Sulphur dioxide sensitivity and plasma antioxidants in adult subjects with asthma

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Abstract

***Objectives*—To screen adult subjects with asthma for sensitivity to inhaled sulphur dioxide (SO_2) and identify subject characteristics associated with that sensitivity. Medication use, symptoms, and plasma antioxidant nutrients between SO_2 responders and non-responders were compared.**

***Methods*—Adult subjects (ages 18-39 years) with asthma were exposed to 0.5 ppm SO_2 for 10 minutes during moderate exercise. Pulmonary function tests and symptom ratings were assessed before and after exposure (n=47). A subject was classified as sensitive to SO_2 if forced expiratory volume in 1 second (FEV_1) showed a drop ⩾8% over baseline. Blood samples were obtained from subjects (n=38) before the SO_2 challenge; plasma ascorbate, α-tocopherol, retinol, carotenoids, and lipids were measured.**

***Results*—Of the 47 subjects screened, 53% had a drop in FEV_1 ⩾8% (ranging from −8% to −44%). Among those 25 subjects, the mean drop in FEV_1 was −17.2%. Baseline pulmonary function indices (FEV_1% of predicted and FEV_1/FVC% (forced vital capacity)) did not predict sensitivity to SO_2. Although use of medication was inversely related to changes in pulmonary function after SO_2 ($p<0.05$), both SO_2 responders and non-responders were represented in each medication category. Total symptom scores after exposure were significantly correlated with changes in FEV_1 ($p<0.05$), FVC ($p<0.05$), and peak expiratory flow (PEF) ($p<0.01$) but not forced expiratory flow between 25% and 75% vital capacity (FEF_{25-75}). Plasma β-carotene concentrations were inversely associated with PEF values and ascorbate concentrations were inversely associated with FEV_1 and FEV_1/FVC ($p=0.05$ in all cases). High density lipoprotein concentrations were positively correlated with FEV_1% of predicted ($p<0.05$) and inversely correlated with change in FEF_{25-75} ($p<0.05$) after SO_2.**

***Conclusion*—These results show that the response to SO_2 among adults with mild to moderate asthma is very diverse. Severity of asthma defined by medication category was not a predictor of sensitivity to SO_2. Lung function values were associated with β-carotene and ascorbate concentrations in plasma; however, plasma antioxidant nutrient concentrations were not associated with sensitivity to inhaled SO_2.**

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Sulphur dioxide (SO_2) is a common ambient and occupational air pollutant. Sources of SO_2 include electric coal fired power plants, smelters, wood pulp manufacturing, and food processing operations.[1] It is one of six common outdoor air pollutants regulated as criteria pollutants by the United States Environmental Protection Agency. About 600 000 workers in the United States are exposed to SO_2 at work.[2] The typical responses to inhaled SO_2 in subjects with asthma are acute bronchoconstriction measured as decrements in forced expiratory volume in one second (FEV_1) or increases in airway resistance.[3 4] Subjects with asthma have significant changes in pulmonary function after brief exposures at concentrations as low as 0.25 ppm whereas subjects without asthma often have no significant change in pulmonary function after exposures below 5 ppm.[5] A recent report determined the prevalence of airway hyperresponsiveness to SO_2 in an adult population of 790 subjects, aged 20–44 years, as part of the European Community respiratory health survey. The prevalence of SO_2 hyperresponsiveness (measured as a 20% decrease in FEV_1) in that population was 3.4%.[6] Of subjects with a methacholine positive response, 22% showed sensitivity to SO_2 whereas only two out of 679 who were not methacholine positive had such sensitivity, although the presence of asthma was not used directly as a risk factor.

Concentrations of vitamins E (α-tocopherol), C (ascorbate), A (retinol), and carotenoids in peripheral blood may be useful biomarkers for predicting the response of adults with asthma to air pollutants. Epidemiological studies have shown a relation between dietary concentrations of vitamin C and pulmonary function values.[7–10] There is evidence that vitamin C intake in the general population is correlated with asthma status and that people with asthma have lower serum vitamin C than people without.[11] Low dietary intake of vitamins C[12] and E[13] are associated with an increased risk of developing asthma. Plasma concentrations of antioxidant vitamins do not always show a good correlation with dietary intake, particularly for lipid soluble antioxidants such as α-tocopherol and β-carotene. However, they serve as good markers of internal dose, as factors other than diet—such as variations in absorption and metabolism—are reflected in plasma concentrations.[14 15]

This paper describes the responses of adult subjects with asthma to a 10 minute SO_2

screening test. The relation between response to SO_2 exposure, medication, symptoms, and plasma antioxidant nutrients are discussed.

Methods

The use of human subjects was approved by the University of Washington Human Subjects Committee. Subjects with a history of asthma aged 18–39 years were recruited from local asthma and allergy clinics, university students, faculty, and staff, and the general population. Forty seven subjects (14 men and 33 women) completed the screening procedure. Use of medication was restricted as follows: use of long acting and short acting β_2 agonist was prohibited within 12 and 6 hours of the screening visit, respectively. Inhaled anti-inflammatory medications were withheld on the screening day.

Subjects inhaled SO_2 by a mouthpiece while wearing noseclips for 10 minutes during moderate exercise on a treadmill. The treadmill was set to achieve about a threefold increase in resting minute ventilation. Minute ventilation was measured continuously during each challenge test. The SO_2 was generated in a gas aerosol generation and monitoring system connected to the mouthpiece described earlier.[16]

Pulmonary function (FEV_1, forced vital capacity (FVC), forced expiratory flow between 25% and 75% vital capacity (FEF_{25-75})) was measured with a computerised spirometer (Spirometrics III) according to American Thoracic Society guidelines. Peak expiratory flow (PEF) was measured with a hand held peak flow meter (Vitalograph). Pulmonary function was measured before and within 10 minutes after the SO_2 challenge. An 8% drop in FEV_1, based on previous studies,[16 17] was chosen as the criterion for categorising subjects as SO_2 responders. Subjects completed a symptom rating form before and after the exposure. Ten symptoms were rated from 0=none to 5=severe, grouped as follows: upper respiratory (nasal discharge, sore throat), lower respiratory (cough, chest pain or burning, dyspnoea, wheeze), and other (headache, fatigue, unusual smell or taste, dizziness).

Non-fasting blood samples were drawn from each subject at the beginning of the screening visit. Plasma ascorbate, α-tocopherol, retinol, carotenoids, and lipids (total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides) were measured. Samples were analysed by the Clinical Nutrition Research Unit at the University of Washington. Plasma concentrations of ascorbic acid were measured enzymatically with a Cobas-Bio centrifugal analysis.[18] Carotenoids,[19] retinol, and α-tocopherol were extracted from plasma in a total lipid fraction and measured by high performance liquid chromatography.[20] A lipid profile was produced by standard clinical laboratory techniques.

Statistical analyses were conducted with the SPSS software package. Changes in pulmonary function changes by medication category were examined by analysis of variance (ANOVA) and a Bonferroni test to compare group means. Significance was set at p=0.05. Associations between medication category and pulmonary function change were measured by Spearman's correlation coefficients (one tailed). Paired *t* tests compared symptom scores before and after SO_2 challenge. Independent sample *t* tests were used to compare symptom scores by SO_2 response groups. Plasma nutrient and pulmonary function partial correlations were adjusted for age, race, and sex. Analysis of varience tests were applied to selected plasma variables (ascorbate, retinol, β-carotene, lycopene) to examine differences by SO_2 response groups and medication categories. A linear regression model (% change in FEV_1=vitamin E+vitamin C+β-carotene+lycopene+constant) was used to test the hypothesis that SO_2 sensitivity, measured by change in FEV_1, is associated with plasma antioxidant concentrations. As plasma cholesterol, in the case of vitamin E, and HDL, in the case of lycopene, account for a substantial proportion of the variance in these two antioxidant nutrients, the model adjusted vitamin E for cholesterol and lycopene for HDL cholesterol.

Results

Based on data on use of medication from the questionnaire, subjects were divided into four groups that closely match the guidelines for the diagnosis and management of asthma.[21] Table 1 shows the medication categories and subject characteristics including age, sex, baseline % predicted FEV_1, baseline FEV_1/FVC ratio, and the % change in FEV_1 after the SO_2 challenge. As seen in table 1, there was an inverse correlation between use of medication category and % predicted FEV_1 (Spearman's r=-0.40, p=0.003).

Percentage changes in measures of pulmonary function among SO_2 responders and SO_2 non-responders, by medication group, are shown in table 2. The change in FEV_1 after SO_2 challenge ranged from a small increase (6%) to a 44% decrement. Of the 47 subjects screened, 53% had a drop in FEV_1 ⩾8% (range −8% to −44%). The mean drop in FEF_{25-75} after the SO_2 challenge was −26% for the SO_2 responders and −7% for the non-responders (p<0.001). Likewise the changes in FVC (−10% *v* −1 %) and PEF (−15% *v* −2%) between the responders and non-responders were significant (p=0.001 and p=0.002, respectively). The SO_2 induced decrements in FEF_{25-75} and FEV_1 were significantly greater (p<0.05) in subjects who used both bronchodilators and anti-inflammatory medication (group 4), compared with those who rarely used medication (group 1). Those who re-

Table 1 Mean (SD) subject characteristics and SO_2 response by category of medication

*Medication category**	*Age (mean, y)*	*n*	*FEV_1 % of predicted†*	*FEV_1/FVC %†*	*SO_2 response (% change FEV_1)*
1	24.4	11	101.5 (16.5)	78.1 (10.3)	−3.4 (4.8)
2	26.5	15	100.3 (14.6)	90.0 (6.0)	−7.8 (6.0)
3	24.3	12	91.7 (13.3)	75.7 (8.4)	−13.3 (13.9)
4	26.6	9	84.6 (9.7)	75.7 (9.3)	−17.6 (15.1)

*1=no regular medication; 2=bronchodilator when necessary; 3=daily bronchodilator; 4=bronchodilator+anti-inflammatory.
†Calculated from prescreening best FEV_1, and best FVC for FEV_1/FVC %.

Table 2 Pulmonary function changes (mean (SD)% before−after) by SO_2 response and medication group

SO_2 Response	Medication category (n)	FEV_1	FVC	FEF_{25-75}	PEF
Yes:					
1	3	−9.2 (1.6)	−7.7 (3.5)	−16.5 (3.6)	−8.2 (4.7)
2	8	−12.4 (2.9)	−3.9 (5.9)	−27.6 (7.4)	−9.3 (13.1)
3	8	−19.4 (13.2)	−12.9 (15.7)	−21.1 (18.3)	−18.6 (17.7)
4	6	−24.7 (13.0)	−14.6 (10.4)	−36.6 (17.1)	−20.9 (25.7)
Group mean		−17.2 (10.9)	−9.8 (11.2)	−26.4 (14.9)	−15.0 (17.6)
No:					
1	8	−1.3 (3.5)	−0.09 (0.8)	−5.4 (7.6)	0.2 (5.8)
2	7	−2.5 (3.6)	−0.6 (2.2)	−10.3 (5.2)	−4.3 (4.1)
3	4	−1.1 (2.5)	−1.8 (3.1)	−1.2 (5.2)	−3.4 (6.7)
4	3	−3.3 (5.5)	−1.7 (4.3)	−11.7 (21.5)	−4.2 (11.4)
Group mean		−1.9 (3.5)	−0.8 (2.3)	−7.1 (9.4)	−2.5 (6.3)
Total	47	−10.0 (11.3)	−5.6 (9.4)	−17.3 (15.9)	−9.1 (14.8)

sponded to SO_2 rated lower respiratory symptoms significantly higher than those who did not respond ($p<0.05$) after the SO_2 challenge (data not shown); this was not the case for upper respiratory or other symptoms.

Blood samples from 38 subjects were obtained for analysis. All correlations discussed were controlled for age, race, and sex. Three plasma variables were correlated with pulmonary function indices before SO_2 challenge. There was a significant inverse association between plasma β-carotene and FEV_1/FVC % ($r=-0.40$, $p=0.02$) and FEV_1 before challenge ($r=-0.34$, $p<0.05$). Concentrations of HDLs were positively associated with FEV_1 % of predicted ($r = 0.35$, $p=0.04$). Plasma ascorbate was inversely associated with PEF before challenge ($r=-0.33$, $p<0.05$).

Mean plasma nutrient concentrations between those who did and did not respond to SO_2 are shown in table 3. Although concentrations of plasma nutrients among subjects were normally distributed, the range of values among SO_2 responders was often at the low end of the distribution. For example, retinol ranged from 220 to 722 μg/l in those who responded (mean (SEM) 508 (27) μg/l) and from 318 to 808 in those who did not respond (mean (SEM) 537 (35) μg/l). Similarly, the values for ascorbate in responders ranged from 0.19 to 1.83 (mean (SEM) 0.99 (0.09)) mg/dl and 0.52–1.85 (mean (SEM) 1.18 (0.08)) mg/dl in the non-responders. A value of <0.2 mg/dl for plasma ascorbate is considered deficient, 0.2–0.4 is marginal, and >0.4, adequate.[22] Plasma concentrations of α-tocopherol were lower in responders than non-responders; however, β-carotene concentrations were higher in the responders.

Table 3 Screening plasma values (mean (SEM)) by SO_2 response

Plasma nutrient	SO_2 responder (n=22)	SO_2 non-responder (n=16)
Plasma ascorbate (mg/dl)	0.99 (0.09)	1.18 (0.08)
α-Tocopherol (mg/l)	8.70 (0.47)	9.22 (2.81)
Retinol (μg/l)	508 (27)	537 (35)
β-Carotene (μg/l)	231.3 (62.8)	195.1 (33.2)
Lycopene (μg/l)	304.8.38 (28.3)	294.1 (25.4)
Total cholesterol (mg/dl)	161.0 (6.2)	182.4 (9.1)
HDL cholesterol (mg/dl)	52.3 (3.0)	48.2 (4.1)
LDL cholesterol (mg/dl)	85.2 (5.4)	106 (6.1)
Triglycerides	117.6 (14.8)	144.1 (16.7)

Results of plasma lipid assays showed that mean LDL cholesterol was significantly lower in the responders ($p=0.02$). Mean total cholesterol concentrations were lower among non-responders than among responders (161 mg/dl *v* 182 mg/dl; $p<0.05$). Concentrations of HDL were inversely correlated with change in FEF_{25-75} ($r=0.38$, $p=0.02$) after SO_2 challenge; associations with changes in other pulmonary function measures (FEV_1 ($r=0.08$), FVC ($r=0.30$), PEF ($r=-0.07$)) were not significant.

A linear regression model applied for representative plasma antioxidants (vitamin E, vitamin C, vitamin A, β-carotene, lycopene) tested the hypothesis that SO_2 sensitivity, measured by pulmonary function changes in FEV_1 in these subjects (n=38), was associated with antioxidant concentrations. None of the associations was significant.

Discussion

Epidemiological studies have shown a relation between dietary concentrations of vitamin C and pulmonary function as described earlier.[7–10] However, we found no significant association between plasma concentrations of ascorbate and baseline pulmonary function values in the 38 subjects in this study for whom there were blood samples. We did not have data on diet from the questionnaire on these subjects. The blood samples were not taken after fasting and that may have influenced the outcome; also, a single measurement is often not a good indication of long term values. This study used plasma nutrient concentrations because obtaining epithelial lung fluid concentrations was beyond our scope. However, positive correlations between lung tissue and serum concentrations of β-carotene, α-tocopherol, and total carotenoids (but not retinol) have been found,[23] adding credence to the concept of use of plasma antioxidant concentrations as a surrogate for lung tissue concentrations, although more research is needed in this area. The people who responded to SO_2 in this study participated in a double blind cross over study of the effects of antioxidant dietary supplementation on ozone induced bronchoconstriction. The response to ozone was found to be less after the combined vitamin C and E regimen compared with placebo[24] again indicating a positive correlation between plasma antioxidant concentrations and lung function.

The plasma lipid profile results in this study indicated some differences relating to SO_2 response. The lower concentrations of total cholesterol and LDL cholesterol among people who did not respond to SO_2, and the inverse association between HDL cholesterol concentrations and change in FEF_{25-75} after exposure to SO_2, may be indirectly explained by the fact that patients with more severe asthma are less likely to exercise regularly, and thus may have a more unfavourable lipid profile. Also, there is evidence that diet may influence severity of asthma, or at least bronchial hyperresponsiveness.[25] Subjects consuming more dietary fats might also eat fewer fruits and vegetables containing antioxidants and micronutrients that seem to have a protective effect in the lung.[7–13]

There was a diverse response among adult subjects with predominantly mild intermittent to mild persistent asthma to the SO_2 challenge test. Slightly more than half (53%) of the young adults reacted to clinically relevant concentrations of SO_2. Although use of medication was inversely related to changes in pulmonary function after SO_2, severity of asthma defined by medication category was not a perfect predictor of SO_2 sensitivity. People who did not respond were represented in each medication category: eight of 11 subjects in category 1; seven of 15 in category 2; four of 12 in category 3; and three of nine in category 4. Neither % predicted FEV_1 nor the FEV_1/FVC ratio predicted sensitivity to SO_2. The magnitude of ratings on the symptom rating scale at baseline was not associated with sensitivity, although the symptom ratings after SO_2 challenge were significantly associated with the % change in FEV_1. This association indicates that the pulmonary function changes in this study are clinically relevant. The large decrements in FEV_1 after SO_2 challenge among the subjects in categories 3 and 4 (>25%, n=6), would result in stopping activity by most people. The inability of severity of asthma to serve as an indicator for sensitivity to SO_2 agrees with a recent epidemiological study which found that severity of asthma was not related to air pollutant response.[26]

As severity of asthma among subjects in this study was based on reported use of medication, we acknowledge the potential for misclassification. When using medication as a surrogate for severity, an optimal treatment regimen is assumed; compliance with prescribed medications is also a potentially problematic underlying assumption. Subjects were required to withhold medications for 6–12 hours before screening visits, however, there is the possibility of an interaction between SO_2 and medication in the subjects on regular anti-inflammatory treatment.

The SO_2 concentration in this study (0.5 ppm) and exposure conditions (10 minutes, 2 mph, 10% grade on treadmill) are comparable with moderate activity during increased ambient concentrations of SO_2 and to certain workplace conditions. This concentration of SO_2 is found in community air for brief periods and would not result in failure to meet the present United States national standards of ambient air quality for SO_2, which is 0.14 ppm for a 24 hour average and 0.03 ppm for an annual average. The Environmental Protection Agency has considered setting a short term standard for SO_2 explicitly to protect people with asthma from brief, increased concentrations of SO_2. The Puget Sound Air Pollution Control Agency governing Seattle, Washington has set short term standards for SO_2: a 1 hour average of 0.40 ppm, never to be exceeded; a 1 hour average of 0.25 ppm not to be exceeded more than twice within 7 days; and a 3 hour average of 0.10 ppm, not to be exceeded more than once a year. The data in this study support the need for short term SO_2 standards to protect people with asthma. Further research is needed to evaluate the association between diet, plasma antioxidants, and sensitivity to air pollutants.

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