

Efficacy and Safety of Ambroxol Lozenges in the Treatment of Acute Uncomplicated Sore Throat

EBM-based clinical documentation

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Abstract

Sore throat is the hallmark of acute pharyngitis. Although usually caused by viral infections, it is frequently treated with antibiotics. Such inappropriate use of antibiotics might best be challenged by offering efficacious and safe symptomatic pain relief instead. However, there is need for robust evidence to support such alternatives.

Presently, the evidence from randomised, placebo-controlled, double-blind clinical trials (RCT) with the local anaesthetic ambroxol (CAS 23828-92-4) in the treatment of sore throat is being reviewed. This relates to five RCT in 1,772 patients; 1,713 were evaluable with regard to efficacy. Treatment with ambroxol lozenges was statistically significantly superior to placebo in reducing sore throat pain intensity with a high level of consistency of the estimated effect across the different studies. The effect had an early onset and lasted up to at least 3 h after a single first lozenge. The pain relief was associated with a statistically superior regression of pharyngeal redness and inflammation; with ambroxol, the overall efficacy was more frequently rated as at least “good”.

Treatment with the ambroxol lozenges was well tolerated. There was heterogeneity in reporting adverse events: in one later study with less severe baseline pain intensity there was more frequent reporting of hypoaesthesia of the oral cavity and

tongue as an untoward phenomenon. In patients with more severe baseline pain this reflection of the medication's pharmacological action was only rarely reported as untoward.

It is concluded that lozenges containing 20 mg ambroxol are a safe and efficacious treatment for acute uncomplicated sore throat of recent onset in adult patients.

Key words

- Ambroxol, lozenge
- CAS 23828-92-4
- Evidence-based medicine
- Local anaesthetics
- Mucoangin®
- Sore throat

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1. Introduction

1.1 Challenges in treating sore throat

Sore throat, i.e. acute pharyngitis, is an inflammatory syndrome of the pharynx and/or tonsils that can be caused by several different groups of microorganisms. Pharyngitis can be part of a generalized upper respiratory tract infection or a specific infection localized in the pharynx. Most cases are caused by viruses and occur as part of common colds and influenzal syndromes.

Sore throat is the most common indication for an unscheduled visit with a physician for the school-age child, adolescent, and adult [1, 2]. On the other hand, fewer than 20% of patients with sore throat or pharyngo-tonsillitis seek medical advice [3–6].

Several factors may cause sore throat (VINDICATE: vascular [as in blood dyscrasias], infection, neoplasma, degenerative diseases, intoxication congenital diseases, allergy, trauma or endocrine disorders [7]). However, most cases of sore throat are caused by infectious pharyngitis and up to 85% of all such infections are considered to be of viral origin.

Many viruses can cause infection of the pharynx. The common respiratory viruses such as respiratory syncytial virus and para-influenza are more notable as causes of bronchiolitis and croup, but they also may cause pharyngitis or naso-pharyngitis. Adenovirus and influenza A are common and severe causes of sore throat. Epstein-Barr virus causes severe pharyngitis most notably in adolescents, but it may cause infection at any age. Herpes simplex is said to account for approximately 15% of cases of pharyngitis in adolescents, and it may be particularly severe. Rhinovirus and corona viruses, which are the most frequent causes of the common cold, also can cause pharyngitis. Finally, the enteroviruses, coxsackie and ECHO, often cause pharyngitis, with or without fever and rash, in the summer and late fall [8].

In regions that have warm summers and cool winters, viral pharyngitis typically peaks during the winter and early spring, a time when people often are close together in poorly ventilated rooms. In this environment, the viruses that cause pharyngitis spread easily in the droplets of coughs and sneezes and on dirty hands that have been exposed to fluids from a sick person's nose or mouth. In most people who are otherwise healthy, simple viral pharyngitis does not last long, goes away on its own and does not cause any long-term complications, although the short-term discomfort can be significant.

Less frequently sore throat is caused by bacterial infections. Group A β -haemolytic *Streptococcus* (GABHS) or *Streptococcus pyogenes* is the most common cause of bacterial pharyngitis in children and adults worldwide. Other less common causes of pharyngitis due to bacterial agents include *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, and *Arcanobacteria haemolyticum*. GABHS-infections are the most frequent cause of bacterial pharyngitis. Such infections mostly occur in school-aged children. They are characterised by acute onset of

fever and sore throat. Headache, abdominal pain, and vomiting also may occur. Rhinorrhoea, cough, conjunctivitis, hoarseness, and diarrhoea are unusual. Tonsils are enlarged and inflamed, with patches of exudate. Petechiae may sometimes be seen on the palate. Anterior cervical lymph nodes may be enlarged on one or both sides and are often tender [8]. Like viral pharyngitis, bacterial pharyngitis can spread quickly and easily within a community, especially during late winter and early spring.

1.2 Antibiotics for sore throat?

There are several guidelines with regard to the management of acute sore throat in adults [9–22]. Most of these focus on the use of antibiotics in sore throat and on the diagnostic procedures to establish the relatively rare need for antibiotics. Most agree that bacterial infections are not a predominant cause of sore throat, but there are fundamental differences among these guidelines with regard to the use of a rapid antigen test or throat culture for diagnosis and the use of antibiotics for treatment [23]. Furthermore, existing guidelines are generally poorly adhered to [24, 25]. Even refined diagnostic algorithms have failed to reduce the inappropriate use of antibiotics [26].

Although GABHS infection is considered an appropriate indication for antibiotic therapy [27,28], only 10% to 20% of sore throat presentations in general practice are culture positive for GABHS [29, 30]. Nevertheless, reports from various countries estimate that an antibiotic is prescribed in 30% to 75% of visits for sore throat [31–34]. Analyses in the USA indicate that antibiotics are being prescribed to about 73% of all adults consulting for sore throat and that only 23% received recommended antibiotics (penicillin or erythromycin) [35].

Viral pharyngitis but also GABHS related sore throat is a self-limited illness in which symptoms are resolving by 3 days independent of whether antibiotics were used or not [33, 36, 37]. Less than half of the patients who sought medical advice for sore throat presented within the first 3 days of their illness [38]. Therefore, antibiotics are unlikely to provide symptom relief other than that resulting from the natural regression of the condition [39, 40]. Systematic EBM (evidence based medicine) reviews confirm that antibiotics confer only slight relative benefits in the treatment of sore throat; protecting sore throat sufferers against suppurative and non-suppurative complications can only be achieved by treating many with antibiotics, most of whom will derive no benefit; antibiotics shorten the duration of symptoms by only about 16 h overall [41]. Furthermore, there is no evidence that antibiotics ought to be prescribed generally to prevent respiratory tract complications [42], rheumatic fever [43] or glomerulonephritis [14, 44], which now are accepted to be very rare. Nevertheless, the need to provide prompt symptomatic relief (rather than protection against complications) is often quoted

as a reason to start antibiotics without or before the results of swab cultures are known [24, 45, 46].

Although physicians are well aware of the questionable benefit-risk relationship of prescribing antibiotics for sore throat, they nevertheless continue prescribing them. The patients' insistent request of antibiotics appears to be a decisive factor in this behaviour [47–50]. A recent survey suggests that patients with acute sore throat who hope for antibiotics may in fact want treatment for pain [51].

1.3 Non-antibiotic treatments for sore throat?

Although self-limited, sore throat caused by viral pharyngitis or GABHS-infection is highly bothersome. Hence, offering prompt, efficient and safe pain relief must be a prime objective in managing sore throat. For the patients who seek medical advice this might help to avoid undue prescription of antibiotics. For the vast majority of the patients who do not seek such advice this is equally important since it reduces incapacitation.

Several simple remedies are generally advocated: getting plenty of rest (either in or out of bed), drinking plenty of water to prevent dehydration, gargling with warm salty water, drinking warm liquids (tea or broth) or cool liquids, eating gelatine desserts or flavoured ice cream, using a cool mist vaporiser to relieve throat dryness, etc.

In cases that are refractory to such remedies, systemic (paracetamol [52], NSAIDs such as acetylsalicylic acid [53], ibuprofen [52, 54–56], niflumic acid [57], tiaprofenic acid [58], morniflumate [59], corticosteroids [60], etc.) might be considered. Systemic medications may have the disadvantage of too low concentrations of the drug substance in the target tissue, whilst sufficiently high systemic doses of such agents (NSAIDs in particular) are bound to cause systemic adverse reactions.

Anaesthetic and disinfecting lozenges, pharyngeal washes, and sprays may be used instead. Pharyngeal washes may have the disadvantage of a relatively short contact time; additionally, pharyngeal washes do not reach the tonsils due to the retching reflex caused by most of the drugs [61]. Inhalations may be an alternative for infectious inflammations of the lower part of the pharyngeal cavity in particular. Due to the increased flux of saliva caused by sucking, drugs administered by lozenges usually are quite capable to reach also the lower part of the pharyngeal cavity. The progressive and protracted release of the active compound by sucking lozenges also contributes to a long and protracted availability at the site of desired action provided the concentrations (even when diluted by saliva) remain sufficiently high [62].

Local NSAIDs such as ibuprofen [63] and flurbiprofen [64, 65, 66] have been proposed, but concern has been expressed that the benefit of their local action might be too small in comparison to the risk related to their untoward systemic effects [67]. Alternatively, local anaesthetics [68, 69] such as lidocaine [70] and benzocaine [71, 72] are often used also to prevent postopera-

tive sore throat resulting from the irritation by endotracheal intubation [73, 74]. However, such local anaesthetics may cause to several side effects [75]: sensitisation [76] and methaemoglobulinaemia [77–79]) have been reported; additionally, the amount of benzocaine in several lozenges is probably too small to be of real benefit [80]. Antiseptic drugs (e.g. benzethonium, cetylpyridinium, hexamidine, hexetidine, chlorhexidine and benzalconium chloride) are quite popular for oral hygiene and dental care [81–83], but carry the risk of causing sensitisation, local irritations or lesions of the mucosa [84, 85]. For this reason, such antiseptic drugs are applied usually in too low, i.e. sub-therapeutic doses.

1.4 Background and rationale for using lozenges containing ambroxol for the treatment of sore throat

Lozenges containing ambroxol (CAS 23828-92-4; ATC R02AD05 – Mucoangin[®], Boehringer Ingelheim) have recently been introduced for the symptomatic treatment of acute sore throat. Galenically, these hard compressed lozenges are particularly well suited for sucking with a progressive release of the medication.

The present publication summarises the clinical evidence on the efficacy and safety of lozenges containing 20 mg ambroxol as documented by five randomised, placebo-controlled, double-blind clinical trials (RCT) conducted in a real-life clinical practice setting. Non-clinical studies provided a sound rationale for the use of lozenges containing ambroxol in this indication [86, 87]. Part of the material presented here has been previously published as separate reports [88, 89].

2. Patients and methods

2.1 Clinical trials

Data are reported from five randomised, placebo-controlled, double-blind, multi-national, multi-centre clinical trials (internal trial numbers BI 18.173, BI 18.174, 18.466, BI 18.468, and BI 18.489). Subjects were assigned at random to treatment with either ambroxol or placebo in a parallel fashion. One trial (BI 18.489) included a further group treated with benzocaine-containing lozenges as active control. The studies were conducted in ambulatory fashion by qualified primary care physicians.

All studies were confirmed to have been carried out in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice (details available on request). All studies were subject to review and approval by an independent ethics committee. Only subjects willing and able to provide informed consent were eligible for enrolment.

2.2 Study population

In order to be eligible, subjects had to have acute uncomplicated sore throat of recent onset without signs suggestive of bacterial infection. Patients with suspected primary or secondary bacterial pharyngitis were excluded on the basis of clinical findings (absence of seropurulent, purulent, fibrous or fibrinous exudate from the pharyngeal mucosa) and time of onset (which had to be within 3 days before the start of treatment).

Table 1: Number of randomised/treated patients, number of patients of the efficacy evaluable dataset (FAS) per treatment group and the overall per-protocol dataset for each of the trials and for the total database.

Trial	Treated	Efficacy-evaluable dataset (FAS)						PP	
	Total	Placebo	5 mg	10 mg	20 mg	30 mg	Benzo	Total	Total
18.174	92	21	23	24	22			90	81
18.173	215	103			105			208	196
18.466	331	92			104	109		305	283
18.468	383	119			123	118		360	325
18.489	751	246			252		252	750	724
All	1772	581	23	24	606	227	252	1713	1609

FAS = full analysis dataset; PP = per protocol dataset; Benzo = benzocaine.

All patients were male or female out-patients, 18 to 80 years of age. Baseline pre-dose sore throat intensity was to be at least 'severe' (BI 18.173, BI 18.174 BI, 18.466, and BI 18.468) or 'moderate' (BI 18.489) scored by a verbal rating scale (VRS, see 2.5.1).

2.3 Study medication

Investigational treatments consisted of a first lozenge (active medication or placebo) followed by pharmacodynamic pain evaluation over the first 3 h after dosing; during this period no further lozenges were taken. Subsequently, up to 6 lozenges could be taken per day at a minimum interval of 0:30 h; treatments lasted 1 day (BI 18.174), 2 (BI 18.173) and 3 days (BI 18.466, BI 18.468, and BI 18.489). In all studies, one group received lozenges containing 20 mg ambroxol. In one study (BI 18.174) further study groups were investigated receiving matched lozenges containing 5 and 10 mg ambroxol. In two studies (BI 18.466 and BI 18.468) both lozenges containing 20 mg and 30 mg ambroxol were investigated. In trial BI 18.489 a further study group was investigated taking lozenges containing 3 mg benzocaine (see Table 1).

In all studies, placebo consisted of a lozenge with matched appearance, but with a peppermint-flavoured taste when sucked. The placebo lozenges were to be sucked in the same fashion as the active medication. Subjects and investigators were blinded in this regard.

2.4 Study schedule and experimental conditions

All subjects were investigated in a real-life primary care practice setting. After screening and assessing baseline pain, eligible subjects were assigned at random to their double-blind medication. The randomisation list was generated with a commercially available and validated randomisation programme. A first lozenge of the assigned medication was taken and pain intensity was scored by VRS 30, 60 (± 5), 120 and 180 (± 10) min after the first lozenge. During this time, the subjects remained in the doctor's office. During this phase, the patients were not allowed to take other medications, suck other lozenges, use toothpaste, mouthwash or breath spray, smoke, chew chewing gum, eat candies, eat or drink.

After completion of the last measurement, the patients were allowed to leave the practice. During the further day and the subsequent days (as applicable; see 0) patients were ambulatory and kept a diary with daily recordings of overall efficacy at the end of each trial day. Use of any further medication and the eventual occurrence of untoward changes were to be recorded.

Within one week after the first investigational day, the subjects were evaluated again to assess medication usage and

compliance (diary records and return of medication containers), usage of other medications (diary records), daily efficacy scores, overall wellbeing and tolerability of the treatments.

2.5 Efficacy and safety criteria

2.5.1 Efficacy criteria

Changes in sore throat intensity after the first lozenge were investigated extensively up to 3 h after dosing. This is a *pharmacodynamic* evaluation of the extent and time course of sore throat relief after a first single lozenge. Subsequent use was only restricted in terms of the total number of daily lozenges (up to 6 per day) and the minimum interval between consecutive lozenges (0:30 h at least). This latter situation represents the likely way of *pharmaco-therapeutic* use. Efficacy evaluations therefore addressed both the response in a pharmacodynamic approach (response to the first lozenge) and a pharmacotherapeutic way (symptomatic relief subsequent to the pharmacodynamic evaluation including relatively free use of the medication during the following days).

Pain intensity was scored by the patient by means of a 6-point VRS (0 = "none", 1 = "hardly any pain", 2 = "moderate pain", 3 = "moderately severe pain", 4 = "severe pain", 5 = "very severe pain", except for study 18.174 with scores 0 = "none", 1 = "slight pain", 2 = "moderate pain", 3 = "severe pain", 4 = "very severe pain", 5 = "intolerable pain"). This approach is similar or comparable to that used in further clinical trials on pain relief. For the pharmacodynamic response to the first lozenge, pain intensity (PI) was scored by VRS before dosing and at 30, 60, 120 and 180 min after the first lozenge.

Pain intensities subsequent to dosing were then expressed as arithmetic changes (PID) from baseline intensity (negative changes reflecting a reduction in PI). The cumulative sum of the post-dosing PID was weighted for the time elapsed since the previous assessment: $SPID_{AUC} = 0.5 \cdot PID_{30} + 0.5 \cdot PID_{60} + PID_{120} + PID_{180}$. Additionally, the relief over the 3 h after the first lozenge was expressed as $SPID_{norm} = SPID_{AUC} / (3 \cdot PI_{baseline})$. This represents the time-weighted average pain relief over the first 3 h after the first lozenge as a ratio of the baseline score; this $SPID_{norm}$ equals the ratio of the achieved $SPID_{AUC}$ relative to the maximum achievable effect; hence, a $SPID_{norm} = -1.0$ means that full pain relief had been achieved already after 30 min and was maintained up to 180 min after dosing.

The treatments were compared for $SPID_{norm}$ as primary criterion and the time course of the VRS (as PI or PID) as secondary efficacy endpoints.

The pharmacotherapeutic evaluation subsequent to the investigation of the response to the first lozenge was based on the daily diary records of overall pain reducing efficacy using a

Table 2: Number (N) and percentage (%) of the patients by baseline pre-dose pain intensity VRS category for each of the trials and for the total database.

Trial	Total	Baseline pain intensity														
		None			Hardly any		Moderate		Moderately severe		Severe		Very severe		Intolerable	
		N	N	%	N	%	N	%	N	%	N	%	N	%		
18.174	90	0	2	2.2	7	7.8	–		58	64.4	22	24.4	1	1.1		
18.173	208	0	0	0.0	3	1.4	9	4.3	176	84.6	20	9.6	–			
18.466	305	0	1	0.3	10	3.3	44	14.4	232	76.1	18	5.9	–			
18.468	360	0	3	0.8	22	6.1	54	15.0	253	70.3	28	7.8	–			
18.489	750	0	0	0.0	310	41.3	282	37.6	125	16.7	33	4.4	–			
ALL	1713	0	6	0.4	352	20.5	389	22.7	844	49.3	121	7.1	1	0.1		

a Slight pain in Trial 18.174.

4-point VRS (1 = very good", 2 = "good", 3 = "not so good", 4 = "poor") relative to the number of lozenges used. At the end of the study, the patients and the physician scored the overall efficacy on a 4-point VRS (1 = "good", 2 = "satisfactory", 3 = "not satisfactory", 4 = "bad").

2.5.2 Safety criteria

Untoward changes reported spontaneously by the patient during the visit or recorded in the diary and related answers to non-leading questions by the physician were listed and analysed as adverse events. At the end of the study, the patients and the physician scored the overall tolerability on a 4-point VRS (1 = "good", 2 = "satisfactory", 3 = "not satisfactory", 4 = "bad").

2.5.3 Statistical analyses

For the responses to the first lozenge, the primary endpoint SPID_{norm} was analysed by means of an analysis of variance with treatment and centre as fixed effects included. The treatments were contrasted by means of the estimated least-square adjusted mean differences of the true treatment means of SPID_{norm} and the corresponding 95% confidence interval (CI).

For the continuous secondary endpoints PI and PID an analysis of covariance including treatment and centre as fixed effects and baseline as covariable was performed. The Kaplan-Meier estimator was presented for the endpoint time to onset of action after the first lozenge and the log rank test used to calculate p values and to test for statistically significant differences between the treatment groups. The Cochran-Mantel-Haenszel test, stratified by the baseline assessment of redness, was applied to analyse the assessment of redness at the end-of-study evaluation. The Wilcoxon rank test was used for the evaluation of the assessment of efficacy and tolerability.

Incidence, severity, and causal relationship of the adverse events were tabulated by system organ class after coding according to MedDRA (Medical Dictionary for Regulatory Activities).

3. Results

3.1 Demography, patient disposition and baseline features

In these five trials 1,777 patients were enrolled; 1,772 patients were randomised and treated. 1,713 were evaluable with regard to efficacy; 95 were discontinued from the trial prematurely; 1,609 were evaluable in terms of efficacy without confounding protocol deviations (see Table 1).

37% of all evaluable subjects were males, 63% females. Within each study, the subjects were on average about 36 years old; overall, ages ranged from 16 to 80 years. No patients were suspected to have a bacterial infection.

On inspection of the throat, redness of the throat was slight in 14.3%, marked in 44.0%, and severe in 36.8% of the patients; in 4.4% there was severe inflammation. In 86% of the patients there was no exudate on throat inspection, whereas there was a serous exudate in 14%. In the earlier studies (BI 18.173 and BI 18.174) about half of the subjects had a serous exudate, while the remaining had none. In the later (larger) studies (BI 18.466, BI 18.468, and BI 18.489) almost all subjects had no exudate. There were no differences between the treatment groups in this regard.

In the first four studies, most subjects had a baseline intensity that was at least moderately severe; in the later study (BI 18.489), about 44% of the patients had a less severe ("moderate") baseline pain intensity (see Table 2). Within each study, there was no difference among the treatment groups with regard to the baseline pain intensity.

3.2 Response to the first lozenge

Administration of the investigational treatments resulted in a distinct relief of pain intensity (Fig. 1). The least-square estimated treatment means and the estimated mean differences vs. placebo (plus 95% CI) of the SPID_{norm} within each study are summarised in Table 3 (see also Fig. 2). In all studies, the administration of placebo (i.e. sucking a matched lozenge with a distinct mint-flavoured taste) was followed by a clear reduction in pain intensity. In trial BI 18.174 lozenges containing doses of 5 and 10 mg ambroxol were no different from placebo; the improvement caused by the lozenge containing 20 mg ambroxol was larger, but failed to reach statistical significance. In all further trials (BI 18.173, BI 18.466, BI 18.468, BI 18.489), the relief of the pain of sore throat by sucking a first lozenge containing 20 mg ambroxol was significantly larger than for placebo. The lozenges containing 30 mg ambroxol (BI 18.466 and BI 18.468) were not superior to the lozenges containing 20 mg.

The pain reduction was statistically significantly superior to placebo already at the first time point of evalu-

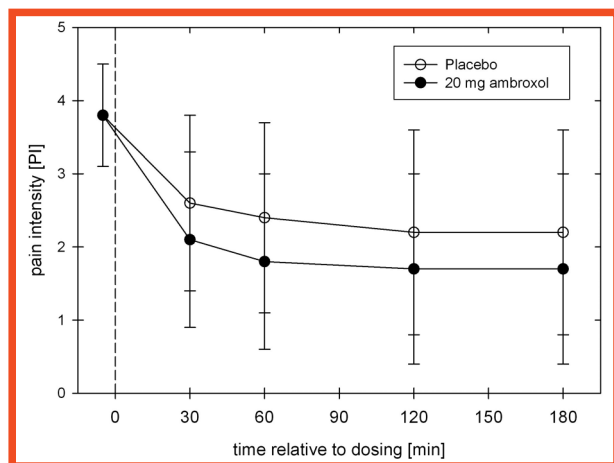


Fig. 1: Time course of the mean (\pm SD) change in pain intensity (PI – maximum score = 5) following the administration of a single lozenge containing 20 mg ambroxol or matched placebo (Trial BI 18.468).

ation (30 min after dosing) in all studies that were evaluable in this regard (p-values: BI 18.173: 0.0054; BI 18.446: 0.0333; BI 18.468: 0.0007; BI 18.489: 0.0099) and lasted at least up to 3 h after dosing (p-values: BI 18.173:

0.0046; BI 18.446: 0.0004; BI 18.468: 0.0066; BI 18.489: 0.0028). In trial BI 18.489, 54% and 73% of the patients had an onset of detectable pain relief within 10 and 20 min after dosing, respectively.

3.3 Overall efficacy

Most of the patients did not report having used other medication. No distinction could be made between the treatments in this regard.

During the ambulatory treatment phase, the subjects recorded their evaluation of the overall treatment efficacy at the end of each day. At the end of the first day, 69% and 53% of the patients reported an overall efficacy that was good or very good for the treatment with ambroxol (20 mg) and placebo, respectively (see Fig. 3). At the end of the second day, 78% and 59% of the patients reported an overall efficacy that was at least good for ambroxol and placebo, respectively. At the end of third day, this was 83% and 67%, respectively.

The throat was inspected before starting the investigational treatment and at the end of treatment. In all studies, there was a clear improvement of pharyngeal redness and signs of inflammation over the course of the treatment. This effect was statistically superior in the patients treated with lozenges containing ambroxol.

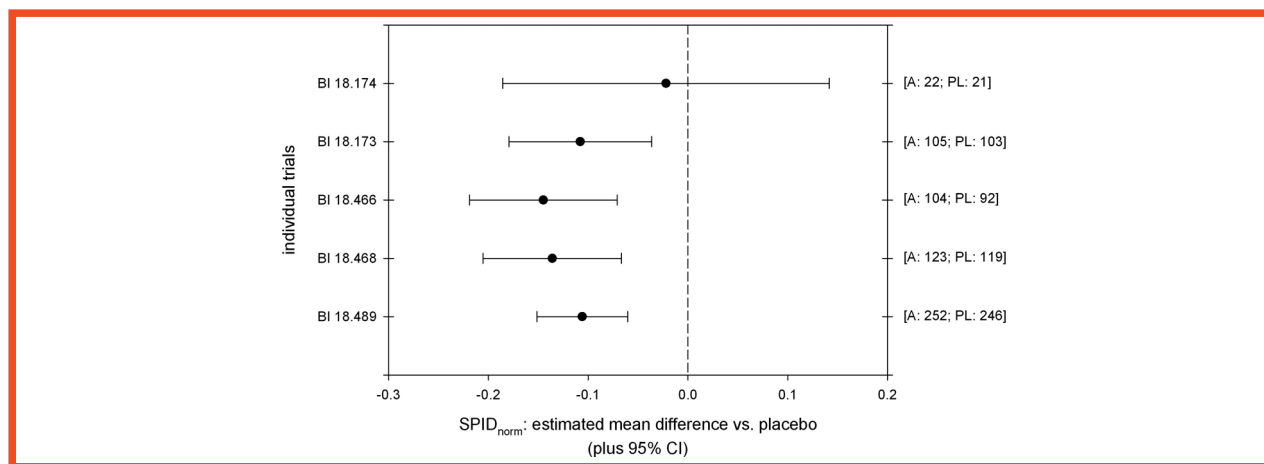


Fig. 2: Point estimate and 95% confidence interval of the true mean difference of SPID_{norm} for active treatment (lozenges containing 20 mg ambroxol) and placebo for the individual trials; values between square brackets indicate the number of subjects per treatment. A: ambroxol; PL: placebo.

Table 3: Number (N) of patients per treatment, least-square adjusted treatment mean (SEM: standard error of the mean) and estimated mean treatment difference (plus 95% confidence interval) of SPID_{norm} for lozenges containing ambroxol and placebo (PL) per trial.

Trial	Placebo (PL)		Ambroxol		Ambroxol minus PL		p-value
	N	Estimated mean (SEM)	Dose (mg)	N	Estimated mean (SEM)	Estimated mean (SEM)	
18.174	21	-0.354 (0.061)	5	23	-0.352 (0.059)	0.001 (0.081)	0.9892
18.174	21	-0.354 (0.061)	10	24	-0.363 (0.057)	-0.010 (0.081)	0.9052
18.174	21	-0.354 (0.061)	20	22	-0.375 (0.059)	-0.022 (0.082)	0.7913
18.173	103	-0.273 (0.031)	20	105	-0.381 (0.032)	-0.108 (0.036)	0.0033
18.466	92	-0.273 (0.041)	20	104	-0.418 (0.039)	-0.145 (0.038)	0.0001
18.468	119	-0.288 (0.041)	20	123	-0.424 (0.040)	-0.136 (0.035)	0.0001
18.489	246	-0.291 (0.018)	20	252	-0.397 (0.018)	-0.106 (0.023)	<.0001
18.466	92	-0.273 (0.041)	30	109	-0.402 (0.038)	-0.129 (0.037)	0.0006
18468	119	-0.288 (0.041)	30 mg	118	-0.494 (0.040)	-0.205 (0.036)	<.0001

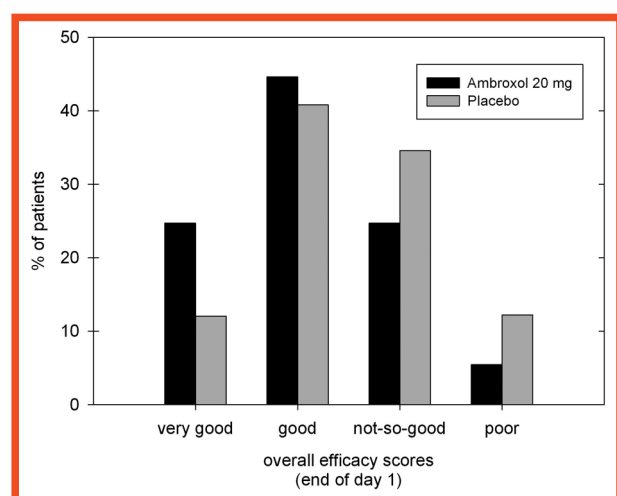


Fig. 3: Percentage of patients with overall efficacy scores as “very good”, “good”, “not so good”, or “poor” at the end of treatment with lozenges containing 20 mg ambroxol or matched placebo.

3.4 Safety and tolerability

The treatments were in general well tolerated. In adults, the safety database relates to five studies involving 1,772 adult patients who were treated and randomised: 23, 24, 620, and 240 patients assigned to treatment with 5, 10, 20, and 30 mg ambroxol, respectively, 613 patients assigned to placebo, and 252 patients assigned to treatment with benzocaine. This dataset is larger than that for the efficacy evaluations since not all patients treated were evaluable for efficacy.

3.4.1 Adverse events

There were no fatal adverse events (AE). One event was reported as serious AE: in trial BI 18.173 one patient treated with ambroxol was refractory to the investigational treatment and developed severe pharyngitis with pharynx oedema, which required hospitalisation and specific treatment. The event was judged not related to the trial medication by the investigator.

95/1,772 (5.4%) patients were discontinued prematurely. Nineteen discontinuations were due to AE (1% of the treated patients): Trial BI 18.173: one patient each with moderate nausea, moderate otitis media and severe pharyngitis treated with ambroxol (20 mg); BI 18.174: moderate abdominal cramps in one patient treated with ambroxol (20 mg); BI 18.466: one patient each with face oedema, upper respiratory tract infection, sinusitis (placebo group), one patient with upper respiratory tract infection (ambroxol 20 mg), one patient each with bronchitis, gastroenteritis and nausea (ambroxol 30 mg). BI 18.468: one patient with rash (placebo), one patient with worsening pharyngitis (ambroxol 20 mg) and one patient with dry mouth (ambroxol 30 mg); BI 18.489: one patient with fever (subsequently developing tonsillitis, nasal oedema, nasal congestion) and one patient patient with mild myalgia and pyrexia (placebo); one patient with moderate oral hy-

poaesthesia, one patient with gastritis, and one patient with eye allergy, increased lacrimation, and allergic rhinitis (benzocaine).

There was heterogeneity in the reporting of adverse events. This heterogeneity relates mainly to the active treatment, and less to placebo; furthermore, it particularly involves the relatively high incidence in trial BI 18.489 (patients with relatively less severe sore throat) in contrast to the low AE incidence in trial BI 18.468 and also – albeit to a lesser extent – BI 18.466 (patients with more severe sore throat) (see Table 4). Pooling the trial data of the patients treated with lozenges containing 20 mg ambroxol (N: 620) compared with those treated with matched placebo (N: 613), AE were reported in 20.2% and 11.9% of the patients treated with ambroxol and placebo, respectively. The main difference between the treatment groups related to adverse reporting of oral hypoaesthesia (ambroxol: 7.3%, placebo: 1.0%) and dysgeusia (ambroxol: 3.6%, placebo: 0.2%). Such reactions were frequently reported in patients with less severe sore throat treated with ambroxol in trial BI 18.489 (oral hypoaesthesia: 18%; dysgeusia: 8%; pharyngeal hypoaesthesia: 4%), whereas this was rarely reported in patients treated with placebo in parallel. In the further trials investigating patients with more severe sore throat

Table 4: Total number of patients and number (and %) of patients with at least one adverse event (AE) per treatment and trial and for the total respective dataset.

Study	20 mg ambroxol			Placebo		
	Total treated	Patients with any AE		Total treated	Patients with any AE	
		N	%		N	%
18.174	22	5	22.7	23	2	8.7
18.173	107	12	11.2	108	7	6.5
18.466	111	7	6.3	108	7	6.5
18.468	128	5	3.9	127	4	3.1
18.489	252	96	38.1	247	53	21.5
Total	620	125	20.2	613	73	11.9

Table 5: Number (N) and percentage (%) of patients for any and leading ($\geq 1\%$ of patients) adverse events (AE) while treated with lozenges containing 20 mg ambroxol or matched placebo.

	20 mg ambroxol		Placebo	
	N	%	N	%
Total treated	620	100.0	613	100.0
Total with any AE	125	20.2	73	11.9
ENT, oral cavity and tongue				
Mouth - hypoaesthesia	45	7.3	6	1.0
Dysgeusia - taste perversion	22	3.5	1	0.2
Pharynx - hypoaesthesia	11	1.8	1	0.2
Pharyngolaryngeal pain	4	0.6	10	1.6
Gastrointestinal tract				
Nausea	13	2.1	11	1.8
General wellbeing				
Headache	7	1.1	14	2.3

ENT = ear-nose-throat.

such findings were sometimes reported for active treatment more frequently than when treated with placebo, but overall far less frequently than in trial BI 18.489. AE (irrespective of the reported causality) that were reported for more than 1% of the pooled patients (in either treatment group) are detailed in Table 5.

3.4.2 Overall tolerability scores

Heterogeneity was also reflected in the patients' and physicians' overall evaluation of tolerability. The physicians scored the overall tolerability as at least "good" in about 69% and as less than satisfactory in about 13% of the patients treated with ambroxol (20 mg) lozenges; there was no difference between the trials in this regard. In contrast, the tolerability of the placebo treatment was considered as at least "good" in 59% and less than satisfactory in about 25% of the patients with severe baseline sore throat (Trials BI 18.173, BI 18.174, BI 18.466 and BI 18.468), but as at least "good" in 83% and less than satisfactory in about 4% of the patients of trial BI 18.489, which enrolled patients with less severe baseline pain intensity. In the first four trials there was little distinction in the patients' assessment of overall tolerability between ambroxol and placebo; however, in trial BI 18.489 the patients scored the tolerability of placebo as at least "good" in 89% and as "not so good" or "poor" in 11%; for the patients treated with ambroxol this was 81% and 19%, respectively.

4. Discussion

Sore throat is the hallmark of acute pharyngitis. Although self-limited, sore throat is a highly bothersome incapacitating condition. Hence, there is need for prompt efficacious and safe symptomatic relief. This also might help reducing the patient's insistent urge to request antibiotic therapy for a predominantly viral infection [51].

In spite of the relevance of establishing appropriate treatment for a common, highly bothersome condition such as sore throat, there is little published robust evidence on the benefit and risk of such interventions [90] that is applicable to the setting of general primary care. This is most evident for various local treatments containing local antiseptics either alone or in combination with anaesthetics. Local anaesthetics have been shown to be efficacious [70], but most remedies for sore throat contain far lower doses. Locally applied anaesthetics and NSAIDs furthermore carry the risk of inducing systemic effects secondary to their systemic uptake [91].

Ambroxol is a local anaesthetic agent [86, 87] with well documented and established secretolytic and secretomotoric actions [92, 93] and ancillary anti-inflammatory [94] and antioxidant properties [95–97].

The present publication summarises the evidence on the efficacy and safety of lozenges containing 20 mg ambroxol as derived from randomised, placebo-controlled, clinical trials in adult patients with acute, uncomplicated sore throat of recent onset without signs or

symptoms suggestive of bacterial infection. In order to secure the relevance of the documentation, these studies were conducted as clinical phase-III trials in a real-life primary care setting. Others have conducted such trials as phase-II investigation in professional human pharmacology research clinics [70]. Such approach might yield higher sensitivity due to more homogenous investigator performance; however, it remains difficult to extrapolate from such stringently standardised experimental conditions to real-life practice.

The data relate to five trials. In these five trials 1,777 patients were enrolled; 1,772 patients were randomised and treated. All treated patients were considered in the safety analyses, 1,713 were evaluable with regard to efficacy: 606 were treated with lozenges containing 20 mg ambroxol, 23 and 24 patients treated with lozenges containing 5 mg and 10 mg ambroxol, 227 patients treated with lozenges containing 30 mg ambroxol; 581 patients were treated in double-blind fashion with matched placebo, whereas in one study, a further group of patients was studied receiving lozenges with a low dose (3 mg) of benzocaine.

The data of these trials were not pooled with regard to efficacy. This was judged preferable in order to make the presence (efficacy) and absence (tolerability) of homogeneity more transparent.

4.1 Efficacy

The underlying condition ('sore throat') is a subjective impairment. This subjectiveness is evaluated at two levels: 'pain intensity' (the pharmacodynamic model based on the 3 h response to a first lozenge) and 'ability to reduce pain effectively' (the pharmacotherapeutic model based on the pain relief during subsequent ambulatory treatment with up to six lozenges per day at an interval of at least half an hour). The responses were recorded each time by an appropriate tool (verbal rating scales). Both approaches, although different, are complementary. Additionally, each is the best suited for the model in which it was used. From the patient's perspective, this subjectiveness is a sufficient and appropriate justification to seek treatment, and a treatment related reduction of this discomfort is a beneficial outcome.

At baseline, the intensity of sore throat was scored (VRS) as at least "moderately severe" (i.e. more than "moderate") in 1,477 patients and as "moderate" in 449 patients. Hence, the database covers the full spectrum of baseline pain intensity (PI), which is relevant to the initiation of active medication. Differences in the baseline pain intensity level result in different PID and SPID_{AUC} responses when treatment causes full pain relief: a larger PID and SPID_{AUC} are needed when the baseline-PI is higher; this undue source of heterogeneity was avoided by expressing the pharmacodynamic pain relief as SPID_{norm}: independent of the baseline PI, a SPID_{norm} of -1.0 means a full resolution of all pain from the first to the last timepoint of evaluation. There was no inconsistency of the treatment efficacy among these severity levels.

Lozenges containing 20 mg ambroxol proved statistically superior to placebo with regard to the extent and duration of the reduction in pain intensity after a first lozenge with an early onset and long duration of the effects. In one early dose-finding study (BI 18.174) investigating doses of 5, 10 and 20 mg ambroxol, there was a statistically significant overall treatment effect, but the superiority of the lozenge containing 20 mg ambroxol relative to placebo failed to reach statistical significance, also due to the small size of the sample. In all further pivotal efficacy studies, the treatment effect was distinct and consistent. Similar superiority relative to placebo was seen also during the subsequent ambulatory phase when the patients took up to 6 lozenges per day at an interval of at least 30 min. The lozenges containing 30 mg ambroxol were not more efficacious than the lozenges containing 20 mg ambroxol.

At least two aspects need to be taken into account when assessing the observed effects in terms of relevance. First of all, sore throat is a self-limiting condition, which heals spontaneously in most subjects over the course of 2–3 days. This is well reflected by the changes from predose baseline observed in the patients treated with placebo. Secondly, the sucking of a placebo lozenge with a distinct mint-flavoured taste is not an “inactive” treatment. Increased salivation by sucking the placebo lozenge has an evident pain-relieving rather than a pain amplifying effect (otherwise eventually evidenced by pain on swallowing). Hence, the observed efficacy of the ambroxol lozenges has several components: the physical actions (sucking, salivation, etc.), the psychological aspects (anticipation of relief) and an effect component, which is specifically attributable to the pharmacological actions of ambroxol. The latter is evidenced by the biostatistically separated and estimated treatment effect. Since these efficacy components are not necessarily additive (especially when the placebo response is already relatively large), the effect component which is specifically attributable to the pharmacological actions of ambroxol might have been underestimated.

In spite of these constraints, the size of the treatment effect appeared large enough to be considered beneficial: at the end of the 3rd day, 78–84% of the patients treated with 20 mg ambroxol scored the efficacy as ‘very good’ or ‘good’ vs. 22–16% of the patients who scored it as ‘not so good’ or ‘poor’; with placebo in contrast, only 55–57% scored it as ‘good’ or ‘very good’ vs. 45–43% who scored it as ‘not so good’ or ‘poor’.

Additionally, the treatment with the ambroxol lozenges was associated with a statistically significantly faster and more complete regression of the local signs of pharyngeal inflammation.

These conclusions are endorsed by the data from a large-scale pharmacy-based post-authorisation survey, which especially emphasized the early onset of the effect [98].

4.2 Safety and tolerability

The treatments were in general equally well tolerated. The AE were mostly mild-to-moderate and regressed readily without sequels. Rarely, the investigational treatments had to be discontinued due to AE. In this regard, there was no noteworthy difference between the treatments with lozenges containing ambroxol and the other treatments (placebo, benzocaine).

There was heterogeneity in the reporting and labelling of adverse events. This mainly affected AE-reporting under active treatment; it particularly involved the comparably low AE-incidence in the earlier trials and the relatively high incidence in the latest trial.

Across all studies, local reactions most likely reflecting the pharmacological actions of the medication were predominant (oral hypoaesthesia [“numbness of the tongue and/or oral cavity”] and changes in taste perception). Such effects were more frequently reported as an AE in the most recent study. At that time, there was already awareness of the possible occurrence of such phenomena from previous studies; additionally, in this trial, patients had less severe baseline pain intensity than in the earlier trials. Patients with rather moderate sore throat might be more likely to experience numbness of the mouth, tongue or throat as a discomfort, whereas patients with a more severe intensity of sore throat might consider this as a desirable phenomenon instead.

Among the other reactions, mild dyspepsia and nausea are the most noteworthy since they were occasionally reported, somewhat more frequently for active medication than for placebo. Lastly, several of the remaining few AE most likely reflect the symptoms of the underlying disease causing sore throat.

4.3 Implications

The clinical documentation on ambroxol lozenges shows that acute sore throat generally regresses spontaneously over 2–3 days. During this time ambroxol lozenges are useful by improving the patients’ comfort since they provide fast and long-lasting relief. In most cases with uncomplicated sore throat such symptomatic treatment will suffice.

A bacterial infectious “Strep” throat is to be suspected if symptoms do not regress readily after 3–4 days, particularly in the presence of fever, white, draining patches on the throat, swollen or tender lymph glands in the neck, otitis and other suppurative infections (mastoiditis for instance). In such protracted and/or complicated cases, there is justification to start antibiotics after having taken materials for culture of throat swabs or having a positive rapid antigen testing (RAT). It is uncertain whether the results of these tests alone should guide the decision to treat with antibiotics.

4.4 Conclusion

On the basis of this extensive documentation it can be concluded that lozenges containing 20 mg ambroxol

used at least 30 min apart with a maximum dose of 6 lozenges per day for up to 3 days of treatment are efficacious, safe and well tolerated for the short-term relief of acute uncomplicated sore throat. This treatment offers a fast onset of action and an effect lasting for at least 3 h. Patients treated with ambroxol lozenges showed more extensive regression of pharyngeal redness than those treated with placebo. This conclusion is based on the best possible external i.e. explicit evidence from double-blind, placebo-controlled randomised clinical trials in real-life clinical practice. It is supported by the ancillary evidence of a large-scale observational study.

It is recommendable that evidence like the present is being taken into account when considering options for an efficacious and safe management of acute sore throat without antibiotics. Similarly, it is recommendable that lack of such evidence calls for caution when considering treatment options for sore throat.

Author contributions

Conception and design of the studies as detailed in the trial protocols were developed by the sponsor under the responsibility of J. M. Vix and H. Peil. Conduct of the studies as well as the data review were done by the sponsor (responsible J. M. Vix and H. Peil) in close co-operation with the investigators. Statistical analysis was the responsibility of H. Peil. Overall evaluation and interpretation of the data was the common work of C. de Mey, H. Peil and J. M. Vix. Preparation of the manuscript was the joint effort of all listed authors as coordinated by C. de Mey. All authors reviewed the manuscript critically and approved the final version to be published.

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