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**References and Figures are available in the above versions.**

From the Berlin-Buch Research Institute for Pulmonary Diseases and Tuberculosis  
(Official Director: Dr. P. Luther)

## **Effect of ascorbic acid on the clinical course of infection-related bronchial asthma and the formation of reactive oxygen metabolites by BAL cells**

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### **Key words**

Infection-related bronchial asthma, ascorbic acid, antioxidant, peak flow, bronchial hyperreactivity, bronchoalveolar lavage, alveolar differential cell count, chemiluminescence, reactive oxygen metabolites

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### **List of abbreviations**

AM Alveolar macrophages  
BAL Bronchoalveolar lavage  
BHR Bronchial hyperreactivity  
CL Chemiluminescence  
DCC Differential cell count  
ROM Reactive oxygen metabolites  
R<sub>AW</sub> Airway resistance (measured by occlusive pressure techniques)

### **Summary (Authors' summary in english)**

Possible anti-asthmatic effectiveness of ascorbic acid was checked, in a double blind study, on patients with infection-related bronchial asthma. Basic medication to 29 out-patients was accompanied by three oral doses of 5 g/day of ascorbic acid, as compared to placebo, through 35 days. Testing periods were randomised by cross-over design with seven-day washout periods. The following parameters were investigated and were evaluated:

- Daily asthma symptom score;
- Four measurements per day of expiratory peak flow, throughout the entire study;
- Three checks throughout study of bronchial hyperreactivity, using histamine provocation;
- Broncho-alveolar lavage at the end of testing periods, with determination of alveolar differential cell count and measurement of metabolic activity of broncho-alveolar cells, using chemiluminescence;
- Global assessment of effectiveness and tolerance by doctor and patient.

Ascorbic acid exhibited merely poor broncholytic action. Symptom scores were slightly improved in the course of treatment, and peak flow values were slightly increased, as well. Hence, clinically relevant anti-asthmatic and, more specifically, broncholytic effects were not observed. However, bronchial hyperreactivity was reduced by uptake of ascorbic acid in 52 percent of all asthma patients involved. Alveolar differential cell count in patients with infection-related bronchial asthma was characterised by alveolar lymphocytosis. Chemiluminescence measurements were applied to alveolar macrophages and revealed reduced chemiluminescence response under the impact of ascorbic acid. These findings are likely to support the assumption that ascorbic acid, an anti-oxidant, reduced the buildup of reactive oxygen metabolites in patients with infection-related asthma and thus counteracted the inflammatory pathogenetic mechanism and, consequently, might be conducive to moderate lowering of bronchial hyperreactivity. The use of ascorbic acid for prophylactic medication on patients with bronchial hyperreactivity or mild forms of asthma appears to be a possible option, as a result of this study. Due consideration should be given to contraindications to administration of anti-oxidants, such as purulent infections.

### **Summary (Translation from German; English translation by original authors above)**

The potential anti-asthmatic effectiveness of ascorbic acid was studied in patients with infection-related bronchial asthma. In addition to the basic medication, 29 outpatients were additionally treated for a period of 35 days with 5 g/day of ascorbic acid in comparison to oral placebo in 3 daily doses. The allocation of the testing periods was randomized by cross-over design with 7-day washout periods. The following parameters were investigated and evaluated: daily asthma symptom score, measurement of the expiratory peak flow 4 times per day during the entire course of the study, testing of bronchial reactivity using histamine provocation at 3 time points during the course of the study, broncho-alveolar lavage at the end of the study periods with determination of the alveolar differential cell count and measurement of metabolic activity of the bronchoalveolar cells using chemiluminescence, and global assessment of the efficacy and tolerability by doctor and patient.

Ascorbic acid exhibited a weak broncholytic effect. During treatment, symptom scores were slightly improved and there was also a slight increase in peak flow values. Hence, a clinically relevant anti-asthmatic and in particular, broncholytic effect was not observed. However, bronchial hyperreactivity was reduced by taking ascorbic acid in 52 percent of the asthma patients. The alveolar differential cell count was characterized by alveolar lymphocytosis in patients with infection-related bronchial asthma. Chemiluminescence measurements of alveolar macrophages revealed a reduced chemiluminescence response under the impact of ascorbic acid. These findings suggest that ascorbic acid, as an antioxidant, reduces the formation of reactive oxygen metabolites in patients with infection-related asthma and thus counteracts the inflammatory pathomechanism and consequently might be able to bring about moderate lowering of bronchial hyperreactivity. The use of ascorbic acid as prophylactic medication for patients with bronchial hyperreactivity or mild forms of asthma appears to be a possibility as a result of this study. Due consideration should be given to possible contraindications to administration of antioxidants, e.g., the presence of purulent infections.

## Introduction

In the past 40 years, a number of works have been published that deal with the effect of ascorbic acid (4, 29) on the clinical course of bronchial asthma or on the histamine, antigen or metacholine induced bronchospasm, although some of the results that were achieved were contradictory. While in some studies, a protective effect (1, 12, 15, 19, 28, 35) of ascorbic acid on the pharmacodynamic or allergen induced bronchospasm or clinical course of bronchial asthma was established, in other cases, no effect of ascorbic acid (16, 17) could be found. The possible positive effect of ascorbic acid on bronchial asthma could be due to its antioxidative properties (2, 3, 5, 9). Lipid peroxide and reactive oxygen metabolites (ROM) ( $O_2^-$ ,  $H_2O_2$ ,  $OCl^-$ ,  $OH^-$ ) which can be formed in excess in the lungs under pathological conditions stimulate, e.g., arachidonic acid metabolism and lead to the formation of cyclo-oxygenase and lipoxygenase products which have a bronchoconstrictive effect, such as prostaglandins and leukotrienes (8, 12).

In general, in vivo, various antioxidants (including ascorbic acid) and antioxidant enzymes, so-called radical scavengers protect the lungs from damage due to reactive oxygen metabolites and lipid peroxide (10). In the presence of increased activity of the pulmonary inflammatory cells (e.g., alveolar macrophages, granulocytes) with bronchial asthma, the equilibrium between oxidative and antioxidative capacity in the lungs may be displaced in favor of the oxidative process, such that additional administration of ascorbic acid at a high dose (5 g/day) and over a longer period of time may be expected to provide a therapeutic effect. In the present work, the hypothesis of an anti-asthmatic effect of ascorbic acid is to be tested (6, 7).

## Materials and methods

A total of 29 patients with infection-related bronchial asthma (18 men and 11 women from 18 to 60 years of age) were recruited for the double blind crossover study under ambulatory conditions. Inhaled and systemic corticosteroids, renal disease and acute and serious purulent infections were considered to be exclusion criteria. The study was conducted over a period of 35 days. It was divided into a 2-week placebo period, 1-week wash-out test and 2-week ascorbic acid period. The sequence of the test periods was chosen at random (Fig. 1).

For the present study, in addition to the basic medication, a daily dose of 5 g ascorbic acid (Ascorvit containing 500 mg) was defined in comparison to oral placebo in 3 individual doses. Coated tablets from VEB Jenapharm, Clinical Research Division, lot numbers 150485 and 050886 were used. The patients received packages furnished with lot numbers that were coded according to the double blind study conditions. The code was not broken during the study.

During a pre-period of 2 weeks, the starting values for pulmonary function parameters were to be determined under the anti-asthmatic treatment up to that time. At the same time during this period, the patients were to learn how to complete the diary and determine the maximum expiratory peak flow with the peak flow meter.

During the 35-day double blind treatment period, the patients were seen 4 times: on the 8<sup>th</sup>, 14<sup>th</sup>, 29<sup>th</sup> and 35<sup>th</sup> day after the start of treatment. In the middle of the verum [HH: verum = active intervention] and placebo periods, measurements of bronchial hyperreactivity were performed again and at the end of the test period, a broncho-alveolar lavage with cytological examination and chemiluminescence measurement were performed.

In principle, the efficacy of an anti-asthmatic agent cannot be determined by a single target parameter. Even asthma symptoms are expressed in distinctly different ways. To record the symptoms, the complaints were listed separately in a diary (Table 1).

Each patient was given a peak flow monitor (Vitalograph) at the start of the study to measure the maximum expiratory velocity during the course of the study. The measurement was performed 4 times a day (6 a.m., 9 a.m., 12 noon, and 6 p.m.) by the patients while sitting. The highest value (l/min) out of each of three measurements was noted in the diary.

The measurement of nonspecific BHR was performed on the Bronchoscreen Measuring Station (Jaeger, Wuerzburg/West Germany) under the use of histamine dihydrochloride at a concentration of 1 mg/ml as the pharmacodynamic provocation substance [20]. The advantage of this method is that in contrast to conventional measuring procedures, better quantification of the bronchial reaction can be achieved with a distinct reduction in time needed for the examination. The histamine aerosol administration was performed breath for breath during the inspiratory phase during spontaneous respiration (nebulizer output per breath: 5  $\mu$ mol). The bronchial reaction was simultaneously determined on the same instrument with the airway resistance method ( $R_{AW}$ ). As target criteria of the BHR, a 50% increase in respiratory tract resistance ( $R_{AW}$ ) in comparison to the starting value with simultaneous exceedance of the  $R_{AW}$  value of 0.3 kPa/(l · s) post provocation was defined. The following pulmonary function parameters prior to inhalative provocation were valid as exclusion criterion for the examination:  $R_{AW} > 0.5$  kPa/(l · s) or  $FEV_1 < 80$  % of the target value. Through pre-testing, BHR to a cumulative histamine dose of  $\leq 8$   $\mu$ mol was demonstrated for all 29 patients. To enable a semiquantitative evaluation in the hyperreactivity zone, during the test periods, the threshold dose for the BHR to 1  $\mu$ mol histamine was determined that corresponds to 40 respirations. The BHR ( $PD_{50R_{AW}}$ ) was defined as positive at a cumulative provocation dose of  $\leq 1$   $\mu$ mol histamine, and negative at  $> 1$   $\mu$ mol histamine.

Broncho-alveolar lavage (BAL): The alveolar macrophages (AM) were obtained under outpatient conditions by broncho-alveolar lavage. The BAL was performed in the medial lobe with a fiber optic bronchoscope under local anesthesia with sterile physiological NaCl solution in individual portions (20 ml 57 times) (18, 20, 21, 31). The rinse fluid was pooled in a siliconized Erlenmeyer flask cooled in ice water, then filtered through a wire sieve (250  $\mu\text{m}$ ) and centrifuged at 4°C (500 g, 10 min). The cell sediment was treated for 10 min. at 4°C with 10 ml sterile erythrocyte lysis buffer (pH = 7.4) and then washed twice with phosphate buffered physiologic saline solution (PBS) and set to a cell density of 106 AM/ml PBS.

Cytologic investigations: The total cell count and the proportion of AM in the cell suspension were determined in the cell chamber according to Neubauer using morphological criteria and by an esterase test with  $\alpha$ -naphthyl acetate. The cell differentiation was performed after staining the cell suspension with a mixture of equal parts of 1 % aqueous Nile blue chloride and thionine tartaric acid solution according to Feyrter (1 g thionine + 0.5 g tartaric acid/100 ml distilled H<sub>2</sub>O) at a 1:1 ratio.

#### *Chemiluminescence (CL) measurement*

*Measuring technique:* The measurement was performed with the liquid scintillation counter Isocap300 (Searle Nuclear Chicago Division, Holland) in out-of-coincidence mode and recycling operating mode. The measuring time per sample was 0.2 min at an interval of approximately 6 min. Polypropylene test tubes (so-called mini vials) were used (measurement temperature 24°C). The work room was completely darkened and equipped with dark room illumination (33).

*Reagents:* As a medium for the CL measurement was veronal buffered physiological NaCl solution with an adjuvant of albumin, glucose, Ca<sup>2+</sup> and Mg<sup>2+</sup> according to information provided by Wulf et al. (34). The yeast cell walls for the stimulation of the AM were isolated from baker's yeast (23). The opsonization of the yeast cell walls was performed with human serum (concentration of the yeast cell wall dispersion 5 mg/1 ml PBS). Luminol (CL intensifier) was brought into solution at a concentration of 6 mg/3 ml PBS with the addition of 24  $\mu\text{l}$  diethylamine by ultrasound treatment. Lucigenin (Cl intensifier) was dissolved in PBS (10.2 mg/2 ml).

*Measuring technique:* 2 ml veronal buffer, 20  $\mu\text{l}$  Luminol or Lucigenin solution and 100  $\mu\text{l}$  of AM suspension ( $1 \cdot 10^5$  AM) were mixed in a measuring tube and pre-incubated for approximately 15 minutes with liquid scintillation counter. Afterwards, the yeast cell wall suspension (500  $\mu\text{g}$ ) was added and the CL measurement performed.

The Luminol and Lucigenin intensified CL was measured in parallel for this<sup>1)</sup>. For quantitative analysis of the measurement results, the peak heights (IPM) and areas under the CL curves (IP) were determined within 200 min after stimulation with the yeast cell wall suspension.

For characterization of the pharmacokinetics of ascorbic acid for the therapy regimen used, the daily profile of the serum level of ascorbic acid was determined enzymatically with the L-ascorbic acid color test (Boehringer, Mannheim, West Germany). Global evaluation of efficacy and tolerability were recorded by patient and physician.

The arithmetic mean ( $\bar{x}$ ) and the standard deviation ( $s$ ) were determined for the statistical analysis of the measured variables.

The statistical comparison of the groups was performed with the paired t-test and the Wilcoxon test.

<sup>1)</sup> The Lucigenin intensified chemiluminescence shows the formation of superoxide anion ( $\text{O}_2^-$ ), while the Luminol dependent chemiluminescence is specific for hypohalogenite.

**Fig. 1:** Schedule for the controlled double blind trial with ascorbic acid/placebo in patients with infection-related bronchial asthma. BHR – bronchial hyperreactivity, BAL – broncho-alveolar lavage

	Pre-period	Test periods				
		Placebo-Verum		Washout period	Verum-Placebo	
Days		8	14	21	29	35
Peak flow diary	4 times a day [over all study]					
Physician consultation	*	*	*		*	*
BHR	*	*			*	
BAL			*			*
Ascorbic acid serum level measurement		*	*		*	*

Note [HH]:

Verum: active treatment, here vitamin C

**Table 1:** Symptom scores

Analysis of asthmatic symptoms:

0 = no symptoms

1 = mild or brief symptoms that do not require additional use of medication

2 = more severe symptoms that are relieved within 15 minutes by additional medication

3 = more severe symptoms that do not respond adequately to or in a delayed manner to additional medication or require repeated use

Symptoms can include: intermittent dyspnea, wheezing, sensation of tightness in the morning or dry irritating cough

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## Results

The overall mean peak flow value for all asthmatics was 410 l/min in the placebo phase and 419 l/min in the verum phase. This slight increase of an average of 9 l/min in the ascorbic acid group was statistically not significant and may also not be clinically relevant. A similar impression resulted from the analysis of the symptom scores. The mean in the placebo phase was 0.72 points and under ascorbic acid it was 0.65 points. Consequently, a slight decrease in symptoms could be observed in the treatment period with ascorbic acid.

The investigations on bronchial hyperreactivity were performed at each of 3 time points, in the pre-period, after 8 days and on the 29<sup>th</sup> day. The course of bronchial hyperreactivity in 23 subjects during the investigation period is presented in Table 2. In 11 asthmatics, no change occurred during both periods. In 12 subjects, bronchial hyperreactivity was detectable during the placebo phase, while in the ascorbic acid phase, a negative reaction was observed. The opposite case did not occur. This asymmetry is significant ( $p \leq 0.0003$ ; test on the basis of the binomial distribution). As a result of this, in 52% of patients with bronchial asthma, bronchial hyperreactivity could be effectively lowered.

The analysis of the bronchial lavage showed that 8 out of 24 patients exhibited an alveolar differential cell count that was commensurate with standards during both test periods. In 5 patients, normalization of the alveolar cell count resulted under ascorbic acid treatment, and in 6 other patients, the alveolar lymphocytes primarily present subsided. In 3 cases, alveolar eosinophilia persisted. Of note, there was considerable lymphocytosis ( $>28\%$ ) in 3 patients during both periods (Table 3).

The results of the CL measurements on AM from the BAL fluid show that under ascorbic acid, a reduction in the chemiluminescence response results with the Lucigenin as well as the Luminol intensification (Table 4).

The difference between the two groups (placebo period, ascorbic acid period) is statistically significant for the peak heights ( $p \sim 0.03$ ).

The changes in the alveolar macrophage activity measured on the basis of the formation of ROM do not correlate or only weakly correlate with the changes in peak flow values and symptom scores ( $|r| < 0.04$  in all cases).

In the analysis of the results, more precise characterization of those patients for whom definite therapeutic or hyperreactivity lowering effects could be proven was attempted (Fig. 2). However, the search for responder-typical commonalities was unsuccessful.

The serum level on the 8<sup>th</sup> day was 13.8–26.8 mg and 10.1–28.4 mg ascorbic acid/l on the 14<sup>th</sup> day, corresponding to the administration rhythm. As was expected, they were considerably above the normal range for men (Fig. 3).

The evaluation of the tolerability of the test preparation by the physician and the patient did not reveal any relevant differences between the test periods.

Only 1 patient complained of nausea during the ascorbic acid period; another indicated increased sensation of thirst over the entire test period. 3 patients noted temperature increases up to 38.2°C once in the evening on the day of the broncho-alveolar lavage.



**Table 2:** Course of bronchial hyperreactivity (BHR) with oral ascorbic acid (5 g/day for 35 days) in comparison to placebo (n = 23)

Positive criteria: PD<sub>50</sub>R<sub>AW</sub> ≤ 1 μmol histamine

		BHP in the vitamin C period		Totals
		Positive	Negative	
BHR in the placebo period	Positive	9	12	21
	Negative	0	2	2
	Totals	9	14	23

**Table 3:** Cell distribution in the broncho-alveolar fluid in patients with infection-related bronchial asthma: 0 = conforms to standards, ↑ = elevated, ↑↑ = strongly elevated (estimation of results based on normal values according to Hunninghake and Crystal [31])

n	Placebo period		Ascorbic acid period	
	Lymphocytes	Eosinophils	Lymphocytes	Eosinophils
8	0	0	0	0
2	0	(5%) ↑	0	0
3	(15%) ↑	0	0	0
3	(15%) ↑	(5%) ↑	0	(5%) ↑
3	(34%) ↑	(3%) ↑	(53%) ↑↑	0
1	(16%) ↑	(8%) ↑	(14%) ↑	(25%) ↑
1	0	(8%) ↑	(18%) ↑	0
1	(17%) ↑	0	0	(5%) ↑
1	0	0	(53%) ↑↑	0
1	(16%) ↑	0	(26%) ↑	(8%) ↑
24 (Total)				

**Table 4:** Comparison of the parameter of the chemiluminescence (CL) curves of the alveolar macrophages of patients with infection-related bronchial asthma (n = 24)

	Area under the CL curve IP 10 <sup>-8</sup> *	Peak height IPM 10 <sup>-6</sup> **
	x ± s	x ± s
<b>Placebo period</b>		
Lucigenin	1.78 ± 1.51	2.11 ± 1.93
Luminol	2.17 ± 2.94	2.23 ± 2.77
<b>Ascorbic acid period</b>		
Lucigenin	1.29 ± 0.74	1.41 ± 0.87
Luminol	1.81 ± 1.72	1.91 ± 2.07
Statistics	a:c p ~ 0.08	a:c p ~ 0.03
Wilcoxon test	b:d p ~ 0.09	b:d p ~ 0.03
* IP = impulses		
** IPM = impulses per minute		

**Fig. 2:** Peak flow course curve of an asthma patient during the entire study

L l/min    Days [Tage]

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**Fig. 3:** Daily profile of the serum level of ascorbic acid in a male asthmatic.

Ascorbic acid [mg/l]

Intake [Einnahme]

14<sup>th</sup> day [14. Tage]

8<sup>th</sup> day [8. Tage]

Normal range for men [Normbereich für Männer]

Time [h.] [Zeit]

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## Discussion

In comparison to the individual studies with ascorbic acid in bronchial asthma to date in which low doses were used over a shorter administration time period (11, 15, 17, 19, 25, 30), for the first time in a complex study a therapeutic effect of ascorbic acid could be proven by including pulmonary function, symptom scores, bronchial hyperreactivity and broncho-alveolar lavage, which is most notably expressed by significant lowering of bronchial hyperreactivity. Bronchial hyperreactivity is an important quantifiable characteristic in asthmatic disease. Hyperreactivity is usually already recognizable before the manifestation of 'clinical asthma' and is consequently causally involved in the pathogenesis of asthma. Nowadays, bronchial hyperreactivity is even considered to be common denominator of all asthma forms (27). The inhaled provocation with histamine has proven to be the established quantitative method for the study of bronchial hyperreactivity (20). A clinically relevant raising of the threshold of bronchial reactivity resulted in 52% of asthmatics, and indeed, in contrast to the placebo period, a hyperreactivity lowering effect could be measured in 11 subjects under ascorbic acid.

An effective reduction in bronchial hyperreactivity must be considered to be a decisive element of asthma prevention measures today (26). At the same time, bronchial hyperreactivity is considered to be the most important determining factor for the course of asthma disease. Pulmonary function studies frequently give varying results depending on external influences, daily rhythm and medication. For this reason, the peak flow value, as a more objective pulmonary function parameter, was measured four times a day and documented in the diary. Relatively rare, selective measurements of pulmonary function parameters by more extensive measuring techniques such as spirometry or body plethysmography, in spite of higher personnel/technical expenditure, do not result in more reliable results than the significantly more frequently measured peak flow value that records the daily variation range of pulmonary function of asthmatics in a more representative manner. The peak flow values and the symptom scores indeed showed a tendency toward improvement during ascorbic acid therapy, but the differences in both test time periods were not significant.

The results of the chemiluminescence measurements on alveolar macrophages demonstrated that under ascorbic acid treatment, a reduced chemiluminescence response resulted. This indicates that ascorbic acid reduces the formation of reactive oxygen metabolites in patients with bronchial asthma and consequently could also have an inhibitory effect on the biosynthesis of cyclo-oxygenase and lipoxygenase products which have a bronchoconstrictive effect. Ascorbic acid probably does not directly reduce the formation of reactive oxygen metabolites e.g., by the NAD(P)H oxidase system of inflammatory cells. The oxygen radicals and toxic oxidants that arise are reduced and are thus rendered innocuous before they can react with the pulmonary cells or the lung tissue. Furthermore, the present study underlines the value of bronchial alveolar lavage in bronchial asthma (13, 24, 32). Statements about the degree of inflammation in infection-related bronchial asthma and the therapeutic effect of anti-asthmatic/allergic acting substances can be made from the alveolar differential cell count (14, 22). From the results, it can be concluded that ascorbic acid at a high dose (5 g/day) is a suitable antioxidant for reduction of radical formation in infection-related bronchial asthma and consequently could favorably affect the clinical course of asthma. This must be further clarified in other comprehensive studies.

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