Allergy 2006: 61: 605–610

Copyright © Blackwell Munksgaard 2006

ALLERGY
DOI: 10.1111/j.1398-9995.2006.01073.x

Original article

The effect of salt chamber treatment on bronchial hyperresponsiveness in asthmatics

Background: Randomized controlled trials are needed to evaluate the effects of complementary treatments in asthma. This study assessed the effect of salt chamber treatment as an add-on therapy to low to moderate inhaled steroid therapy in asthma patients with bronchial hyperresponsiveness (BHR).
Methods: After a 2-week baseline period, 32 asthma patients who exhibited BHR in the histamine inhalation challenge were randomized: 17 to 2-week active treatment, during which salt was fed to the room by a salt generator, and 15 to placebo. The salt chamber treatment lasted 40 min and was administered five times a week.
Results: Median provocative dose causing a decrease of 15% in Fev_1 ($PD_{15}FEV_4$) increased significantly in the active group ($P = 0.047$) but not in the placebo group. The difference in changes between the active and placebo groups was significant ($P = 0.02$). Nine patients (56%) in the active group and two patients (17%) in the placebo group exhibited at least one doubling dose decrease in BHR ($P = 0.040$). Six patients (38%) in the active group and none in the placebo group became non-hyperresponsive ($P = 0.017$). Neither the peak expiratory flow (PEF) values measured just before and after the treatment, nor FEV_1 values measured before the histamine challenges, changed. The reduction in BHR was not caused by changes in the baseline lung function.
Conclusions: Salt chamber treatment reduced bronchial hyperresponsiveness as an add-on therapy in asthmatics with a low to moderate dose of inhaled steroids. The possibility that salt chamber treatment could serve as a complementary therapy to conventional medication cannot be excluded.

J. Hedman[1], T. Hugg[2], J. Sandell[2], T. Haahtela[3]

[1]Department of Pulmonary Diseases, South Karelia Central Hospital, Lappeenranta, Finland; [2]South Karelia Allergy and Environment Institute, Joutseno, Finland; [3]Department of Allergy, Helsinki University Central Hospital, Helsinki, Finland

Key words: asthma; bronchial hyperresponsiveness; complementary treatments; salt chamber; speleotherapy.

Dr J. Hedman
Department of Pulmonary Diseases
South Karelia Central Hospital
Valto Käkelänkatu 1
53130 Lappeenranta
Finland

Accepted for publication 13 January 2006

Complementary and alternative medicine is widely used in the treatment of asthma. However, data on the efficacy of these treatments are usually lacking. Randomized controlled trials are needed for exploring their possible effects (1, 2). They can also lead to undertreatment, and it is important to verify if they have any value in the treatment of asthma.

Bronchial hyperresponsiveness (BHR) gives valuable information on the patient's symptoms and airway inflammation (3). It has been used to assess the effect of some complementary treatments; e.g. Sahaga yoga has been shown to be beneficial (4) but short-term acupuncture therapy not so (5).

Subterranean environment therapy is called speleotherapy. Halotherapy is a form of speleotherapy, which makes use of the microclimatic conditions in a salt cave. Natural karst caves have been used for treating asthmatic patients in Germany, Switzerland, Hungary, Bulgaria, the former Yugoslavia and the former Soviet Union. The main therapeutic factors of speleotherapy in caves and mines are thought to be air quality, underground climate and radiation. Different combinations of temperature, relative humidity, pressure, radiation and aerosols are also vital elements.

The effects of salt mine treatment on health in the village of Solotvino, in the Carpathian Mountains have been investigated by Russian scientists. Natural dry sodium chloride dust which formed as a result of convection diffusion from salty walls was proposed to be the main microclimatic treatment factor. A 'halochamber' was constructed to simulate the microclimate of salt mines (6).

The Cochrane Database of Systematic Reviews evaluated the efficacy of speleotherapy in the treatment of asthma (7). It included controlled clinical trials that compared the clinical effects of speleotherapy with either another type of intervention or no intervention at all. Three trials on a total of 124 asthmatic children met the inclusion criteria, but only one trial had reasonable methodological quality (8). In the study by Novotny et al. (8), slight improvement of the lung function was observed at the end of the 3-week treatment period in the

speleotherapy group compared with the control group. In two other trials, it has been reported that speleotherapy had a beneficial short-term effect on lung function as well. It was not possible to assess any other outcome. The conclusion was that the available evidence is insufficient to show speleotherapeutic interventions as an effective treatment measure for chronic asthma. Randomized controlled trials with long-term follow up are necessary (7).

We assessed the effect of the salt chamber treatment as an add-on therapy in patients with persistent asthma who exhibited BHR in the histamine challenge in spite of a low to moderate inhaled steroid dose.

Material and methods

Patients

We selected adult patients who remained hyperresponsive in the histamine inhalation challenge in spite of regular treatment with inhaled steroids. Female and male asthmatics aged ≥18 years were eligible for inclusion if: (1) they used inhaled glucocorticosteroids at a constant daily dose of ≥200 μg for ≥30 days before entry; and (2) they were histamine challenge-positive ($PD_{15}FEV_1 \leq 1.6$ mg). Before the histamine challenge, they had to have a baseline forced expiratory volume in 1 s (FEV_1) of ≥70% predicted.

Exclusion criteria included respiratory infection or worsening of asthma within 30 days before entry into the study, current smoking or a history of smoking ≥10 pack-years, other respiratory disease, or severe dysfunction in other organs. Pregnant and lactating women, as well as women of childbearing potential unable to use acceptable contraceptives were excluded.

Subjects were recruited through a local newspaper advertizement (231 responses). After a telephonic interview with a research nurse and doctor, 153 patients were excluded (124 because of inclusion or exclusion criteria, while 29 subjects cancelled their participation before the histamine challenge). Seventy-eight asthmatics underwent a histamine inhalation challenge test for evaluatation of airway responsiveness (Fig. 1). Forty-six of the patients were challenge-negative and were hence excluded. Thirty-two patients (41%) were challenge-positive and were randomized in the study – 17 to the active salt chamber treatment and 15 to the placebo treatment. Baseline characteristics of study subjects are given in Table 1. Nine

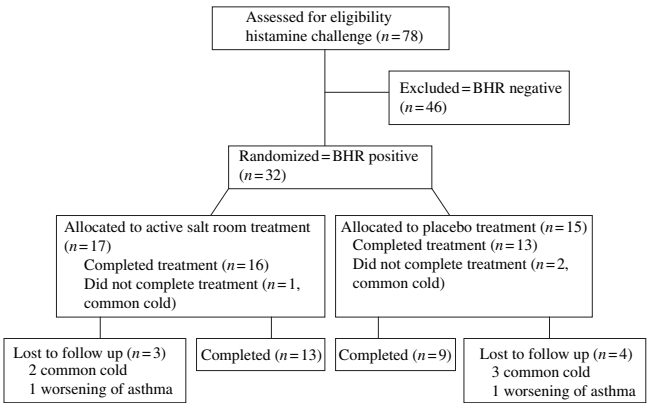


Figure 1. Flow of subjects through study.

Table 1. Baseline characteristics of the study subjects

	Active ($n = 17$)	Placebo ($n = 15$)
Age, years	53.2 (12.2)	52.1 (14.9)
Female, *n*	15	14
Atopy, *n**	10	9
Duration of asthma treatment, years	8.8 (5.9)	9.6 (7.2)
Inhaled steroid dose, mg†	0.894 (0.506)	0.733 (0.232)
Long-acting beta-2 agonist	9	6
FEV_1, l	2.61 (0.77)	2.54 (0.48)
FEV_1, % predicted‡	89.5 (17.1)	91.9 (8.5)
FVC, l	3.25 (0.97)	3.21 (0.54)
FVC, % predicted‡	90.4 (15.2)	95.6 (7.1)
Morning PEF, l/min	441 (78.2)	438 (68.7)
Evening PEF, l/min	455 (94.1)	448 (63.6)
$PD_{15}FEV_1$, mg	0.488 (0.407)	0.588 (0.407)
Short acting bronchodilator use, *n*/2 weeks	2.8 (2.8)	1.4 (2.2)
Nocturnal awakenings, *n*/2 weeks	2.9 (5.4)	0.4 (0.8)
Symptom score, 2 weeks	3.8 (5.2)	3.6 (5.0)

Data are presented as group mean (SD) values and patient numbers.
*Allergic rhinitis or atopic eczema reported by the subject.
†Expressed as bechlometasone equivalent dose (1.0 mg budesonide or 0.5 mg fluticasone equivalent to 1.0 mg bechlomethasone).
‡Viljanen et al. (9).

patients in the active group and six patients in the placebo group used long-acting beta-2 agonists but none of the subjects used aminophylline or leucotriene receptor antagonists. There were no significant differences between the groups.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The Ethics Committee of South Karelia Central Hospital approved the study protocol and all patients gave their written consent prior to the commencement of the study.

Study design

A parallel-group, double-blind, randomized placebo-controlled trial was conducted. After a 2-week baseline period, patients were randomized to either a 2-week active salt chamber treatment or the placebo. The randomization of patients was carried out in groups of four and the treatment was blinded to the patients, study nurse and investigator. Patients underwent 40 min of treatment every day, five times a week, in the salt chamber of Lappeenranta Spa.

Patients continued their original asthma medication throughout the study and the salt chamber treatment acted as an add-on therapy. If there was a need for increasing the steroid dose because of the worsening of the asthma, the patient was excluded from the study.

Conditions

The salt chamber was 12.5 m^2 in area with a volume of 27.5 m^3. The roof, walls and partly also the floor were covered with 20–50-mm-thick coating of salt (rock salt, NaCl 98.5%). Both the active and the placebo treatments were administered in the same salt chamber. During the active treatment, 3 g of salt was fed into the salt generator (Polar and Iris salt generator; Polar Health Oy, Nummela, Finland; IndiumTop LLC, Tallinn, Estonia) at intervals of 4 min, first being pulverized and then being blown into the chamber through the feed channel. Indoor dust emission, determined by isokinetic samples according to standard EN 13284-1 in the front of the feed channel, ranged from 1.6 to 3.3 mg/s (three measurements).

Table 2. Salt concentrations (mg/m^3) in the salt chamber

Measurements mean	Feeding speed of salt	Blasting volume of the salt generator	Concentration (mean range)
1	3 g/3 min	1/1	14.7
2	3 g/4 min	1/2	7.1 (5.9–8.4)
3	3 g/4 min	3/4	7.6 (6.7–8.1)
4	3 g/4 min	1/4	7.4 (7.3–7.5)

During the placebo treatment, salt was not fed into the salt generator. The generator was, however, running and patients could hear its sound.

The air blast volume of the salt generator and the feeding speed of the salt affected the salt concentration (Table 2). A feeding rate of 3 g every 4 min and a blasting volume of one-fourth of the salt generator resulted in conditions similar to those reported and used in treatment units of eastern and central parts of Europe (8).

The treatments were administered, on average, at a temperature of 23.0°C (range 18.0–27.3°C, $n = 304$) and at 41% relative humidity (range 25–51%, $n = 304$). Indoor air temperature (U-type thermistor probe; Grant Instruments Ltd, Shepreth, UK) and relative humidity values (Vaisala HMP 35 AG, Vaisala Oyj, Finland) were recorded with a datalogger (Squirrell 1000 series; Grant Instruments Ltd).

During the active treatment, the mean salt concentrations of the indoor air of the salt chamber fluctuated from 7.1 to 7.6 mg/m^3 (range 0–31.5 mg/m^3; $n = 7$). During the placebo treatment, the mean salt concentration was 0.3 mg/m^3 ($n = 3$). Salt concentrations were restored to zero level (0–1 mg/m^3, $n = 7$) during the 20 min of enhanced ventilation after each treatment period.

Stationary inhalable dust samples were collected with IOM (SKC Inc., Eighty Four, PA, USA) samplers. The sampling head is designed to meet the ACGIH and EN 481 criteria for inhalable dust at a sampling flow rate of 2.0 l/min. Time-dependent variation of dust concentrations was measured with a Respicon TM-SE (Helmut Hund GmbH, Wetzlar, Germany). The sampler is designed to meet the ACGIH and EN 481 criteria for size-selective sampling of occupational dusts. Particle size distribution was determined by a six-stage cascade impactor. The cut-off points were 10, 5, 2.5, 1.3, 0.65 and 0.3 μm at a sampling rate of 20 l/min. Salt dust concentration, time-dependent variation of salt dust concentration and particle size distribution were measured 1 m above the ground between the seats. While the measurements were being taken, one to four persons stayed in the chamber, simulating the treatment protocol. A particle size < 5 μm (aerodynamic diameter) constituted 35–45% of the total particle mass, and a particle size < 20 μm correspondingly 88–97% ($n = 4$). Depending on the measurement time, the median of the particle size distribution ranged from 6 to 8 μm ($n = 4$). According to the measurements, both the salt dust concentration and particle size distribution were evenly distributed inside the chamber. Measurement of the conditions was carried out by the Lappeenranta Regional Institute of Occupational Health.

Outcome measurements

The main outcome parameter was BHR. Patients underwent a histamine inhalation challenge three times: at the baseline, at the end of the 2-week treatment, and 2 months after the treatment. The study was conducted outside the pollen season.

The histamine challenge method has been described in detail elsewhere (10). In short, an automatic inhalation-synchronized dosimetric jet nebulizer with the known lung deposition of the aerosol was used to administer histamine and to control breathing (Spira Elektro 2; Respiratory Care Center, Hämeenlinna, Finland). The non-cumulative doses of histamine were 0.025, 0.1, 0.4 and 1.6 mg, administered within 0.4 s following the tidal inspiration of 100 ml of air. FEV_1, measured with flow/volume spirometry (Medikro, Kuopio, Finland), was used to determine the response. The $PD_{15}FEV_1$ was calculated from logarithmically transformed histamine doses using linear interpolation.

Peak expiratory flow (PEF) measurements, use of a rescue bronchodilator (puffs per 24 h) and asthma symptoms (wheezing, dyspnoea), were recorded each morning and evening by the patients on diary cards during the study. The number of nocturnal awakenings were also recorded. Wheezing and dyspnoea were each graded on a scale of 0–3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). Total asthma symptom score (on a scale of 0–6) was the sum of wheezing and dyspnoea scores. Baseline diary data for 2 weeks were collected before randomization. The PEF was measured using a mini-Wright peak flow meter (Clement Clark, Harlow, UK), and the highest of three values was recorded. The PEF was also measured just before and after salt chamber treatment.

Statistical analyses

Non-parametric statistics were mainly used. A comparison of the active and placebo groups was made using either the Mann–Whitney *U*-test or the Fischer's exact test, as appropriate. The Wilcoxon signed-rank test was used to analyse the effect of treatments in the two groups. A per-protocol analysis (excluding all participants who failed to complete the protocol) was also carried out using paired (within-treatment effect) and unpaired (between-treatment effect) *t*-tests. If a patient was a non-responder ($PD_{15}FEV_1 > 1.6$ mg) in the 2-week or in the 2-month histamine challenge, an arbitrary $PD_{15}FEV_1$ value of 3.2 mg was used. A *P*-value of < 0.05 was considered statistically significant. All tests were performed using GBSTAT software Version 6.5 (Dynamic Microsystems, Silver Spring, MD, USA).

Results

Sixteen asthmatics in the active group and 13 in the placebo group completed the 2-week salt chamber treatment. One patient in the active group and two in the placebo group failed to complete the treatment (all because of respiratory infections).

Bronchial hyperresponsiveness

After the 2-week treatment, the median $PD_{15}FEV_1$ value increased significantly in the active group but decreased in the placebo group compared with the baseline. In the active group, median (range) the $PD_{15}FEV_1$ value before and after treatment was 0.460 mg (0.020–1.57) and 0.595 mg (0.022 to > 1.6) ($P = 0.047$); and in the placebo group 0.720 mg (0.016–1.42) and 0.630 mg (0.085–1.25) ($P > 0.05$). The difference between the changes occurring during the treatment with the salt chamber and the placebo was significant ($P = 0.02$) (Table 3).

The BHR decreased by at least one doubling dose in nine patients (56%) in the active group and in two patients (17%) in the placebo group (Fischer's exact,

Table 3. Per-protocol analysis of changes in spirometric indices, PEF values, bronchodilator use, nocturnal awakenings and symptom scores over 2 weeks active and placebo salt chamber treatment

	Active ($n = 16$)	Placebo ($n = 13$)	Active *vs* placebo difference
FEV_1, l	0.04 (−0.18 to 0.10)	0.01 (−0.08 to 0.06)	0.03 (−0.12 to 0.18)
FVC, l	−0.04 (−0.07 to 0.15)	−0.04 (−0.05 to 0.13)	0.001 (−0.13 to 0.13)
Morning PEF, l/min	7.0 (−0.09 to 14.1)	4.4 (−6.0 to 14.7)	2.7 (−9.3 to 14.7)
Evening PEF, l/min	9.3 (2.7 to 15.8)**	4.0 (−5.4 to 13.4)	5.5 (−5.6 to 16.4)
Treatment PEF, l/min	0.8 (−2.5 to 4.1)	4.0 (−0.8 to 8.8)	−3.1 (−8.6 to 2.4)
Short-acting bronchodilator use, *n*/2 weeks	1.5 (−0.2 to 3.2)	1.1 (−0.2 to 2.3)	0.4 (−1.6 to 2.4)
Nocturnal awakenings, *n*/2 weeks	2.2 (0.4 to 4.0)*	0.2 (−0.2 to 0.7)	2.0 (0.1 to 3.8)
Symptom score, 2 weeks	1.7 (−1.6 to 4.9)	2.5 (−0.8 to 5.9)	−0.9 (−5.3 to 3.6)

*$P < 0.05$, **$P < 0.01$ (within-group difference from baseline).

$P = 0.040$). Six patients (38%) in the active group and none in the placebo group became non-responsive to histamine (Fischer's exact, $P = 0.017$). The changes in the individual BHR in the active and placebo groups are given in Fig. 2.

A follow-up histamine challenge was performed 2 months after the salt chamber treatment. There were three dropouts in the active group (two due to common cold and one to worsening of asthma) and four dropouts in the placebo group (three due to common cold and one to worsening of asthma). In the active group, the median (range) $PD_{15}FEV_1$ value was 0.580 mg (0.067 to >1.6) and in the placebo group 0.620 mg (0.110 to >1.6). There were no more significant changes compared with the baseline in the within-group or in the between-group analyses. Four of 13 patients in the active group and one of nine patients in the placebo group were non-responsive to histamine ($PD_{15}FEV_1$ >1.6 mg) ($P > 0.05$).

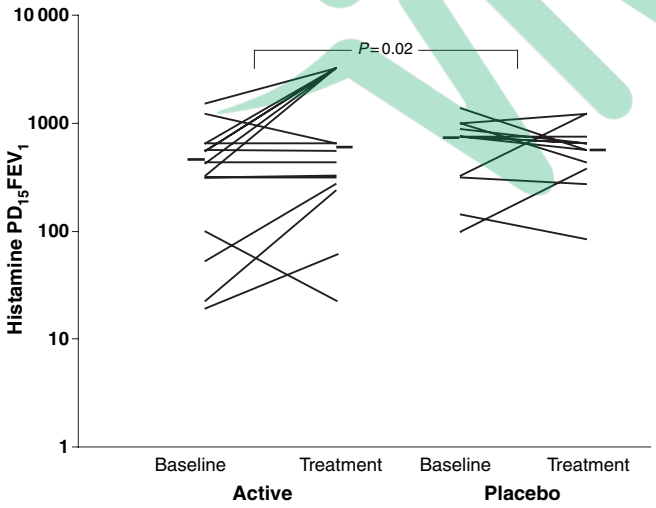


Figure 2. Changes in airway responsiveness to histamine in the active and placebo salt chamber treatment groups. $PD_{15}FEV_1$ (μg histamine) at baseline and after the 2-week treatment. An arbitrary value of 3200 μg was used in subjects who were challenge-negative. Thick lines represent median values.

Other outcome measures

Changes in spirometric indices, PEF values, bronchodilator use, nocturnal awakenings and symptom scores over 2 weeks of active and placebo salt chamber treatment are given in Table 3. No significant changes in between-group analysis were observed. Statistical significant differences in evening PEF values ($P = 0.0085$) and in nocturnal awakenings ($P = 0.020$) were detected in within-group analysis of active group.

Discussion

This study is the first controlled trial investigating the effect of salt chamber treatment on BHR. A 2-week salt chamber treatment reduced BHR as an add-on therapy on a low to moderate dose of inhaled steroids.

The number of patients was small, which increases the risk of error due to chance, and hence our results should be taken as preliminary only. BHR did not differ statistically between active and placebo groups in the baseline. There is, however, a more reactive group in the active treatment group and therefore any change could tend to favour the active group. Being in a trial environment may also have helped compliance and this would have again favoured the active treatment group. The 2-week baseline period may have been the factor leading to an apparent improvement, too. The duration of the effects on BHR and asthma control cannot be reliably estimated as the sample size became too small during the 2-month follow-up. As respiratory viral infections may increase BHR (11), these patients were excluded from the follow-up.

The mechanisms of the effect of salt chamber treatment are unclear and can only be speculated. BHR is a surrogate marker of bronchial inflammation. Sont et al. have stressed the value of a methacholine challenge in guiding treatment; reducing BHR leads to better control of asthma (12). Airway responsiveness to direct bronchoconstrictor stimulus as histamine or methacholine is, however, only loosely related to inflammation (13, 14). Further studies are needed to assess the effect of salt

chamber treatment on more direct inflammatory parameters (e.g. exhaled NO or inflammatory markers in induced sputum).

Airway calibre depends on the balance between the force generated by airway smooth muscle (ASM) and a number of opposing factors, mainly autonomic nervous mechanisms tending to limit ASM tone and mechanical forces opposing ASM shortening (15). Salt chamber treatment did not cause any bronchodilation. Neither the PEF values measured just before and after the treatment, nor the FEV_1 values measured before the histamine challenges changed. Therefore, the reduction in BHR was not caused by changes in baseline lung function as could have been one possible explanation (16, 17).

Bronchial hyperresponsiveness can be reduced by directly affecting airway smooth muscle contractility (18). Some cytokines may act directly or indirectly on ASM cells and alter myocyte function by modulating contractile agonist-induced calcium signalling in human ASM cells (18). There is also a strong positive correlation between bronchial reactivity and the level of intracellular magnesium: magnesium intervenes in the calcium transport mechanism and intracellular phosphorylation reactions (19). Whether these mechanisms are involved in the salt chamber treatment is unknown.

Inhalation of hypertonic saline can cause bronchoconstriction (20). Dry powder sodium chloride has even been used to assess BHR in asthmatics (21). As the resting ventilation is 6–10 l/min, the NaCl dose inhaled by the patients during a 40-min treatment period was about 18–30 mg. This is less than the provocative dose of NaCl causing the FEV_1 to fall 20% from the baseline in an inhalation challenge test using dry NaCl (mean 103 mg) in the study by Andersson et al. (22). It is also far less than the daily sodium intake of female (2.36 g) and male (3.15 g) asthmatics in the study by Sausenthaler et al. (22). In that study, the sodium intake did not alter BHR assessed as PD_{20} to methacholine but might have increased mild BHR assessed as PD_{10} (22). In our study, no bronchoconstriction because of the salt chamber treatment was observed. It is, however, possible that increasing salt concentrations eventually cause bronchoconstriction in sensitive individuals. Salt inhalation may have a U-shaped effect, small and moderate doses being beneficial but higher doses causing adverse effects.

It is possible that the symptomatic relief the patients reported from salt chamber treatment is associated with the reduction in BHR. All patients used inhaled steroids but still showed a reduction in BHR to an extent which is not easy to attain by any drug treatment. The idea that salt chamber treatment could serve as a complementary therapy to conventional medication cannot be ruled out. No side-effects were observed.

Salt chamber treatment is, however, neither simple nor cost-free. The conditions in the individual salt chambers should be measured and standardized as we did in our study. The possible dose–response effect of salt concentrations should be studied in further trials. The optimum duration or regularity of treatments needed are not known. In practice, the length of individual salt treatments vary widely from 20 min to hours and last five to 25 sessions. The length and regime of our study mirrors the common practice in Estonia and in the salt chamber of Lappeenranta Spa. Health economic aspects should be evaluated. There might be benefits linked to the better control of asthma and reduced use of asthma medication. Expenses linked to the salt chamber treatment, as well as travel costs to the treatment centres, should be evaluated. In future studies, the cost benefit should be compared with other treatment modalities, including the improvement of existing drug treatment.

Acknowledgments

The authors would like to thank K. Mynttinen and J. Paananen for assistance and S. Rautio for the measurement of conditions. The study was supported by research grants from Finland's Slot Machine Association and The Social Insurance Institution of Finland.

References

1. Bielory L. Replacing myth and prejudice with scientific facts about complementary and alternative medicine. Ann Allergy Asthma Immunol 2002;**88**:249–250.
2. Gyorik SA, Brutsche MH. Complementary and alternative medicine for bronchial asthma: is there new evidence? Curr Opin Pulm Med 2004;**10**:37–43.
3. Banik AN, Holgate ST. Problems and progress in measuring methacholine bronchial reactivity. Clin and Exp Allergy 1998;**28**(Suppl. 1):15–19.
4. Manocha R, Marks GB, Kenchington P, Peters D, Salome CM. Sahaja yoga in the management of moderate to severe asthma: a randomised controlled trial. Thorax 2002;**57**:110–115.
5. Shapira MY, Berkman N, Ben-David G, Avital A, Bardach E, Breuer R. Short-term acupuncture therapy is of no benefit in asthma with moderate persistent asthma. Chest 2002;**121**:1396–1400.
6. Chervinskaya AV, Zilber NA. Halotherapy for treatment of respiratory diseases. J. Aerosol Med 1995;**8**:221–232.
7. Beamon S, Falkenbach A, Fainburg G, Linde K. Speleotherapy for asthma (Cochrane Review). The Cochrane Library, Issue 4. Chichester: John Wiley & Sons, Ltd, 2004.
8. Novotny A, Krämer E, Steinbrugger B, Fabian J, Eber E, Sandri B et al. Der therapeutische Einfluss von Radon-Inhalation und Hyperthermie im Gasteiner Heilstollen auf das Asthma bronchiale im Kindesalter. Die Höhle 1994;**48**(Suppl.):198–202.

9. Viljanen AA, Haittunen PK, Kreus KE, Viljanen BC. Spirometric studies in nonsmoking, healthy adults. Scand J Clin Lab Invest 1982;**42**(Suppl. 159):5–20.
10. Sovijärvi ARA, Malmberg P, Reinikainen K, Rytilä P, Poppius H. A rapid dosimetric method with controlled tidal breathing for histamine challenge. Repeatability and distribution of bronchial reactivity in a clinical material. Chest 1993;**104**:164–170.
11. Grunberg K, Smits HH, Timmers MC, de Klerk EP, Dolhain RJ, Dick EC et al. Experimental rhinovirus 16 infection. Effects on cell differentials and soluble markers in sputum in asthmatic subjects. Am J Respir Crit Care Med 1997;**156**:609–616.
12. Sont JK, Willems LNA, Bel EH, van Krieken JHJM, Vandenbroucke JP, Sterk PJ, AMPUL Study Group. Clinical control and histopathology outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. Am J Respir Crit Care Med 1999;**159**:1043–1051.
13. Crimi E, Spanevello A, Neri M, Ind PW, Rossi GA, Brusasco V. Dissociation between airway inflammation and airway hyperresponsiveness in allergic asthma. Am J Respir Crit Care Med 1998;**157**:4–9.
14. Cockcroft DW. How best to measure airway responsiveness. Am J Respir Crit Care Med 2001;**163**:1514–1515.
15. Brusasco V, Crimi E, Pellegrino R. Airway hyperresponsiveness in asthma: not just a matter of inflammation. Thorax 1998;**53**:992–998.
16. Hogg JC, Pare PD, Moreno R. The effect of submucosal edema on airway resistance. Am Rev Respir Dis 1987;**135**:54–56.
17. James A, Ryan G. Testing airway responsiveness using inhaled methacholine or histamine. Respirology 1997;**2**:97–105.
18. Amrani Y, Panettieri RA Jr. Cytokines induce airway smooth muscle cell hyperresponsiveness to contractile agonists. Thorax 1998;**53**:713–716.
19. Dominguez LJ, Barbagallo M, Di Lorenzo G, Drago A, Scola S, Morici G et al. Bronchial reactivity and intracellular magnesium: a possible mechanism for the bronchodilating effects of magnesium in asthma. Clin Sci 1998;**95**:137–142.
20. Covar RA, Spahn JD, Martin RJ, Silkoff PE, Sundstrom DA, Murphy J et al. Safety and application of induced sputum analysis in childhood asthma. J Allergy Clin Immunol 2004;**114**:575–582.
21. Anderson SD, Spring J, Moore B, Rodwell LT, Spalding N, Gonda I et al. The effect of inhaling a dry powder of sodium chloride on the airways of asthmatic subjects. Eur Respir J 1997;**10**:2465–2473.
22. Sausenthaler S, Kompauer I, Brasche S, Linseisen J, Heinrich J. Sodium intake and bronchial hyperresponsiveness in adults. Respir Med 2005;**99**:864–870.

VIVASALT