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Clinical efficacy of Broncho-Vaxom® in adult patients with chronic purulent sinusitis – a multicentric, placebo-controlled, double-blind study

B. Heintz[1], W. W. Schlenter[2], R. Kirsten[3] and K. Nelson[3]

[1] *Internal Medicine II, University of Aachen, Aachen, FRG*
[2] *ENT Department, Medical University of Lübeck, Lübeck, FRG*
[3] *Clinical Pharmacology, University of Frankfurt, Frankfurt, FRG*

Abstract. This study was designed to test the clinical effectiveness of Broncho-Vaxom® (an orally applicable bacterial lysate) in a large number of adult patients suffering from chronic purulent sinusitis. Broncho-Vaxom® or placebo was administered to 284 patients presenting with chronic purulent sinusitis within the bounds of a multicentric, randomized double-blind study. Patients were clinically examined before admittance to the study and at 1, 2, 3 and 6 months after treatment initiation (one capsule daily for a period of 10 days per month during 3 consecutive months). The sinuses were x-rayed before and at 3 and 6 months after therapy began. Patients assessed the severity of their symptoms on a scale of 0 to 4: 0 = no symptoms, 1 = light symptoms, 2 = moderate symptoms, 3 = severe symptoms, 4 = very severe symptoms. The average severity score for coughing during the course of Broncho-Vaxom® therapy decreased in the third month of treatment from 2.34 before treatment to 0.85, compared to placebo before treatment (2.41) and after treatment (1.24). The score decreased further to 0.61 in the sixth month after the initiation of Broncho-Vaxom® therapy, with no further decrease as a result of placebo therapy (1.25). Comparable average score courses for expectorations and headache also occurred. In the first month of Broncho-Vaxom® therapy, a decrease was already apparent in the severity of the main sinusitis symptom: purulent nasal discharge. The score was 1.55 in the first month of Broncho-Vaxom® treatment compared to 1.80 in the placebo group. A continuous decrease to 0.58 after Broncho-Vaxom® therapy in the 6th month occurred, compared to 1.29 after placebo therapy. Six months after therapy began, the average number of reinfections in the placebo group was almost double that occurring in the Broncho-Vaxom®-treated group. The number of patients with obstructed sinuses decreased from 54 to 9 in the Broncho-Vaxom® group and from 46 to 25 in the placebo group. Side effects were minimal. Broncho-Vaxom® proved to be an effective therapy in alleviating symptoms and recurrence of sinusitis.

Key words: Broncho-Vaxom® – sinusitis – immune system – bacterial infections

Introduction

Respiratory tract infections are treated either symptomatically by alleviation of cough, fever, headache, increased expectoration, nasal obstruction; or in the case of serious infection, with the help of antibiotics. A new therapeutic approach, aimed at preventing the recurrence of respiratory infections, stimulates the patient's immune system by the oral application of bacterial lysates.

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Reprint requests to Dr. B. Heintz.

Treatment with Broncho-Vaxom® (a bacterial immunostimulant) has been shown to increase the number of circulating T- and B-lymphocytes [Clot and Andary 1980, Girard and Fleury 1979, Magyar et al. 1985, Martin du Pan and Koechli 1984], increase the number of eosinophils [Hajicek 1980], decrease the number of neutrophils [Hajicek 1980], decrease the number of micro-organisms in the sputum [Hajicek 1980], stimulate immunglobulin production in sputum and serum [Puigdollers et al. 1980], increase the number of phagocytes [Fontanges 1977] and induce interferon production [Martin du Pan et al. 1982].

Clinical studies have corroborated the positive effects of Broncho-Vaxom® on the immunological

Table 1. Severity of symptoms (mean values of scores 0–4) during the 6 months of study

Severity of symptoms		Begin	Month 1	Month 2	Month 3	Month 6
Headache						
P	n	138	128	127	126	128
	$\bar{x}$	2.42	1.56	1.34	1.08	1.15
	SD	1.00	1.20	1.14	1.15	1.22
BV	n	140	130	132	128	134
	$\bar{x}$	2.48	1.55	1.21	0.76	0.56
	SD	0.91	0.97	0.96	0.95	0.80
	p	NS	<0.05	<0.05	<0.05	<0.001
Purulent nasal discharge						
P	n	136	126	125	123	121
	$\bar{x}$	2.57	1.80	1.56	1.37	1.29
	SD	1.04	1.24	1.21	1.24	1.36
BV	n	139	130	129	128	127
	$\bar{x}$	2.50	1.55	1.09	0.74	0.58
	SD	1.01	0.97	0.98	0.89	0.76
	p	NS	<0.01	<0.01	<0.001	<0.001
Coughing						
P	n	127	125	122	119	114
	$\bar{x}$	2.41	1.76	1.44	1.24	1.25
	SD	1.15	1.21	1.22	1.23	1.30
BV	n	128	127	126	124	124
	$\bar{x}$	2.34	1.59	1.22	0.84	0.61
	SD	1.25	1.15	0.90	0.91	0.76
	p	NS	NS	<0.01	<0.01	<0.001
Expectoration						
P	n	131	124	123	121	115
	$\bar{x}$	2.21	1.63	1.29	1.15	1.08
	SD	1.09	1.16	1.16	1.12	1.23
BV	n	129	127	126	124	124
	$\bar{x}$	2.19	1.54	1.11	0.71	0.51
	SD	1.09	1.05	0.87	0.86	0.69
	p	NS	NS	<0.05	<0.01	<0.001

P = Placebo, BV = Broncho-Vaxom®, n = number of details; statistical comparison: BV compared with P

system. Prevention of recurrent chronic bronchitis [Keller and Hinz 1984, Magyar et al. 1985], tracheobronchitis, tonsillitis [Ruah 1981] and asthmoid bronchitis [Hajicek 1980] has been observed. Two studies on a small number of children have also reported a decrease in sinusitis incidence during Broncho-Vaxom® therapy [Gsell 1980, Ruah 1981]. This study was designed to test the clinical effectiveness of Broncho-Vaxom® in a large number of adult patients suffering from chronic purulent sinusitis.

Patients and methods

Broncho-Vaxom®, containing 7 mg of a lyophilized extract of 8 bacterial species (Diplococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae and ozaenae, Neisseria catarrhalis, Staphylococcus aureus, Streptococcus pyogenes and viridans), or placebo, was administered to 284 patients (141 placebo, 143 Broncho-Vaxom®) of both sexes, aged 16 years and over. Patients presenting with chronic purulent rhino-sinusitis, persistent sinusitis after unilateral sinus puncture, accompanying bronchitis, sinu-bronchial syndrome, chronically swollen sinus mucosa and/or adenoid sinusitis were treated within the bounds of a randomized, placebo-controlled, multicentric double-blind study. Patients were admitted into the study beginning in February and at the latest, 8 weeks after admittance of the first patient. The observation period extended over 6 months after admittance. Patients were instructed to take one capsule daily for a period of 10 days per month during 3 consecutive months. No placebo or Broncho-Vaxom® capsules were administered in the 4th, 5th or 6th month of the observation period.

Exclusion criteria were extended to patients who had taken part in a drug testing program within the previous 2 months, who were known to be allergic to the bacterial species contained in Broncho-Vaxom®, and those who had had intestinal disturbances, operations on the intestinal tract (except for appendix), renal insufficiency, diabetes, hyperthyroidism or other endocrine disturbances, malignancy, chronic alcoholism, acute alcohol poisoning within the previous month, medication dependency, immunoglobuline deficiency syndrome of genetic origin and/or autoimmune diseases. Pregnant patients were also excluded from the study.

Patients were clinically examined before admittance to the study and at 1, 2, 3, and 6 months after treatment initiation. The sinuses were x-rayed before admittance to the study and at 3 and 6 months after therapy commencement.

Patients were asked to assess the severity of their symptoms during the course of the study on a scale of 0 to 4: 0 = no symptoms, 1 = light symptoms, 2 = moderate symptoms, 3 = severe symptoms, 4 = very severe symptoms. The average score was calculated from all reporting patients.

The statistical analysis was done using the chi-square test. In both groups, the 6-month data were missing for approximately 10% of the case report forms. These patients were excluded from the statistical tests.

The patients were informed of the nature of the study and gave informed consent to participate in the study.

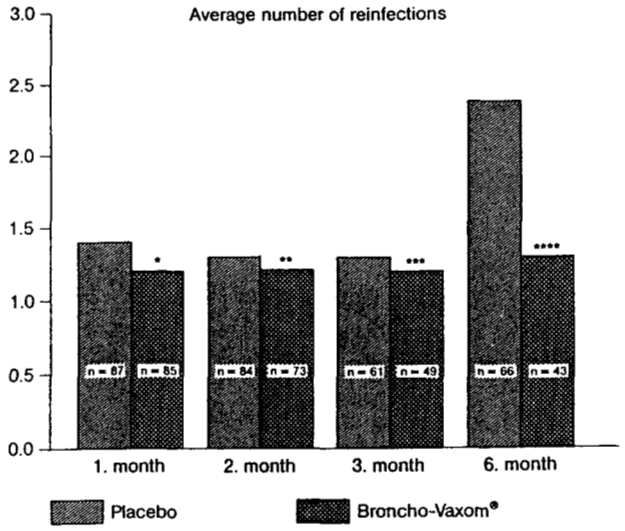

Fig. 1. Average number of reinfections during the 6 months of study, n = total number of reinfections statistical comparison: BV compared with P, * = NS, ** = NS, *** = NS, **** = p <0.01

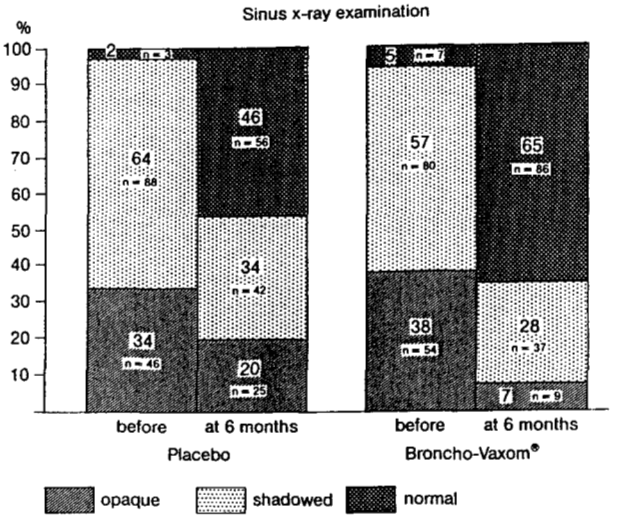

Fig. 2. Sinus x-ray examination (opaque, shadowed, normal) during the 6 months of study. Results are given in percent of patients. n = number of patients

Results

During a period of 6 months preceding the study, no differences in the per patient average number of infections (3.7 – placebo, 3.8 – Broncho-Vaxom®), average length of infections in days (12.3 – placebo, 12.1 – Broncho-Vaxom®), average number of sinus punctures (0.16 – placebo, 0.18 – Broncho-Vaxom®) or average number of irrigations (4.5 – placebo, 4.7 – Broncho-Vaxom®) were observed between the two groups.

The average severity score of coughing, expectoration, headache and purulent nasal discharge during the course of Broncho-Vaxom® and placebo therapy over a period of 6 months on a scale of 0 to 4 is shown in Table 1.

No differences in scores were observed during the first month of Broncho-Vaxom® therapy compared to placebo with respect to coughing. In the second and third month of therapy, a decrease in the severity score was observed as a result of Broncho-Vaxom® therapy (month 3: 1.24 for placebo compared to 0.84 with Broncho-Vaxom®; $p < 0.01$). The severity score decreased further to 0.61 in the sixth month after initiation of Broncho-Vaxom® therapy, whereas, it did not change as a result of placebo therapy (1.25; $p < 0.001$).

A similar course was observed in the average severity score of expectorations. During the third month of treatment, Broncho-Vaxom® caused the score to decrease to 0.71 compared to 1.15 for placebo ($p < 0.01$). A further decrease to 0.51 during Broncho-Vaxom® therapy occurred in the sixth observation month compared to 1.08 in the placebo group ($p < 0.001$). Table 1 shows a comparable average severity score course for headache.

The average severity score for purulent nasal discharge during the course of Broncho-Vaxom® therapy is also shown in Table 1. In the first month of therapy, a decrease was already apparent. The score for purulent nasal discharge was 1.55 in the first month of Broncho-Vaxom® treatment compared to 1.80 in the placebo group ($p < 0.01$). A continuous decrease to 0.58 on the severity scale occurred after Broncho-Vaxom® therapy in the 6th month, compared to 1.29 after placebo therapy ($p < 0.001$).

The average number of reinfections occurring during the 6-month observation period is depicted in Figure 1. The number of reinfections was comparable in both the placebo and Broncho-Vaxom® groups, except after 6 months where the number of reinfections in the placebo groups was almost double that occurring in the Broncho-Vaxom®-treated group ($p < 0.01$).

Sinus status as determined by x-ray examination during the course of the study is shown in Figure 2. The number of patients with empty sinuses (normal) increased from 7 to 86 patients after 6 months with Broncho-Vaxom® treatment, compared to an increase from 3 to 56 patients with empty sinuses in the placebo group. The number of patients with full sinuses (opaque) decreased from 54 to 9 in the Broncho-Vaxom® group and from 46 to 25 in the placebo group.

The following side effects were encountered during Broncho-Vaxom® therapy: two patients

reported light nausea, one reported a return attack of trigeminal neuralgia, another reported headache and stomachache, one patient reported larger blisters on the lower lip after the second Broncho-Vaxom® treatment period and one patient reported smell and taste "differences".

In the placebo group, the following side effects were observed: one patient reported after the second treatment of loss of hair, poor general condition (1), nausea after intake in the morning disappearing after breakfast (1), shivers (1), increased coughing and difficult breathing (1), nausea (1), perhaps due to Gelomyrtol, and one patient had fever on one day (38.2° C).

Discussion

Patients suffering from recurrent infections of the respiratory tract may be equipped with a less than normally effective immunoglobulin-response-system, which can be artificially activated by an immunostimulant.

Several studies have shown that Broncho-Vaxom® activates the immune system [Puigdollers et al. 1980], stimulating the production of IgA, IgG and IgM. The connection between activation of enteral immunocytes in healthy volunteers and increased IgA-secretion in the bronchial tract cells via IgA-plasma cells has been described [Kohl 1985, Lamm et al. 1982]. It is also evident that the number of T-lymphocytes is an important factor for the body's defense against pathogens [Magyar et al. 1985]. A hypothetical decrease in the number or activity of T-lymphocytes in patients with chronic respiratory infections compared to the normal population might account for their immune deficit.

Maestroni and Losa [1984] have found that children with propensity towards respiratory infections exhibit a reduced lymphocyte response to alloantigens when compared to normal children. This defect responded to the application of Broncho-Vaxom®. Clot and Andary [1980] have also presented data, showing that patients with selective IgA-deficiency responded to Broncho-Vaxom® with normalization of T-lymphocytes and recovery of altered membrane properties.

Previous studies have shown both subjective and objective improvement in respiratory disease as a result of Broncho-Vaxom® therapy. Among these diseases, chronic and asthmoid bronchitis, pharyngitis and tonsillitis [Gsell 1980, Orlandi 1985, Hajicek 1980] are influenced positively by Broncho-Vaxom® therapy. Two limited studies on sinusitis in children have also reported a positive influence of Broncho-Vaxom® [Gsell 1980, Ruah 1981]. This study, comprising a large number of patients, confirms these reports which indicated a positive effect of Broncho-Vaxom® on the recurrence and severity of infectious pharyngeal and nasal symptoms [Girard and Fleury 1979, Keller and Hinz 1984]. The results presented here show that a discontinuous three-month treatment with the immunostimulant Broncho-Vaxom® reduced the severity of symptoms associated with sinusitis. Subjective improvement was not the only therapeutic gain, but extended to a decrease in the degree of sinus filling, determined by x-ray examination.

Since seasonal weather changes and placebo treatment substantially influence the frequency and severity of respiratory diseases, this study was conceived as a placebo-controlled study with an observation period of 6 months. Due to the considerable variation of clinical symptoms, a large patient population was included in the study.

The main symptom of sinusitis, purulent nasal discharge, began to decrease in severity in the first month after Broncho-Vaxom® treatment and steadily decreased throughout the course of the study, with a maximal decrease in severity occurring 6 months after treatment commencement.

Other symptoms of sinusitis such as coughing, headache and expectoration, began to subside 1–2 months after initiation of therapy and reached maximally observed improvement 6 months after treatment began.

Further studies should be directed towards the identification of. morphological changes in the upper respiratory tract as a result of Broncho-Vaxom® therapy. The duration of improvements and whether repeated cures are necessary to stabilize and prolong the achieved state should be examined. It would also be of interest to investigate why some patients do not respond to immunostimulus.

Immunostimulants are a promising therapy for respiratory disease. The development of Broncho-Vaxom®, an orally applicable immuno-stimulant, as a further improvement of parenterally applicable drugs, will allow the treatment of a larger group of patients.

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