

Assessment of palatability of two sublingual diluents in allergic patients: A prospective pilot study

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ABSTRACT

Background: Taste of diluents could have an effect on the ultimate patient compliance and acceptability of allergenic extract formulations used in sublingual allergy immunotherapy. This study assessed the palatability and compared the flavor and taste preferences of two sublingual diluents in allergic adult patients.

Methods: This was a prospective, randomized, double-blinded pilot study. Diluents A (50% glycerin and water) and B (0.4% phenol and water) were tested. Three drops were placed in the sublingual area beneath the tongue for 2 minutes before swallowing. A 5-point analog scale was used to allow ranking of the degree of taste acceptance. Patients were then given a 10-minute break where unsalted crackers and bottled water were provided to cleanse the palate between tasting periods. After tasting both samples, patients were asked to answer a final question regarding taste preference.

Results: Of the 30 patients, there were 15 men and 15 women with a mean age of 38 years (range, 18 to 61 years). For diluent A, 18 (60.0%) patients graded the diluent as having a "pleasant" taste, 8 (26.7%) patients gave a grade of "very pleasant," and 4 (13.3%) patients said that they were "not sure." For diluent B, 16 (53.3%) patients gave a grade of "unpleasant" and only 6 (20.0%) patients gave a grade of "pleasant." Finally, 28 (93.3%) of the 30 patients chose diluent A over diluent B as the preferred diluent of choice ($p < 0.0001$).

Conclusion: Fifty percent glycerin had better taste attributes and phenolated saline induced unpleasant oral sensation on sublingual dosing.

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Allergic rhinitis is a global health problem, affecting between 10 and 40% of the world's population.^{1,2} In industrialized countries it is the most common allergic condition affecting ~20% of the population.³ The prevalence of hay fever (seasonal allergic rhinitis) has increased for many decades but appears to have stabilized in recent years.⁴ Current guidelines of the European Academy of Allergy and Clinical Immunology Working Party on the Management of Rhinitis and Allergic Rhinitis and Its Impact on Asthma initiative state that antihistamines and nasal steroids are the current first-line therapy for allergic rhinitis.^{5,6} However, although debated for some time, it is increasingly clear that allergic rhinitis is not a simple complex of minor symptoms but is significantly linked to asthma morbidity. Allergen-specific immunotherapy administered by s.c. injection significantly reduces the morbidity of asthma with a clinical effect approximately equal to that of inhaled steroids. Injection site reactions, rash, and other adverse events including rare fatal allergic reactions limit the general use of this therapy.⁷ Although immunotherapy by s.c. dosing of allergenic extracts has been practiced for >50 years and is proven to be effective, patient compliance and safety concerns have prompted the investigation of alternative routes of administration.

Sublingual dosing has gained widespread popularity throughout Europe in pursuit of a convenient, safe, and effective therapy that can be embraced by a higher percentage of allergic patients. The 2010 Cochrane analysis expanded to 60 placebo-controlled clinical trials and confirms that sublingual immunotherapy (SLIT) significantly reduces symptom and medication scores in both adults and children.⁸ Significant allergy symptom reduction requires doses above 5 μ g of primary allergen daily and recent studies more commonly involve daily sublingual doses around 20 μ g of primary antigen. Temporary local symptoms with rare reports of systemic reaction and no adverse event requiring adrenaline remain consistent with sublingual dosing as a safe option for immunotherapy at home in a higher proportion of

allergic adults and children than those willing to undergo routine injections.

Although pharmacologic efficacy of immunotherapy is a major factor in symptom management, clinical efficacy is dependent on several additional factors. This includes the availability of an easily dosed formulation, such as a solution or suspension of an acceptable taste and texture. With the emergence of sublingual dosing of allergenic extracts, drops have been prepared using existing formulations without full consideration of the relative factors for an optimal oral formulation. Allergenic extracts for injection are formulated with various diluents with 50% glycerin and 0.4% phenol representing two disparate preservative options. For s.c. injection, 0.4% phenol is used more commonly than 50% glycerin, but the basis for this selection may not be applicable when the route of administration is sublingual rather than s.c.. Both 0.4% phenol and 50% glycerin provide antimicrobial preservation of allergenic extracts but phenol is known to accelerate protein degradation while glycerin stabilizes protein integrity. At room temperature, the rate of protein degradation is significantly accelerated in the presence of 0.4% phenol.⁹ Although 50% glycerin provides optimal protein stabilization, 0.4% phenol is more commonly used for s.c. immunotherapy because phenol allows the injection of isotonic solutions and hypertonic glycerin solutions create pain on injection. However, when dosed sublingually, 50% glycerin formulations would not be expected to produce discomfort; therefore, phenol-free glycerin-based formulations could represent a good option for SLIT. No studies have been conducted to examine the potential differences in palatability associated with the common diluents used for immunotherapy. The objective of this study was to evaluate the palatability and to compare the flavor and taste preferences of two commonly used sublingual diluents.

Others have investigated patient preference in orally administered medications. In a taste comparison study, comparing between a strawberry-flavored tablet and a peppermint-flavored syrup, >92% of children aged 6–11 years preferred the strawberry-flavored lansoprazole delayed-release orally disintegrating tablet, either dissolved in a small amount of water or allowed to dissolve on the tongue, over the peppermint-flavored ranitidine syrup.¹⁰ This product preference suggests that preferential use of these medications may improve treatment compliance as well as outcome. For the purpose of this study, we assessed the palatability of two sublingual diluents in allergic adult patients using methods similar to that used in the comparison of lansoprazole versus ranitidine.

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SETTING AND SUBJECT SELECTION

This was a prospective, randomized, double-blinded pilot study approved by the Medical University of South Carolina Institutional Review Board (HR 19205). Inclusion criteria were (1) patients with positive allergy testing (either skin-prick test or elevated IgE measured by modified radioallergosorbent test) from 18 to 99 years of age and able to provide informed consent, perform scale assessment, and answer questions related to taste preference and (2) patients need to have been fasting for at least 30 minutes before study start. Exclusion criteria were (1) any known food or drug allergies or allergies to the active or inactive ingredients in the test products and (2) a current medical condition that would interfere with the ability to swallow and/or to discriminate taste (*e.g.*, common cold or sinus or bronchial infection).

Each patient placed 3 drops (pumpfuls) in the sublingual area beneath the tongue for 2 minutes before swallowing. After each sample, the subjects were provided a 5-point analog scale to allow ranking of the degree of taste acceptance. In addition, the subjects were able to document any adverse event immediately after the 2-minute swallowing period. After recording the answer, study staff provided the patient with unsalted crackers and bottled water at ambient temperature to cleanse the palate. Patients were given a 10-minute break between the two tasting periods. If a 10-minute break was not adequate to fully eliminate carryover taste or sensation, then the interval was extended up to 1 hour with the time required to clear the aftertaste recorded in minutes. If the time required to clear the aftertaste extended beyond 1 hour, the subject was asked to return for the second treatment at least 24 hours later.

After tasting both samples, patients were asked to answer a final question regarding taste preference. A physician or physician assistant was available throughout the study to ensure the safety of the patient. Patients were monitored after the completion of sample tasting for any potential adverse reactions. Any adverse events occurring during the taste testing session were recorded. Disease information and demographic variables, such as age, ethnic group, and sex, were collected.

DILUENTS

Diluents A and B were in a prepackaged box for each subject, furnished by the sponsor. The research staff had no knowledge of the properties in each diluent. The order of assignment were randomized in 1:1 ratio between A before B (AB) and B before A (BA) using randomized assignments enclosed in sealed opaque envelopes opened at the time of subject enrollment.

Diluent A: Glycerin, 50% in water

Glycerin 99.7% USP: 52.5% v/v

Sodium chloride: 0.95% w/v

Sodium bicarbonate: 0.24% w/v

Sterile water for injection USP: q.s.

Diluent B: Normal saline with 0.4% phenol

Phenol: 0.4%

Sodium chloride: 0.9%

Water for injection: q.s.

All ingredients listed previously are included in the Food and Drug Administration (FDA) list of approved inactive ingredients and are within the concentrations approved for use. It is noted that phenol is cleared by FDA for use in i.m. or i.v. formulations at concentrations up to 2.5% and for s.c. formulations at concentrations up to 0.5%. As an inactive ingredient phenol is not listed in any oral formulations. In oral formulations, phenol is considered an active ingredient, typified by

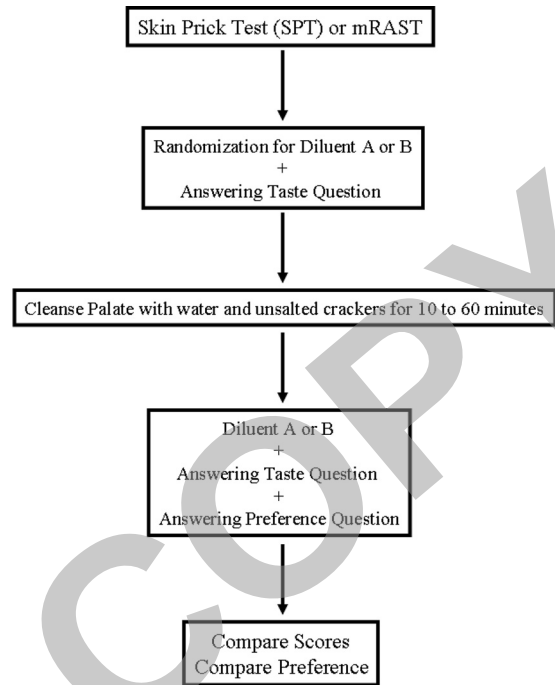


Figure 1. Flowchart detailing study procedures.

Chloraseptic spray (Prestige Brands Inc., Irvington, NY), which incorporates phenol at 1.5% concentrations as an oral anesthetic/analgesic. The concentration proposed in this study is threefold, which is a safe concentration for phenol. Chloraseptic spray will not be found in the FDA Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations because this product is an old, grandfather clause product marketed in the United States without a new drug application.

A modified linear scale previously used in other studies¹¹⁻¹³ was used to assess palatability in this study. The first question is scored from 1 (very unpleasant) to 5 (very pleasant). The second question asks for preference of either oral diluent A or oral diluent B. We also assessed for any potential side effects, such as burning, tingling, nausea, *etc.*

BIOSTATISTICAL ANALYSIS

All analyses and graphs were performed with Sigma Stat 3.5, Sample Power 2.0, and Sigma Plot 10.0 (SPSS, Chicago, IL.). Categorical variables such as preference were compared using chi-square or Fisher's exact test. Continuous variables such as taste scores were compared using the *t*-test.

RESULTS

Fifteen men and 15 women with a mean age of 38 years (range, 18–61 years) were enrolled in this study (Fig. 1). Of the 30 patients, one was Asian (3.3%), 9 (30.0%) were black, and 20 (66.7%) patients were white. All but one of the patients was a nonsmoker (Fig. 2). For diluent A (50% glycerinated), 18 (60.0%) patients graded the diluent as having a "pleasant" taste, 8 (26.7%) patients gave a grade of "very pleasant," and 4 (13.3%) patients said that they were "not sure." For diluent B (0.4% phenol), 16 (53.3%) patients gave a grade of "unpleasant" and only 6 (20.0%) patients gave a grade of "pleasant" (Fig. 3). Regarding side effects (Fig. 4) to diluents A and B, the majority of patients (29 or 96.7% versus 25 or 83.3%) did not have any side effect. Only one person described diluent A as having a "tingling" on the tongue. For diluent B, 2 (6.7%) patients described the diluent as causing "tingling" and 3 (10.0%) patients described it as causing "nausea." The results were overwhelming with 28 (93.3%) of the 30 patients choosing

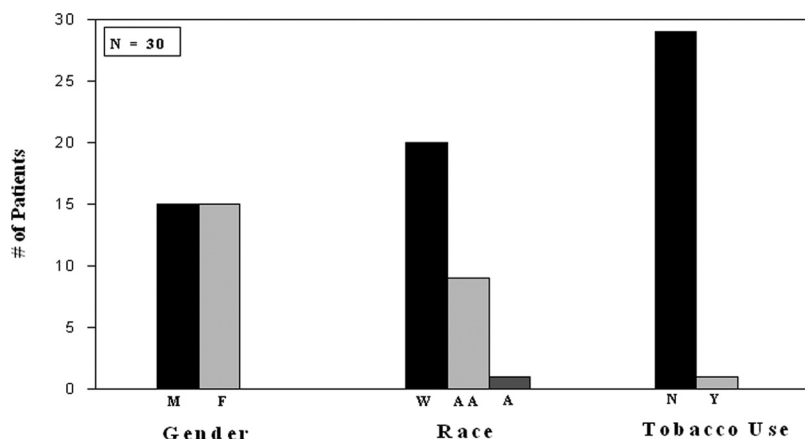


Figure 2. Sublingual study demographics—gender, race, and tobacco use.

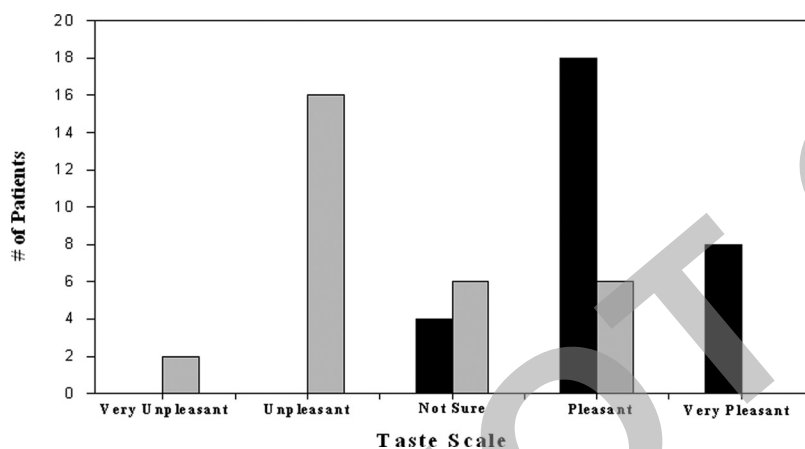


Figure 3. Taste Scale—Diluent A versus diluent B.

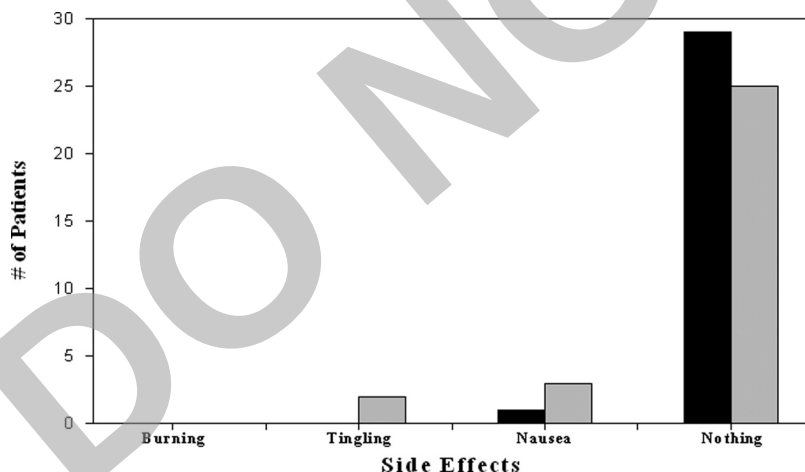


Figure 4. Side effects—Diluent A versus diluent B.

diluent A over diluent B as the preferred diluent of choice ($p < 0.0001$; Fig. 5). Finally, of the 28 patients that had preference for diluent A, all patients stated that the reason for choosing diluent A over diluent B was because of the taste of diluent A. All 30 patients completed the study and left the clinic without any complaints.

DISCUSSION

The choice of diluent for allergenic extract formulation represents a primary difference among commercial allergenic extracts. With respect to protein stability preservation, 50% glycerin has been shown to provide the most complete protection against loss of antigen potency, but 50% glycerin is known to create more pain on injection than

phenolated saline. However, when the intended route of allergenic extract dosing is sublingual, 50% glycerin appears to be a better option than phenolated saline.

In the current study, the subjective response to sublingual dosing of 50% glycerin diluent was compared with that of phenolated saline. When taken sublingually, taste attributes were significantly better for 50% glycerin than for phenolated saline. Unpleasant oral sensation or nausea that could be characterized as potential adverse events were less commonly reported with 50% glycerin than with phenolated saline. Although phenol-containing diluents could be argued to be preferable for avoidance of pain on injection, phenolated diluent is not optimal for formulation of SLIT drops.

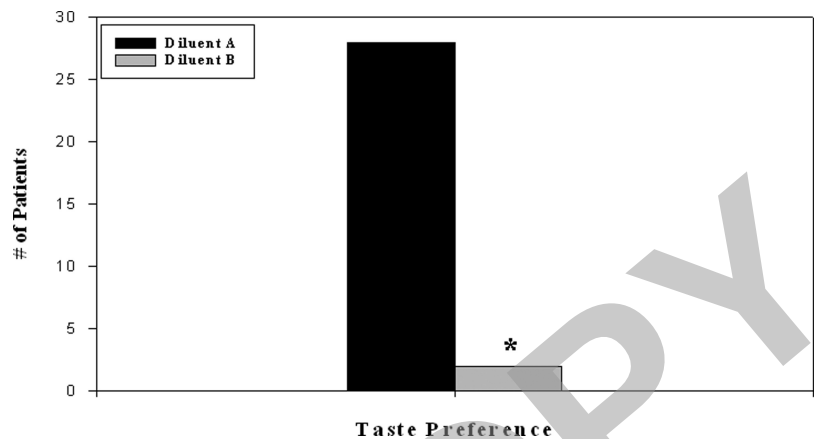


Figure 5. Taste preference—Diluent A versus diluent B.

Although bad taste and poor compliance are popularly linked, data do not support a clear correlation between poor taste and compliance.¹⁴ Other factors, such as severity of disease and patient awareness of ramifications of noncompliance, which is responsive to effective communication between clinician and patient, blurs any simple correlation between bad medication taste and noncompliance. That said, however, when given an option, it seems unreasonable to present the less preferred over the more preferred formulation. Beyond simple taste preference for glycerin versus phenol, however, use of phenol in sublingual formulations could introduce needless complexity to sublingual dose finding and continuation without adverse events. It is helpful to recall that phenol is the active ingredient in Chloraseptic Sore Throat Spray. Although present in lower concentrations in allergenic extracts, phenol taste has been shown in this study to be clearly perceptible with concentrations as low as 0.4%. In addition to simply creating a bad taste, the generalized effect of phenol on oral sensation could complicate the assessment of oral adverse event sensations that underlie the determination of dose using escalation of oral doses to attain maximum tolerated dose, which represents one proposed method for determining individualized dose for SLIT.¹⁵

Beyond the subjective effects on taste and mouth sensation, the deleterious effects of phenolated saline on allergenic protein stability represents a significant pharmaceutical problem when sublingual drops are maintained at room temperature. When solutions are maintained at room temperature, antigen potency falls quickly in formulations prepared using phenolated saline but are maintained without change in excess of practical beyond-use dates for containers formulated with 50% glycerin. For these reasons it is practical to recommend the use of 50% glycerin and the avoidance of phenol when preparing formulations of allergens intended for sublingual dosing.

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