not the case, perhaps because the instrument is not sensitive enough and misses small alterations. It is also possible that a learning effect in distinguishing between capsaicin and placebo masks a possible decrease in capsaicin sensibility. This latter phenomenon was observed in a group of normal individuals who were not treated with capsaicin but only repeatedly tested for capsaicin sensitivity (unpublished data).

Taking into account the results on the objective parameters of PNIF, acoustic rhinometry and CDA provocation in this study, it seems that the most important underlying pathophysiology that results in symptoms in IR patients is increased hyperreactivity of the nasal mucosa rather than decreased patency. This may also be an explanation for the correlation between the decrease in nasal reactivity measured by CDA provocation and nasal complaints, as well as for the absence of a significant change in PNIF and TMMCA2. Furthermore, it seems that the values of PNIF and acoustic rhinometry do not differ from values found in normal controls in other studies (22, 23).

During the trial, we paid a lot of attention to safety data in order to identify adverse side-effects. Because the concentration of capsaicin in the nasal mucosa could reach higher values in group A, a different, possibly more negative, effect on the safety data compared with group B was a possibility. We therefore collected values for blood pressure, heart rate, olfactory function and mucosal sensibility and compared them before and after treatment in and between the two groups. No significant differences were found so we conclude that local capsaicin application seems safe in both treatment regimens.

We conclude that local capsaicin nasal spray significantly reduces nasal complaints in IR patients and that five treatments of capsaicin on a single day is at least as effective as five treatments of capsaicin in 2 weeks, and even more effective in the reduction of nasal complaints measured with a VAS. We also conclude that intranasal capsaicin seems safe to use.

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