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Anti-inflammatory activity of 1.8-cineol (eucalyptol) in bronchial asthma: a double-blind placebo-controlled trial

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Abstract Airway hypersecretion is mediated by increased release of inflammatory mediators and can be improved by inhibition of mediator production. We have recently reported that 1.8-cineol (eucalyptol) which is known as the *major* monoterpene of eucalyptus oil suppressed arachidonic acid metabolism and cytokine production in human monocytes. Therefore, the aim of this study was to evaluate the anti-inflammatory efficacy of 1.8-cineol by determining its *prednisolone equivalent potency* in patients with severe asthma. Thirty-two patients with steroid-dependent bronchial asthma were enrolled in a double-blind, placebo-controlled trial. After determining the effective oral steroid dosage during a 2 month run-in phase, subjects were randomly allocated to receive either 200 mg 1.8-cineol t.i.d. or placebo in small gut soluble capsules for 12 weeks. Oral glucocorticosteroids were reduced by 2.5 mg increments every 3 weeks. The primary end point of this investigation was to establish the oral glucocorticosteroid-sparing capacity of 1.8-cineol in severe asthma. Reductions in daily prednisolone dosage of 36% with active treatment (range 2.5–10 mg, mean: 3.75 mg) *vs.* a decrease of only 7% (2.5–5 mg, mean: 0.91 mg) in the placebo group ($P=0.006$) were tolerated. Twelve of 16 cineol *vs.* four out of 16 placebo patients achieved a reduction of oral steroids ($P=0.012$). Long-term systemic therapy with 1.8-cineol has a significant steroid-saving effect in steroid-depending asthma. This is the first evidence suggesting an anti-inflammatory activity of the monoterpene 1.8-cineol in asthma and a new rational for its use as mucolytic agent in upper and lower airway diseases.

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Keywords 1.8-cineol (eucalyptol); secretolysis; asthma; anti-inflammatory therapy; glucocorticosteroid.

INTRODUCTION

In nature, essential oils are widely known as mixtures of various monoterpenes that are used traditionally in man in consequence of their secretolytic properties. Irritation of the airways and acute bronchospastic reactions following inhalation or ingestion of these natural mixtures of monoterpenes has limited their clinical use. By contrast, saturated monoterpenes, such as 1.8-cineol (eucalyptol), the major constituent of eucalyptus oil is well tolerated. This volatile oil has been used in traditional medicine as a secretolytic remedy for bronchitis, sinusitis, and colds.

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Biochemical, 1.8-cineol, and other terpenes such as menthol or camphor are isoprenoids (C_5) consisting of 2-isoprene subunits (C_{10}). They are related to human isoprenoids such as sesquiterpenes (C_{15}), steroid hormones ($2 \times C_{15}$), as well as glucocorticosteroid and tocopherols (C_{20}), each of which contains increasing numbers of isoprene subunits. Inhibition of the cyclooxygenase pathway was reported as first evidence of a potential anti-inflammatory activity of 1.8 cineol (1). Since inflammatory mediators are known to induce hypersecretion by stimulation of Cl^- secretion into the airways (2,3), we have recently reported that the monoterpene 1.8-cineol revealed a steroid-like suppression of arachidonic acid metabolism and cytokine production *in vitro* (4). Furthermore, 1.8-cineol showed a dose-dependent inhibition of monocyte mediator production at therapeutic plasma levels *in vitro* with a magnitude of inhibition comparable to that of budesonide (5). Further controlled studies revealed a significant improvement in lung

function tests (6,7) and in a non-controlled study significant inhibition of LTB_4 and IL-1β in stimulated monocytes *ex vivo* after additional therapy with 200 mg 1.8-cineol t.i.d. administered in enteric-coated capsules (8).

In Germany, 1.8-cineol is registered as *a licensed medicinal product* and available since many years in small gut-soluble capsules (Soledum™ capsules, Cassella-med, Cologne, Germany) containing 100 mg cineol per capsule for the treatment of acute and chronic bronchitis, sinusitis, and respiratory infections. 1.8-Cineol is well tolerated at a dosage of 600 mg/day (3×2 capsules), and should be taken with cold water about 20 min prior to eating to prevent epigastric pain. Overweight may be critical to achieve steady-state plasma concentrations, which are normally reached following 2–3 days of dosing because of the highly lipophilic nature of the substance. 1.8-Cineol is extensively distributed into tissues and has a long terminal half-life, which reflects the slow release of the monoterpene from these tissues back into plasma after dosing has ceased. Following chronic administration (800 mg/day), no accumulation of cineol is known in the plasma.

To establish whether the inhibitory effects of 1.8-cineol on inflammatory mediator production may also translate into clinically relevant anti-inflammatory efficacy, we performed a randomised, placebo-controlled trial to determine the oral glucocorticosteroid-saving efficacy of long-term cineol therapy in patients with severe asthma.

PATIENTS AND METHODS

Study subjects

Thirty-two patients aged 32–75 years who met NHLBI criteria for the diagnosis of bronchial asthma (9) were recruited from our asthma outpatient clinic at Bonn University Hospital. Three asthmatics were aspirin-sensitive and eight patients had chronic rhinosinusitis, with or without nasal polyps, equally distributed in both groups; six patients were smokers ($2 < 5$ and $4 < 10$ cigarettes/day). Body weight in the placebo group (74 ± 2 kg) was not statistically different (P=0.36) from the verum group (78 ± 14 kg). Previous treatment with 1.8-cineol was at least withdrawn 6 weeks before patient selection. All asthmatics were receiving between 5 and 24 mg prednisolone daily as the lowest maintenance dose. Both groups were treated not statistically different with high doses of inhaled corticosteroids from metered dose inhalers expressed as equivalent doses to beclomethasone dipropionate (BDP) in the verum and placebo groups (Table 1). One puff BDP ($100\,\mu g \times puff^{-1}$=valve dose) was calculated as equivalent to 1 puff flunisolide ($250\,g \times puff^{-1}$), 1 puff budesonide ($100\,\mu g \times puff^{-1}$) and 1 puff fluticasone propionate ($50\,\mu g \times puff^{-1}$). Additionally, patients were on appropriate asthma treatment including long-acting inhaled β-agonists and/or theophylline. Dosages were kept constant throughout the study except for short-acting β-agonists, which were used as required with an average frequency of 3×2 puffs/day. Daily prednisolone dosage and concomitant asthma

Table 1. Baseline demographics and concomitant therapy*

	Cineol	Placebo	*P*-value
Male : Female	12:4	6:10	0.0277
Age (years)	59 ± 10	56 ± 15	0.5349
Prednisolone dose (mg)	10.3 ± 4.4	11.9 ± 5.7	0.2834
FVC [l]	4.6 ± 1.4	3.4 ± 1.0	0.0869
FEV_1 [l]	2.8 ± 1.4	2.2 ± 0.9	0.117
%FEV_1 pred	85 ± 30	78 ± 26	0.6501
FEV_1/FVC	61 ± 16	63 ± 13	0.9750
PEFR [l/min]	388 ± 186	353 ± 107	0.8139
RAW (kPa/(l/s))	0.31 ± 0.16	0.37 ± 0.13	0.2115
Concomitant daily asthma medication (n Pt.)			
Inhaled steroids (μg)	830 ± 190 (16)	1100 ± 200 (16)	0.1941
Theophylline (mg)	796 ± 97 (14)	716 ± 75 (15)	0.6496
Formoterol (μg)	19.6 (10)	18.7 ± 0.8 (11)	0.5463
Ipratropium bromide (μg)	167 ± 15 (13)	154 ± 14 (14)	0.1088

*Data are presented as mean ± SD unless otherwise indicated.

medications did not differ in the two groups (Table 1). For patient inclusion, a reversibility of at least 15% in forced expiratory volume in 1 s (FEV_1) 10 min after inhalation of 200 μg fenoterol, and an airway resistance (RAW) below 0.6 kPa(l/s) was required. Lung function criteria and values conformed to ATS guidelines. Prior to patient inclusion and at the end of the study, blood counts and complete chemical analyses were performed. 1.8-Cineol in small gut-soluble capsules taken 20 min before eating at a daily dosage of 3×200mg had no taste or smell in patients with a body weight >60 kg.

Exclusion criteria were *BMI index* >27, pregnancy and lactation, known hypersensitivity to essential oils, *treatment with other secretolytic agents and leucotriene antagonists*. No further changes in asthma medication were allowed during the last 4 weeks prior to starting study medication. Patients with respiratory infections within 6 weeks before study entry were excluded.

All patients gave written informed consent to take part. The Human Ethics Committee of Bonn University Hospital approved the study. The trial was conducted in accordance with current good clinical practise (GCP) guidelines.

Study design

This was a prospective, randomised, double-blind, and placebo-controlled trial. Each participant was randomly assigned either to 1.8-cineol (Soledum™ Capsules, Cassella-med, Cologne, Germany) 200 mg t.i.d. (at 8 a.m., 2 p.m., and 8 p.m.) or placebo capsules (Cassella-med) of identical appearance. Cineol was taken in small gut-soluble capsules with no taste or smell, if taken 20 min prior eating. Randomisation of patients and allocation concealment was made using the rancode system (IDV, Gauting, Germany). The Study visits were performed on recruitment and at 3, 6, 9, and 12 weeks as outpatients. All patients were assigned to a run-in phase of 2 months with an additional visit (-4 week) to ascertain that the asthma was stable at the lowest effective systemic steroid dose. Stable asthma was assured prior to randomisation and at each following visit using measurements of lung function, peak flow and asthma scores on validated scales. Compliance was monitored in both groups by counting the remaining study medication at each visit of the randomisation phase.

Each patient used a mini-Wright peak-flow meter to measure (best of three expiratory manoeuvres) daily morning and evening PEFR (peak expiratory flow rate). Use of short-acting inhaled bronchodilators for relief of acute dyspnoea was also documented. Asthma symptoms were derived from validated scales to assess the intensity and frequency of dyspnoea and the severity of cough. Using these validated scales, patients and the study physician were asked to assess the efficacy of treatment at the end of study (or withdrawal from the study).

Each study visit was planned to take place between 8 and 10 a.m. Lung function tests including bodyplethysmography (Masterscreen, Jäger, Germany) were performed at each visit, and venous blood was taken to determine blood-cell counts and biochemical profiles at study entry and at the final study visit.

GLUCOCORTICOSTEROID REDUCTION PROTOCOL

Prior to randomisation, all patients were stable on the minimal effective systemic steroid dose for at least 4 weeks. After randomisation, the study physician at the outpatient clinic saw the patients at 3-week intervals and in addition, if asthma symptoms had increased in between two visits. Provided their asthma was stable (RAW <0.6 kPa/(l/s), average morning/evening peak flow $<20\%$, increase in β_2-adrenergics use by $<30\%$), oral steroids were reduced by 2.5 mg at each visit (or 5 mg, if the long-term dosage was $\geq$20 mg/day) for the following 3 weeks up to the next visit. Exacerbations compared to baseline were decrease in the average morning/evening peak flow by $>30\%$, decrease of mean daily peak flow by $>30\%$, or increased use of inhaled β-agonists as rescue medication by $>30\%$, or increase in RAW by $>30\%$ at the time of the 3-week revaluation. In case of a worsening trend in patients not reaching the exact criteria, prednisolone 2.5 mg was reduced, and the patient was informed to see the study physician if symptoms increased.

Statistical analysis

For each patient, the lowest oral glucocorticosteroid dosage which maintained stable clinical conditions for at least 3 weeks was determined, as was the duration of tolerated steroid reduction. Primary outcome measure was the change from the baseline of oral steroid dosage. Secondary efficacy criteria were duration of dose reduction tolerated and stable lung function as determined by bodyplethysmography, stable clinical condition as measured by outpatient PEFR, symptom scores and bronchodilators use, and overall assessment of efficacy by the patient and the study physician. Outcome measure size was based on an estimated difference of 3 mg steroid reduction between the two groups ($\alpha \leq 0.05$, $\beta \leq 0.10$) resulting from a sample size estimation of 16 patients for each group (statistics N, IDV, Gauting, Germany). The minimal clinical relevant difference was estimated *a priori* by 2.5 mg prednisone that was equal to one steroid reduction step. For analysis of diary-card data of each patient, means of daily PEFR, the average morning/evening PEFR and symptom scores were calculated for each 3-week

interval. Differences between the 1.8-cineol and the placebo recipients were assessed with the Wilcoxon Signed Rank test (StatView 5.01, SAS Institute Inc., NC, USA). Survival analysis (Kaplan–Meier) was used to examine the effects of 1.8-cineol and placebo over time. Differences were considered significant if P was less than 0.05.

RESULTS

Baseline characteristics

Thirty-three patients meeting the entry criteria were included in the study and randomised to receive study medication. One patient withdrew consent due to a supervening illness, so the per protocol analysis was based on 32 patients.

Patient demography, lung function and glucocorticosteroid medication at baseline are summarised in Table 1. Glucocorticosteroid dosages and concomitant asthma medication were equally distributed between the groups, and lung function tests revealed comparable results. Only the male:female ratio differed in the two groups, resulting in a non-significant lower FEV_1 in the placebo group. All concomitant therapy was unchanged on exit from the study.

Glucocorticoid-saving effects (Table 2)

Individuals on 1.8-cineol had their oral glucocorticosteroid reduced by a mean of 3.75 mg (95% CI: 2.15–5.35 mg) while maintaining a stable clinical condition, whereas the tolerated reduction was significantly lower in the placebo group (mean: 0.91 mg, 95% CI: 0.03–1.85 mg, P=0.006). The individual dosages at start and end of treatment are shown in Fig. 1. The cumulative dosage reductions achieved in each group throughout the 12-week study were 60 mg per day for 1.8-cineol as compared to 14.5 mg for placebo treatments. Cumulative reductions of prednisolone dosages (2.5 mg/3 weeks) as compared to randomisation (visit 1) were tolerated in the verum group at visit 2 (32.5 mg in 13 patients, P=0.0022), at visit 3 (40 mg in eight patients, P=0.0117), at visit 4 (30 mg in four patients, P=0.0679), and visit 5 (30 mg in three patients, P=0.1088). In the placebo group, the tolerated reduction of prednisolone dosages as compared to randomisation (visit 1) was much less at visit 2 (10 mg in four patients, P=0.0679) and visit 3 (5 mg in one patient).

Only four patients treated with 1.8-cineol did not tolerate any decrease in glucocorticosteroid dosage in contrast to 12 patients given placebo. Compared to placebo, cineol recipients maintained their lung function four times longer despite receiving lower dosages of prednisolone (Table 2).

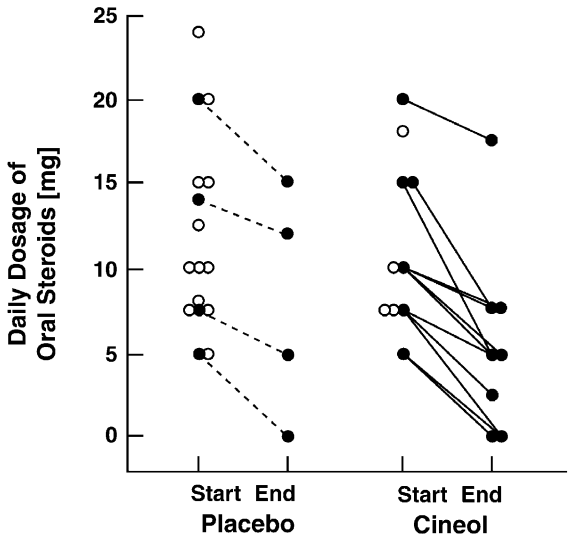

Fig 1. Individual steroid doses before and after treatment. Patients who tolerated a reduction in oral steroid dosage are indicated with dark symbols and patients who withdrew from the study due to clinical deterioration as clear symbols. Twelve patients receiving 1.8-cineol and four placebo patients had their steroid dosages reduced as shown by the connecting lines. Steroid dosages are not depicted for all cineol patients, if they were the same: one patient on 20 mg was reduced to 17.5 mg; two patients on 15 mg, one of each was reduced to 7.5 and 5 mg; four patients on 10 mg, two patients of each were reduced to 7.5 and 5 mg; three patients on 7.5 mg, one patient of each was reduced to 5, 2.5 and 0 mg; two patients on 5 mg were reduced to 0 mg.

Clinical effects of glucocorticosteroid reduction

Reduction of prednisone 2.5 mg every third week (e.g. visits 1–5) had no significant impact on lung function and PEFR in the verum group, if all patients in each group at the different visits were statistically compared to baseline (Table 3a). In this group, prednisone reduction also did not significantly increase regular daily use of salbutamol. By contrast, in the placebo group, PEFR was significantly lower in 15 out of 16 patients after the first reduction (visit 2) of prednisolone 2.5 (Table 3b). Reduction of prednisolone in the placebo group did not provoke any adverse effects on lung function measurements compared to baseline. However, in this group, the use of salbutamol as rescue medication almost increased 2-fold as compared to baseline and this was significant after reduction of only 2.5 mg at visit 2 (Table 3b).

Scores for frequency of dyspnoea (0=never, 1=rare, 2=occasional, 3=often, 4=very often, 5=persistent) before glucocorticosteroid reduction (visit 1) were not significantly (P=0.29) different in the placebo (1.5 ± 1.2, n=16) and the verum (0.8 ± 0.7, n=16) groups. After reduction of prednisolone 2.5 mg (visit 2), the score of

Table 2. Efficacy parameters[a]

	Cineol	Placebo	*P*-value
Tolerated dose reduction per patient (mg)	3.75	0.91	0.006
Cumulative tolerated dose reduction steps in relation to total possible steps[b]	27/ 55	5/ 55	0.0001
Days stable on reduced dose	36.6	8.3	0.006
Patient's global assessment of efficacy[c]	2.2 ± 1.2	3.3 ± 0.8	0.01
Study physician's global assessment of efficacy	2.2 ± 1.2	3.7 ± 0.7	0.007

[a]Data are presented as mean or mean ± SD.
[b]One step was equivalent to 2.5 mg except in one patient with initial steroid dosages of > 20 mg in whom the initial step was 5 mg. In one patient, initial prednisolone of 14 mg/day was reduced by 2 mg. The total number of possible dose reduction steps was determined considering the patient's initial dose and the duration of the study. For example, if the initial dosage was 7.5 mg, three reduction steps (to 5, 2.5, and 0 mg) were possible throughout the study.
[c]On a 4-point scale (1: very good, 2: good, 3: moderate, 4: deterioration).

Table 3. Comparison of lung function tests and rescue salbutamol before and after prednisone reduction*

Reduction of prednisolone (mg/3 weeks)	*n*	FEV_1 (L)	*P*-value	RAW kPa/(l/s)	*P*-value	PEFR (l/min)	*P*-value	Rescue salbutamol (puffs/day)	*P*-value
(a) Verum group									
0	16	2.81 ± 1.4	—	0.316 ± 0.158	—	388 ± 186	—	2.6 ± 3,1	—
2.5	16	2.95 ± 1.2	0.7532	0.289 ± 0.122	0.4955	318 ± 130	0.5303	3.2 ± 3.2	0.2249
5	12	2.75 ± 1.4	0.6465	0.32 ± 0.13	0.3465	418 ± 206	0.0630	3.4 ± 3.8	0.5839
7.5	6	2.75 ± 1.5	0.138	0.282 ± 0.19	0.2489	362 ± 85	0.0796	1.8 ± 3.5	0.1797
10	4	2.65 ± 2.0	0.2733	0.297 ± 0.223	0.4652	353 ± 95	0.1441	2.0 ± 3.5	1.0
(b) Placebo group									
0	16	2.18 ± 0.89	—	0.371 ± 0.124	—	353 ± 107	—	3.7 ± 3.2	—
2.5	15	2.16 ± 0.69	0.9547	0.381 ± 0.144	0.7548	269 ± 90	0.0329	6.3 ± 3.8	0.0093
5	4	2.22 ± 0.43	0.4652	0.37 ± 0.133	0.0679	295 ± 149	0.6547	6 ± 2	0.1797
7.5	0	—		—		—		—	

*Changes compared to baseline in lung function measurements and use of salbutamol (mean ± SD) for all patients in each group after reduction of prednisone 2.5 mg every third week.

dypnoea was significantly (P=0.0063) higher in the placebo group (2.8 ± 1.3, n=15) compared to the verum group (1.3 ± 1.3, n=16).

Safety

1.8-Cineol was generally well tolerated. There were 12 adverse events in nine patients throughout the study: Three patients on 1.8-cineol and two on placebo experienced upper respiratory tract infections, two patients had back pain, severe headache, gastritis and heartburn in the 1.8-cineol group or abdominal discomfort and tonsillitis during placebo treatment. Side effects considered by the study physician to be possibly attributable to cineol were heartburn and gastritis. There were no serious adverse events (SAEs) or any clinically relevant abnormalities in routine blood test parameters.

Discussion

In the present double-blind trial, the majority of patients with chronic asthma receiving oral 1.8-cineol 200 mg t.i.d. remained clinically stable despite a mean reduction of oral steroid dosage of 36% equivalent to 3.8 mg/day. This was in sharp contrast to the placebo group (7% equivalent to 0.9 mg/day), in which 12 of 16 patients were not able to tolerate any decrease of oral steroids according to pre-defined stability criteria. The mean duration of the tolerated dose reduction during 1.8-cineol was four times that in the placebo group with a four times greater reduction of cumulative steroid doses in the verum group. Therefore, this is the first report to suggest a clinically relevant anti-inflammatory activity of 1.8-cineol in bronchial asthma.

Only four out of 16 patients receiving placebo tolerated a reduction of their steroid dosages by 2.5–5 mg.

This reflects the fact that almost all patients were on the lowest effective steroid dose and represented a group of steroid-dependent asthmatics. The placebos were indistinguishable from the active drug unless the capsules were a bit apart. Concomitant medication was also comparable at baseline and was kept unchanged as long as patients remained in the study.

Before randomisation, the two groups studied were comparable in the severity of their asthma as determined by long-term systemic use of prednisolone, concomitant asthma medication including on demand use of short-term β_2-agonists, lung function tests, daily measurements of peak expiratory flow, scores for frequency of dyspnoea and body weight. The groups studied differed only in that the male:female ratio was reversed, but by the entirely comparable asthma parameters in both groups, gender seems to be very unlikely to have affected the severity of asthma in this study. Adverse events occurred infrequently. Heartburn and gastritis were the sole side effects, which the study physician considered to be attributable to cineol. There were no severe adverse events at any time during the study.

Until recently, however, the scientific literature has contained very little clinical or experimental data on 1.8-cineol or related terpenes as anti-asthma medications. Relatively high concentrations of systemic 1.8-cineol were recently reported to display an inhibitory effect on the classic types of experimental inflammation in rats, i.e. paw oedema by carrageenan and cotton pellet-induced granuloma (10). Though 1.8-cineol has no acute bronchodilators activity, a controlled study reported on surprisingly strong bronchodilators effects in patients with asthma following oral therapy with 1.8-cineol for 7 days (6). In a single-blind study, in patients with mild and moderate asthma, additional therapy with 1.8-cineol over 3 days also improved lung function and suppressed *ex vivo*-stimulated inflammatory mediator production in short-term cultures of peripheral monocytes (8). These studies gave first evidence that 1.8-cineol could interfere with inflammatory mediator production as the underlying mechanism of its mucolytic activity. As indicated by the present study, long-term therapy with 1.8-cineol is well tolerated and mediates an anti-inflammatory activity equivalent to about 3 mg prednisolone. In this view, there is new evidence to support long-term systemic therapy with 1.8-cineol that might be therapeutically useful for treatment of asthma and COPD. Since systemic glucocorticosteroids were reduced in our present study, the bronchodilators activity of 1.8-cineol was only seen in one proportion of the patients studied in the verum group at visit 2 despite reduction of prednisolone to 2.5 mg.

The chemical relationship between the monoterpene 1.8-cineol and glucocorticosteroids, also members of the terpene family, raise the possibility that there is a common mechanism of inflammatory mediator suppression for their anti-inflammatory efficacy. Further findings from our own laboratory revealed that not only 1.8-cineol, but also pure L-menthol, which is the major constituent of mint oil was able to suppress inflammatory mediator production in stimulated monocytes *in vitro* (11). By contrast, mint oil and its derivatives containing menthol, were shown to induce prostaglandin and leukotrienes production *in vitro*, indicating potential pro-inflammatory activities of natural mixtures of monoterpenes (11). L-menthol was also shown in a double-blind, placebo-controlled trial in patients with mild asthma to reduce airway hyperresponsiveness and improve asthma (12).

The leukotrienes (LT) LTC_4 and LTD_4, their precursors (5-HETE), prostanoids (PGD_2, PGF_2), and certain cytokine stimulate mucus production by human airway epithelial cells (2,13,14). Therefore, our previous reports suggested that the known mucolytic effects of 1.8-cineol might be mediated through inhibition of inflammatory mediator production (4,8). By contrast, mixtures of various monoterpenes known as essential oils may induce hypersecretion by increased cell activity and stimulation of inflammatory mediator production, rather than by single secretolysis. This is supposed to be a major cause for known side effects of essential oils in asthma.

In conclusion, the present study supports for the first time a clinically relevant anti-inflammatory activity of the terpenoid oxide 1.8-cineol and offers new perspectives for its long-term therapeutic use in airway diseases, such as asthma. Its potential role for early systemic anti-inflammatory treatment of intermittent and mild persistent asthma requiring high doses of inhaled glucocorticosteroid still needs to be defined. Additional studies with 1.8-cineol in various inflammatory and steroid-sensitive disorders, such as allergic rhinitis and inflammatory bowel disease, seem necessary to better define its therapeutic efficacy in chronic inflammatory diseases.

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