

Effect of changing dietary sodium on the airway response to histamine

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ABSTRACT The airway response to histamine has been shown to be related to the 24 hour urinary excretion of sodium. To assess whether this relation is likely to represent a direct causal association a randomised double blind crossover trial of slow sodium (80 mmol/day) was compared with placebo in 36 subjects having a low sodium diet. The dose of histamine causing a 20% fall in FEV₁ (PD₂₀) was 1.51 doubling doses lower when the men were taking sodium than when they were taking placebo ($p < 0.05$). On the basis of PD₁₀ values, the difference in men was 1.66 doubling doses of histamine ($p < 0.05$). There was no corresponding effect in women. Regressing PD₁₀ against urinary excretion of electrolytes with data from the two occasions during the trial and the measurements made before the trial showed a significant association with sodium excretion after allowance had been made for any effect associated with potassium or creatinine excretion, the latter being a marker of the completeness of the urine collection. Again there was no corresponding effect among women. These findings are compatible with the differences in regional mortality data for England and Wales, which show a relation between asthma mortality and regional per person purchases of table salt for men but not for women.

Introduction

The airway response to inhaled histamine is correlated with the 24 hour urinary excretion of sodium, a high rate of sodium excretion being associated with increased reactivity of the airway.¹ This might explain the strong association between regional mortality from asthma and purchases of table salt per person in England and Wales, an association that has been shown for adult men and children of both sexes, but not for adult women.² It might also explain the relative lack of asthma in some of the world's poorest areas.³⁻⁶

As the evidence for this association comes entirely from observational studies, however, it could be due to confounding.¹ We report here the results of an experimental study designed to test whether a change in the sodium content of the diet leads to a change in the airway response to histamine.

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Methods

SUBJECTS

Volunteers of both sexes were recruited from outpatient clinics and hospital and medical school staff and from two local general practices. Subjects all had moderately severe asthma. Thirty five were taking inhaled beta agonists, 12 inhaled corticosteroids, eight cromoglycate, five theophylline, and three anti-histamines. None was taking oral corticosteroids at the time of the trial.

ASSESSMENT

Subjects were assessed on four occasions. At each assessment measurements included bronchial response to histamine, blood pressure, and skin sensitivity to common inhaled allergens. Twenty four hour collections of urine were made immediately before the second, third, and fourth visits and used to obtain estimates of 24 hour urinary sodium, potassium, and creatinine excretion.

HISTAMINE CHALLENGE

FEV₁ and forced vital capacity (FVC) were measured

with a dry spirometer (Vitalograph, Buckingham), the greater of two technically acceptable measurements within 5% of each other being used. The airway response to histamine was measured by a method similar to that described by Yan *et al.*,⁷ with a hand held nebuliser. The FEV₁ was measured after an inhalation of normal saline, followed by doubling doses of histamine starting at a dose of 0.015 μ mol and continuing until either the FEV₁ fell to 80% of the post-saline value or a maximum dose of 0.72 μ mol had been administered. The doses that provoked a 10% and 20% fall in FEV₁ from the post-saline value (PD₁₀, PD₂₀) were calculated by fitting a curve to the dose-response data as described by Chinn *et al.*,⁸ with extrapolation to a dose of 1.45 μ mol. Subjects were asked not to use beta agonist inhalers in the six hours before the tests.

SKIN SENSITIVITY

Skinprick tests were performed for type I (immediate) hypersensitivity to *Dermatophagoides pteronyssinus*, house dust, cat fur, *Aspergillus niger*, and mixed grass pollen, with diluent control. The maximum weal diameter and that at 90° to it were measured at 10 minutes and the mean for all five allergens was calculated as the mean skin weal diameter. Subjects were asked not to use antihistamines within 24 hours of any test.

24 HOUR URINE SPECIMENS

Subjects were given verbal and written instructions on how urine should be collected. After voiding urine first thing in the morning they were asked to note the time and collect all their urine up to and including the first specimen of the following day, after which they were asked to record the time. The urine bottles contained methiolate preservative. Urine volume was measured and the concentration of sodium and potassium was estimated by means of ion specific electrodes. The creatinine concentration was measured by means of a modified Jaffe rate reaction.

BLOOD PRESSURE

Blood pressure was measured in the left arm by sphygmomanometry after the patient had been seated for at least 10 minutes. The second of two measurements made at least two minutes apart was recorded. Measurements were taken to the nearest 2 mm Hg.

PROTOCOL

The study had a double blind randomised crossover design. One week after the initial assessment subjects had a second assessment; they were put on a low sodium diet and asked to take either slow sodium (80 mmol/day in two doses) or placebo tablets. After

two weeks of this regimen a third assessment was carried out and the subjects changed to the alternative regimen. The fourth assessment was made after a further two weeks.

The study was approved by the local ethics committee. All subjects signed a consent form after the purpose of the research procedures and likely side effects had been explained.

STATISTICAL METHODS

For all estimates within subject analysis was used. Histamine PD₁₀ and PD₂₀ were transformed to the log₁₀ scale and values for the slow sodium and placebo periods were compared. The significance of the difference was estimated by a paired *t* test. When one treatment is given more commonly before another this may lead to bias if the order of the treatment itself influences the response. In one analysis where this was a possibility the effect was also calculated after account had been taken of the order in which treatments had been given. This and subsequent analyses of variance were performed with the program GLIM.⁹ Where data on the airway response to histamine were censored (when PD₁₀ and PD₂₀ were greater than the highest dose for which an estimate was possible) the values were put at the censoring limit (1.45 μ mol). When both PD₂₀ or PD₁₀ values were censored the subject had to be excluded as change in reactivity could not be estimated. This accounts for the variable number of subjects in the different analyses.

Histamine PD₁₀ was regressed against the 24 hour urinary excretion of sodium, potassium, and creatinine on the three occasions on which this information was collected. This was done in two ways: first by setting all censored values at the censoring limit as before, and secondly by using maximum likelihood to estimate the regression coefficients, a normal distribution of log PD₁₀ values within subjects being assumed.¹⁰ This second analysis allowed use of the additional information that censored values were at or above rather than at the censoring limit. Similar analyses were performed to assess the relation of electrolyte excretion to airway reactivity after account had been taken of initial lung function, time since last bronchodilator, and whether the subjects were having a low salt diet.

Systolic and diastolic blood pressure were regressed against urinary electrolyte excretion.

Results

Of the 41 subjects recruited to the study, four had values for PD₁₀ that were greater than the censoring limit on all four occasions or on all but the first occasion, and one failed to collect a urine specimen on the second and third occasions. These five subjects

Table 1 Characteristics at the end of the introductory week of the 36 subjects included in the analysis

	Men	Women
Number	14	22
Median (range) age (y)	29.5 (19-47)	30 (18-53)
Smoking history		
Number (%) of current smokers	3 (21)	6 (27)
Number (%) of ex-smokers	4 (29)	6 (27)
Number (%) of never smokers	7 (50)	10 (46)
Mean (SD) skin wheal diameter (mm)	3.82 (1.57)	2.85 (1.69)
Number (%) taking inhaled bronchodilator	14 (100)	21 (95.5)
Number (%) taking inhaled steroid	5 (36)	7 (32)
Mean (SD) urinary excretion (mmol/24 h)		
Sodium	100.5 (46.3)	108.5 (54.3)
Potassium	44.5 (19.1)	47.0 (16.7)
Creatinine	8.7 (3.1)	8.1 (3.3)
Mean (SD) blood pressure (mm Hg)		
Systolic	118.4 (21.1)	107.9 (14.8)
Diastolic	72.1 (10.6)	68.5 (12.0)

were excluded from further analysis, leaving 36 subjects in the study (14 men and 22 women). Details of these subjects are shown in table 1. Two further women failed to collect a urine specimen, one after taking placebo and the other after low sodium. Their results were not available for the comparison of these two regimens, though the information that was available was used to assess the within person association of airway reactivity and electrolyte excretion.

The mean sodium excretion at visit 2 before the introduction of the diet or tablets was 106 mmol/24 hours (fig 1). After adoption of a low salt diet there was a mean (SEM) reduction in sodium excretion of 32 (17) mmol/24 hours in men and of 35 (9) mmol/24 hours in women. On taking the sodium tablets the men showed a mean increase in urinary sodium of 47 (15) mmol/24 hours and the women a mean increase of 43 (12) mmol/24 hours compared with the period of the low sodium diet and placebo tablets.

There was an increase in PD_{10} in the men having the low sodium diet and a fall in PD_{10} after they had started the slow sodium tablets ($p < 0.05$). These changes were not seen among the women.

The PD_{20} when the men were taking sodium tablets was 1.51 (95% CI = 0.31 to 2.72) doubling doses lower than when they were on placebo. The comparable figure for PD_{10} was 1.66 (95% confidence interval (CI) = 0.38 to 2.95) doubling doses in men (fig 2, table 2). Women had slightly higher PD_{20} and PD_{10} values when taking sodium than when they were having placebo tablets, though the difference was not significant (fig 2, table 2). The effect of sodium on PD_{10} and PD_{20} was significantly different in men and women ($p < 0.05$). Adjustment for the order in which the treatments were given made no difference to the conclusions of the analysis.

Table 3 shows the association within subjects between PD_{10} and the urinary excretion of sodium,

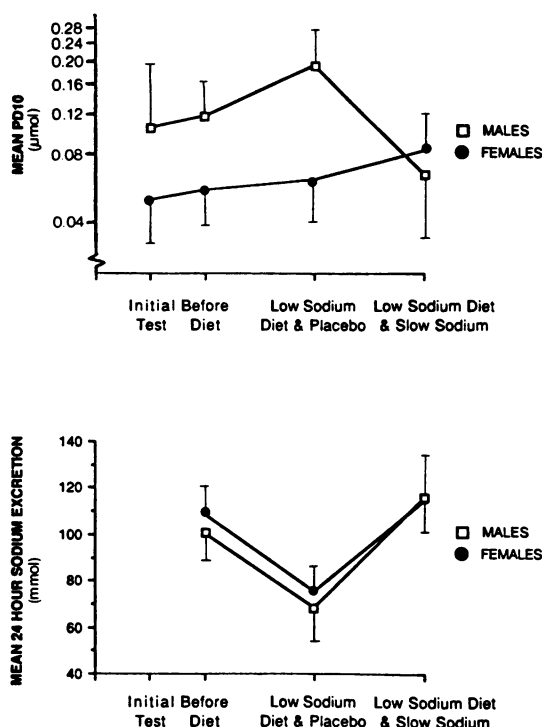


Fig 1 Geometric mean PD_{10} values (airway reactivity) and 24 hour sodium excretion at different stages of the trial (the last two regimens were given in random order and not in the order shown by the diagram). Because of missing values taken account of in the estimation of mean differences in sodium excretion given in the text, those shown in the diagram are not exactly equivalent. The error bars represent between subject standard errors.

potassium, and creatinine. There was a significant negative relation between PD_{10} and urinary excretion of sodium for men but not for women. The relation with potassium is positive but not significant for both men and women. Adjustment for urinary excretion of creatinine allowed for variation in the completeness of the specimens collected but had little effect on the estimates.

There was a slight fall in the baseline FEV₁ during the course of the study irrespective of diet and a further slight fall when subjects were taking the sodium tablets. These changes were, however, small and not significant. Allowing for the change in FEV₁ made little difference to the relation between bronchial reactivity and sodium excretion (table 4).

All subjects were asked not to use beta agonist inhalers within six hours of a challenge test. Two men and three women used their inhalers within this period at some time during the trial. Adjusting for changes in

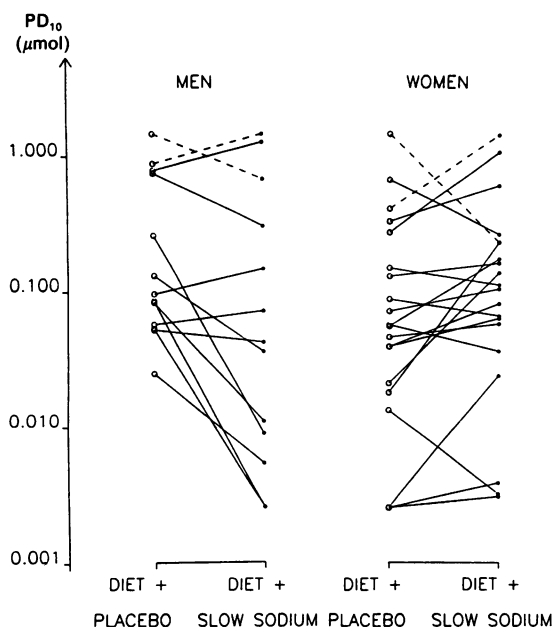


Fig 2 Changes in PD values (airway reactivity) for men and women taking slow sodium and placebo tablets. Broken lines represent subjects for whom one estimate of PD_{10} was censored.

the period in which people had used inhalers made no difference to the results.

The magnitude of the relation between bronchial reactivity and sodium excretion was not dependent on age or mean skin weal diameter. The age range in this study was narrow, however, and all but four of the subjects were atopic.

There was no significant association between systolic or diastolic blood pressure and sodium excretion

Table 2 Differences in dose of histamine required to provoke a 20% (PD_{20}) or 10% (PD_{10}) fall in FEV_1 during the slow sodium and the placebo period

	Change in provoking dose (95% confidence interval) expressed as doubling concentration of histamine	
	Mean change	(95% confidence interval)
Men		
PD_{20} (n = 11)*	-1.51	(-2.72 to -0.31)
PD_{10} (n = 13)	-1.66	(-2.95 to -0.38)
Women		
PD_{20} (n = 20)	0.12	(-0.99 to 1.23)
PD_{10} (n = 20)	0.62	(-0.15 to 1.39)

*One man had two censored PD_{10} values and three had two censored PD_{20} values and so could not be included in these analyses. PD_{20} , PD_{10} —provocative doses of histamine causing FEV_1 to fall by 20% and 10%.

Table 3 Association within subjects between PD_{20} as the dependent variable and urinary excretion of sodium (Na^+), potassium (K^+), and creatinine

Method	Regression coefficient (SE)		
	Na^+	K^+	Creatinine
Men			
(n = 14) GLIM†	-0.0050* (0.0019)	0.0017 (0.0089)	0.0163 (0.0431)
WOLYNETZ‡	-0.0055** (0.0017)	0.0058 (0.0083)	0.0137 (0.0384)
Women			
(n = 22) GLIM	0.0013 (0.0021)	0.0077 (0.0063)	0.0054 (0.0480)
WOLYNETZ	0.0019 (0.0018)	0.0062 (0.0054)	0.0130 (0.0406)

†Used with censored values set to the censoring limit and assumed exact.

‡Incorporates the knowledge that censored values were known only to be $\geq 1.45 \mu\text{mol}$ (see text).

* $p < 0.05$; ** $p < 0.01$.

for either sex (table 5). In men there was a negative association between diastolic blood pressure and urinary excretion of potassium ($p < 0.05$). The associations between blood pressure and urinary excretion of potassium in women were weak, positive, and not significant.

Discussion

In a randomised, double blind, crossover challenge the bronchial response to histamine was greater in men on a low sodium diet while they were taking slow sodium than when they were taking placebo. Similar changes were not seen in women. Change in airway reactivity in the men was associated with change in urinary sodium excretion.

The sodium excretion of the subjects was low at the beginning of the trial. The mean excretion was 106 mmol/24 hours compared with 170 mmol/24 hours in a sample of 138 men living in North

Table 4 Effect of adjusting for other variables on the regression coefficients (PD_{10}) for sodium (Na^+) excretion (estimates used maximum likelihood to take account of censoring)*

	Regression coefficient for sodium excretion (SE)	
	Men	Women
$Na^+ + K^+ + \text{cr}$	-0.0055** (0.0017)	0.0019 (0.0018)
+ initial FEV_1	-0.0054** (0.0016)	0.0027 (0.0019)
+ last dose of bronchodilator	-0.0054** (0.0017)	0.0012 (0.0017)
+ diet	-0.0057** (0.0018)	0.0024 (0.0018)

*All models are within subject analyses and are adjusted for the effects of potassium (K^+) and creatinine (cr) excretions in table 3.

** $p < 0.01$.

Table 5 Within subject regression of blood pressure against 24 hour urinary electrolytes

<i>Regression coefficients (SE)</i>			
	<i>Na⁺</i>	<i>K⁺</i>	<i>Creatinine</i>
<i>Men (n = 14)</i>			
Systolic	0.065 (0.042)	-0.298 (0.198)	1.48 (0.96)
Diastolic	0.019 (0.025)	-0.255* (0.118)	0.91 (0.57)
<i>Women (n = 22)</i>			
Systolic	0.036 (0.041)	0.091 (0.124)	-0.45 (0.95)
Diastolic	0.008 (0.027)	0.069 (0.081)	-0.54 (0.62)

*p < 0.05.

Hampshire¹ and in a similar trial looking at the effect of altering sodium intake on blood pressure.¹¹ This may have been due to the selection of subjects. Alternatively, as all the subjects were told the hypothesis when they gave their consent to the study, some may have reduced their sodium intake during the initial week of the study even though they were asked not to. This low initial level of sodium excretion may explain the relatively small mean fall in sodium excretion of about 35 mmol/24 hours with the change to a low sodium diet. The mean increase in sodium excretion during the slow sodium period compared with the placebo period was also smaller than might have been expected. The total daily dose of sodium was 80 mmol, but the mean increase in sodium excretion was only 47 mmol/24 hours in men and 43 mmol/24 hours in women. Compliance as judged by pill counts at the end of each period was good and lapses in compliance could not explain such a small change. Possibly the increase in sodium intake caused by the slow sodium tablets reduced the appetite for salt and made it easier to comply with the low salt diet.

All the subjects included in the analysis were moderately reactive to inhaled histamine. Less reactive subjects were excluded on clinical criteria and by the requirement that at least one of the last three estimates of PD₁₀ should be uncensored—that is, less than 1.45 μmol of histamine. The censoring value was lower than usual because of an error in making up the histamine solutions. The censoring value was set at twice the maximum cumulative dose of histamine administered as this degree of extrapolation has been shown to give estimates that are no less reliable than those confined to doses less than the maximum cumulative dose.⁸

Where values of PD₁₀ were greater than 1.45 μmol a more exact estimate was not possible and this caused difficulties in analysing the data. Fixing these values at the censoring limit of 1.45 μmol underestimates the differences from any values below the censoring limit. Excluding subjects with any censored values, however, loses valuable information on the minimum difference between the two values. Provided that the within

person distribution of log PD₁₀ can reasonably be assumed to be normal, maximum likelihood methods can be used to estimate regression coefficients where the dependent variable has censored values.¹⁰ As would be expected, the regression coefficients were slightly greater when estimated in this way and the standard errors slightly less.

When censored values have to be set to the censoring limit PD₁₀ may be preferred to PD₂₀ if this leads to fewer censored values in the analysis. Differences between a censored value that has been set to the censoring limit and another value will always underestimate the true difference and will therefore provide biased estimates of the overall effect. In this study there was little difference in the estimated effect whether PD₁₀ or PD₂₀ was used for men, among whom two subjects had censored information on one occasion each in the trial whichever measurement was used. On the other hand, the differences among the women were greater; this is in part due to the censoring of values from only one woman when PD₁₀ was used but from four women when PD₂₀ was used.

In the regression of reactivity against urinary electrolytes, one subject had all the last three values of PD₂₀ censored and had to be excluded from that analysis. When maximum likelihood estimates of the regression coefficients were used to minimise the effect of censoring, reactivity measured by PD₂₀ was also significantly associated with sodium excretion ($\beta = -0.0041$, SE = 0.0017; n = 13; p < 0.05) in men.

An association was found between bronchial reactivity and sodium excretion for men but not for women. The difference between the two sexes is significant and is in keeping with the relation between salt purchases and asthma mortality.² This differs from the results of Javadi *et al*, who also found an increase in bronchial response to histamine when subjects increased dietary sodium, but no difference between the response of six men and four women.¹² This study, however, was small, open, and unrandomised, making it difficult to interpret with confidence.

Nevertheless, as the basic pathogenetic mechanisms are likely to be the same for both sexes, this difference requires some explanation. The most likely explanation is some confounding factor obscuring the underlying relation between the two variables in the women. As our measurements were taken two weeks apart possibly our results are confounded by an effect of the menstrual cycle. But although asthmatic symptoms have been shown to vary with the menstrual cycle¹³⁻¹⁶ reactivity has generally not varied¹⁶⁻¹⁷ though there are clearly some exceptions.¹⁸ We analysed data on the two sexes separately because of the discrepancy between the sexes in the regional mortality data showing an association between asthma mortality and table salt consumption for men and for children of

both sexes but no such association for adult females.² An additional cyclical source of within subject variability, presumably common to most women of childbearing age, would not be expected to obscure an effect of sodium consumption on annual asthma mortality. A second possibility therefore is that airway responsiveness in women is not affected by an increased sodium intake.

There is some support for this from the difference in the relation between blood pressure and electrolyte excretion that has been reported for men and women. Belgian¹⁹ and British²⁰ studies have noted that blood pressure is related to urinary potassium excretion in men, but not in women unless they are taking a contraceptive pill.²⁰ Our findings give some support to these observations, though the numbers are small. Diastolic blood pressure was related negatively to potassium excretion in men ($p < 0.05$), whereas the relation was weak and positive for the women. The discrepancy between the sexes in the effects of dietary electrolytes may therefore be a general one, not confined to an effect on either airway reactivity or blood pressure. Here again, however, the data are not all consistent. Neither the Intersalt study²¹ nor the Scottish heart health study²² show the same discrepancy between the effects of sodium or potassium on blood pressure.

This study supports the hypothesis that a high sodium diet increases bronchial reactivity in men but not in women and suggests that moderate restriction of sodium intake in asthmatic men would reduce bronchial reactivity. The analysis of mortality data² suggests that this may also be true for children and that an overall reduction in sodium intake might reduce mortality from asthma in these groups.

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