

Safety and Efficacy of a Traditional Herbal Medicine (Throat Coat[®]) in Symptomatic Temporary Relief of Pain in Patients with Acute Pharyngitis: A Multicenter, Prospective, Randomized, Double-Blinded, Placebo-Controlled Study

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ABSTRACT

Objective: To investigate the safety and efficacy of Throat Coat[®] (Traditional Medicinals[®], Sebastopol, CA), a traditional demulcent herbal tea, in comparison with a placebo tea in the symptomatic treatment of acute pharyngitis.

Design: Multicenter, prospective, randomized, double-blinded, placebo-controlled, two-armed, parallel-group clinical trial.

Settings: Three primary care clinics in Duluth, MN, Madison, WI, and Middleton, WI.

Subjects: Patients of both genders (≥ 18 years of age) with clinical diagnoses of acute pharyngitis.

Interventions: Patients ($n = 60$) were randomly assigned to receive 5–8 oz of Throat Coat ($n = 30$) or a placebo ($n = 30$), four to six times daily. The study period was 2 to 7 days with a window for the follow-up visit of 2–10 days accounting for the variable duration of sore throat symptoms.

Outcome measures: Primary efficacy parameter: sum of pain intensity differences (SPID) for pain in throat on swallowing, calculated as the area under the curve (AUC) of pain intensity difference scores (assessed at 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, and 30 minutes after treatment). Secondary efficacy parameter: total pain relief (TOTPAR), calculated as the AUC from time 0 (baseline) to 30 minutes of pain relief (assessed at 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, and 30 minutes).

Results: Compared to placebo, intensity of throat pain when swallowing was significantly reduced by Throat Coat in intention to treat and valid for efficacy analysis (VEA). Significant differences in change from baseline pain were observed at 5 min ($p = 0.007$), 10 min ($p = 0.005$), 15 minutes ($p = 0.01$), 20 minutes ($p = 0.05$), and 30 minutes ($p = 0.04$) after completion of the first dose (VEA analysis). There was a statistically significant improvement of SPID in the Throat Coat-treated group: Least square means \pm standard error of the means (SEM) of SPID were -16.5 ± 13.9 in the placebo group and -43.8 ± 11.9 in the Throat Coat-treated group ($p = 0.012$). TOTPAR was also significantly higher in the Throat Coat-treated group: Least square means \pm

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SEM of TOTPAR were 32.4 ± 12.8 in the placebo group and 53.6 ± 10.9 in the Throat Coat-treated group ($p = 0.031$). This study shows that Throat Coat is significantly superior to placebo and provided a rapid, temporary relief of sore throat pain in patients with pharyngitis.

INTRODUCTION

Acute pharyngitis is characterized by an inflammation of the mucous membranes of the pharynx and the surrounding lymphoid tissue. Acute sore throat is a common affliction accounting for up to 5% of pediatric office visits and 40 million annual adult visits to medical facilities in the United States. It is a frequently presented condition among patients seen at emergency departments (O'Brien et al., 1993). Pain in throat on swallowing is the most prominent clinical symptom of sore throat. The intensity of symptoms is experienced as mild to moderate discomfort in the majority of cases, but acute pharyngitis can also be incapacitating with a feeling of general malaise and an inability of swallowing (O'Brien et al., 1993).

Approximately one quarter (10%–40%) of acute pharyngitis cases in adults is caused by Group A streptococci, in 40%–45% it is a concomitant symptom of viral infections, and in one third of cases the causative agent could not be identified (Carroll and Reimer, 1996). Current therapy consists of antibiotics when indicated, internal analgesics, topical anesthetics, and antipyretics. Antibiotic treatment aims at the eradication of *Streptococcus*, and thereby at preventing consecutive immunologic diseases, such as rheumatic fever and glomerulonephritis (O'Brien et al., 1993). A recent systematic review of trials, by the Cochrane Collaboration, involving a total of 10,484 cases of sore throat treated with antibiotics concluded that the absolute benefits of antibiotics are modest (Del Mar et al., 2000). Standard treatment of pain and inflammation components with analgesics, anti-inflammatory drugs and even steroids (Marvez-Valls et al., 1998) has potential risks and side-effects. Although topical anesthetics do not cause systemic side-effects, allergic reactions have been reported (Catterall and Mackie, 1996). There is clearly a need for alternative and safer therapies to achieve relief of symptoms in acute pharyngitis.

To date, little strong scientific evidence is available to support the generally recognized

action of demulcents on sore throat pain. Demulcents are agents that soothe and relieve irritation, especially of the oral and pharyngeal mucosa. Demulcent herbs have demonstrated mucilaginous effects, whereby the polysaccharides occurring in the aqueous extract adhere to irritated mucous membranes forming a coating (Schmidgall et al., 2000).

The investigational product in this study is classified as a dietary supplement in the United States, while in Canada it is an over-the-counter (OTC) drug (Health Canada Therapeutic Products Programme, 2002) meeting the Drugs Directorate definition and guidelines for authorized "Traditional Herbal Medicines" (Health Canada Drugs Directorate, 1995). It contains a combination of three herbs and one dry extract with reported demulcent activity: (1) Elm bark (*Ulmus rubra* Muhlenberg) is generally recognized as a safe and effective OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat (Food and Drug Administration [FDA], 1982) and an official standards monograph (Elm USP) is published in the *United States Pharmacopeia* (USP; United States Pharmacopeial Convention, 2002). Official standards published in the USP designate that the article has an FDA-approved or USP-accepted use (United States Pharmacopeial Convention, 1999); (2) Licorice root (*Glycyrrhiza glabra* L.) is categorized as a demulcent in the *Indian Pharmacopoeia* (Government of India Ministry of Health and Family Welfare, 1996), and it is indicated for relief of cough with phlegm in the *Pharmacopoeia of the People's Republic of China* (Pharmacopoeia Commission of the People's Republic of China, 1997). Additionally, licorice root tea is an approved non-prescription drug in Germany for catarrhs of the upper respiratory tract (Blumenthal et al., 1998; Braun et al., 1996) and an official standards monograph is published in the *European Pharmacopoeia* (2002) as well as in the *United States National Formulary* (United States Pharmacopeial Convention, 2002); (3) A monograph for licorice root extract is published in the *Pharmacopoeia of the People's Republic of China* indi-

cated for the treatment of bronchitis, pharyngitis, and laryngitis, among other conditions (Pharmacopoeia Commission of the People's Republic of China, 1997); (4) Marshmallow root (*Althaea officinalis* L.) tea is an approved non-prescription drug in Germany for irritation of the oral and pharyngeal mucosa with associated dry cough (Blumenthal et al., 1998; Braun et al., 1996) and an official standards monograph is published in the European Pharmacopoeia (2002). Schmidgall et al. (2000) recently reported that an aqueous extract of marshmallow root demonstrated significant bioadhesive effects on buccal mucous membranes *ex vivo* confirming that mucilaginous effects on epithelia can occur. *Ex vivo* tests are conducted outside the living body using an organ or tissue sample.

The aim of this study was to investigate the safety and efficacy of a traditional demulcent herbal tea, in comparison with a placebo tea to evaluate if there is a significant difference in effectiveness of immediate relief of sore throat pain between the experimental group (Throat Coat,[®] Traditional Medicinals,[®] Sebastopol, CA) and the control group (placebo).

MATERIALS AND METHODS

This study was conducted in accordance with Institutional Review Board (IRB) regulations, good clinical practice and the Declaration of Helsinki. The study was approved by the Dean IRB (Middleton, WI) and the St. Mary's/Duluth Clinic IRB (Duluth, MN) and all subjects gave written consent prior to participation. All herbs used in this trial are either classified as generally recognized as safe (GRAS) for use in foods by the FDA and/or are permitted for use in dietary supplement products according to the provisions of the Dietary Supplement Health and Education Act of 1994.

Study design

This trial was designed as a multicenter, prospective, randomized, double-blind, placebo-controlled, two-armed, parallel-group clinical trial to investigate the effects of a traditional demulcent herbal preparation (Throat Coat) on sore throat pain in patients diagnosed with acute pharyngitis.

Subjects

Eligible participants were recruited from December 2000 to May 2001 in Duluth, MN, through the St. Mary's Medical Center, a hospital clinic that serves residents of northern Minnesota, northern Wisconsin and Upper Michigan. Patients were also recruited in the Madison, WI, area through the Dean Foundation for Health, Research and Education, a non-profit organization that conducts clinical trials through its participating physicians in the Dean Health System.

Adult patients of both genders ages 18 years and older were examined by one of the clinical study investigators (a medical doctor) or by one of the clinical study coordinators [e.g., certified clinical research coordinator, certified medical assistant, or registered nurse] and were enrolled into the study according to the inclusion and exclusion criteria described in Table 1. This study was purposely designed to include patients based on a clinical diagnosis regardless of etiology (i.e., viral or bacterial) to investigate

TABLE 1. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

1. ≥ 18 years of age
2. Diagnosis of acute pharyngitis established by a physician or under the protocol of a physician.
3. Baseline pain score of ≥ 5 , assessed on a 0–10 rating scale at the time of randomization when evaluating the intensity of pain in the throat on swallowing.
4. Patient must be able to understand and give written informed consent and report adverse events and concomitant medication for the duration of the study.

Exclusion Criteria

1. Patient has suffered from sore throat for more than 7 days.
2. Patient has taken any medication for relief of sore throat including herbs or dietary supplements within 4 hours prior to study initiation.
3. Patients who are on analgesic or anti-inflammatory regimen requiring treatment with analgesics; nonsteroidal anti-inflammatory drugs, or steroids.
4. Symptoms of sore throat caused by local irritation of mucous membranes as a result of gastroesophageal reflux or ingestion of caustic substances.
5. Patient is pregnant, nursing, or a woman of childbearing potential not practicing adequate contraception. Women, who are uncertain if they are pregnant, may participate in the study, if they undergo a pregnancy test, which shows a negative result.
6. Patient has comorbid condition, uncontrolled metabolic condition or psychiatric condition that might make tolerance or evaluation of the dietary supplement difficult.

the effects of the herbal preparation in a representative population. No routine laboratory safety evaluations were performed. At the start of the study, throat swabs were taken on 11 patients for an evaluation of streptococcus infection. Three were positive (all ending up in the Throat Coat-treated group). No other medications were prescribed. Written informed consent was obtained by the investigator and study coordinator. A flowchart illustrating the study procedures is provided in Table 2.

Sixty (60) subjects were randomized in a double-blinded manner to one of two parallel treatment groups (Throat Coat or placebo). The regular treatment period was 2–10 days, depending on the continued intake of the investigational product because of persistent pharyngeal symptoms. The patients visited the clinic a second time after 7 days (visit 2) with a window of 2–10 days. At both visits, patients gave an assessment of their throat pain on

swallowing and completed the questionnaire for acute pharyngitis shown in Table 3.

The first treatment with either Throat Coat or placebo was at visit 1, in the clinic. Patients were followed-up in the clinic for 30 min after the first dose; they gave repeated ratings of pain on swallowing and of pain relief during this period. From visit 1 until visit 2, patients used either Throat Coat or placebo 4–6 times per day; they documented pain on swallowing and completed a pharyngitis questionnaire in a diary. The subjects were instructed to avoid taking analgesics, anti-inflammatory drugs, steroids (except for ophthalmic drugs and rectal preparations), and any other medication for the relief of sore throat including lozenges and herbal dietary supplements.

The study coordinator supervised the patients' assessments and reviewed patient diary information regarding efficacy of the product. As a check on compliance, the patients were

TABLE 2. FLOWCHART OF STUDY PROCEDURES

Day #	0	2–10	Time (days)
Visit #		1	2
Diagnosis of acute pharyngitis established by physician		x	
Inclusion/exclusion criteria confirmed		x	
Written informed consent		x	
Randomization		x	
Supply of investigational product to the patient		x	
Medication accountability assessed			x
Evaluations at clinic			
Pharyngitis-specific questionnaire assessed		x	x
Reporting of adverse events		x	x
Assessment of pain intensity and pain relief		x	x
Assessment of symptom-specific concomitant medication		x	x
Patient diary for efficacy assessment			
Diary dispensed		x	
Diary returned and evaluations recorded			x
Additional assessments:			
At visit 1: Assessment of pain in throat on swallowing 1, 5, 10, 15, 20, and 30 minutes after drinking the first cup of tea.			
In patient diary after 3 and 24 hours, and every consecutive day until visit 2: Assessment of pain in throat on swallowing, and of pharyngitis questionnaire.			

TABLE 3. SORE THROAT QUESTIONNAIRE

<i>Patient No.</i> 	<i>Patient Initials</i> <i>First Last</i>	<i>Date of Visit</i> <i>M M D D</i>	<i>SORE THROAT QUESTIONNAIRE Visit 1</i>
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Sore Throat Questionnaire

Please indicate the extent to which you are bothered by any of these symptoms by placing a check in the appropriate box.

	Symptoms	Not at all	Very little	Little	Moderately	Much	Very much	Extremely
1	Pain or discomfort in throat on swallowing							
2	Sensation of swelling in the throat							
3	Difficulty in swallowing							
4	Hoarseness							
5	Extension of throat pain to ear or head							
6	Influenza-like symptoms (headache, fever, sweats, muscle aches)							
7	To what extent did your sore throat affect your overall well-being?							
	When did the pain in throat on swallowing disappear completely?	Date _/_/___		Time of day _:__				

Further comments on symptoms:

asked to bring in all unused study investigational products to the clinic on visit 2.

Randomization

The randomization list for this double-blinded, randomized study was computerized and the patients were allocated in blocks. The allocation sequence was generated by the clinical research organization (Narayana Research, Hørsholm, Denmark), and the details were unknown to the study investigators and coordinators.

The randomization code for each patient was stored in two sealed envelopes. One set of envelopes was kept by Narayana Research in a

fireproof place. The other set of envelopes was kept at the study centers for emergency situations, in the event that knowledge of the actual treatment were to become medically necessary. Breaking the code for one patient would not automatically break the code for the other patients.

Two copies of the randomization list were put into two sealed envelopes. One was kept by Narayana Research; the other was forwarded to Traditional Medicinals' quality control manager for labeling the investigational product. The randomization list was transcribed on a list that identified which patients receive the same treatment, without revealing whether placebo or active treatment was given.

This sequence list was also placed in a sealed envelope and kept by the clinical research organization.

Each study center was provided with a list of randomization numbers (patient identifying numbers) prepared in advance. This list contained the randomization numbers to be used by this center (e.g., 01, 02, 03, etc., or 41, 42, 43, etc.), but not the corresponding allocation to one of the two treatment groups. This randomization number was the patient number throughout the study. Once a patient was randomized, the patient numbers were added to the case report forms from visit 1.

Packages with the test and reference treatment were supplied to each study site. Each package was labeled with the patient number (randomized number). The patient number thereby controlled which study treatment the patient received, without unblinding individuals at the centers.

Interventions

Patients with acute pharyngitis were randomized to receive either placebo or Throat Coat at a dose of 5–8 fl. oz. (prepared from 2 g of dried herbal mixture) 4–6 times daily for as long as pain or discomfort in the throat persisted. All study personnel and patients were blinded to treatment assignment throughout the course of the study.

Throat Coat (Lot # A6350) and placebo (Lot # A6351) were supplied as homogeneous mixtures of dried botanicals packaged in an unbleached double-pouch filter tea bag, individually sealed in a plain white tamper-evident overwrap. Labels of the test and reference product were identical. Production of the investigational products was carried out according to good manufacturing practice and the quality standards of the botanical raw materials are documented in their written specifications according to current pharmacopoeial standards. Additionally, identification of the botanical ingredients was confirmed through an independent laboratory (Alkemists Pharmaceuticals, Costa Mesa, CA) using high-performance thin-layer chromatography with photo documentation and microscopy with digital photo-determination. Certificates of analysis are available upon request.

Each single-dose of Throat Coat contained 960 mg of a pharmacopoeial-grade herbal demulcent mixture as follows: 760 mg of licorice root; 80 mg of elm inner bark; 60 mg of marshmallow root; and 60 mg of licorice root aqueous dry extract. (Lanzhou Taibao Pharmaceutical Factory, Gansu Province, People's Republic of China). Raw materials used for extraction were large, dried, mature roots of Chinese licorice (*Glycyrrhiza uralensis* Fisch. ex DC) grown in Gansu Province. The drug-to-extract ratio was 8:1 (w/w). The extraction solvent was water. The excipient was dextrin made from Chinese yam rhizome (*Dioscorea oppositifolia* L.). The trial preparation also contained a proprietary mixture of the following nondemulcent botanical ingredients in order of predominance: wild cherry bark (*Prunus serotina* Ehrh.); fennel fruit (*Foeniculum vulgare* Miller); cassia bark (*Cinnamomum aromaticum* Nees); and sweet orange peel (*Citrus sinensis* (L.) Osbeck). The placebo preparation was a licorice-flavored nonmedicinal beverage tea designed to taste, smell, and appear indistinguishable from the trial preparation with identical packaging and mode of administration. The placebo preparation contained food ingredients that, based on a review of the medical herbalism literature, have not been shown to exhibit demulcent activity. In addition no evidence was found regarding any traditional use as demulcents. These ingredients included barley (*Hordeum vulgare* L.), roasted chicory root (*Cichorium intybus* L.), sweet orange peel (*Citrus sinensis* (L.) Osbeck), natural licorice flavor, star anise fruit (*Illicium verum* J.D. Hook. f.), and stevia leaf (*Stevia rebaudiana* (Bertoni) Hemsl.). The amount of natural licorice "flavor" contained in the placebo preparation was 160 mg per serving, a typical food flavor-enhancer level.

At visit 1, the first dose was prepared for, and dispensed to, the patients by a clinical study coordinator. Subsequent doses were prepared by the patients at home following written instructions received from the clinical study coordinators. The patients were given one package with 64 individually sealed tea bags as well as 1 standard tea infusion cup with a lid for home preparation. The patients were instructed to prepare 1 cup of tea, 4–6 times daily,

according to the following instructions: "Pour 150–240 mL (5–8 oz.) of boiling water over 1 tea bag in a heat-resistant porcelain cup (cup and lid provided). Cover the cup with a lid and allow to steep for 15 minutes. Gently squeeze the tea bag over the cup with a spoon or kitchen tongs to release any remaining extractive from the herbs. Do not add sweetener of any kind to the tea. Drink tea slowly and gargle before swallowing."

The reason that patients were instructed not to add sweetener of any kind is because honey is traditionally added to medicinal herbal teas as both a flavor enhancer and, in some cases, also to enhance therapeutic effects. The addition of honey to the placebo tea would have presented a significant confounding factor due to its known pharmacologic actions. In several studies, honey has demonstrated antibacterial effects (Therapeutic Goods Administration, 1998) including activity against viridans streptococci (Tichy and Novak, 2000). In various systems of traditional medicine, honey is used as a demulcent in cough mixtures (Leung and Foster, 1996) and in Chinese medicine it is specifically indicated for dry cough among other conditions (Pharmacopoeia Commission of the People's Republic of China, 1997).

Efficacy variables

Patients assessed the intensity of pain they felt in the throat on swallowing. Assessments were made at baseline, and at the following time-points after drinking the first cup of investigational tea: after 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 3 hours, 24 hours, and every consecutive day until visit 2 as long as pain symptoms persisted. The intensity of pain was assessed using an 11-point numerical scale (0 = no pain to 10 = most severe pain imaginable).

In addition, patients assessed the extent of pain relief compared to baseline after 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 3 hours, 24 hours, and every consecutive day until visit 2 as long as pain symptoms persisted.

Assessments of pain intensity and pain relief up to 30 minutes postbaseline and at visit 2 were noted on the case report form. At inter-

mediate time-points between visits 1 and 2, patients entered the ratings in their patient's diaries. Patients were asked to perform the daily ratings at the same time of the day as when they performed their baseline pain rating at the clinic. The pain ratings were to be performed no earlier than 5 minutes after drinking the tea and no later than 15 minutes after the last sip of tea.

Adverse reactions were summarized by incidence of patients in the two parallel treatment groups. All adverse reactions were coded according to adverse reaction terminology (ART) of the World Health Organization (WHO), assigning each adverse reaction to standard adverse events within corresponding body system classes.

Sample size calculation

No clinical trial data existed on the efficacy of Throat Coat or for any of its individual demulcent botanicals. Based on two previous clinical studies examining the effectiveness of steroids for pain relief in acute pharyngitis (Marvez-Valls et al., 1998; O'Brien et al., 1993), the following assumptions were made in sample size estimation:

- Mean baseline pain scores of 8.4 on an 11-point numeric rating scale
- Mean follow-up control scores of 4.8
- Mean follow-up case scores of 2.7
- Standard deviation of 2.5.

These assumptions were made on the basis of studies that used different methods and examined different products than in the current study, and thus could be used for estimation only (Marvez-Valls et al., 1998; O'Brien et al., 1993). Using these assumptions, a minimum sample size of 48 was needed to examine efficacy in a two-tailed test. To allow for a dropout rate of approximately 20%, the target sample size was 60 patients.

Statistical analysis

The primary efficacy parameter was the sum of pain intensity differences (SPID) for pain in throat on swallowing, calculated as the area under the curve of pain score changes from base-

line for pain in throat on swallowing (assessed at 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, and 30 minutes after treatment), according to the trapezoidal rule from time 0 (baseline) to 30 minutes.

The secondary efficacy parameters included total pain relief (TOTPAR) calculated as the AUC of pain relief scores regarding the improvement of pain in throat on swallowing (assessed at 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, and 30 minutes after treatment), according to the trapezoidal rule from time 0 (baseline) to 30 minutes.

Both the SPID and TOTPAR have been used in several other clinical studies assessing pain (Benrimoj and Langford, 2001; Desjardins et al., 2000; Farrar et al., 2000; Hersh et al., 2000; Schachtel et al., 1991).

Other exploratory, secondary efficacy parameters included the results of the pharyngitis questionnaire employing a 7-point Likert scale ranging from "not at all" (0), "very little" (1), "little" (2), "moderate" (3), "much" (4), "very much" (5) to "extremely" (6). The change from baseline (visit 1) to 24 hours and 48 hours and at visit 2 was analyzed using an analysis of variance (ANOVA) test with treatment and stratification of patients who were streptococ-

cus-positive ("yes/no") in the model statement. The change from baseline was calculated for each patient and was summarized.

A *p*-value of 0.05 or less was considered to be statistically significant and was used to evaluate all treatment comparisons.

RESULTS

Demographics

A total of 60 subjects were recruited during a period of 6 months: 30 were randomized to the Throat Coat group and 30 to the placebo group. Patient groups were similar in terms of age, weight, and gender distribution. There were no significant differences among patients in the two groups in terms of total severity of symptoms. Demographic and baseline characteristics are shown in Table 4.

There were no exclusions as a result of adverse reactions. All patients supplied data post-baseline and were, thus, included in the intention to treat (ITT) analysis (30 per group). One patient (placebo, female) had to be excluded from the valid for efficacy analysis (VEA) of the primary endpoint (visit 1) because she continued to drink tea during the repeated ratings.

TABLE 4. BASELINE DEMOGRAPHIC AND CHARACTERISTICS OF PARTICIPANTS (INTENT-TO-TREAT POPULATION)

Variable	Unit	Treatment in ITT*			
		ThroatCoat®		Placebo	
		Mean	SD	Mean	SD
Study population	(n)	30		30	
Demographics					
Age	years	34.6	14.0	32.2	13.6
Gender					
Male	%	37		43	
Female	%	63		57	
Ethnicity					
Caucasian	%	87		87	
Noncaucasian	%	13		13	
Weight	kg	76.8	19.3	87.4	19.2
Height	cm	168.9	8.9	171.0	8.5
BMI	kg/m ²	26.8	5.8	30.0	6.8
Test on streptococcus					
Performed	%	30		7	
Positive	%	10		0	
Baseline values					
Pain when swallowing	0–10	6.6	1.0	6.1	1.2
Pharyngitis questionnaire	0–42	22.5	5.9	23.2	6.4

ITT, intention to treat; SD, standard deviation; BMI, body-mass index.

TABLE 5. ANALYSIS OF SUM OF PAIN INTENSITY DIFFERENCES (SPID)—POPULATION: INTENT-TO-TREAT

	Placebo (N = 30)	ThroatCoat® (N = 30)	P-value ^a
N	30	30	
Mean	-39.90	-59.23	
Standard deviation	42.270	42.443	
Median	-29.50	-55.50	
Minimum, maximum	-158.0, 37.5	-165.5, 5.0	
Least square mean	-20.60	-43.80	0.041
Standard error of least square mean	14.866	12.748	

SPID is calculated as the area under the curve (AUC) of pain intensity difference scores assessed after 1, 5, 10, 15, 20, and 30 minutes of treatment. Negative AUC means patient scores improved from baseline. Positive AUC means patient scores worsened from baseline.

^aTreatment comparison using an analysis of variance model with terms for treatment and strep.

Therefore the VEA analysis for the primary endpoint included 59 patients (Throat Coat: $n = 30$; placebo: $n = 29$).

With regard to the secondary endpoints, two patients were lost to follow-up because they did not show up for visit 2 (1 placebo and 1 Throat Coat; one patient mailed the diary to the clinic), which did not affect the primary efficacy analysis. Four patients with data available were excluded from the VEA analysis for data from 3 hours postrandomization onward. Additionally, four patients had taken disallowed concomitant medication (analgesics) at specific time points. Therefore, the ratings given at these time points were excluded from the VEA analysis.

Efficacy

Primary efficacy parameter. Change from baseline pain on swallowing was assessed at 1, 5, 10, 15, 20, and 30 minutes after drinking the first cup of test preparation. In the ITT analysis, Throat Coat differed significantly from

placebo at 5 minutes ($p = 0.02$) and 10 minutes ($p = 0.03$), and just missed the significance level at 15 minutes ($p = 0.051$). The primary efficacy endpoint, SPID, for throat pain on swallowing, also improved to a statistically significant degree in the Throat Coat–treated group: least square means \pm standard error of the mean (SEM) of SPID were -20.6 ± 14.9 in the placebo group and -43.8 ± 12.7 in the Throat Coat–treated group ($p = 0.041$), as shown in Table 5. In addition, significant differences in change from baseline pain in throat on swallowing between Throat Coat and placebo were observed in the VEA analysis at 5 minutes ($p = 0.007$), 10 minutes ($p = 0.005$), 15 minutes ($p = 0.01$), 20 minutes ($p = 0.05$), and 30 minutes ($p = 0.04$) after completion of the first dose. SPID also improved to a statistically significant degree in the Throat Coat–treated group: least square means \pm SEM of SPID -16.5 ± 13.9 for placebo and -43.8 ± 11.9 for Throat Coat ($p = 0.012$), as shown in Table 6.

TABLE 6. ANALYSIS OF SUM OF PAIN INTENSITY DIFFERENCES (SPID)—POPULATION: VALID FOR EFFICACY

	Placebo (N = 29)	ThroatCoat® (N = 30)	P-value ^a
N	29	30	
Mean	-35.83	-59.23	
Standard deviation	36.541	42.443	
Median	-29.50	-55.50	
Minimum, maximum	-106.0, 37.5	-165.5, 5.0	
Least square mean	-16.53	-43.80	0.012
Standard error of least square mean	13.938	11.897	

SPID is calculated as the area under the curve (AUC) of pain intensity difference scores assessed after 1, 5, 10, 15, 20, and 30 minutes of treatment. Negative AUC means patient scores improved from baseline. Positive AUC means patient scores worsened from baseline.

^aTreatment comparison using an analysis of variance model with terms for treatment.

TABLE 7. ANALYSIS OF TOTAL PAIN RELIEF—POPULATION: VALID FOR EFFICACY

	Placebo (N = 29)	ThroatCoat® (N = 30)	P-value ^a
N	29	30	
Mean	48.67	66.65	
Standard deviation	32.816	39.200	
Median	46.50	58.00	
Minimum, maximum	0.0, 141.0	0.0, 150.5	
Least square mean	32.39	53.62	0.031
Standard error of least square mean	12.769	10.899	

Total pain relief is calculated as the area under the curve of pain-relief scores assessed after 1, 5, 10, 15, 20, and 30 minutes of treatment.

^aTreatment comparison using an analysis of variance model with terms for treatment and stratification of patients with strep throat.

Secondary efficacy parameter. In the VEA analysis, significant differences in pain relief between Throat Coat and placebo were observed at 10 minutes ($p = 0.005$), 15 minutes ($p = 0.05$) and 30 minutes after completion of the first dose ($p = 0.02$). TOTPAR was significantly higher in the Throat Coat–treated group: least square means \pm SEM of TOTPAR for placebo: 32.4 ± 12.8 ; for Throat Coat: 53.6 ± 10.9 ($p = 0.031$), as shown in Table 7.

In the ITT analysis, differences between groups were significant at 10 minutes ($p = 0.02$) and just missed the significance level at 30 minutes ($p = 0.052$). TOTPAR was higher, though not statistically significant, in the Throat Coat group: least square means \pm SEM of TOTPAR were 35.1 ± 13.1 in the placebo group and 53.6 ± 11.3 in the Throat Coat group ($p = 0.064$), as shown in Table 8.

Pharyngitis questionnaire

Based on patients' entries in their diaries, changes to baseline in the pharyngitis questionnaire were evaluated after 24 and 48 hours of treatment and at visit 2. The score continuously improved over time in both groups, as shown in Table 9. As standard deviations were large, the median describes data more precisely. Although there was a trend in favor of Throat Coat over placebo, no statistically significant group differences were observed in either the VEA or ITT analysis ($p > 0.05$). The use of a pharyngitis questionnaire at 24 and 48 hours and at visit 2 was intended to be exploratory beyond the hypotheses of immediate short-term pain relief. The fact that pain relief was not sustained according to the results of the pharyngitis questionnaire confirms the re-

TABLE 8. ANALYSIS OF TOTAL PAIN RELIEF—POPULATION: INTENT-TO-TREAT

	Placebo (N = 30)	ThroatCoat® (N = 30)	P-value ^a
N	30	30	
Mean	51.37	66.65	
Standard deviation	35.461	39.200	
Median	46.50	58.00	
Minimum, maximum	0.0, 141.0	0.0, 150.5	
Least square mean	35.08	53.62	0.064
Standard error of least square mean	13.141	11.268	

Total pain relief is calculated as the area under the curve of pain-relief scores assessed after 1, 5, 10, 15, 20, and 30 minutes of treatment.

^aTreatment comparison using an analysis of variance model with terms for treatment and stratification of strep throat patients.

TABLE 9. ANALYSIS OF CHANGE FROM BASELINE IN TOTAL PHARYNGITIS SCORE FROM THE SORE THROAT QUESTIONNAIRE—POPULATION: INTENT-TO-TREAT

Scheduled time		Placebo	ThroatCoat®	P-value ^a
24 Hours	N	30	29	
	Mean	-9.30	-8.69	
	Standard deviation	8.205	5.770	
	Median	-8.50	-9.00	
	Minimum, maximum	-27.0, 6.0	-24.0, 4.0	
	Least square mean	-8.36	-7.94	0.829
	Standard error of least square mean	2.546	2.184	
2 Days	N	29	28	
	Mean	-13.52	-12.89	
	Standard deviation	9.203	9.167	
	Median	-12.00	-14.50	
	Minimum, maximum	-39.0, 8.0	-28.0, 9.0	
	Least square mean	-13.58	-12.94	0.802
	Standard error of least square mean	3.314	2.832	
Visit 2	N	29	29	
	Mean	-20.21	-19.03	
	Standard deviation	7.456	7.962	
	Median	-19.00	-20.00	
	Minimum, maximum	-38.0, -6.0	-31.0, 7.0	
	Least square mean	-18.33	-17.54	0.709
	Standard error of least square mean	2.763	2.359	

Scores were collected on a 7-point Likert scale from 0 (Not at all) to 6 (Extremely). Total scores were calculated by summing each of the seven individual scores.

^aTreatment comparison using an analysis of variance model with terms for treatment.

sults of the primary efficacy parameter, which showed immediate short-term relief.

Compliance

An average of four to six tea bags per day represented a treatment compliance of 100%. Related to duration of treatment, mean compliance was $110 \pm 23\%$ in the placebo group and $101 \pm 27\%$ in the Throat Coat group.

Safety

The average dosage of Throat Coat used in this study was 4–6 cups per day over a period of up to approximately 1 week. Throat Coat was very well-tolerated within this dosage range in a patient population with acute pharyngitis. The clinical study coordinator coded all reported adverse events according to ART of the WHO. No serious adverse events occurred in this study. Of the 60 patients entered, 12 (20%) reported 17 adverse events, which were predominantly mild-to-moderate in severity. In the placebo group ($n = 30$), 10 events (7 patients, 23.3%) were reported. In the

Throat Coat–treated group ($n = 30$), 7 events (5 patients, 16.7%) were reported. Body systems involved were the body as a whole (2 events), nervous system disorders (4 events), gastrointestinal system disorders (2 events), hearing and vestibular disorders (1 event), respiratory system disorders (7 events), and vision disorders (1 event). Neither Throat Coat nor placebo caused significant changes in diastolic or systolic blood pressure, body weight, or heart rate, shown in Table 10. Although we were aware of some case reports of adverse events associated with licorice candy overdose (Chamberlain and Abolnik, 1997; de Klerk et al., 1997; Eriksson et al., 1999), we did not expect any significant changes in blood pressure in this study involving licorice root and extract used within normal therapeutic dosage ranges. According to the WHO monograph, no adverse reactions have been associated with licorice root when used within the recommended dosage (5–15 g daily) and treatment period limits (not longer than 4–6 weeks). On prolonged use (>6 weeks) at overdose levels (>50 g/day), hypertension may occur (World Health Organization, 1999).

TABLE 10. CLINICAL CHARACTERISTICS OF PARTICIPANTS

Parameter	ThroatCoat®		Placebo	
	Study start	Study end	Study start	Study end
Weight (mean kg ± SD)	76.8 ± 19.3	76.5 ± 19.1	87.4 ± 19.2	86.0 ± 17.4
Body temperature (mean °C ± SD)	36.9 ± 0.5	36.8 ± 0.4	36.9 ± 0.5	36.7 ± 0.4
Heart rate (mean bpm ± SD)	75.5 ± 8.1	75.7 ± 10.5	76.1 ± 11.3	76.3 ± 8.6
Systolic blood pressure (mean mmHg ± SD)	116.8 ± 9.7	117.3 ± 10.2	120.4 ± 13.1	119.4 ± 12.5
Diastolic blood pressure (mean mmHg ± SD)	73.0 ± 8.5	73.8 ± 9.4	76.6 ± 9.0	75.3 ± 9.0

Body weight, body temperature, heart rate, and systolic and diastolic blood pressure were determined at visit 1 (study start) and visit 2 (end of study). No significant changes in these parameters were observed during the study. SD, standard deviation.

Nine events in the placebo group and six events in the Throat Coat–treated group were mild or moderate. Only one adverse event per group was classified as severe (one case of sinusitis each). It is assumed that these two events were symptoms of the disease under study; they were judged unrelated to the study medication by the investigators.

The investigators considered two events in one patient (3.3%) of the placebo group related to therapy and one event in one patient (3.3%) of the Throat Coat–treated group. In the placebo group, these were one case of headache and one case of gastroenteritis in one patient each. The one event considered related to Throat Coat was a case of mild diarrhea, which lasted for 1 day. No specific corrective action was undertaken. This patient acknowledged drinking more than the recommended 6 cups of study medication per day.

While this study, in and of itself, cannot establish safety because of the relatively small cohort ($n = 30$), sufficient evidence of product safety existed prior to conducting this study. The herbs contained in Throat Coat have been classified as either GRAS for use in foods by the FDA (e.g., licorice and licorice derivatives) (Food and Drug Administration, 1998) or *generally recognized as safe and effective* (e.g., Elm USP) as an OTC active ingredient (Food and Drug Administration, 1982; United States Phar-

macopeial Convention, 2002). The investigational product has long-term marketing experience (since 1974) with widespread use in the United States and Canada and to a lesser extent in Australia, New Zealand, and the United Kingdom with an approximate 11.4 million doses ingested annually. There has never been a serious adverse event report associated with the use of Throat Coat and the company receives and investigates an average of 1 nonserious adverse event report per approximately 13.7 million doses ingested (Traditional Medicinals®, 2001). Additionally, the investigational product meets current European guidelines for well-established herbal medicinal products with an acceptable level of safety.*

DISCUSSION

The results of this study show that Throat Coat, an herbal demulcent remedy, is an efficacious and safe symptomatic treatment for sore throat pain in patients suffering from acute pharyngitis. In the majority of cases acute pharyngitis is a viral infection while a bacterial infection is shown in approximately 25% of cases, mostly group A streptococcus (Carroll and Reimer, 1996). Nevertheless, antibiotics are frequently prescribed, as physicians may want to fulfill (putative) patients' expectations (But-

*European Agency for the Evaluation of Medicinal Products. Draft points to consider on the evidence of safety and efficacy required for well-established herbal medicinal products in bibliographic applications. London, UK: The European Agency for the Evaluation of Medicinal Products Ad Hoc Working Group on Herbal Medicinal Products. January 28, 1999; EMEA/HMPWP/23/99 draft.

ler et al., 1998; Graham and Fahey, 1999). Recovery, however, is little influenced by antibiotic use (Little et al., 1997a). On the contrary, reattendance to the clinic may even be higher following a course of prescribed antibiotics, as such prescriptions may "medicalize" a self-limiting disease (Little et al., 1997b). Additionally, the use of antibiotics is associated with side-effects affecting the individual and the community (e.g., diarrhea, rashes, candidiasis, unplanned pregnancy secondary to oral contraceptive failure) (Graham and Fahey, 1999) as well as an increase in multiresistant bacterial strains attributed to antibiotic overprescription (Benrimoj, et al., 2001). Considering their impact on bacterial resistance, the use of antibiotics for sore throat is not without risks (Graham and Fahey, 1999). In this situation a form of therapy influencing the subjective symptoms of acute pharyngitis without the negative aspects of antibiotics is considered appropriate and advantageous.

Herbal demulcent preparations have been established for the treatment of sore throat over generations in many systems of Traditional Medicine and they offer a safe alternative to other therapies. Throat Coat, one of the well-established traditional herbal preparations for acute pharyngitis available in North America, has been evaluated in this study under double-blinded and placebo-controlled conditions. The study has shown that Throat Coat is significantly superior to placebo and provided a rapid temporary relief of pain.

CONCLUSION

Throat Coat was superior to placebo in the primary efficacy endpoint of this study. During the 30 min after drinking the preparation, it reduced pain on swallowing to a significantly greater extent than placebo. This superiority could be verified in the ITT and the VEA analysis. Also in total pain relief over this period, Throat Coat was superior to placebo; significance was observed in the VEA population only.

Throat Coat was found to be more effective than placebo for the temporary relief of pain on swallowing in patients with acute pharyngitis.

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