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Clinical assessment of the warming sensation accompanying flavor 316282 in a cold and cough syrup containing paracetamol, phenylephrine hydrochloride, and guaifenesin

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Abstract

Objective: The primary objective was to assess the warming sensation caused by flavor 316282 in a cold and cough product in the target population.

Methods: A single-cohort, single-treatment arm, open-label study. Subjects received one 30-mL dose of syrup containing flavor 316282, paracetamol, phenylephrine hydrochloride, and guaifenesin and recorded onset and disappearance of any warming sensation in the mouth/throat. Subjects' assessment of strength and appeal of the sensation, taste, texture, and acceptability of the product as a cold and cough remedy was investigated using questionnaires.

Results: A total of 51 subjects were included; 47 (92.1%) experienced a warming sensation. The median duration of the warming sensation was 100 s (95% confidence interval = 82 s, 112 s). The majority of subjects rated the syrup as excellent, good, or fair for treatment of cough and cold symptoms (96.1%), taste (80.4%), and texture (98.0%). There were no safety concerns, and the syrup was well tolerated. Most subjects liked the warming sensation.

Conclusions: Flavor 316282 in a cold and cough syrup is associated with a warming sensation. The syrup is well tolerated, safe, and palatable.

Keywords

Flavor 316282, warming, cough, cold, syrup

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Introduction

The treatment of mild, self-limiting medical conditions, such as colds and coughs, by patients saves health-care resources for those in more urgent need of medical treatment and is, therefore, encouraged in most health-care systems. Products available over-the-counter (OTC) for the treatment of colds and coughs must be not only effective in bringing about symptomatic relief but pleasant to take, in order to encourage compliance.

A new syrup formulation for the short-term symptomatic relief of colds, chills, and influenza with productive cough has been developed containing paracetamol, phenylephrine hydrochloride, and guaifenesin. These active ingredients are well-established pharmaceutical agents, which in combination products can relieve several concurrent symptoms of colds and flu, such as sore throat, headache, body pains and aches, fever, nasal congestion, and cough. The inactive ingredients are also well established for use OTC syrups: acesulfame K, alcohol, citric acid, edetate disodium, FD&C blue #1, FD&C red #40, IFF flavor 316282 (International Flavor and Fragrances, Shrewsbury, NJ, USA), glycerin, maltitol solution, propylene glycol, purified water, sodium benzoate, and sodium citrate.

The flavoring in this product, flavor 316282, causes a warming sensation in the mouth and back of the throat, which was demonstrated by surveys of subjects testing base formulations that included the flavor but not the active ingredients (data on file; Novartis Consumer Health, Inc., Parsippany, NJ, USA). This agent is included for the orange taste of the product, but may also have a soothing effect appropriate to the indication. The use of warming sensation to soothe patients suffering from cough, chills, cold, and flu

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is well known anecdotally, and there is a small body of literature suggesting that warm liquids and warming salves (e.g., chicken soup, teas, and chest rubs) help patients feel better.[1–4] Overall, the message is one of patient comfort, which may have a greater meaning for certain populations and cultures. There are no studies to date that have evaluated warming sensation of liquids, rubs, or drug ingredients in terms of patient acceptability and preference.

The primary objective of this study was to assess the warming sensation caused by the excipient flavor 316282 in a syrup containing paracetamol, phenylephrine hydrochloride, and guaifenesin, in people with cold and cough symptoms. The syrup contains 0.15% weight/volume of the warming flavor. The secondary objectives were to assess subject acceptability, as well as the safety and tolerability of the warming syrup formulation.

Methods and materials

Study population

Subjects (12 years of age and older) suffering from symptoms of an upper respiratory tract infection (URTI) were recruited. At dosing, eligible subjects had to have a productive cough plus one or more symptoms in each of two categories: (1) mild-to-moderate body pain, fever, or sore throat; (2) nasal congestion (blocked nose) with or without rhinorrhea (runny nose) or sneezing. Subjects were excluded if they had severe throat pain or cough, assessed as scoring 3 on a 4-point ordinal scale where 0 = not present and 3 = severe.

Before any assessments were performed, subjects had to show an understanding of the study procedures, provide written informed consent, and indicate their willingness to complete the required assessments. Informed consent was signed by one or both parents or legal guardian for adolescents, who also were asked to sign an informed assent. The recruitment target was 56 subjects in order to obtain a minimum of 50 evaluable subjects from two centers.

Study design

The study used a single cohort, single-treatment arm, open-label design carried out over 1 day at two centers. Screening occurred when the subjects were seen at the clinic for symptoms of a URTI, and eligible subjects received treatment between 30 min and 6 h after being screened.

Study treatment

Each 30-mL dose of study medication contained the active ingredients: paracetamol, 500 mg, phenylephrine hydrochloride, 10 mg, and guaifenesin, 200 mg. The syrup also contained 0.15% weight/volume of the warming flavor 316282. While being observed, each subject swallowed a single 30-mL dose of the study medication over a period of 1 min or less, immediately followed by a 1-h observation period. Drinks other than 200 mL of water at room temperature were prohibited from 1 h before dosing to the end of the assessment period.

Study assessments

Pre-dose. Eligible subjects had a short physical examination, which included evaluation of the oropharynx, vital signs (blood pressure, pulse, and temperature), and height and weight measurements (to confirm minimum weight for adolescents). Baseline severity scores were recorded using a 4-point scale (0 = not present; 1 = mild; 2 = moderate; 3 = severe) for each of the following symptoms of a URTI with productive cough: runny nose, sneezing, blocked nose, sore throat, dry cough, headache, fever, and body pain.

The baseline score for warming sensation intensity was determined by the subject following ingestion of 30 mL of water at room temperature. Subjects indicated the warming sensation intensity by making a vertical mark on a 100-mm visual analogue scale (VAS), which ranged from "no warming sensation" (= 0 mm) to "strongest possible warming sensation" (= 100 mm).

Post-dose. Two stopwatches were started at the point when the study medication was swallowed (time zero). Subjects were asked to stop one stopwatch as soon as they felt a warming sensation at the back of their throat, and to stop the second stopwatch as soon as that sensation had disappeared. In addition, subjects were asked to indicate the warming sensation intensity at 60 s after dosing by making a vertical mark on the VAS.

Ten minutes post-dose, subjects were asked to assess the strength of the warming sensation using the following ratings: from 5 (much too strong) to 1 (much too weak). They also rated their overall opinion of the warming sensation on a 9-point scale, where 9 = liked extremely and 1 = disliked extremely.

A second physical examination, including assessments of the oropharynx and vital signs, was carried out 1 h after dosing, and adverse events were recorded. At this time, the subject's overall opinion of the medication was evaluated using a 5-point scale, from 4 = excellent to 0 = unacceptable, and based on the following query: "Taking into account all the benefits and any side effects which you attributed to your study medication, how would you rate the syrup you took for treating cold symptoms?" The subject's overall opinion of syrup taste and texture was recorded separately using a similar scale.

Statistical analysis

The intensity of warming sensation at baseline and at 60 s post-dose and the onset and duration of warming sensation were summarized. For the intensity of warming sensation, the n, arithmetic mean, standard deviation (SD), median, minimum, and maximum values were calculated for pre-dose, post-dose, and for the difference (post-dose − pre-dose). For the onset and duration of warming sensation, the n, minimum,

Table 1. Study population demographics (N = 51).

Demographic variable	
Age in years, mean (SD)	32.0 (12.65)
Sex, n (%)	
Male	25 (49.0%)
Female	26 (51.0%)
Race, n (%)	
Caucasian	45 (88.2%)
Asian	3 (5.9%)
Black	2 (3.9%
Native American	1 (2.0%)
Body mass index (kg/m^2), mean (SD)	25.39 (6.061)
Smoking history, n (%)	
Never smoked	22 (43.1%)
Ex-smoker	14 (27.5%)
Current smoker	15 (29.4%)

SD: standard deviation.

25th percentile, median and its 95% confidence interval (CI), 75th percentile, and maximum values were calculated. The median, its 95% CI, and the lower and upper quartiles were estimated using the Kaplan–Meier survival analysis method.

Results

Study population

A total of 51 subjects with a mean age of 32 years (range = 15–64 years) were recruited and included in the analyses (Table 1). The majority of the subjects were over 18 years of age (98.0%) and Caucasian (88.2%). The numbers of males and females were similar.

Cold and flu symptoms

The presence of URTI symptoms in the study population pre-dose is summarized in Table 2. All symptoms were mild or moderate. Besides productive cough, which was present in all subjects and required for entry into treatment, the three most common symptoms were sore throat pain (94.1%), blocked nose (94.1%), and runny nose (86.3%). Only one subject (2.0%) had fever.

Warming sensation

In total, 47 (92.1%) subjects experienced a warming sensation. The median time to onset of warming sensation was 9 s (95% CI = 8 s, 15 s), with time for individual subjects ranging from 2 to 53 s. The interquartile range (Q25 to Q75) was 6–20 s.

The mean (SD) intensity of warming sensation pre-dose was 1.6 mm (3.16 mm), range = 0–17 mm. At 60 s post-dose, the mean (SD) intensity was 36.2 mm (27.61 mm), range = 0–98 mm. In total, 38 subjects (74.5%) reported an increase in the intensity of the warming sensation at 60 s post-dose, 13 subjects did not. The latter included four (7.8%) who experienced no warming sensation at all and nine (17.6%) for whom the warming sensation had already subsided.

Table 2. Presence of mild or moderate upper respiratory tract infection symptoms pre-dose (N = 51).

Symptom	n (%)
Productive cough[a]	51 (100)
Sore throat pain	48 (94.1)
Blocked nose	48 (94.1)
Runny nose	44 (86.3)
Sneezing	40 (78.4)
Headache	38 (74.5)
Body pain	35 (68.6)
Dry cough	21 (41.2)
Fever	1 (2.0)

[a]All patients were required to have productive cough to be eligible for treatment.

Table 3. Subjects' assessments of strength of warming sensation (N = 51).

Strength of warming sensation	n (%)
Much too weak	3 (5.9)
Too weak (not warming enough)	6 (11.8)
Just about right (pleasantly warming)	34 (66.7)
Too strong (too warming)	8 (15.7)
Much too strong	0

Table 4. Subjects' overall opinions of warming sensation (N = 51).

Opinion of warming sensation	n (%)
Dislike extremely	0
Dislike very much	0
Dislike moderately	1 (2.0)
Dislike slightly	7 (13.7)
Neither like nor dislike	7 (13.7)
Like slightly	10 (19.6)
Like moderately	19 (37.3)
Like very much	7 (13.7)
Like extremely	0

In total, 47 (92.1%) subjects experienced a warming sensation. The median duration of warming sensation was 100 s (95% CI = 82 s, 112 s), with duration for individual subjects ranging from 16 to 1052 s (17.5 min). The interquartile range was 59–125 s.

The majority (34, 66.7%) of subjects described the warming sensation as "pleasantly warming or just about right" (Table 3), although 8 (15.7%) described the sensation as "too strong" (too warming) and 6 (11.8%) as "too weak" (not warming enough).

Overall, 36 (70.6%) subjects liked the warming sensation experienced with the syrup, 7 (13.7%) subjects neither liked nor disliked the warming sensation, and 8 (15.7%) subjects disliked the sensation (Table 4).

Table 5. Subjects' opinions of effectiveness of syrup for treating symptoms of upper respiratory tract infection after 1 h (N = 51).

Rating	n (%)
Excellent	7 (13.7)
Good	27 (52.9)
Fair	15 (29.4)
Poor	1 (2.0)
Unacceptable	1 (2.0)

Table 6. Subjects' assessments of acceptability of syrup taste and texture (N = 51).

Rating	Syrup taste, n (%)	Syrup texture, n (%)
Excellent	4 (7.8)	14 (27.5)
Good (i.e. better than expected)	21 (41.2)	21 (41.2)
Fair (i.e. as expected)	16 (31.4)	15 (29.4)
Poor (i.e. worse than expected)	10 (19.6)	1 (2.0)
Unacceptable	0	0

Acceptability of the syrup

The results of assessments of the acceptability of the syrup to the subjects are summarized in Tables 5 and 6. The majority of patients (34, 66.7%) rated the syrup as good or excellent for treating their URTI symptoms after 1 h. In all, 15 (29.4%) rated the syrup as fair, and 2 subjects (4%) rated the treatment as poor or unacceptable. Taste and texture of the syrup were also rated as good or excellent by the majority of subjects: 25 (49.0%) and 35 (68.6%), respectively. Taste was considered fair (i.e. as expected) for 16 (31.4%) of the subjects, with 15 (29.4%) giving a similar rating for texture. In all, 10 (19.6%) subjects considered the taste to be poor (defined as worse than expected), and 1 (2.0%) subject rated the texture as poor, but no subject felt that the taste or texture was unacceptable.

Safety

Four (7.8%) subjects experienced treatment-emergent adverse effects (TEAEs): two (3.9%) had pyrexia, one (2.0%) nausea, and one (2.0%) headache. The nausea and headache were mild in severity and suspected of being study drug related. One pyrexia event was mild and the other was moderate in intensity. There were no severe or serious adverse events. Mean changes in systolic and diastolic blood pressure and body temperature were small. Mean pulse rate fell by 5.0 bpm at 1 h post-dose.

Discussion

The purpose of this study was to evaluate the perception of the warming sensation associated with a flavoring agent when combined with 500 mg paracetamol, 10 mg phenylephrine hydrochloride, and 200 mg guaifenesin and its impact on the acceptability of the product for the treatment of colds and cough. This is the first documented study of perception of warming sensation associated with an OTC cough cold product.

The majority of the study population experienced a warming sensation after swallowing the syrup, and most described the sensation strength as "pleasantly warming." Interestingly, about 18% of subjects described the sensation as "not warm enough," suggesting that a sensation of warmth may be a desirable attribute for a cough and cold product for them. Whether this reflects cultural attitudes about treatment for chills, colds, coughs, and flu cannot be determined, but warrants further study—specifically with regard to whether the perception of a "soothing sensation" (e.g., warmth) for an OTC drug product might influence patient preference and/or produce a placebo effect.

A high proportion of subjects in this study were satisfied with the syrup as a treatment for their cold symptoms at 1 h post-dosing, and most found the taste and texture to be acceptable. There were no safety concerns resulting from this study.

This was an open-label study, and the lack of a control group—that is, the unflavored syrup—limits interpretation of the findings. It is difficult to provide appropriate controls for these types of studies. Ideally, two control groups should have been included—a vehicle control with the inactive ingredients (including the warming flavor) as well as the unflavored cough and cold syrup. The utility of the unflavored syrup is questionable, however, as the active ingredients are well used and do not cause warming, and the lack of an added flavor would likely make the syrup unpalatable for most subjects. Comparison to similar products with other flavoring agents that are not warming might be suggested, but analyses of patient acceptance, preference, and opinions of effectiveness would be complicated by the differences in formulation. Prior consumer acceptance surveys of prototype formulations (without the active ingredients, but

with the flavoring agent) were considered warming by a majority of subjects, and showed no adverse events or safety signals (data on file; Novartis Consumer Health, Inc.).

Conclusion

This study confirms that most people perceive IFF flavor 316282 as producing a pleasant warming sensation in a cold and cough remedy containing 500 mg paracetamol, 10 mg phenylephrine hydrochloride, and 200 mg guaifenesin, and that this combination is an acceptable product for the treatment of colds and flu with productive cough. The localized warming sensation effect demonstrated by flavor 316282 in this medication may increase the acceptability and hence compliance in those seeking relief from the symptoms of colds and flu with productive cough.

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Declaration of conflicting interests

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