

Effect of alterations of dietary sodium on the severity of asthma in men

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Abstract

Background—There is some evidence of a positive association between increased dietary salt consumption and both increased bronchial reactivity and mortality from asthma in men. This study assesses the effects of alterations in dietary salt consumption on the clinical severity of asthma in adult male asthmatic patients.

Methods—A randomised, double blind, placebo controlled, crossover design was employed. Twenty seven mild to moderate asthmatic patients were established on a low sodium diet (80 mmol/day) at the end of a 4-5 day run in period and then randomised to receive 200 mmol/day slow sodium or matching placebo for five weeks, crossing over to the alternative regime for a further five weeks. Patients used diary cards to record twice daily peak expiratory flow rates, daily symptom scores, and bronchodilator consumption. Spirometry and degree of bronchial responsiveness (methacholine challenge test) were measured at screening and at the end of each treatment period. Twenty four hour urinary sodium excretion was measured at screening and in duplicate for each treatment period.

Results—Twenty two patients completed the study. For these patients the mean (95% confidence interval (CI)) difference in 24 hour sodium excretion between treatments was 204 (175 to 235) mmol. Compared with placebo, sodium supplementation resulted in deleterious alterations of all measured parameters. Bronchial reactivity rose on slow sodium with a 0.73 (0.2 to 1.3) doubling dose methacholine difference compared with placebo. Estimated median (95% CI) difference in bronchodilator consumption was 1.3 (0.4 to 2.1) puffs per day, the estimated median difference in symptom score was 0.6 (0.2 to 0.9), and mean forced expiratory volume in one second fell by 0.21 (0.05 to 0.37) l. The peak expiratory flow rate rose on placebo and fell on slow sodium. Median differences between treatments were 5.6% (2.2% to 9.8%) for morning and 7.8% (3.9% to 12.9%) for evening peak expiratory flow rate.

Conclusions—Our results suggest that large increases in dietary sodium result in physiological deterioration and increased morbidity in male asthmatic patients.

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There is a strong association between regional figures for mortality from asthma and purchases of table salt per person for adult men and children of both sexes (but not adult women) in England and Wales.¹ The degree of bronchial responsiveness to histamine is positively correlated with the 24 hour urinary sodium excretion in men² and rises with increased dietary sodium.^{3,4} Severity of asthma correlates with the degree of bronchial responsiveness⁵ and it is therefore possible that the severity of asthma can be influenced by alterations in dietary sodium consumption. This study was designed to assess the effect of changes in dietary sodium on the severity of symptoms of asthma, bronchodilator requirements, lung function, and bronchial responsiveness to methacholine.

Methods

SUBJECTS

Twenty seven stable male asthmatic patients aged between 12 and 68 years were recruited with consent from their general practitioners. All gave a history of intermittent wheeze, shortness of breath, and chest tightness relieved by bronchodilator therapy, had previously been given a diagnosis of asthma, and were taking asthma medication at the time of the study. Only one gave a history of smoking and he had stopped several years previously.

All were taking inhaled β sympathomimetic agonists and 12 inhaled corticosteroids. Four were taking inhaled sodium cromoglycate and three oral theophyllines. No patient was using oral β agonists, antihistamines, or steroids at the time of the study.

The patients gave written informed consent to the study which was approved by the local ethics committee.

STUDY DESIGN

A double blind randomised crossover design was used to compare sustained release

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sodium (slow sodium) with placebo in patients receiving a low sodium diet.

Assessment

Before entry subjects underwent clinical examination and blood was taken for routine haematological and biochemical analysis. Discretionary chest radiographs and electrocardiograms were performed. No subject was entered into the study who had a history of or clinical or laboratory evidence of renal, hepatic, cardiovascular disease, hypertension, or electrolyte imbalance, or who was taking diuretic therapy.

Randomisation

Paired treatment courses were assigned a unique number from 1 to 30. Each number coded for placebo treatment crossing to slow sodium or vice versa was allocated by a random draw. At randomisation patients were consecutively assigned a treatment number starting at 1.

Protocol

At the initial assessment a methacholine challenge test was performed (see below) and subjects were instructed in the use of a peak flow meter (mini-Wright) and diary card. After 4–5 days, during which patients recorded peak flow rates (PEF) and collected a 24 hour specimen of urine for sodium analysis, they were placed on a low sodium diet (80 mmol supervised by a dietician) and randomised to receive either slow sodium (200 mmol daily in two doses) or matching placebo for five weeks, followed by the alternative regimen for a further five weeks. Subjects recorded morning and evening PEF (best of three) and completed the diary cards recording symptoms and bronchodilator consumption daily throughout the 10 week study period. Forced expiratory volume in one second (FEV₁, best of three) and methacholine challenge tests were performed at weeks 5 and 10, and 24 hour urine samples were collected at weeks 3, 5, 8, and 10.

Subjects were asked to use inhaled bronchodilators on an "as required" rather than a regular basis and all other medication was kept constant during the study period. They were asked not to use Ventolin within four hours of PEF recordings where possible.

Symptom scores

Daily symptom scores were recorded on a scale from 0 to 5 where 0 = no symptoms and 5 = symptoms so severe that the patient either could not go to work or could not perform normal daily activities.

Methacholine challenge tests

Airway responsiveness to methacholine was measured by the method of Yan *et al.*⁶ Subjects were asked to avoid inhaled bronchodilators for six hours and oral theophyllines for at least 12 hours before the challenge tests. Baseline FEV₁ was measured with a dry wedge spirometer (Vitalograph, Buckingham UK). Subjects then inhaled three puffs of

saline from a DeVilbiss No 40 hand held nebuliser (delivering 0.0025–0.0035 ml per actuation) followed by incremental doubling doses of methacholine from 0.012 μ mol to a maximum of 12.24 μ mol or until a 20% fall in FEV₁ from the maximum value after saline was recorded. Spirometry was repeated at one minute intervals after each dose.

All subsequent bronchial challenge tests on an individual subject were performed at the same time of day.

24 hour urine specimens

On receipt of specimens the volume was measured and concentrations of sodium and potassium were measured by ion specific electrodes. Creatinine was measured by a modified Jaffe rate reaction.

ANALYSIS

Comparisons between placebo and slow sodium were made for symptom scores, bronchodilator consumption, and PEF values using combined data for all daily recordings from the last 21 days of each treatment period. A two week washout period was effectively introduced by this strategy. Available data did not allow comparisons with pretrial baseline results for symptom scores and bronchodilator consumption.

Analysis of variance for repeated measures (SPSS) revealed a significant treatment/period interaction for the paired PEF data. These data were therefore analysed as parallel groups for the first period only ($n = 11$ for both slow sodium and placebo). The percentage change of the mean of the 21 PEF recordings for individuals from their pretrial baseline value was analysed by the Mann-Whitney two sample test. Percentage change was used to provide a relative measure as the groups were not well matched at baseline. The pretrial values were taken as the mean of the four days' recordings before randomisation. PEF recordings made within four hours of using bronchodilator were omitted from analysis.

Between treatment comparisons of FEV₁ and PD₂₀ methacholine (dose of methacholine producing a 20% fall in FEV₁ from the post saline value) were compared by the paired Student's *t* test (after logarithmic transformation of reactivity data). The PD₂₀ methacholine was calculated by linear interpolation on a plot of percentage fall in FEV₁ from the post saline value against the dose of methacholine on a logarithmic scale.

Creatinine excretion was used to assess the completeness of 24 hour urine samples, those showing excretion relative to body mass outside the laboratory reference range being excluded from analysis.

With the exception of the peak flow data our analyses detected no significant period or sequence of treatment effects or interactions.⁷

Results

Twenty two subjects of mean age 36 (range 12–68) years completed the study. Five were

Changes in sodium excretion, lung function, reactivity, symptoms, and bronchodilator consumption

Measurement	Baseline (n = 22)	Low sodium diet + slow sodium (n = 22)	Low sodium diet + placebo (n = 22)
Mean (SD) 24 hour urinary sodium excretion (mmol)	159 (42)	292 (68)	88 (31)****
Mean (SD) FEV ₁ (l)	2.68 (1.2)	2.61 (1.2)	2.82 (1.2)*
Geometric mean PD ₂₀ (μmol) (range)	0.53 (0.05–7.00)	0.39 (0.03–9.00)	0.65 (0.05–6.20)*
Median daily symptom score (25th to 75th percentiles)	–	2.0 (1.5 to 2.9)	1.5 (0.7 to 2.0)**
Median puffs per day of bronchodilator (25th to 75th percentiles)	–	5.9 (3.9 to 8.3)	5.0 (3.6 to 7.3)**

FEV₁—forced expiratory volume in one second; PD₂₀—dose of methacholine producing a 20% fall in FEV₁; *p < 0.05; **p < 0.01; ****p < 0.0001 for differences between slow sodium and placebo.

withdrawn from the study during the first period, one because of exacerbation (while taking slow sodium), and four because of poor compliance.

SODIUM CONSUMPTION

Compared with baseline mean (95% CI) 24 hour sodium excretion rose by 133 (99 to 168) mmol on slow sodium (p < 0.0001) and fell on placebo by 71 (46 to 97) mmol (p < 0.0001). The difference in sodium excretion between placebo and sodium supplements was 204 (175 to 235) mmol (p < 0.0001). All indices measured showed significant improvements with placebo compared with slow sodium (table).

LUNG FUNCTION

FEV₁

There was a mean rise in FEV₁ of 0.21 l (8%) on placebo compared with slow sodium (p < 0.05). Compared with the pretrial baseline, mean FEV₁ rose on placebo by 0.14 (95% CI 0.03 to 0.25) l (5%) (p < 0.05) and

fell on slow sodium by 0.07 (–0.22 to 0.07) l (2.6%) (p > 0.1).

PEF

Changes in PEF over time by treatment group for the first period are shown in the figure. PEF rose on placebo and fell on slow sodium. The results according to the planned analysis of combined data for weeks 3–5 are set out below.

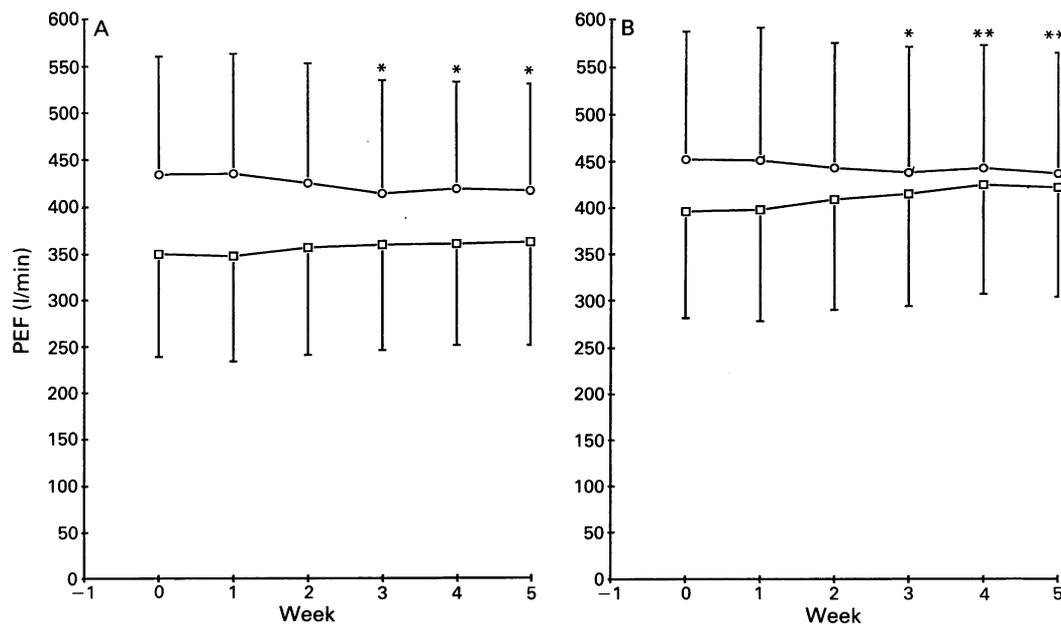
Morning PEF: the mean (SD) morning PEF on placebo (n = 11) rose from 352 (111) l/min at baseline to 361.5 (112) l/min. The mean morning PEF for the slow sodium group (n = 11) fell from 434 (126) l/min at baseline to 419 (116) l/min. In terms of percentage change from baseline the placebo group showed a median (25th to 75th percentiles) increase of 2.6% (–3.0% to 6.1%) compared with a fall of 3.2% (–6.7% to 0.6%) for the slow sodium group. The median (95% CI) difference between treatments was 5.6% (2.2% to 9.8%) (p < 0.05).

Evening PEF: the mean (SD) evening PEF on placebo rose from 396 (115) l/min at baseline to 420 (117) l/min. The slow sodium group showed a fall from 452 (135) l/min at baseline to 439 (133) l/min. The median (25th to 75th percentiles) percentage changes from baseline were thus +4.0% (1.6% to 8.4%) for placebo and –4.5% (–4.8% to 0.9%) for slow sodium. The median (95% CI) difference was 7.8% (3.9% to 12.9%) (p < 0.01).

BRONCHODILATOR CONSUMPTION AND SYMPTOM SCORE

Overall there was an estimated median (95% CI) reduction in bronchodilator consumption of 1.3 (0.4 to 2.1) puffs per day (p < 0.01) for placebo compared with slow sodium. Correspondingly, in comparison with slow sodium there was a decrease in estimated median symptom score on placebo of 0.6 (0.2 to 0.9) (p < 0.01).

Mean (SD) peak expiratory flow rate (PEF) by study week (± one day) in (A) morning and (B) evening. *p < 0.05 and **p < 0.01 for differences between sodium and placebo (% change from baseline). □, placebo; ○, sodium.



BRONCHIAL REACTIVITY

Geometric mean (range) PD_{20} was 0.53 (0.05–7.00) μmol at baseline. This fell on slow sodium to 0.39 (0.03–9.00) μmol and rose on placebo to 0.65 (0.05–6.20) μmol . The difference between slow sodium and placebo was equivalent to 0.73 (95% CI 0.2 to 1.3) doubling doses methacholine.

Discussion

Recent epidemiological evidence indicates an association between mortality from asthma and high dietary sodium intake.¹ Subsequent experiments have shown that bronchial reactivity is increased on high sodium diets.^{3,4} This evidence is clearer for men than for women as it is for the relationship between sodium and hypertension. For this reason we confined our study to male asthmatic patients.

A change from a high sodium to a low sodium intake resulted in reduced bronchial reactivity, bronchodilator requirements, and symptoms, with concurrent improvement in lung function. The daily PEF recordings suggest that most of the effects occurred in weeks 2 and 3 after dietary change. There were little or no additional effects observed beyond the third week. The changes in PEF were sustained to week 5 indicating no tendency toward tolerance.

Our study was not strictly designed to assess the effect of reductions of dietary sodium from normal ranges and we lack useful baseline data on bronchodilator consumption and symptom scores. Initiation of a low sodium diet was likely to affect dietary factors in addition to sodium. In order to make relatively unconfounded comparisons between baseline and the two treatment periods, a prolonged single blind run in period would have been necessary. Such a protraction may have jeopardised the study because of a fall off in compliance or greater loss of subjects.

Comparisons with baseline data should be made with caution for these reasons, and the possible effects of unblinded patient/observer assessment bias and modification of patient behaviour on entry to a research study—for example, increased compliance with usual therapy.

Notwithstanding these potential problems, comparisons between baseline and the low and high sodium treatments suggest a continuous dose-response effect. Although the magnitude of the improvements with a low sodium diet (placebo) compared with sodium supplement may be clinically useful, the changes in peak flow, FEV_1 and bronchial reactivity from baseline to placebo were modest. The changes observed for these parameters were less than would be expected for seasonal alterations⁸ and low dose budesonide treatment.⁹ These results indicate that sodium restriction as a therapeutic intervention may only be of use in asthmatic patients with high daily sodium intakes. The normal range of daily sodium excretion for British adults is 100–250 mmol.¹⁰ The probable degree of sodium restriction necessary to

achieve a useful response, and the limited number of asthmatic subjects for whom such restriction would be appropriate or tolerated further, lessens the therapeutic usefulness of sodium restriction.

Our findings do not agree with those of Lieberman and Heimer¹¹ who found no change in PEF with alterations in dietary sodium in an open crossover study. Their negative findings may be explained by differences in study design and patient selection. Their treatment periods were considerably shorter and no washout intervals were included between treatments. The changes in sodium intake were smaller than in our study. Fewer patients were studied and half were women who, previous work would suggest, are less likely to show a response. No other measures of asthma were assessed which may have helped to qualify the findings in PEF.

The mechanism of the effect of dietary sodium on bronchial reactivity is unknown. Animal experiments have shown that the hyperreactivity of sensitised bronchial smooth muscle is associated with an exaggerated influx of sodium across the cell membranes.¹² It is possible that this inhibits the exchange mechanism of sodium and calcium ions¹³ resulting in raised intracellular calcium and thus increased contractility. High sodium consumption may enhance this abnormality. High sodium intake has been shown to inhibit Na^+/K^+ ATPase in erythrocytes of normotensive males.¹⁴ The resulting inhibition of the Na^+/K^+ pump would be expected to increase levels of intracellular sodium and, in turn, to increase intracellular calcium via inhibition of Na^+/Ca^{++} exchange. Increased airway smooth muscle contractility with pump inhibition is supported by animal experiments,^{15,16} but has not been shown in studies in human subjects.¹⁷

Intracellular calcium concentrations influence aspects of inflammatory cell functions.¹⁸ High calcium levels would tend to result in hyperexcitability providing an alternative or additional speculative explanation for physiological deterioration in asthmatic subjects as the result of increased sodium loads.

The mechanism of Na^+/K^+ ATPase inhibition is unclear and may be due directly or indirectly to hormonal or chemical changes associated with increased sodium loads, or to changes in physical properties of cell membranes with intravascular volume expansion. Plasma sodium levels change little with alterations in intake. It is therefore unlikely that the effects observed are due to the direct effects of sodium.

The association between dietary salt and asthma may help to explain geographical variations in the prevalence of asthma and the rise in prevalence in underdeveloped populations as they adopt a western lifestyle.¹⁹ While research continues to unravel the mechanisms of physiological changes due to alterations in dietary sodium, further long term and dose-response studies are needed to assess the usefulness of sodium restriction in both sexes.

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