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Efficacy and Safety of Ketoprofen Lysine Salt Mouthwash Versus Benzydamine Hydrochloride Mouthwash in Acute Pharyngeal Inflammation: A Randomized, Single-Blind Study

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ABSTRACT

Background: Pharyngodynia, or sore throat, is one of the symptoms most frequently reported by patients to primary care physicians.

Objective: The purpose of this study was to compare the efficacy and tolerability of mouthwash formulations of ketoprofen lysine salt (KLS), an anti-inflammatory agent, and benzydamine hydrochloride (BH), a local anesthetic, in patients with acute inflammation of the pharyngeal cavity.

Methods: In this randomized, multicenter, parallel-group, single-blind study, patients (who were blinded) were assigned to receive undiluted BH 15 mL (22.5 mg) or KLS 10 mL (160 mg) diluted in 100 mL of water. Both agents were gargled twice daily until pain remission or up to 7 days. A physical examination of the oropharyngeal cavity was performed, and severity of edema and hyperemia was assessed after 3 days of treatment and, if symptoms had not resolved, after pain remission.

Results: Of the 241 patients (120 KLS, 121 BH), 239 were included in the safety analysis and 232 were in the intent-to-treat population. The differences between groups in the duration of analgesic effect after the first dose of drug and the time course of pain were found to be statistically significant ($P = 0.006$ and $P = 0.017$, respectively), favoring KLS. Adverse drug-related effects reported included numbness of the tissues in the oral cavity, sensation of tingling in the tissues in the oral cavity, dry mouth, thirst, and nausea. A significantly greater proportion of BH-treated patients reported adverse events ($P = 0.001$ for all adverse events and drug-related adverse events).

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Conclusions: KLS mouthwash exerts a significantly longer first-application analgesic action with significantly greater local tolerability than BH in patients with pharyngeal pain of inflammatory and/or infectious origin.

Key words: ketoprofen lysine salt, benzydamine hydrochloride, pharyngitis, topical analgesics, mouthwash, pharyngodynia. (*Clin Ther.* 2001;23:1508–1518)

INTRODUCTION

Sore throat, or pharyngodynia, due to acute pharyngitis and laryngitis is one of the symptoms most frequently reported by patients to primary care physicians, and accounts for a high percentage (>60%) of the workload of these outpatient facilities.[1,2] The most commonly accepted etiology of sore throat is a viral upper respiratory tract infection. Bacterial pharyngitides, for which antibiotics are indicated, account for <10% of cases. Viral forms of pharyngitis are self-limiting and resolve spontaneously. Treatment is therefore limited to symptomatic control of the pain and dysphagia accompanying the syndrome. The most widely used medications for treatment of symptoms are analgesic and/or anti-inflammatory drugs, which are available as tablets and solutions for oral administration and in the form of mouthwashes for washes and gargles of the pharyngeal cavity.[3,4]

In the treatment of viral pharyngitis, a mouthwash formulation has several advantages over oral formulations, including reduced side effects and drug interactions, and provides maximum activity at the oropharyngeal tissues, where the main endogenous inflammation mediators (E_2 prostaglandins) are present.[5] In addition, mouthwash formulations have fewer side effects related to systemic absorption or contact with the gastric mucosa.

The rationale for using a mouthwash in viral pharyngitis is to relieve pharyngodynia and the resulting difficulty in eating and to reduce the duration and intensity of local inflammation. Some mouthwashes used for this indication, such as benzydamine hydrochloride (BH), act exclusively on a patient's perception of pain through their local anesthetic properties. In contrast, analgesic anti-inflammatory drugs such as ketoprofen lysine salt (KLS) act by blocking the inflammatory process itself; such agents act not only on pain, but also on the symptoms of inflammation.

KLS is a nonsteroidal anti-inflammatory drug (NSAID) derived from 2-arylpropionic acid that has anti-inflammatory, analgesic, and antipyretic properties.[6–10] KLS has been found to be effective in reducing inflammatory symptoms (edema reduction, 61%; burning sensation reduction, 51%; pain reduction, 57%) after 3 days of treatment, leading to complete resolution of symptoms within 7 days of observation.[4] Its tolerability profile was also favorable in all cases studied.[6–8] In particular, this formulation demonstrated diffusion comparable to gastrointestinal absorption within minutes in the oropharyngeal mucosa, with no systemic involvement.[11] An analysis of the literature, carried out using major medical databases (eg, PubMed, MedHunt), revealed that most clinical studies focused only on the efficacy of systemic administration of KLS.[12] In this therapeutic area, the only drug for which the efficacy of the mouthwash formulation has been tested is BH.

The purpose of this study was to compare the efficacy and tolerability of treatment with mouthwash formulations of KLS versus BH in patients with acute inflammation

of the pharyngeal cavity. The primary study end point was analgesic effect after the first drug dose. Secondary end points were time to remission of symptoms (pain, edema, and hyperemia in the pharyngeal region) and incidence of adverse events.

PATIENTS AND METHODS

Patient Population

Patients 18 to 70 years of age with acute pharyngitis or pharyngolaryngitis, moderate or severe pain in the pharyngeal region (score ≥70 mm on a 100-mm visual analog scale [VAS]), and with edema and/or hyperemia of moderate or severe intensity (score ≥2 on a categorical scale from 0 to 3) were selected for study participation.

Study Design

This was a multicenter, single-blind, randomized, parallel-group study of 2 active drugs. The study was conducted in compliance with the Declaration of Helsinki (Hong Kong and, during the course of the study, Somerset West revisions) and the Ethics Committee and Good Clinical Practice guidelines. The ethics committees in each participating center approved the trial protocol and the informed consent form. Outpatients of 23 ENT departments were enrolled. All investigators were at least qualified ENT assistants and their specific skills were comparable.

Exclusion criteria were presence of a microbial infection requiring specific antimicrobial treatment; treatment with either study drug during the week before enrollment; hypersensitivity to study drugs, chemically related drugs, NSAIDs, or to mouthwashes in general; treatment with corticosteroids or antibiotics during the week before enrollment; inability to properly fill in the patient diary every day as required by the protocol; pregnancy; and lactation.

Patients who gave their informed consent were entered into the screening phase, which included a detailed physical examination and medical history. Eligible patients entered the treatment phase and received a bottle of either KLS or BH mouthwash according to the randomization scheme. Patients took pure BH 15 mL (22.5 mg) or KLS 10 mL (160 mg) diluted in 100 mL water. Patients gargled twice daily with the study drugs until pain remission up to 7 days. During the treatment phase, the use of topical or systemic corticosteroids, NSAIDs, and any other type of mouthwash was prohibited.

At the interim visit after 3 days of treatment, a physical examination of the oropharyngeal cavity was performed, and severity of edema and hyperemia was assessed according to a scale from 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). Based on the results of the interim assessment, the investigator could decide whether treatment was complete or needed to continue up to 7 days. Physical examination and assessments were repeated at the end of the treatment period.

Diary Card Assessment

During the treatment phase, patients recorded morning and evening VAS pain assessments, symptom assessment scores, adverse events, and use of concomitant or rescue medications in a diary.

Visual Analog Scale: Pain Assessment

Patients assessed pain severity using a 100-mm VAS. On the first day of treat-

ment, VAS assessment was performed immediately before and 0.5, 1, 2, 3, 4, 5, and 6 hours after the morning application of the solution. The aim of this part of the study was to evaluate the duration of analgesic effect. The conventional 50% reduction of baseline pain[13] was considered a clinically significant decrease. From these data, the following values were estimated: (1) beginning of analgesic effect, the time of the first observation at which the VAS score was <50% of the score recorded before administration; (2) end of analgesic effect, the time of the first observation (after the onset of analgesic effect) at which the VAS score was ≥50% of that recorded before administration; and (3) duration of analgesic effect, the difference in hours between the end and beginning of analgesic effect as defined previously.

After the first drug application, VAS assessments were performed twice daily (morning and evening), 1 hour after drug application. Pain remission was considered to have occurred the day on which 2 consecutive (morning and evening) VAS pain scores were <10 mm. Mean daily VAS scores were also calculated.

Symptoms Assessment

Patients recorded all adverse effects and symptoms daily and rated their severity according to a 3-point scale (1 = mild; 2 = moderate; 3 = severe). The incidence of specific adverse events and symptoms, including numbness of the tissue in the oral cavity, sensation of tingling in the tissues of the oral cavity, dry mouth, thirst, nausea, and abdominal pain, was assessed through the use of a questionnaire in the patient diary. Adverse events spontaneously reported by patients were also assessed.

Compliance Assessment

Patients were instructed to take the prescribed drug twice daily until pain remission. Only 2 missed doses were allowed, provided these were not consecutive. Compliance was evaluated by daily diary data assessments and by measurement of unused mouthwash after each patient completed treatment. The volume of unused mouthwash was used to calculate the actual quantity used during treatment. Knowing the starting volume of each preparation, it was possible to establish a compliance tolerance range (consumed volume/number of remaining gargles). A theoretical difference of 20% was accepted.

Statistical Analysis

The duration of analgesic effect was assessed by analysis of variance (ANOVA) followed by a *t* test for 2 independent samples. The same test was applied to the number of days required to obtain remission. The time course of pain intensity (VAS score) recorded 1 hour after each drug application was analyzed by repeated-measures ANOVA using the prestudy VAS value as covariate. A chi-square test was performed (and, if appropriate, the relative risk with its 95% CI was calculated) for the proportion of patients reporting resolution of inflammation signs, the proportion of patients experiencing adverse events, and the proportion of patients withdrawn due to adverse events in the 2 treatment groups.

RESULTS

Patient Characteristics

Of the 241 patients with moderate to severe pharyngeal pain enrolled in the

study, 120 patients were assigned to the KLS group and 121 patients were assigned to the BH group. The safety population included 239 patients who had ≥1 application of study drug, and the intent-to-treat (ITT) population for the primary variable included 232 patients (118 treated with KLS and 114 treated with BH). The per-protocol analysis was not performed because the difference between the size of the ITT and per-protocol populations was marginal (223/232 patients [96.1%] in the per-protocol population). The demographic and clinical characteristics of this patient population were similar to the overall population profile of patients with moderate to severe pharyngeal pain in several other clinical trials.[11–14] There was no evidence of a statistically significant or clinically relevant difference between treatment groups (Table I).

Efficacy

The difference between treatment groups (including patients who did not reach the analgesic threshold) in duration of analgesic effect after the first drug ad-

Table I. Demographic and baseline characteristics of the safety population.

	Ketoprofen Lysine Salt (n = 119)	Benzydamine Hydrochloride (n = 120)	*P*
Sex			
Male	46	49	
Female	73	71	0.73*
Age, y, mean ± SD	37.0 ± 12.1	37.8 ± 12.5	0.61†
Diagnosis, no. (%)			
Pharyngitis	108 (91)	109 (91)	0.99‡
Laryngitis	–	1 (1)	
Pharyngitis/laryngitis	6 (5)	6 (5)	
Pharyngitis/other	5 (4)	4 (3)	
VAS pain score, mm, mean ± SD	81.9 ± 7.4	81.4 ± 7.3	0.59†
Edema, no. (%)			
None	5 (4)	9 (8)	0.69*
Mild	34 (29)	31 (26)	
Moderate	70 (59)	68 (57)	
Severe	10 (8)	12 (10)	
Hyperemia, no. (%)			
Mild	2 (2)	7 (6)	0.22‡
Moderate	65 (55)	67 (56)	
Severe	52 (44)	46 (38)	

*Chi-square test.
†Analysis of variance.
‡Fisher exact test.

ministration was statistically significant (1.02 hours for KLS vs 0.47 hour for BH; $P = 0.006$) despite the small overall number of responders (ie, patients with a pain reduction >50%) (Figure 1). When only responders were considered (37 KLS, 29 BH), the duration of analgesic effect after the first application in the KLS group was significantly longer than in the BH group (3.24 vs 1.84 hours; $P = 0.013$) (Figure 1).

The time course of VAS pain score 1 hour after each drug application was significantly different between groups, as was the mean daily VAS score ($P = 0.017$), with a significant and specific correlation between duration of treatment and efficacy in both groups (Figure 2).

For the secondary end points, there were no detectable differences between groups in the number of treatment days required to obtain pain remission (4.16 KLS vs 4.39 BH; $P = 0.21$), the proportion of patients with pharyngeal edema or hyperemia reduced to mild or absent (97% KLS vs 94% BH; $P = 0.30$), or the proportion of patients who completely recovered from both symptoms (75% KLS vs 66% BH; $P = 0.15$) at the end of the study.

Safety

Safety evaluation was performed using data from 239 patients who took ≥1 dose of study drug. As expected for symptoms monitored through a predefined questionnaire (in this case, the patient's diary), the most frequently reported adverse events were those specifically monitored in the

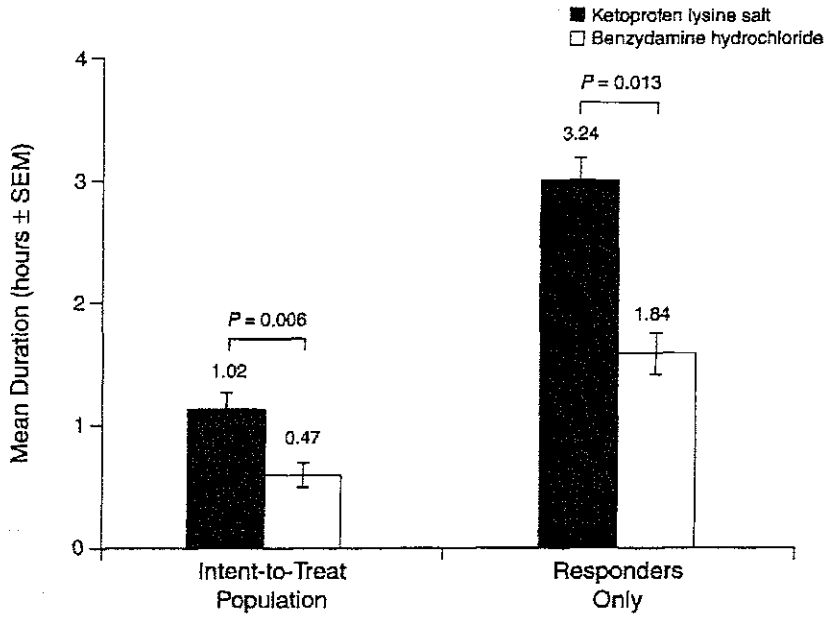

Figure 1. Mean duration of analgesic effect of ketoprofen lysine salt and benzydamine hydrochloride in the intent-to-treat population (n = 232) and in responders (n = 66).

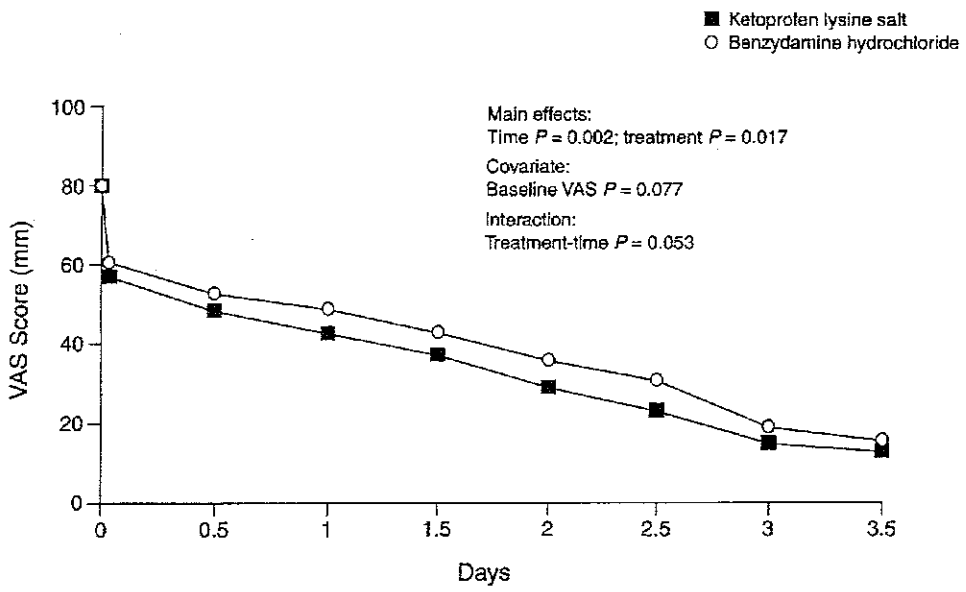

Figure 2. Time course of pain as measured by visual analog scale (VAS) score reported 1 hour after drug administration.

diary itself. These events were generally localized and included numbness of the tissues in the oral cavity, sensation of tingling in the tissues in the oral cavity, dry mouth, thirst, and nausea. A significantly greater proportion of BH-treated patients than KLS-treated patients reported adverse events ($P = 0.001$ for all adverse events and for those classified as drug-related).

The estimated relative risk (RR) of adverse events for patients in the BH group compared with those in the KLS group was 1.88 (95% CI, 1.48–2.39). This was attributed primarily to the higher risk in the BH group of experiencing local sensitivity disorders such as numbness in tissues and tingling sensation in the oral cavity (RR, 2.46; 95% CI, 1.77–3.43) and dry mouth (RR, 2.17; 95% CI, 1.27–3.70) (Table II, Figure 3).

Only 1 patient (treated with BH) experienced a serious adverse event (moderate pharyngolaryngeal edema requiring hospitalization) and consequently withdrew from the study. Two other BH-treated patients also withdrew from the study due to adverse events (worsening of the underlying disease). No clinically significant changes were observed in vital signs (diastolic and systolic blood pressure and pulse rate), physical findings, and other safety variables.

DISCUSSION

Painful conditions of the oropharyngeal cavity caused by underlying inflammatory or infectious disorders are often treated with mouthwash formulations. Mouthwashes are widely available and often do not require a prescription. Because

Table II. Adverse event (AE) summary.

	Ketoprofen Lysine Salt (n = 119)	Benzydamine Hydrochloride (n = 120)	*P*	Relative Risk (95% CI)
Overall AEs	48	91	0.001	1.88 (1.48–2.39)
Drug-related AEs	39	83	0.001	2.11 (1.59–2.80)
Local sensitivity disorders	31	77	0.001	2.46 (1.77–3.43)
Dry mouth	16	35	0.003	2.17 (1.27–3.70)

the concentration of active agent in mouthwash formulations is considerably lower than in oral formulations, they are not considered to pose a serious risk of adverse events. The 2 most widely used drug classes for these conditions are local anesthetics and anti-inflammatory agents.

Both drugs tested in the present study were administered in their commercial formulations with anonymous labels. Since the 2 drugs differ in their physical

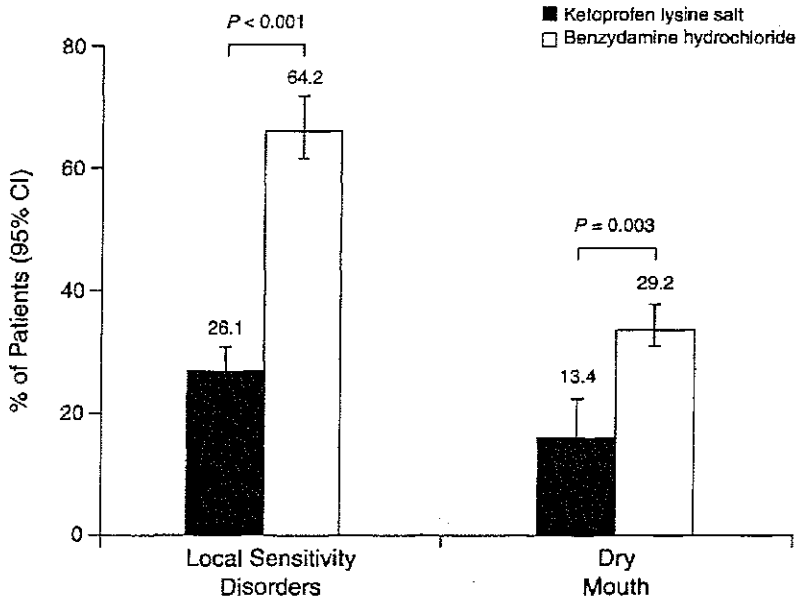

Figure 3. Percentage of patients reporting local sensitivity disorders and dry mouth during treatment with ketoprofen lysine salt or benzydamine hydrochloride mouthwash.

and manufacturing characteristics, we had to resort to a single-blind design—experimenters were able to identify the randomization groups, whereas patients were blinded with respect to study drug (assuming that only patients who never used the 2 drugs were included in the study). The hypothesis for a single-blind study of KLS versus placebo was strongly contested by the ethical committees of the 23 medical institutions in which the study was performed. Drug-versus-placebo studies must be able to provide information about the clinical efficacy of the drug, but they also should guarantee the possibility of a *t*-test data analysis in both the ameliorative and pejorative sense (as is the case in a double-blind study). The use of a *t* test in a single-blind study excludes the possibility that the drug could have the same or less effect than placebo; that is, we would have to consider, as the only possibility, that the drug is necessarily more active than placebo. For these reasons, the ethical committees deemed it useless to treat patients with an inactive substance (placebo), preferring a direct comparison between KLS and a known active mouthwash (BH). Notwithstanding the single-blind design, the investigators, clinical monitors, and clinical research associates did not know the randomization sequence a priori, but obtained these data only after treatments were assigned. To obtain a complete double blind it would have been necessary to undertake a double-dummy study with the following randomization scheme: KLS + placebo-BH; placebo-BH + KLS; BH + placebo-KLS; placebo-KLS + BH. This hypothesis was rejected for its scarce applicability in this specific analysis of a local topical treatment. In fact, a placebo mouthwash administered immediately after an active drug would have produced a mucosal washing effect; this would have reduced the therapeutic effect of the administered drug, and final data analysis would have been unreliable. Moreover, the need for 2 subsequent gargles would have likely reduced compliance. A crossover design was not applicable in this study because of the rapid course of pharyngeal infections.

In the present study, the application of an anesthetic or anti-inflammatory mouthwash yielded a remarkably lower response in terms of analgesia compared with that reported in the literature.[1,8,10,14] At variance with our expectations, only 25% of patients using BH and 32% of those using KLS experienced a decrease in subjective pain of ≥50% within 6 hours of application.

The time course of pain intensity (as measured by VAS scores) indicated a decrease in subjective pain among patients who used KLS. Among KLS-treated patients, the duration of protocol-defined analgesic effect was 2.2 times longer than among the BH-treated patients. However, in comparing these results with those obtained in studies of KLS oral solution,[14] on which the protocol had been based, only the effect in responders was considered. The calculated duration of analgesic effect after KLS treatment was 1.8 times longer than after BH, and reached the expected 3.5 hours. This agrees with previous investigations of BH mouthwash, in which the duration of analgesia was short (~1.5 hours) and applications had to be repeated every 3 hours.[1,2,15]

This trial also showed that the tolerability of low concentrations of locally applied active substances should be considered differently if local effects, and not only systemic adverse effects, are evaluated.

The use of a specific questionnaire in the diary that inquired about particular adverse events may have disproportionately increased the reporting (and hence the calculation of incidence) of these adverse events. In the absence of such a questionnaire, patients may underestimate the incidence of adverse treatment effects, dismissing them as part of the clinical profile of the disease. However, there is no reason to believe that this deviation from normal reporting of adverse events was different in the 2 treatment groups. Similarly, there is no reason to suggest that the physician's classification of the adverse events as treatment-related or non–treatment-related could be influenced by the use of a questionnaire that probes specific adverse events. The high incidence of local adverse events in the BH-treated patients (64.2%) is not surprising. Indeed one of the characteristics of BH is its marked local anesthetic activity at or below approved dosages,[16] despite its lack of structural similarity to standard local anesthetics. This property accounts for the rapid onset and transience of analgesia with BH, as well as for its local side effects.

The results of this study suggest that the anti-inflammatory agent KLS applied locally is clinically more appropriate to treat oropharyngeal pain than the local anesthetic BH. The duration of analgesic effect of KLS was approximately twice as long as that of BH, and the risk of local adverse events was approximately half that of BH. This result, however, cannot be extended to the whole class of anti-inflammatory mouthwash formulations. Although KLS is an anti-inflammatory agent, the presence of lysine has been reported to profoundly modify the ability of its anion to penetrate the superficial tissues (and the systemic circulation when administered by systemic routes[14,15]) as well as its persistence in the tissues (half-life).

CONCLUSIONS

KLS mouthwash, an anti-inflammatory agent, has a significantly longer analgesic action after first application and greater local tolerability than BH, a local anesthetic mouthwash, in patients with pharyngeal pain of inflammatory and/or infectious origin.

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