Eur Respir J
1989, 2, 229–233

Effects of vitamin C on airway responsiveness to inhaled histamine in heavy smokers

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Effects of vitamin C on airway responsiveness to inhaled histamine in heavy smokers. C. Bucca, G. Rolla, E. Caria, W. Arossa, M. Bugiani.
ABSTRACT: Histamine bronchial threshold, the provocation concentration of histamine causing a 25% fall in maximal expiratory flow at 50% of forced vital capacity from the control value ($PC_{25}MEF_{50}$), was measured in seven heavy smokers and in seven sex- and age-matched nonsmokers before and one hour after ingestion, double-blind, of vitamin C (2 g) or placebo. Smokers had significantly lower baseline values of serum ascorbate, maximal expiratory flow at 50% of forced vital capacity (MEF_{50}) and $PC_{25}MEF_{50}$: the latter was negatively related to serum ascorbate ($r=-0.85$; $p<0.001$). Acute treatment with vitamin C produced a significant decrease in $PC_{25}MEF_{50}$ in smokers (95% confidence limit (CL) from 4.87–3.36 to 2.91–2.01 $mg \cdot ml^{-1}$; $p=0.017$), whilst it had no effect in nonsmokers. A preliminary open study on the effect of prolonged administration of vitamin C (1 g daily) was performed in smokers. One week of treatment produced a further significant decrease in $PC_{25}MEF_{50}$ ($p<0.0001$). Our results suggest that in heavy smokers histamine bronchial responsiveness may be attenuated by chronic ascorbate deficiency. In these circumstances, acute and short-term treatment with vitamin C may increase the bronchoconstrictive response to inhaled histamine.
Eur Respir J., 1989, 2, 229–233.

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Keywords: Airway responsiveness to histamine; antioxidants; ascorbic acid deficiency; cigarette smoking; vitamin C.

Received: February, 1988; accepted after revision 24 November, 1988.

It has been postulated that vitamin C (ascorbic acid) may have a role in the regulation of airway tone and modulation of airway reactivity [1–4]. This assumption is based on some metabolic actions of vitamin C, such as participation in maintaining lung redox state [4], modulation of prostanoid metabolism [5, 6], promotion of nonenzymatic histamine degradation [7]. Human studies show that ascorbic acid has a protective effect against the increase in bronchial responsiveness induced by the oxidants ozone [1] and nitrogen dioxide (NO_2) [2]. Trials to reduce bronchial hyperreactivity in asthmatics with vitamin C have yielded conflicting results [3, 8–11].

Epidemiological studies have shown the effect of heavy smoking in reducing ascorbic acid levels in blood [12]. This finding has been attributed [13] either to the increased need for reducing agents imposed by the chemical oxidants contained in tobacco smoke [14, 15], such as carbon particles, acetaldehyde and NO_2, or to some metabolic properties of nicotine. Ascorbic acid, in fact, participates in the biosynthesis of serotonin and catecholamines the release of which is stimulated by nicotine [13].

We wondered whether vitamin C deficiency may contribute to the increase in nonspecific bronchial responsiveness found in heavy smokers [16, 17]. We performed a double-blind study on the acute effect of vitamin C on histamine airway responsiveness in seven heavy smokers as compared to seven sex- and age-matched nonsmokers. We also performed a preliminary open study on the effect of a one week administration of vitamin C in smokers.

Subjects and methods

Seven heavy smokers (more than 20 cigarettes per day) and seven sex- and age-matched nonsmokers, members of the hospital staff, gave informed consent to take part in the study. The smokers were mildly symptomatic (mild cough and sputum in the morning). Baseline spirometry was within the normal range in all subjects. None reported an asthmatic and atopic history or any airway infection in the last two months. No subject was taking vitamin C supplements or bronchoactive drugs.

The acute effect of vitamin C on airway reactivity to inhaled histamine was studied against placebo, in a double-blind randomized fashion. Subjects were examined on two consecutive days, in the morning at the same hour. On each day, spirometry and histamine bronchial threshold were measured before and after oral intake of either vitamin C (2 g) or placebo. Ascorbic acid and placebo were formulated in chewable tablets with orange and lemon flavours. The second challenge was performed one hour apart or later if forced expiratory volume in one second (FEV_1) had not returned to baseline. A blood sample was collected on day 1, before treatment, for the measurement of serum ascorbic acid and analysed within 4 h by a colourimetric method based on the reduction of a tetrazolium salt (Boehringer Biochemia, Mannheim).

A preliminary open study on the effect of prolonged treatment was performed in smokers by repeating the inhalation challenge after one week administration of vitamin C (1 g daily).

Baseline readings of lung volumes and flows, taken as the best of five measurements, were obtained by a computerized OHIO 840 spirometer. Forced vital capacity (FVC), FEV_1 and the maximal expiratory flow at 50% of FVC (MEF_{50}) were calculated from the curves. Reference values were obtained form QUANJER [18] for FVC and FEV_1 and from KNUDSON *et al.* [19] for MEF_{50}.

Bronchial challenges to inhaled histamine were carried out using a modification of the American Thoracic Society (ATS) procedure [20]. Histamine was delivered in doubling concentrations of 0.25, 0.5, 1, 2, 4, 8, 16 and 32 $mg \cdot ml^{-1}$, by a compressed air nebulizer controlled by a breath actuated MEFAR dosimeter. The dosimeter was set to nebulize for 0.6 s; the mass median diameter of the particles was 3.5–4 μm. Each dose of histamine was inhaled by taking five slow vital capacity breaths from the nebulizer. FEV_1 and MEF_{50} were measured 2 min after each nebulization; the interval between one dose and the next was about 5 min. The test was stopped when FEV_1 had dropped by 20% or the highest histamine concentration was reached. Smokers refrained from smoking at least 1 h before each test.

Analysis of results

Histamine responsiveness was assessed on the basis of changes in MEF_{50}, according to the finding that flows in the lower half of FVC are more sensitive in detecting an induced bronchoconstriction in smokers [17]. To account for changes in FVC, the maximum expiratory flow/volume curves were matched at total lung capacity. The provocation concentration of histamine causing a 25% fall in MEF_{50} from the control value ($PC_{25}MEF_{50}$) was calculated from the dose/response curve. The abscissa represented the histamine concentration on a logarithmic scale and the ordinate the percentage change in MEF_{50}. Bronchial hyperreactivity was diagnosed when the $PC_{25}MEF_{50}$ was 8 $mg \cdot ml^{-1}$ or lower. Logarithmic transformation of $PC_{25}MEF_{50}$ was used for statistical analysis. Geometric means of $PC_{25}MEF_{50}$ and means±SEM of the other variables were used in reporting results.

The differences in baseline lung function values between smokers and nonsmokers were evaluated by Student's t-test for unpaired data. One-way analysis of variance was used to assess the reproducibility of baseline lung function and $PC_{25}MEF_{50}$ and to evaluate the influence of vitamin C on prechallenge lung function in each subject. The influence of serum ascorbic acid or prechallenge MEF_{50} on $PC_{25}MEF_{50}$ was evaluated by linear regression analysis. Two-way analysis of variance with replications (ANOVA) was used to compare the effect of active treatment and placebo in smokers and nonsmokers. A value of $p<0.05$ was considered to be statistically significant. The 95% confidence limits (CL) of $PC_{25}MEF_{50}$ before and after vitamin C were computed to verify the validity of the significant differences.

Results

General characteristics and mean baseline values of serum ascorbate, FEV_1 and MEF_{50} (expressed as % of predicted) of smokers and nonsmokers are reported in table 1. Smokers had significantly lower values of serum ascorbic acid, MEF_{50}, and $PC_{25}MEF_{50}$; five of the seven smokers had bronchial hyperreactivity. In smokers, log-$PC_{25}MEF_{50}$ was negatively related to serum ascorbic acid ($r=-0.85$; $p<0.001$), (fig. 1). In the nonsmokers, serum ascorbate was in the normal range and was unrelated to

Table 1. – Comparison between baseline results in smokers and nonsmokers (mean and SEM)

		Smokers n=7	Nonsmokers n=7
Age	yrs	39.9 (4.9)	33.0 (3.7)
Males/females	n	3/4	3/4
Cigarettes·day⁻¹	n	25.4 (3)	-
Pack-years	n	20.6 (4.7)	-
Ascorbic acid in serum	$mg \cdot 100\ ml^{-1}$	0.21 (0.04)	0.72 (0.07)**
FEV_1	% pred	106 (8)	125 (7)
MEF_{50}	% pred	78 (10)	119 (10)*
$PC_{25}MEF_{50}<8\ mg \cdot ml^{-1}$		5/7	1/7*

*: $p<0.05$; **: $p<0.001$; n: number; FEV_1: forced expiratory volume in one second; MEF_{50}: maximal expiratory flow at 50% of forced vital capaity; $PC_{25}MEF_{50}$: provocation concentration of histamine causing a 25% fall in MEF_{50} from control value.

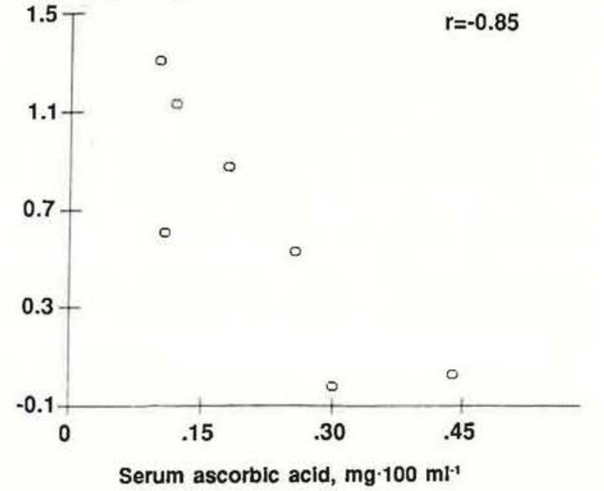

Fig. 1. – Relationship between $logPC_{25}MEF_{50}$ and serum levels of ascorbic acid in smokers. For abbreviations see table 1.

Table 2. – Geometric mean and 95% CL of $PC_{25}MEF_{50}$ observed in smokers and nonsmokers during study A

	Before placebo		After placebo		Before vitamin C		After vitamin C	
	Mean	95% CL mg·ml⁻¹	Mean	95% CL mg·ml⁻¹	Mean	95% CL mg·ml⁻¹	Mean	95% CL mg·ml⁻¹
Smokers	4.22	3.79 4.69	4.04	3.63 4.50	4.19	3.77 4.66	2.42	2.17 2.69
Nonsmokers	14.45	12.99 16.09	14.53	13.05 16.17	14.69	13.20 16.35	13.78	12.38 15.33

$PC_{25}MEF_{50}$ was significantly lower in smokers than in nonsmokers (p=0.018). The $PC_{25}MEF_{50}$ of smokers was significantly lower after vitamin C than in baseline conditions or after placebo (p=0.017). 95% CL: 95% confidence limits.

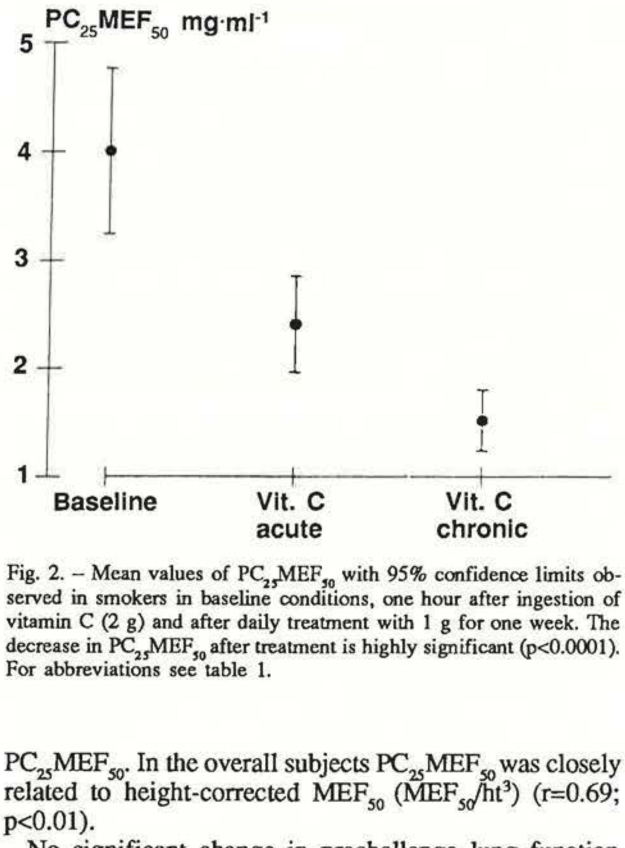

Fig. 2. – Mean values of $PC_{25}MEF_{50}$ with 95% confidence limits observed in smokers in baseline conditions, one hour after ingestion of vitamin C (2 g) and after daily treatment with 1 g for one week. The decrease in $PC_{25}MEF_{50}$ after treatment is highly significant (p<0.0001). For abbreviations see table 1.

$PC_{25}MEF_{50}$. In the overall subjects $PC_{25}MEF_{50}$ was closely related to height-corrected MEF_{50} (MEF_{50}/ht^3) (r=0.69; p<0.01).

No significant change in prechallenge lung function values was observed after placebo or vitamin C in either smokers or nonsmokers. The results of two-way analysis of variance on the acute effect of vitamin C or placebo on $PC_{25}MEF_{50}$ in the two groups are reported in table 2. conditions, and after acute and chronic treatment with vitamin C were highly significant (p<0.0001). As shown in figure 2, the 95% CL of $PC_{25}MEF_{50}$ in baseline conditions, after acute and after one week's treatment with vitamin C, did not overlap.

Discussion

This study confirms previous observations that heavy smokers have greater histamine bronchial responsiveness [16, 21] and lower serum levels of ascorbic acid [12] than nonsmokers. Several mechanisms have been claimed to explain ascorbate deficiency in heavy smokers [13], such as increased oxidation by oxidants and free radicals contained in tobacco smoke, increased biosynthesis of catecholamines and serotonin induced by nicotine, and inadequate dietary intake. At present, it is not known whether vitamin C deficiency has any influence on airway tone and responsiveness. In our smokers, the levels of endogenous ascorbic acid were negatively correlated with $PC_{25}MEF_{50}$, indicating that chronic deficiency attenuated rather than increased their airway responsiveness. In addition, acute treatment with vitamin C caused a significant increase in their histamine-induced bronchoconstriction, which was not observed after placebo. In contrast, no change in $PC_{25}MEF_{50}$ was observed in nonsmokers after active treatment or placebo. The results obtained in smokers after one week of treatment with vitamin C, although preliminary and not tested against placebo, support those of the acute study, showing a further significant increase in airway responsiveness.

These effects of ascorbic acid in smokers were rather unexpected in view of its metabolic properties. Moreover, we are not aware of other investigations reporting such a negative effect of vitamin C on normal or asthmatic airways. In fact, a decrease in airway responsiveness, or at least no change, would have been more expected in smokers after treatment, for several reasons.

Firstly, as a reducing agent, vitamin C should attenuate the noxious effects induced by oxidants contained in the gas phase of tobacco smoke. In this regard, studies in healthy subjects experimentally exposed to ozone [1] or NO_2 [2] demonstrate that vitamin C protects against oxidant-induced increase in airway responsiveness.

Secondly, vitamin C could attenuate the bronchoto enhance that of the dilator prostaglandin E_2 (PGE_2) [5] and prostacyclin (PGI) [22]. In fact, inhibited synthesis of PGE, but not of PGF_2 has been found in alveolar macrophages from smokers [23]. On the other hand, modulation of prostaglandin synthesis has been claimed to explain the attenuation of airway hyperreactivity by ascorbic acid observed in some instances in normal and asthmatic subjects [3, 4, 10]. However, although release of PGE by histamine has been shown in guinea-pig trachea [24], prostanoids do not seem to alter histamine dose/response curves in humans [25].

A decrease in histamine-induced bronchoconstriction by vitamin C could also be expected due to its ability to promote non-enzymatic histamine degradation [7]. On the contrary, an increase in nicotine-induced release of catecholamines by ascorbic acid [13] could not be observed in our study, as subjects refrained from smoking for at least 2 h before the second challenge.

Thus, it is difficult to explain the increase in histamine responsiveness produced by ascorbic acid in our smokers. An increase in airway tone is unlikely, as no change in prechallenge lung function was observed after treatment.

A possible explanation is offered by the results of experimental observations in guinea-pigs maintained on a scorbutic diet. After 30 days, the animals developed a considerable reduction in the conversion of histidine to histamine and in airway sensitivity to histamine aerosol [26]. These findings support our hypothesis that histamine responsiveness in smokers was attenuated by vitamin C deficiency. In another study it was reported that histamine sensitivity could be restored to normal by treatment with vitamin C [27]. We may thus suppose that the decrease in the $PC_{25}MEF_{50}$ of smokers after treatment could be the consequence of restoration of histamine sensitivity, which might be weakened by their deficiency status. However, even if this explanation is attractive, its validity has to be verified in humans. Moreover, the supposed decrease in airway sensitivity in our smokers has to be placed against their increased bronchoconstrictive response to histamine. In this regard, most authors agree that bronchial hyperresponsiveness in smokers develops as a consequence of altered geometry of the airways, chronically injured by tobacco smoke [21, 28–31]. Our findings in smokers are in agreement with this hypothesis, in that their decreased MEF_{50} indicates the presence of structural changes in peripheral airways [32] and its close relationship with $PC_{25}MEF_{50}$ suggests that the decrease in peripheral airway calibre was responsible for their increased responsiveness.

On the other hand, a reduced sensitivity to inhaled irritants in smokers has also been proposed by others. This hypothesis is based on the findings that young asymptomatic smokers responded less to histamine than did matched nonsmoking controls [28] and that smokers with chronic airflow limitation and a histamine threshold comparable to that of asthmatics were significantly less responsive to methacholine than asthmatics [16]. The authors suggested that the decrease in sensitivity could be attributed to an inhibitory effect of nicotine on parasympathetic ganglia, like that produced by other ganglion blockers [33], or on irritant receptors. Histamine-induced bronchoconstriction, in fact, is thought to be the result of both a direct action on the smooth muscle and of a parasympathetic reflex initiated at the irritant receptors [34].

Whether vitamin C increased histamine responsiveness of our smokers by contrasting these effects of nicotine remains a speculation.

In conclusion, our results suggest that in heavy smokers airway responsiveness to histamine may be attenuated by chronic ascorbate deficiency. In these circumstances acute and short-term treatment with vitamin C, by restoring histamine sensitivity, may increase the bronchoconstrictive response to the inhaled agent.

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Effets de la vitamine C sur la réactivité des voies aériennes à l'histamine inhalée chez les grands fumeurs. C. Bucca, G. Rolla, E. Caria, W. Arossa, M. Bugiani.

RÉSUMÉ: Le seuil de réactivité bronchique à l'histamine ($PC_{25}MEF_{50}$) a été mesuré chez 7 grands fumeurs et chez 7 non fumeurs répartis de façon égale pour l'âge et le sexe, après l'absorption en double aveugle de 2 g de vitamine C ou de placebo. Les valeurs basales d'ascorbate, de MEF_{50} et de $PC_{25}MEF_{50}$ sont abaissées chez les fumeurs. $PC_{25}MEF_{50}$ est en relation avec le taux d'ascorbate sérique ($r=-0.85$, $p<0.001$). Un traitement aigu à la vitamine C a produit une diminution significative du $PC_{25}MEF_{50}$ chez les fumeurs (limite de confidence 95% depuis 4.87–3.36 vers 2.91–2.01 $mg \cdot ml^{-1}$, $p=0.017$), alors qu'il n'avait aucun effet chez les non fumeurs. Une étude ouverte préliminaire sur l'effet de l'administration prolongée de 1 g de vitamine C par jour a été conduite chez les fumeurs. Un traitement d'une semaine a produit une diminution complémentaire significative de $PC_{25}MEF_{50}$ chez les fumeurs ($p<0.0001$). Nos observations suggèrent que chez les grands fumeurs l'hyperréactivité bronchique à l'histamine peut être atténuée par une déficience chronique en ascorbate. Dans ces circonstances, un traitement aigu à court terme à la vitamine C pourrait augmenter la réponse bronchoconstrictive à l'histamine inhalée.

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