Nedocromil Sodium Worsens Ozone-Induced Lung Function Changes in Healthy Non-Smoking Subjects

H. Canan Hasanoglu[1], MD, Ghassan Noureddine[2], MD, Adnan Hasanoglu[3], MD,

William L. Eschenbacher[2], MD, FCCP

Ozone exposure can result in acute reversible restrictive and obstructive lung functions changes. The mechanism for these changes may be related to release of neuropeptides from sensory nerve endings in the airway. Nedocromil sodium may act by inhibiting neuropeptide release and thus could possibly prevent ozone-induced decrements in lung function. Four responders (non-smoking volunteers with >15% decline in FEV_1 to ozone exposure) and 5 non-responders (<5% decline in FEV_1 to ozone) were exposed to 30 minutes of exercise in 0.25-0.30 ppm ozone after receiving 2 days of nedocromil sodium with the last dose immediately before O_3 exposure. In both the responders and non-responders, pre-treatment with nedocromil sodium subsequent ozone exposure resulted in greater decreases in FEV_1 and FVC than with ozone exposure alone ($p<0.05$). Nedocromil sodium which is thought to work in part by inhibiting release of neuropeptides from airway sensory nerve endings worsened O_3^- induced pulmonary function changes in nonsmoking volunteers. [Journal of Turgut Özal Medical Center 1998;5(1):34-39]

Key Words: *Ozone, Nedocromil sodium, pulmonary function tests*

Nedocromil sodium'un ozonun neden olduğu solunum fonksiyon değişiklikleri üzerine etkisi

Hava kirliliği sonucu oluşan ozon, akciğerleri etkiler ve solunum fonksiyonlarında akut reverzibl restriktif ve obstrüktif tipte değişiklikler meydana çıkabilir. Bu değişikliklerin havayollarındaki sinir uçlarından nöropeptid salgılanması sonucu olabileceği düşünülmüştür. Nedocromil sodium (NS)'un etki mekanizmaları arasında nöropeptid salınım inhibisyonu bildirilmektedir ve ozonun sebep olduğu solunum fonksiyon bozukluklarına karşı koruyucu etkisi olabileceği düşüncesi ile çalışmamız düzenlenmiştir. Araştırma; 4'ü ozondan etkilenen (FEV_1'de azalma >%15) ve 5'i ozondan etkilenmeyen (FEV_1'de azalma <%5) toplam 9 sigara kullanmayan gönüllüde yapıldı. Herbirine 2 gün NS tedavisi (14 mg/gün) verildikten sonra özel olarak hazırlanmış odacık içinde, 30 dakika egzersiz ile 0.25-0.30 ppm ozon uygulandı. Her iki grupta da NS ile tedavi edilen olgularda; ilaç kullanılmadan uygulanan ozon sonucunda oluşan solunum fonksiyon değişikliklerine göre özellikle FEV_1 ve FVC'de anlamlı azalma saptandı ($p<0.05$). Sonuçlarımıza göre; nedocromil sodium'un ozonun solunum fonksiyonları üzerindeki olumsuz etkilerini arttırdığı kanısına varıldı. [Turgut Özal Tıp Merkezi Dergisi 1998;5(1):34-39]

Anahtar Kelimeler: *Ozon, nedocromil sodium, solunum fonksiyon testleri*

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1 İnönü University School of Medicine Department of Internal Medicine, Malatya, Turkey
2 Baylor College of Medicine The Methodist Hospital, Houston, Texas USA
3 İnönü University School of Medicine Department of General Surgery, Malatya, Turkey

Ozone is the major component of most polluted outdoor environments in the world. This photochemical oxidant is formed by atmospheric reactions from other pollutants including volatile organic compounds and oxides of nitrogen (1,2).

Ozone exposure can result in significant adverse health effects including hypersecretion, inflammation, epithelial cell damage, increased airway responsiveness, edema and bronchoconstriction. Although the mechanism of these effects isn't well known, it is suggested that some metabolites of ozone like oxygen radicals may stimulate cells or neural elements to cause the release of inflammatory mediators. Some studies demonstrated these mediators in the bronchial lavage of subjects after ozone exposure (3-6).

Nedocromil sodium (NS) is a newer and more potent analog of chromolyn sodium. Both of these agents may be effective by either stabilizing mast cells or by inhibiting neuropeptide release from nerve endings such as C-fibers (7,8).

Nedocromil sodium may act by inhibiting neuropeptide release and thus could possibly prevent ozone induced decrements in pulmonary functions. The study is planned to show the effect of NS in human pulmonary functions with ozone exposure.

SUBJECTS AND METHOD

Approval for this study was obtained from the Human Research Committee of Baylor College of Medicine. Subjects were between 18-45 yr. of age, nonsmokers and had no medical condition that would make exercise hazardous. All subjects underwent an evaluation of a history and physical examination. The subjects that had no allergy and pulmonary disease history and having normal physical examination and pulmonary function tests were included to the study. Informed consent was obtained prior to entry.

It is known from the previous studies that there is a variability of responsiveness among human subjects to the physiological effects of ozone exposure. Some normal subjects are quite responsive (>15% decline in forced expiratory volume 1 second (FEV_1) to ozone exposure) whereas other subjects can be quite insensitive to ozone (<5% decline in FEV_1 to ozone exposure). The volunteers first characterized according to their response to ozone exposure. This exposure consisted of 30 minutes of exercise on a cycle ergometer (Mijnhardt model Kem-3) in an environmental chamber (2.1x1.9x1.1 meter stainless steel chamber located at the Methodist hospital) at an ozone concentration of 0.25-0.30 ppm. An ozone generator (OREC model V5AR) was connected to the chamber. Ozone concentration was continuously monitored with an ozone photometer (Dasibi Model 1008 analyzer). The workload on the cycle ergometer was adjusted so that each subject achieved a minute ventilation of 30 liters/min/m^2 of body surface. Spirometry performed before and after exposure. Resistance of airways (Raw), total lung capacity (TLC), expiratory residual volume (ERV), residual volume (RV) were determined by using a variable pressure body plethysmograph. Then 5 nonresponders and 4 responders were included to the study.

Study was done according to these steps:

Step I: Every subject exercised 30 minutes on a cycle ergometer (adjusted as mentioned above) in the room air.

Step II: Every subject exposed to 0.25-0.30 ppm ozone on a cycle ergometer in the environmental chamber for 30 minutes.

Step III: Every subject exposed to 0.25-0.30 ppm ozone on a cycle ergometer in the environmental chamber for 30 minutes after 2 days of nedocromil sodium inhalation therapy with the last dose immediately before ozone exposure (4x2 puff/day, 14 mg/day).

Spirometry was performed before and after every exercise in the three steps and at least 2 weeks interval was given between every step.

The characteristics of the subjects were shown in Table 1. Eight male and 1 female were included to the study, ages were between 24 and 44 with a mean age

Table 1. Characteristics of the subjects

	Sub No	FEV_1 diff (%)	Race		Sex		Age	Hight (Inch)	Weight (Lb)
			B	C	M	F			
Responder	4	-25.75	1	3	4		27.25 ± 2.36	68.75 ± 7.45	173.0 ± 19.3
Nonresponder	5	-0.8	1	4	4	1	36.8 ± 3.4	70.00 ± 5.09	172.6 ± 20.4
	9	p<0.05	p>0.05		p>0.05		p<0.05	p>0.05	p>0.05

of 32.55±6.89.

The symptoms of the subjects after ozone exposure and NS+ozone exposure were asked, inspected and classified as;

0: no symptom, **1**: mild, **2**: moderate, **3**: severe, **4**: very severe.

Wilcoxon paired sample and Mann-Whitney U tests were used for statistical analysis.

RESULTS

Pulmonary function changes after ozone exposure and ozone exposure after 2 days of Nedocromil sodium therapy in 9 healthy nonsmoker subjects were compared in Figure 1. Pretreatment with NS and subsequent ozone exposure resulted in greater decreases in FEV_1 and forced vital capacity (FVC) than with ozone exposure alone ($p<0.05$). ERV, IC, TLC was decreased and RV, Raw was increased both in NS+ozone exposure and ozone exposure alone.

When the responders and nonresponders were compared FEV_1 and FVC were significantly lower in the responders than the nonresponders after ozone exposure ($p<0.05$). Decline of FEV_1 and FVC after NS+ozone exposure was significantly higher than the decline after ozone exposure alone in the nonresponders ($p<0.05$) (Table 2).

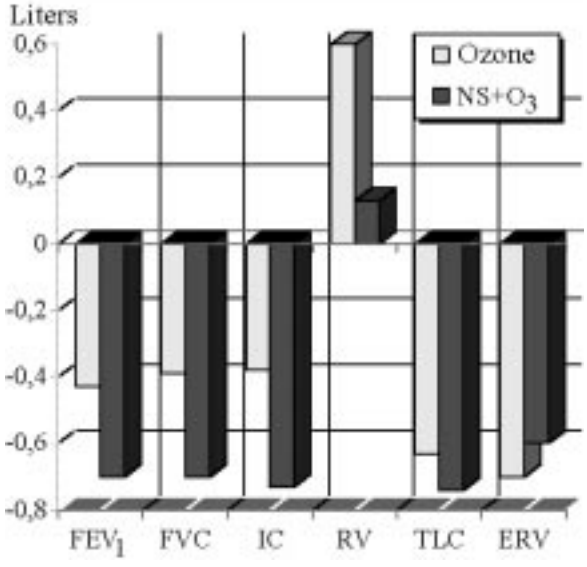

Figure 1. Comparison of pulmonary function test differences before and after ozone exposure and nedocromil sodium + ozone exposure in 9 subjects

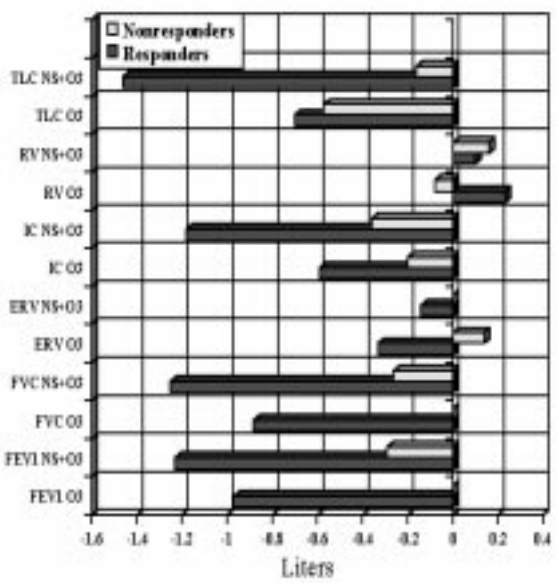

Figure 2. Comparison of pulmonary function tests between responders and non-responders after $NS+O_3$ and O_3

FEV_1, FVC, IC, and TLC both decreased in the responders and nonresponders, but more after the NS treatment+ozone exposure than the ozone exposure alone. Raw and RV increased both after the ozone exposure and NS+ozone exposure in responders; but in nonresponders Raw and RV increased only after NS+ozone exposure (Fig. 2).

Cough, chest tightness and throat irritation were the most common symptoms after ozone exposure (Table 3). This symptoms worsened after the nedocromil treatment+ozone exposure (Figure 3). Symptoms were more severe in the responders than the nonresponders. The mild and moderate symptoms healed in 1 or 2 hours, while the effects of ozone continued 24 or 48 hours in the subjects having severe and very severe symptoms.

DISCUSSION

Ozone is less water-soluble than other pollutants and penetrates more peripherally. Ozone concentration peaks is between 10 AM and 5 PM in the day time and highest levels are in summer, spring and higher in urban than nonurban areas (1,2). Exposure to ozone can result in decreases in lung function, increases in airway resistance and increases in bronchial responsiveness, inflammatory responses and cellular damage in the epithelium of the

Table 2. Comparision of pulmonary function test differences before and after, ozone exposure and nedocromil sodium+ozone exposure in reponders and nonresponders.

		Responders (n=4)	Nonresponders (n=5)	p
FEV_1 (lt)	O_3	-0.97 ± 0.28	0 ± 0.04	<0.05
	$NS+O_3$	-1.23 ± 0	-0.29 ± 0.03	<0.05
FVC (lt)	O_3	-0.88 ± 0.30	0 ± 0.04	<0.05
	$NS+O_3$	-1.25 ± 0.63	-0.26 ± 0.05	>0.05
FEV_1/FVC %	O_3	-7 ± 1.78	-0.2 ± 0.37	<0.05
	$NS+O_3$	-7.5 ± 3.28	-1.2 ± 2.13	>0.05
Raw cm H_2O. 1^{-1} .s	O_3	1.29 ± 0.61	-0.52 ± 0.47	<0.05
	$NS+O_3$	1.07 ± 0.44	0.25 ± 0.21	>0.05
ERV (lt)	O_3	-0.33 ± 0.08	0.14 ± 0.14	<0.05
	$NS+O_3$	-0.14 ± 0.24	0 ± 0.05	>0.05
IC (lt)	O_3	-0.59 ± 0.25	-0.2 ± 0.34	>0.05
	$NS+O_3$	-1.18 ± 0.53	-0.36 ± 0.09	>0.05
RV (lt)	O_3	0.23 ± 0.11	-0.08 ± 0.16	>0.05
	$NS+O_3$	0.1 ± 0.2	0.16 ± 0.09	>0.05
TLC (lt)	O_3	-0.7 ± 0.18	-0.57 ± 0.26	>0.05
	$NS+O_3$	-1.46 ± 0.45	-0.16 ± 0.18	<0.05

The values are mean differences before and after exposure ± SE

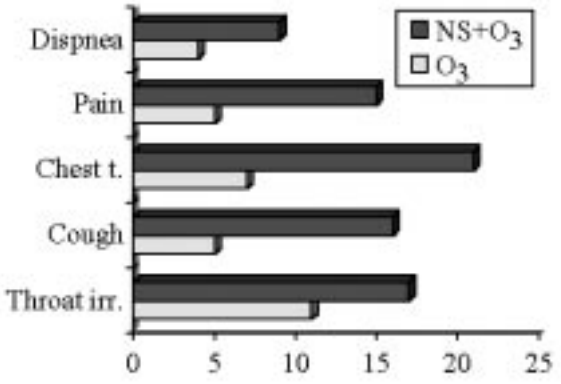

Figure 3. Comparison of the symptoms of 9 subjects after $NS+O_3$ and O_3 exposure alone

conductive airways (3,4,9,10-12). These effects of ozone are more obvious when ozone level is more than 0.2 ppm (3).

The mechanism responsible from these ozone induced pulmonary changes are not well understood. Recent studies have shown that the neuromediator substance-P and 8 epiprostoglandin F_{2alpha} (a marker of oxidative stress) are increased in the conductive airways in normal subjects after ozone exposure (6). These results suggest that ozone can activate C-fibers (sources of substance-P) and there is a correlation between the presence of substance-P and the degree of oxidative stress. Other studies have suggested that certain mast cell mediators may be released after ozone exposure and could account for some pulmonary changes noted (9). But one of the studies showed that cyclooxygenase products of arachidonic metabolites didn't increase after ozone exposure (13).

Nedocromil sodium is a potent inhibitor of mucosal and connective tissue mast cells in primates and it inhibits antigen-induced bronchoconstriction in man (8). It is also a potent inhibitor of reflex bronchoconstriction induced by inhaled sulfur dioxide and bradykinin both of which may act by stimulating airway C-fibers (14).

It was demonstrated before that some of the normal population have sensitivity to ozone, some others not (15,16). We supposed to inhibit the ozone effects on pulmonary functions with NS treatment especially in the responders since some animal studies showed that NS may inhibit some side effects of ozone exposure and respiratory resistance can be diminished by 50% with cromolyn sodium pretreatment (13). Surprisingly, the results of the pulmonary function tests revealed that the decreases in FEV_1 and FVC worsened after the NS treatment The nonresponders in our study who weren't sensitive to ozone became sensitive after two days NS treatment and showed pulmonary function changes like responders. FEV_1, FVC, IC and TLC decreased whereas RV and Raw increased. Also the symptoms of the responders and nonresponders deteriorated after pretreatment of NS with ozone exposure.

Capsaicin the active ingredient of red pepper, in animals has been shown to stimulate C-fibers and causes in man cough and bronchoconstriction (17,18). Hansson's study showed that NS treatment failed to inhibit the cough and bronchoconstriction induced by inhaled capsaicin (17). Our study results also suggested that NS effects may be from a different way than the C-fibers. Jackson's study demonstrated that inhaled NS do not inhibit but stimulates C fiber endings (19). This study can help us to understand the mechanism of NS effects in ozone induced pulmonary function changes. In the other hand, NS was found effective in the asthmatic patients troubled by exercise induced symptoms in many studies (20-22). Rubinchik and colleagues demonstrated that mast cells activation can be inhibited by NS in vitro (23). One in vitro study indicated that NS inhibits IgE synthesis (24). Also many studies confirmed that NS or cromolyn

Table 3. Comparison of the symptoms after O_3 exposure and NS+O_3

		Throat irritation		Cough		Chest thightness		Pain		Dispne	
	Name	**O_3**	**NS+O_3**	**O_3**	**NS+O_3**	**O_3**	**NS+O_3**	**O_3**	**NS+O_3**	**O_3**	**NS+O_3**
RESPONSE	GN	4	4	2	4	2	4	2	4	4	4
	EB	1	1	2	2	0	1	2	2	0	0
	AW	0	2	0	2	0	3	0	2	0	1
	KJ	1	1	0	0	1	2	1	2	0	0
	AH	2	3	0	2	1	2	0	0	0	0
	MK	1	2	0	2	0	2	0	1	0	1
	CM	0	1	0	0	1	3	0	2	0	1
	JL	0	1	0	1	1	1	0	1	0	1
	JL	2	2	1	3	1	3	0	1	0	1
	Total	10	17	5	16	7	21	5	15	4	9

sodium are both significantly effective for treatment of mild to moderate asthma (25-27).

According to our study results, NS didn't inhibit the bronchoconstriction and restrictive pulmonary effects of ozone. Controversy, NS increased these effects of ozone and also provoked the ozone response in nonresponders and they also became sensitive to ozone.

In conclusion; nedocromil sodium which is thought to work in part by inhibiting release of neuropeptides from airway sensory nerve endings that is known to be released after ozone exposure, worsened O_3 induced pulmonary function changes in nonsmoking subjects. The mechanism is uncertain but will be studied further by measuring neuropeptides in the airway lining fluid after O_3 exposure with and without pretreatment with Nedocromil sodium.

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Correspondence : H. Canan HASANOĞLU, MD
İnönü University School of Medicine
Department of Internal Medicine
44069 Kampüs, MALATYA
Fax : + (422) 341-0610
E-Mail Address : ahasanoglu@ihlas.net.tr