Research Contract Executive Summary to

State of California Air Resources Board

Title of Contract: Airway Responses to Atmospheric Pollutants:

Sulfur Dioxide and Ozone

Contract No: A1-133-33

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ABSTRACT

Although our previous finding that people with asthma have greater bronchomotor sensitivity to sulfur dioxide than healthy people was widely accepted, the relevance of the finding to standards regulating atmospheric concentrations of sulfur dioxide was disputed on the grounds that our exposure conditions (use of mouthpiece or facemask) did not mimic those of ordinary exposure, especially in that they altered the fraction of ventilation passing through the nose, a highly efficient filter for removing sulfur dioxide. The greater part of the studies conducted under this contract were aimed at examining the validity of this criticism. In a study of 10 subjects with mild asthma exposed to sulfur dioxide while performing moderate exercise and breathing freely in an exposure chamber, we found that 0.50 ppm of sulfur dioxide caused significant bronchoconstriction, similar in degree to that induced with breathing the same concentration through a facemask. This result establishes the relevance of our earlier work, for it shows that people with asthma performing moderate exercise and breathing without encumbrance may develop bronchoconstriction on inhaling levels of sulfur dioxide that are occasionally exceeded in ambient air. In a study of 19 subjects with mild asthma we found no significant bronchoconstriction due to exposure to 0.25 ppm of sulfur dioxide, even when the subjects exercised vigorously. Thus, the threshold value for the bronchomotor effect of sulfur dioxide in people with mild asthma lies between 0.25 and 0.50 ppm. We next examined the importance of another of our earlier findings, that the airway effects of sulfur dioxide are potentiated when it is inhaled in cold, dry air. In our study of 8 subjects we confirmed that this effect was statistically significant even for low concentrations of sulfur dioxide (0.1-0.25 ppm), but the magnitude of the potentiation was so small as to be of doubtful clinical importance. Thus, even when inhaled in cold, dry air, the threshold of sulfur dioxide causing symptomatic bronchoconstriction in people with mild asthma is probably greater than 0.25 ppm but less than 0.50 ppm.

The final study of human subjects in this contract examined whether anesthetizing the upper airway (pharynx and larynx) by injecting xylocaine around the superior laryngeal nerves would alter the response to inhalation of sulfur dioxide, as would be predicted from animal studies showing that sulfur dioxide stimulates afferent nerve endings in the larynx. Our initially promising results later appeared to be largely due to the placebo effect of the injection, but the ultimately negative result of the study is difficult to interpret in the absence of a "gold standard" allowing the conclusion that conduction in the superior laryngeal nerves was indeed blocked.

Studies of laboratory animals constituted a small part of the research effort, but these studies established that inhalation of sulfur dioxide provokes an increase in secretion of mucus from bronchial submucosal glands -- an effect that may be important in people with diseases associated with a disturbance in mucus secretion (cystic fibrosis, asthma, chronic bronchitis) -- and that sulfur dioxide alters the pattern of breathing as well as the caliber of airways.

In summary, the work done under this contract extends the work done in previous contract periods and establishes the fact that under "real world"

conditions of exposure, people with asthma may develop bronchoconstriction on inhaling 0.50 ppm of sulfur dioxide, a level that may be exceeded under National Ambient Air Quality Standards.

INTRODUCTION

The projects proposed in Contract A1-133-33 included studies of both human volunteers and of laboratory animals and were aimed primarily at determining the degree to which people with asthma would be sensitive to adverse effects of low concentrations of sulfur dioxide under ambient conditions and while pursuing ordinary activities. Secondary aims of the studies were to determine the mechanims by which sulfur dioxide causes bronchoconstriction in people with asthma, to examine whether pre-exposure to ozone alters the response to subsequent inhalation of sulfur dioxide, and to determine whether inhalation of sulfur dioxide causes an increase in secretion from airway submucosal glands as well as contraction of airway smooth muscle.

STUDIES OF HUMAN SUBJECTS

Background

Our finding that people with asthma have heightened bronchomotor responsiveness to sulfur dioxide [1] was the result of our interest in the bronchial hyperreactivity that has long been known to characterize asthma and that is now thought to be fundamental to the pathogenesis of the disease [2,3]. Our findings that asthmatic subjects develop greater bronchoconstriction on inhaling sulfur dioxide than do healthy people [1] and that exercise potentiates this increased responsiveness [4] were not disputed. What was disputed was the relevance of the findings to "real world" conditions of exposure. Because our studies involved use of a mouthpiece or facemask [1,4-6], the conditions did not precisely mimic those of ordinary exposure, where breathing through the nose and mouth is unimpeded [7]. This fact was considered important because of the efficiency of nasal mucous membranes in removing sulfur dioxide from the air inspired [8].

Although we granted the theoretical validity of this argument, we thought it was of little practical importance because of the increase in oral ventilation that occurs with exercise and because of the high incidence of obstructive nasal pathology in people with asthma [9]. However convincing our arguments may have been, the issue was one that could only be settled with data, especially if the results of studies of adverse effects of sulfur dioxide are to be used in shaping policy regulating air quality. The major purpose of this contract, then, was to determine the relevance of our earlier work to conditions more nearly mimicking those of "real world" exposure. To this end we proposed to analyze the effects of facemask exposure on the airway response to sulfur dioxide by comparing the respones obtained with the subject inhaling 0.50 ppm sulfur dioxide while breathing in a chamber to that obtained breathing through a facemask. We also proposed to analyze the influence of varying degrees of severity of asthma on the response and to analyze the

determinants of oronasal distribution of breathing. A single study of human subjects was devoted to examining the mechanism by which sulfur dioxide produces bronchoconstriction. In this study, we analyzed the effect of application of topical anesthesia to the upper airway on the response to subsequent inhalation of sulfur dioxide.

Study Reports

In the first study, we determined the specific airway resistance of 10 mildly asthmatic volunteers before and after they exercised in an exposure chamber for 5 min at a work rate of 750 kilogram meters/min on two different days. On one day a subject breathed filtered air, and on the other day similar air containing 0.50 ppm sulfur dioxide. The order of administration of air with and without sulfur dioxide was randomized and was blinded. We thus were able to determine the degree of bronchoconstriction induced by 0.50 ppm sulfur dioxide above that induced by exercise alone. We were also able to compare the degree of bronchoconstriction induced by 0.50 ppm sulfur dioxide during free breathing to that induced by 0.50 ppm sulfur dioxide during breathing from a facemask under similar conditions. The latter data came from a previous study.

We found that 0.50 ppm sulfur dioxide causes bronchoconstriction in freely breathing people with asthma exercising for 5 min at 750 kilogram meters/min. The bronchoconstrictor response to sulfur dioxide during free breathing was similar in degree to that during breathing from a facemask.

Table. The change in specific airway resistance (L x cm H_2O/L/s) (mean $\pm$ SD) from before to after exercise

	No sulfur dioxide	0.5 ppm sulfur dioxide
Exposure chamber	2.24 $\pm$ 2.34	13.55 $\pm$ 9.18
Facemask	1.11 $\pm$ 4.46	9.54 $\pm$ 8.27

These data were presented at the American Physiologic Society fall 1982 meetings in San Diego and have been published in the American Review of Respiratory Disease [10].

Several laboratories have recently searched for the threshold concentration of sulfur dioxide that will cause bronchoconstriction in people with asthma. Studies reported by Linn et al. [11] and by Witek et al. [12] found that 0.50 ppm sulfur dioxide did not cause bronchoconstriction in exercising people with asthma. The difference between these two studies and the one reported here is that our subjects exercised at a higher work rate during exposure to sulfur dioxide. Finding the threshold concentration of sulfur dioxide that causes bronchoconstriction is an elusive goal. The degree of bronchoconstriction induced by sulfur dioxide depends not only on the concentration of sulfur dioxide inhaled but also on the work rate of exercise performed during exposure, on the oral-nasal distribution of inhaled air, on the underlying

degree of airway hyperreactivity, and possibly on the presence of other irritating agents. Determining the threshold concentration of sulfur dioxide causing bronchoconstriction is nonetheless important for regulatory agencies responsible for establishing air quality standards ensuring a margin of safety for sensitive subgroups in the population. Since our findings on the effects of 0.50 ppm sulfur dioxide in freely breathing asthmatic subjects already established the relevance of our earlier work to "real world" conditions, we considered it more important to examine the effects of a lower concentration of sulfur dioxide (0.25 ppm) on asthmatic subjects performing various levels of exercise than to pursue what had become a somewhat academic question as to the determinants of oronasal distribution of breathing (see Progress Report on A1-133-33, December 2, 1982). Because we anticipated that the effect of this lower concentration of sulfur dioxide would be smaller, we anticipated that a larger number of subjects would have to be studied. We also investigated the effects of 0.25 ppm in subjects performing high levels of exercise (750-1000 kilogram meters/min), for if no effect were seen at those levels, none would be expected with lower levels of exercise. Accordingly, we had 19 asthmatic volunteers exercise at 750 kilogram meters/min for 5 min in an exposure chamber that contained filtered air or, on another day, filtered air plus 0.25 ppm sulfur dioxide. The order of exposure to sulfur dioxide and to filtered air alone was randomized and the experiments were double-blinded. Specific airway resistance, measured by constant-volume, whole-body plethysmography, increased from 6.38 $\pm$ 2.07 cm H_2O x s (mean $\pm$ SD) before exercise to 11.32 $\pm$ 8.97 after exercise on days when subjects breathed filtered air alone and from 5.70 $\pm$ 1.93 to 13.33 $\pm$ 7.54 on days when subjects breathed 0.25 ppm sulfur dioxide in filtered air. The increase in specific airway resistance was not significantly different on the two days. Nine subjects then repeated the experiment exercising at 1000 instead of 750 kilogram meters/min. Specific airway resistance increased from 6.71 $\pm$ 2.25 to 13.59 $\pm$ 7.57 on days when subjects breathed filtered air alone and from 5.23 $\pm$ 1.23 to 12.54 $\pm$ 6.17 on days they breathed 0.25 ppm sulfur dioxide in filtered air. Again, the increase in specific airway resistance on the two days was not significantly different. We conclude that 0.25 ppm sulfur dioxide does not cause bronchoconstriction in most freely breathing, heavily exercising subjects with mild asthma.

These findings have not yet been presented at a public forum but a manuscript describing them has been submitted to the American Review of Respiratory Disease.

We then turned to examine another issue related to the response of asthmatic subjects to sulfur dioxide inhaled under "real world" conditions. The results of our study of the interaction between cold air and sulfur dioxide (Contract A0-156-33) showed that cold air dramatically potentiated the bronchoconstriction produced by 0.50 ppm of sulfur dioxide [10]. In that study, we only examined the effects of a single concentration of sulfur dioxide (0.50 ppm) at a single minute ventilation, and we did not separate the effects of inspired air temperature and of inspired water content on the bronchomotor response. We therefore undertook a study to determine the separate effects of decreased inspired air temperature and decreased inspired water content on sulfur dioxide concentration-response curves in subjects with asthma. In addition, to determine whether low concentrations of sulfur dioxide (0.10 and 0.25 ppm) would potentiate dry

air-induced bronchoconstriction, we constructed ventilation-response curves for each subject for dry air alone and for dry air with 0.10 and 0.25 ppm sulfur dioxide. From the results of this study, we anticipated that we would be able to predict whether the threshold level of sulfur dioxide causing bronchoconstriction would be lower on cold days, as in the winter months, when sulfur dioxide levels are generally higher and air, water content is lower.

Our study was of 8 subjects with mild asthma. On three separate days, we measured specific airway resistance (SRaw) before and after the subject performed voluntary eucapnic hyperpnea at a constant minute ventilation (30-40 L/min) for successive 3-min periods with doubling concentrations of sulfur dioxide in dry, cold air (-20°C, 0% relative humidity), in dry, room temperature air (22°C, 0% relative humidity), and in partially humidified, room temperature air (22°C, 70% relative humidity). On a fourth day, we measured SRaw before and after the subject performed each of six successive 3-min periods of voluntary eucapnic hyperpena at the same minute ventilation breathing dry, cold air without sulfur dioxide. We calculated the concentration of sulfur dioxide that caused a 100% increase in SRaw (PC_{100}) by linear interpolation. and analyzed differences in the values obtained under different conditions for statistical significance by a two-factor analysis of variance and the Student Newman-Keuls multiple range test. Both the PC_{100} for dry, cold air with sulfur dioxide (0.50 $\pm$ 0.20, mean $\pm$ SD) and the PC_{100} for dry, room temperature air with sulfur dioxide (0.60 $\pm$ 0.41) were significantly lower than the PC_{100} for partially humidified, room temperature air with sulfur dioxide (0.87 $\pm$ 0.41). The PC_{100} for dry, cold air with sulfur dioxide and that for dry, room temperature air with sulfur dioxide did not differ significantly. Repeated hyperpnea with dry, cold air without sulfur dioxide at the same ventilation had no effect on SRaw.

We then had the same subjects perform voluntary eucapnic hyperpnea at successively increasing levels of ventilation on three different days with dry air alone, dry air with 0.10 ppm sulfur dioxide, or dry air with 0.25 ppm sulfur dioxide and calculated the ventilation that caused an 80% increase in SRaw under each condition (PV_{80} -- we used this value since in four experiments SRaw never increased by 100%). The PV_{80} for hyperpnea with 0.10 and with 0.25 ppm sulfur dioxide were signficantly lower than those for dry air without sulfur dioxide but these differences were small.

We conclude that sulfur dioxide causes bronchoconstriction at lower concentrations when it is inhaled in dry air than when it is inhaled in partially humidified, warm air. Furthermore, at least with oral breathing, concentrations of sulfur dioxide as low as 0.10 ppm may cause modest potentiation of the bronchoconstriction produced by airway drying or cooling. These effects, however, were generally small and are of uncertain clinical significance.

A manuscript describing these findings has been submitted to the American Review of Respiratory Disease.

The final study was designed to determine whether the bronchomotor response to inhalation of sulfur dioxide is due to stimulation of afferent receptors located in the laryngeal mucosa. We therefore determined whether percutaneous injection of a topical anesthetic agent around the superior

laryngeal nerves, blocking afferent innervation of the mucosa of the larynx rostral to the vocal folds, reduces or abolishes the bronchomotor response to inhalation of sulfur dioxide in asthmatic subjects.

Five subjects with mild asthma were studied with the following protocol. On day 1, baseline specific airway resistance (SRaw) was measured in a body plethysmograph. Subjects hyperventilated 0.50 ppm sulfur dioxide in filtered, humidified, room temperature air for 3 min at a minute ventilation (MV) previously shown to cause at least doubling of baseline SRaw in each individual. On day 2, baseline SRaw was measured. Subjects received an injection (1.5-2 ml) of a 1% xylocaine solution just anterior to the superior cornu of the thyroid cartilage on both sides of the neck to block conduction in the superior laryngeal nerves. Inhalation of 0.50 ppm sulfur dioxide for 3 min was repeated at the same MV as on day 1. The day 3 protocol was a repeat of day 1.

Results

The injection of xylocaine around the superior laryngeal nerves caused no change in baseline SRaw, and the baseline value for SRaw immediately prior to inhalation of sulfur dioxide on the three study days also did not differ significantly. The responses to sulfur dioxide on the three days were as follows.

Day	n	MV (L/m)	SD	ΔSRaw (L x cm H_2O/L/s)	SD	%ΔSRaw (L x cm H_2O/L/s)	SD
1	5	47.7	8.2	10.38	2.36	162.8	38.8
2	5	48.0	8.0	4.90	2.88	93.4	62.7
3	4	46.3	8.9	11.45	2.92	184.5	94.5

Three volunteers who participated in the study described above were further studied on a second occasion, but instead of receiving an injection of 1% xylocaine, they were injected with 1.5-2.0 ml of normal saline. They were not told of this change in the injected material.

A comparison of the responses observed after xylocaine was injected and after saline was injected is as follows.

Injection	n	MV (L/m)	SD	ΔSRaw (L x cm H_2O/L/s)	SD	%ΔSRaw (L x cm H_2O/L/s)	SD
xylocaine	3	50.2	17.7	3.82	3.4	87.3	78.0
saline	3	50.7	7.9	3.79	1.9	60.3	31.5

These results showed that there was no significant difference in the bronchomotor response to sulfur dioxide with percutaneous injection of xylocaine rather than saline in the region of the superior laryngeal

nerves, and that the apparent reduction in responsiveness in the first study was probably due to the effects of suggestion caused by the injection itself. A difficulty with interpreting this "negative" result stems from the lack of any independent criteria confirmed that the conduction in superior laryngeal nerves was indeed blocked by the injections. In exploratory studies in two healthy individuals, we found that the combination of topical application of xylocaine to the posterior pharyngeal wall (by gargling), of inhalation of xylocaine aerosol, and of injection of the superior laryngeal nerves can produce blockade of the gag and cough reflex responses to mechanical irritation of the larynx but that this combination also produced dysphagia in both subjects and inspiratory stridor in one subject. For these reasons, we have not conducted further study of the effects of greater doses of xylocaine on the bronchomotor responsiveness to sulfur dioxide in asthmatic subjects.

STUDIES ON SULFUR DIOXIDE IN DOGS

These studies were designed to determine whether pulmonary responses to inhaled sulfur dioxide are altered by a 1- to 2-h exposure to 0.75 ppm of ozone in dogs. In order to answer this question, we first had to characterize the pulmonary responses to inhaled sulfur dioxide before ozone.

Bronchomotor and Secretomotor Responses

In a preliminary group of studies, we found that the bronchomotor response to inhaled sulfur dioxide was variable. This indicated that we would not be able to study the effect of ozone on the bronchomotor response to inhaled sulfur dioxide. Therefore, we embarked on a study of the effect of sulfur dioxide on mucus secretion from airway submucosal glands.

To determine whether sulfur dioxide increases secretion from submucosal glands, we anesthetized 14 mongrel dogs with chloralose (100 mg/kg) and urethane (500 mg/kg), inserted a cannula in the lower trachea, and ventilated them artificially. To visualize the secretions from submucosal gland duct openings, we exposed the mucosa of the upper trachea and coated its surface with powdered tantalum. Secretions from the glands formed elevations in the tantalum layer (hillocks) with time. Through a dissecting microscope, we counted the number of hillocks per 1.2 cm^2. We applied 500 ppm of sulfur dioxide only to the lower airways for 2 min, but observed gland secretion for 4 min. Starting from the same baseline (9.3 $\pm$ 2, mean $\pm$ SE), the number of hillocks became significantly greater during ventilation with sulfur dioxide than during ventilation with air (1 min: 45 $\pm$ 9 vs 28 $\pm$ 4; 2 min: 65 $\pm$ 8 vs 48 $\pm$ 6; 3 min: 81 $\pm$ 8 vs 60 $\pm$ 7; 4 min: 93 $\pm$ 8 vs 72 $\pm$ 8). Cooling the vagus nerves in the neck below the efferent secretomotor nerves to the upper trachea abolished the effects of sulfur dioxide which returned when the vagi were rewarmed. After i.v. atropine (0.1 mg/kg), hillock numbers no longer increased during application of sulfur dioxide (2 min: control 35 $\pm$ 13; sulfur dioxide: 34 $\pm$ 13; 4 min: 69 $\pm$ 29 vs 68 $\pm$ 26; n = 5). We conclude that sulfur dioxide reflexly stimulates gland secretion via vagal cholinergic pathways. This work has been presented to the American Physiology Society [13,14].

Effect of Sulfur Dioxide on the Control of Breathing

We investigated the effects of sulfur dioxide on ventilation in two dogs walking on a treadmill (1.4 mph). We applied 25-300 ppm sulfur dioxide for 4 min through a tracheostomy tube while continuously recording ventilatory variables breath by breath. Responses were dose dependent and showed a typical time course with coughing at 0.5 min and peak effects at 2 and 5 min. With 200 ppm, there were significant decreases in: time of inspiration, Ti (1.16 ± 0.07, 0.78 ± 0.09, 0.56 ± 0.06 s, control, 1st and 2nd peak, mean ± SE, n = 10); time of expiration, Te (1.61 ± 0.07, 0.95 ± 0.20, 0.48 ± 0.09), total time of breath, Tt (Ti + Te), tidal volume, V_T (447 ± 17, 303 ± 31, 261 ± 34 ml), and significant increases in: V_T/Ti (0.40 ± 0.02, 0.45 ± 0.04, 0.54 ± 0.02), Ti/Tt (0.42 ± 0.01, 0.48 ± 0.02, 0.56 ± 0.02) and ventilation (10.1 ± 0.7, 13.1 ± 1.9, 18.9 ± 2.0 L/min). The acceleration of breathing at each peak culminated in further brief coughing. Cooling both cervical vagi to +1°C prevented all of these responses but they were unaffected by the inhalation of terbutaline (0.2 mg/ml, 10 min). In one experiment in each dog, we introduced a Foley catheter (with its tip cut off above the balloon) through the tracheostomy into the upper trachea. After intubation of the lower trachea, we applied sulfur dioxide alternately to the upper and lower airways. A stream of 4 L/min sulfur dioxide (25 ppm) delivered to the upper airways produced effects similar to 12-14 L/min sulfur dioxide (300 ppm) inhaled into the lower airways. At 2 min, Ti decreased from 1.36 ± 0.16 to 0.90 ± 0.18 s (300 ppm: 1.16 ± 0.36 to 0.70 ± 0.18), Te from 1.81 ± 0.31 to 0.70 ± 0.08 s (1.84 ± 0.66 to 0.72 ± 0.18) and V_T from 536 ± 18 to 389 ± 80 ml (453 ± 120 to 351 ± 21). Coughing was more prominent with upper than with lower airway spplication (41 ± 1 vs 34 ± 8 coughs/4 min), and it persisted long after the exposure. We conclude that, in dogs, sulfur dioxide delivered to the lungs causes coughing and rapid shallow breathing through vagal afferent pathways, that the reaction is independent of bronchoconstriction and that sulfur dioxide applied to the upper airways produces similar responses at much lower concentrations, suggesting that reflex effects of low concentrations of sulfur dioxide inhaled through the mouth is mediate by receptors in the upper rather than in the lower airways. This work was presented to the American Thoracic Society [15].

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