

PHARMCOTHERAPY

Patients with Asthma Benefit from Concomitant Therapy with Cineole: A Placebo-Controlled, Double-Blind Trial

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Background and Aims. Cineole is the main constituent of eucalyptus oil, and it is mainly used as a mucolytic agent in inflammatory airway diseases. With its known mucolytic, bronchodilating, and anti-inflammatory effects, cineole reduces the exacerbation rate in patients suffering from chronic obstructive pulmonary disease. Based on these pharmacodynamic effects, we arrived at the hypothesis that asthma patients would benefit from concomitant therapy with cineole. **Methods.** As part of a double-blind, placebo-controlled, multicenter study, 247 patients with confirmed asthma were randomly selected according to the guidelines for this study. All patients were administered 200 mg of cineole, or a placebo, three times per day as a concomitant therapy over a period of 6 months. The combined primary outcome measures, which were implemented as a multiple criteria testing process, were improvement of lung function, asthma symptoms, and quality of life. **Results.** Following the completion of the 6-month treatment period, it was noted that the patient group treated with cineole showed significantly more improvements to the multiple testing criteria than the patients in the placebo group ($p = .0027$). The statistical significance of the individual outcome measures could also be proven in accordance with the Wei–Lachin procedure (i.e., for Forced expiratory Volume 1 Second (FEV₁), $p = .0398$; for asthma symptoms, $p = .0325$; and for Asthma Quality of Life Questionnaire (AQLQ), $p = .0475$). **Conclusion.** Concomitant therapy using cineole can lead to notable improvement in lung function and health condition as well as to reduce dyspnea in asthma patients.

Keywords anti-inflammatory effects, asthma, concomitant therapy, monoterpenic cineole

INTRODUCTION

Asthma is characterized by an inflammatory process, which induces bronchial hyper-responsiveness, and a generally reversible airway obstruction. The established treatment guidelines recommend the regular use of inhaled corticosteroids (ICS) in order to control the asthma and suppress airway inflammation. The clinical effectiveness of these drugs has been repeatedly proven in controlled clinical studies and is established (1, 2).

The primary aim of asthma management remains, however, the continual improvement of symptom control. Therefore, as cineole accelerates the beat frequency of the cilia in the mucus membrane, as well as acting as both bronchodilating and anti-inflammatory agents, it can be postulated that it may also be effective in treating symptoms in asthma patients (3–8). Therefore, in order to investigate the therapeutic effects of cineole in a real-life population of asthmatics, we conducted a randomized, placebo-controlled, multicenter study using a concomitant prescription of cineole, the main component of eucalyptus oil. As primary endpoint, a multiple criteria method of measurement was implemented, which represents relevant parameters for asthma control as improvement of lung function, asthma symptoms, and quality of life.

PATIENTS AND METHODS

Study Design

This randomized, double-blind, placebo-controlled, parallel group study was conducted in four general practitioner's practices and seven specialist pneumologist's practices representing a real-life population. In accordance with the Helsinki Declaration, the study was approved by the appropriate authorities and ethics committees, responsible for the 11 respective participating centers. Furthermore, all patients provided an explicit, written consent form prior to their participation and the commencement of the study.

Patients were randomly assigned to one of the two treatment groups with stratification according to the clinical centers. Patients were then given the necessary dose of capsules each containing either 100 mg cineole or no active ingredient. The dosage for each group amounted to two capsules, taken three times daily, resulting in a total dose of 600 mg of cineole per day, as a concomitant therapy. The placebo control group received an equal dose of placebo capsules. In order to avoid patients from recognizing the smell of cineole, all patients were instructed to take the gastro-resistant capsules half an hour before meals, so that cineole will be released in the small intestine. Capsules with both active substances, as well as the placebos, were organoleptically identical and sealed in blister stripes. All patients visited the practices at the beginning of the study, as well as in the subsequent 1, 2, 3, 4, 5, and 6 months.

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Enrolment of Participants

The diagnosis of asthma was confirmed according to the current guidelines of Global Initiative for Asthma (GINA) and the German Airway League (1, 2). The study was limited to adult patients, aged 18–65 years, with a certified, diagnosed history of asthma of more than 2 years. All eligible participants were controlled since at least 2 weeks prior to the onset of the study and had a reversibility of airflow obstruction after inhalation of β -agonists (at least 200 μ g Salbutamol or equivalent), and of at least 15% and more than 200 ml in FEV₁. Patients were excluded if they had severe medical conditions, such as bronchial carcinoma, myocardial infarction, alcoholism, and heart failure, or if they were not under the control of their physician for at least 2 weeks.

Outcome Measures

The primary endpoint was structured as a multiple criteria measurement composed of the parameters lung function, asthma symptoms, and quality of life. These were specified in terms of increases of FEV₁, changes to sum of scores of nocturnal asthma, as well as to the amelioration of the quality of life during the 6 months treatment period.

Nocturnal asthma was assessed by scores (0 = never, 1 = rarely (up to two times a month), 2 = occasionally (up to once a week), 3 = often (2–3 times per week), 4 = very often (4–5 times per week), and 5 = nearly continuously (6–7 times per week)) and compared as the sum of scores between visit following the first month, until the final visit after 6 months of treatment. Diagnosis-related quality of life was determined according to the Asthma Quality of Life Questionnaire (AQLQ), comparing potential changes in condition before and after 6 months of treatment between both the groups (9, 10).

The secondary outcome measures the forced vital capacity (FVC) and the vital capacity (VC). Additionally, symptom scores were determined for the dyspnea frequency and intensity during rest, and after exercise (scores: 0 = caused no problems, 1 = occasional problems, 2 = caused a lot of problems, and 3 = the most important problem the patient had). The frequency of dyspnea during the course of a week was also gauged and converted into qualitative scores (scores: 0 = no day was good, 1 = 1–2 days were good, 2 = 3–4 days were good, 3 = nearly every day was good, and 4 = every day was good). Coughing and the propensity to cough were also determined, and given by scores (0 = no cough, 1 = in the morning without complaints, 2 = in the morning with complaints, 3 = in the morning and over the day (moderate), 4 = in the morning and over the day (severe), 5 = continuously during whole day (moderate complaints), and 6 = continuously during whole day (relevant complaints)). Quantity of secretion was determined and measured against the following scores (0 = none, 1 = <2 ml (very modest), 2 = <5 ml (modest), 3 = <10 ml (moderate), and 4 = >10 ml (distinctive)).

Visits and Randomization

Randomization was sequentially assigned in balanced blocks of four from a computer-generated list (random; idv-Data Analysis and Study Planning, Gauting, Germany). After the randomization, the following details of the patients were recorded: height, weight, age, and time from the first diagnosis of asthma symptoms; documentation of allergies; concomitant disease; prescribed medication; assessment of the quality of life; and the current maintenance therapy. Control visits were carried out after 1, 2, 3, 4, 5, and 6 months, when adverse events were recorded, and compliance with the treatment plan, as well as potential changes to therapy were addressed. At the beginning of the study, as well as after 3 and 6 months, respectively, a full spirometry was carried out, in order to provide measurable results. The quality of life, however, was determined at the beginning and at the end of the study.

Statistical Analysis

The proposed sample size for this study was 240 patients for both the treatment groups (nnpar (non-parametric); idv-Data Analysis and Study Planning). An analysis of efficacy was performed with the intention-to-treat population including all eligible patients who received at least one dose of medication and had at least one follow-up visit. The primary outcome measure was composed of the increase of FEV₁, a reduction of the sum of the individual scores for nocturnal asthma, and the amelioration of quality of life during the period of treatment. The statistical analysis of the data was performed according to Wei–Lachin’s directional test for multiple criteria (equally weighted) (Testimate; idv-Data Analysis and Study Planning) (11). All secondary outcome measures were analyzed using the Wilcoxon–Mann–Whitney *U*-test. In addition, some secondary outcome measures were also analyzed exploratory at multiple endpoints according to Wei–Lachin’s directional test. All data are expressed as mean values (with SD) and all tests were two tailed. A *p*-value of .05 or less was considered to indicate statistical significance.

RESULTS

A total of 247 patients—representing a real-life population—were randomized between November 2006 and January 2009 and received at least one dose of the study medication. Both the treatment groups were well matched with respect to the baseline characteristics (Table 1). The mean age of the participants at entry was 52.3 and 53.5 years in the respective groups. The mean duration of the patient’s asthma condition was 14.7 and 15.3 years, respectively, and the basic prescribed medication (i.e., ICS, combinations of ICS with long-acting β -agonist (LABA), anticholinergics, and theophylline) was balanced between the two groups (Table 2). The medication generally was not

TABLE 1.—Base line characteristics of the patients.

Characteristic	Placebo (N = 121)	Cineole (N = 126)
Age—yr		
Mean (SD)	53.5 (12.8)	52.3 (14.0)
Sex—M/F	57/64	42/86
Weight—kg		
Mean (SD)	77.7 (16.0)	76.0 (15.8)
Height—cm		
Mean (SD)	169.6 (9.3)	168.8 (8.9)
Years since detection of asthma		
Mean (SD)	15.3 (13.2)	14.7 (12.9)
FEV ₁		
Mean (SD)	2.35 (0.83)	2.30 (0.82)
FEV ₁ —% of predicted value		
Mean	82	81
Reversibility (increase of FEV ₁ after inhalation of β -agonist) [%] (l)	22.5% (0.52 l)	24.6% (0.54 l)
Smoker/exsmoker	16	21
Patients with allergies	63	72

TABLE 2.—Constant concomitant therapy (number of patients).

Therapy	Placebo (N = 121)	Cineole (N = 126)
Inhaled corticosteroids (ICS)	53	50
Fixed combination of ICS and LABA	41	45
LABA	23	17
Theophylline	11	12
Anticholinergics	11	9
Oral corticosteroids	4	3
Inhaled Short Acting β -Agonists (SABA) including combinations (except ICS)	65	62

changed during the treatment period, except in the occurrence of exacerbations. The baseline lung function and reversibility of airflow limitation in both groups were comparable with an increase of FEV₁ after inhalation of β -agonists of 0.54 and 0.52 l, respectively. Treatment compliance was determined by counting the study medication at each visit and was found to be high and comparable across the treatment groups.

Primary Outcome Measures

Primary outcome measure was composed of lung function, asthma symptoms, and quality of life. After 6 months of treatment the mean increase of FEV₁ was 0.31 l in the cineole group, and 0.20 l in the placebo group (Table 3). Over the same period, amelioration of the sum of all scores of nocturnal asthma was 3.1 versus 5.2, while the AQLQ was also found to have decreased from 5.2 to 2.6. The statistical analysis of the multiple criteria showed significance at $p = .0027$. The statistical significance of the individual parameters could also be proven, when calculated and analyzed in accordance with Wei-Lachin procedure (i.e., for FEV₁, $p = .0398$; for asthma symptoms, $p = .0325$; and for AQLQ $p = .0475$).

TABLE 3.—Primary outcome measures composed by mean of change of FEV₁, AQLQ, and assessment of nocturnal asthma during 6 months of treatment with Cineole and Placebo.^a

	Placebo	Cineole	Wei-Lachin's directional test
	Mean	Mean	P-value*
Mean of improvement of FEV ₁ [l]	0.20 (0.48)	0.31 (0.36)	.0398
Mean of improvement of AQLQ	2.6 (8.1)	5.2 (8.1)	.0475
Sum of assessment of noctur- nal asthma (score) ^b	5.22 (8.1)	3.10 (3.8)	.0325
Wei-Lachin's directional test			.0027

^aMeans plus-minus SD.

^bThe sum of the nocturnal asthma assessment is calculated by the addition of the documented mean of the scores during treatment (scores: 0 = none, 1 = rarely, 2 = occasionally, 3 = frequently, 4 = very frequently, and 5 = each night).

*P-values are for the comparison between the two groups.

Secondary Outcome Measures

Lung Function. After 6 months of treatment, the difference between the mean increase of FVC by 0.29 l administering a cineole therapy, when compared with 0.16 l following the placebo treatment, was statistically significant ($p = .0226$). The difference concerning change of VC between both the treatment groups was not statistically significant ($p = .0682$). Increase of peak flow rate was 1.00 and 0.72 (l/sec) in the cineole and the placebo group, respectively, which reflected a significant difference between the two groups ($p = .0197$).

Dyspnea. Baseline dyspnea scores in the morning, trouble in breathing, dyspnea at rest, and dyspnea during exercise were all similar in both the groups, indicating a moderate level of a dyspnea for most patients at the beginning of the treatment period. Calculating the sum of all values during treatment period, the perceived difference between both the treatment groups was statistically significant for dyspnea at rest and dyspnea during exercise. The differences between both the groups after 6 months of treatment are summarized in Table 4.

Quality of Life. At a treatment period of 6 months, the mean improvement of quality of life according to AQLQ was statistically significant (Table 2). Furthermore, four single parameters of the composed test—mainly concerning breathlessness—showed a statistically significant improvement too. These parameters were breathlessness, breathlessness during exercise, and breathlessness at contact with other people as well as travelling to communal places.

Other Findings. A comparison of hypersecretion (quantity of secretion) during the treatment period at multiple endpoints shows a statistically significant difference of 5.2 and 7.4 ml ($p = .0015$). Therefore, comparing coughing, or rather the cough frequency at multiple endpoints also showed to be statistically significant ($p = .0007$) (Table 5).

TABLE 4.—Secondary outcome measures during 6 months of treatment with Cineole or Placebo for change of lung function and dyspnea symptoms.^a

Lung function and symptoms	Placebo			Cineole			<i>P</i> -value*
	Base line	3 months	6 months	Base line	3 months	6 months	
PFR [l/sec]	4.36 (2.14)	5.01 (2.31)	4.94 (2.41)	4.12 (1.78)	4.83 (2.22)	5.02 (2.31)	.0197
FVC [l]	3.07 (0.94)	3.30 (0.97)	3.26 (0.98)	2.95 (0.96)	3.13 (0.98)	3.21 (1.019)	.0222
Cough^b	2.30 (1.59)	2.19 (1.54)	1.59 (1.39)	2.06 (1.48)	1.50 (1.34)	1.16 (1.21)	.0011
Mean of dyspnea at rest^c	0.52 (0.70)	0.38 (0.67)	0.21 (0.45)	0.42 (0.61)	0.22 (0.53)	0.17 (0.48)	.0198
Mean of dyspnea during exercise^c	2.08 (0.96)	1.71 (1.03)	1.37 (0.93)	1.95 (0.92)	1.39 (1.01)	1.19 (0.93)	.0446

^aMeans plus-minus SD. Higher scores on the symptoms-sum-score indicate more disease activity.

^bScores: 0 = no day was good, 1 = 1–3 days were good, 2 = nearly every day was good, and 3 = every day was good in a week.

^cScores: 0 = did not cause any problems, 1 = sometimes caused problems, 2 = caused a lot of problems, and 3 = the most important problem the patient had.

**P*-value calculated for the comparison of the changes from baseline to 6 months between the two groups (Wilcoxon–Mann–Whitney *U*-test).

***P*-value calculated for the comparison of the sum of values during treatment between the two groups (Wilcoxon–Mann–Whitney *U*-test).

TABLE 5.—Effects on cough and secretion during treatment period with Cineole and Placebo.

	Placebo	Cineole	Wei–Lachin's directional test
	Mean	Mean	<i>P</i> -value
Secretion (quantity)^a	7.35 (5.07)	5.22 (4.14)	.0015
Cough^b	11.8 (6.58)	8.35 (6.04)	.0007

^aSum of score mean values at all visits; during treatment: scores: 1 = none, 2 = <1 ml, 3 = <5 ml, 4 = <10 ml, and 5 = >10 ml.

^bSum of score mean values at all visits; during treatment: 0 = none, 1 = rarely, 2 = occasionally, 3 = frequently, 4 = very frequently, and 5 = each night.

Side Effects

A safety examination was carried out on all patients who were administered the study medication. Within the placebo group, it was assumed that seven of the recognized and recorded adverse events were not related to the study medication, whereas a further six were interpreted as being related to an intolerance of the study medication (i.e., itching, diarrhea, cough, urticaria, and heartburn). During the treatment with cineole, six adverse events were reported as not being related to the study medication. Four patients showed signs of nausea, stomach ache, and heartburn, which were interpreted as being related to the study medication. It has to be noted that the difference between the two treatment groups was neither clinically relevant nor statistically significant. Safety examinations of the study and all participating patients highlighted no notable difference between the two treatment groups. Furthermore, a high level of compliance was noted among all patients throughout the 6-month treatment period.

DISCUSSION

Pharmacotherapy of asthma has traditionally focused on the treatment, and control of airway obstruction and airway inflammation, as a key means of controlling symptoms, and improving the health condition of the patient. ICS and β -agonists have, therefore, been established as the

mainstay of pharmacotherapy. Though, mucociliary dysfunction has direct clinical implications on the pathophysiological mechanisms of asthma, research is not focused on this topic except by Fahy and Dickey (12). Thus, based on the known anti-inflammatory and bronchodilating effects of the natural substance cineole, it was assumed that this substance could be therapeutically beneficial for patients with asthma. The results of this study provide new and important evidence for an additional therapeutic efficacy of cineole as a concomitant therapy. Based on the statistical significance of our data, our study has successfully proved that a concomitant therapy with cineole improves the lung function, the symptoms of asthma, cough, hypersecretion, and ALQL.

The interpretation of the results of this study corroborates the modern statistical test procedure as composed parameters calculated by the Wei–Lachin method. The increase of FEV₁, the amelioration of nocturnal asthma assessment, and the improvement of AQLQ were all statistically significant ($p < .05$). However, the combination, and testing of these parameters as a multiple criteria is shown to lead to a more strongly significant result, as shown impressively by a *p*-value of .0027.

In light of the findings within the literature on the treatment of patients suffering from sinusitis and chronic obstructive pulmonary disease (COPD), the results showing the efficacy of cineole are not surprising. We can therefore conclude that a concomitant application of cineole can be seen to yield a better control of the symptoms of asthma. This proof of efficacy is an important contribution to the generally accepted pharmacological properties of cineole, which is thus not simply limited to the properties of a mucolytic agent. In order to understand the pharmacological properties and the full applicability of cineole more closely, this study has to be viewed in the context of the results of other clinical and preclinical studies in this field (3–8) and recent research by Serafino et al. (13).

The individual mechanisms of the substance's functionality are most probably based on both the known anti-inflammatory and other potential pharmacological effects of this monoterpene, which reach beyond its established mucolytic activity. Consequently, anti-inflammatory

activity of long-term treatment with cineole 200 mg t.i.d. was shown equivalently to 2.8 mg prednisolone in severe asthma (GINA IV), facilitating an effective reduction in the need for systemic requirement of corticosteroids (7).

Patients with asthma participating in this study represent a real-life population with real-life medication. Therefore, about 20% of our patients did not receive ICS but had other effective medications. Severity of asthma was mild to moderate as FEV₁ as a mean was calculated more than 80% of the predictive value in both the groups. The proportion of current smokers was 15% and former smokers was 26% over all patients, which is lower than in a recent study with a real-life population with 19% of current smokers and 38% of former smokers of the patients with asthma (14). Our results underline that, in a real-life study, multiple endpoints may characterize asthma control more evident than a single endpoint only.

CONCLUSION

The known pharmacological and clinical effects of cineole can neither be explained by, nor limited to, the established effects related to mucociliary clearance. It is essential therefore to focus our analysis and interpretation on cineole's properties as an anti-inflammatory agent, which were postulated in this study with asthma patients. Based on the findings, of all clinical studies in patients with COPD, asthma, and sinusitis, we can assume that the main therapeutic effect of cineole is represented by its anti-inflammatory activity.

These results have to be viewed in the context of the overall socioeconomic situation, given that asthma has a high prevalence rate of ~5% within the industrialized nations. Therefore, concomitant therapy using cineole is recommendable in light of both the low level of negative side effects and the relatively low treatment costs. Asthma control can thus be ameliorated and implemented without significant cost increases or additional risks. Cineole may provide a useful treatment option for asthma, which may be viewed as complementing in the established guidelines for asthma therapy.

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DECLARATION OF INTEREST

The authors declare they have no conflicts of interest.

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