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A Randomized, Double-Blind, Placebo-Controlled Pilot Clinical Study on ColdZyme® Mouth Spray against Rhinovirus-Induced Common Cold

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Abstract

Common colds incur significant costs in terms of sick leave and personal discomfort for affected individuals. This study investigated the performance of ColdZyme® Mouth Spray (ColdZyme), a protective barrier against common cold, in rhinovirus-inoculated healthy volunteers. This randomized, double-blind, placebo-controlled pilot study was conducted on 46 healthy volunteers inoculated with rhinovirus 16 via the nose. Subjects self-administered ColdZyme or placebo 6 times daily for 11 days. Symptoms were recorded daily in a diary. Rhinovirus 16 in nasal and oropharyngeal samples at days 0, 3, 4, 6, 7 and 10 were quantified by RT-qPCR. The primary outcome measure was the reduction in viral load in oropharyngeal samples. Rhinovirus 16 was only detected in 35 out of 46 inoculated subjects. Exploratory analysis measuring the total viral load (*i.e.*, area under the curve (AUC)) for days 3 - 10 in successfully inoculated subjects found that ColdZyme treatment resulted in a lower total viral load in the oropharynx ($p = 0.023$). In subjects who experienced symptomatic common cold, irrespectively, if virus were detected, treatment with ColdZyme resulted in a reduction in the number of days with common cold symptoms from 6.5 to 3.0 days ($p = 0.014$) in comparison to placebo. ColdZyme reduced virus infection in the oropharynx and reduced the number of days with common cold symptoms and highlights the possible importance of the oropharynx in common cold infections. Suitable outcome measures for a feasible study on ColdZyme are total viral load in the oropharynx in subjects having detectable virus present in nasal or oropharyngeal samples.

Keywords

Common Cold, Rhinovirus, ColdZyme® Mouth Spray

1. Introduction

The common cold is one of the most commonly encountered infectious syndromes of human beings. Colds are usually self-limiting to previously healthy individuals, but there are also recognized complications such as asthma exacerbations [1]. Despite the benign nature of the illness in the majority of cases, it is still a significant economic burden on society. It leads to increased consultations with clinicians, increased absence from school and work and a subsequent loss in earnings [2]. Common colds can be caused by a number of viruses (e.g., rhinoviruses, coronaviruses, influenza viruses and others). The majority of colds are caused by rhinovirus, which is responsible for approximately half of all colds in adults [3] [4].

Epithelial cell layers in oral and nasal cavities form a physical and innate immune barrier against bacteria and viruses [5]. However, viruses can infect the mucosal cells in this area resulting in cold symptoms. Hence, strengthening the natural epithelial barrier may be of benefit in order to inhibit viral entry into host cells by free virus particles in the throat mucosa. ColdZyme® Mouth Spray (ColdZyme) is a medical device against the common cold. It is designed to deposit a viscous solution containing primarily glycerol and cod trypsin onto the throat, which, thereby, reduces the probability of catching a cold and helps shorten the duration of a cold by forming a thin protective barrier on the oropharyngeal mucous membrane.

This is the first randomized, double-blind study to test ColdZyme against common cold using an experimental rhinovirus challenge model where healthy volunteers were infected via nasal inoculation. We evaluated methods, procedures and suitable outcome measures to assess the effect of depositing a ColdZyme barrier on the oropharyngeal mucosal membrane to protect against viral entry into cells and to reduce total virus load and common cold symptoms *in vivo* in relation to placebo.

2. Methods

2.1. Subjects

This study was conducted in spring 2013 at the Ear, Nose & Throat Department, Skåne University Hospital, Lund, Sweden. Written informed consent was obtained from all subjects before study entry, which was conducted in compliance with the principles of the Declaration of Helsinki/International Conference on Harmonisation Guidance for Good Clinical Practice and Swedish law. The study protocol and accompanying documents were reviewed and approved by the Regional Ethics Committee in Lund, Sweden. Based on viral load parameters from

a similar study [6], a total sample size of 46 was calculated to be sufficient. After signing informed consent, 82 subjects were screened for serum neutralizing antibodies against rhinovirus 16, of whom 46 seronegative subjects between the ages of 20 - 46 years were included. The investigator judged the definition of healthy by detailed medical history and physical examination. Further inclusion criteria for the study were the willingness and ability to complete the study and the perception of having had at least one cold per year.

Volunteers were excluded if they met any of the following criteria: smoker during the last 12 months; any cold symptom within the last month such as sore throat, sneezing, rhinorrhea, malaise, nasal obstruction or cough; presence of serum neutralizing antibodies against rhinovirus 16 at screening (blood samples were collected and were screened at National Heart and Lung Institute, Imperial College London, UK); active allergic rhinitis, asthma or chronic obstructive pulmonary disease during the previous year; positive responses to cat or dog allergens (if subject was likely to come in contact with the specific pet) and/or dust-mite allergens in a skin prick test at screening; nasal disease (e.g., nasal polyposis, significant septum deviation, chronic rhinosinusitis, etc.); females who were pregnant, breastfeeding or intended to become pregnant during the study; active autoimmune disease during the previous year; evidence or history of drug or alcohol abuse; use of any prescribed or non-prescribed medication (except for contraceptives, paracetamol and ibuprofen) within 2 weeks prior to the first administration of investigational product until the end of study; use of any over-the-counter cold prophylaxis products such as vitamin C, zinc or Echinacea within 1 month prior to the first administration of investigational product until the end of study; and participation in any other clinical studies within 60 days. Subjects were free to withdraw their consent at any time without affecting future treatments. Demographic data were collected and analyzed using descriptive statistics. No formal hypothesis testing was performed for these parameters.

2.2. Study Design and Objectives

The study was a double-blind, randomized, placebo-controlled, parallel-group pilot study. Subjects were randomized 1:1 to use either ColdZyme or a placebo mouth spray. The objectives of this study were to investigate the effect of ColdZyme on rhinovirus replication in the pharyngeal mucosa and on common cold symptoms *in vivo*. A study flow scheme is shown in **Figure 1**. Enrolled subjects began treatment with ColdZyme or placebo at the randomization visit. On the day following randomization, the subjects were inoculated on a single occasion with a single vial of stored inoculum [7], divided equally between the two nostrils. A dose of 100 TCID50 (tissue infective dose) was used per subject. The inoculation procedure was performed slowly with sufficient intervals between each spray to ensure maximum contact time between the spray and the nasal and pharyngeal mucosa. Subjects were asked not to swallow during the procedure to ensure maximal pharyngeal contact. Subjects were also asked to sniff gently at each actuation to encourage the delivery of inoculum particles to the

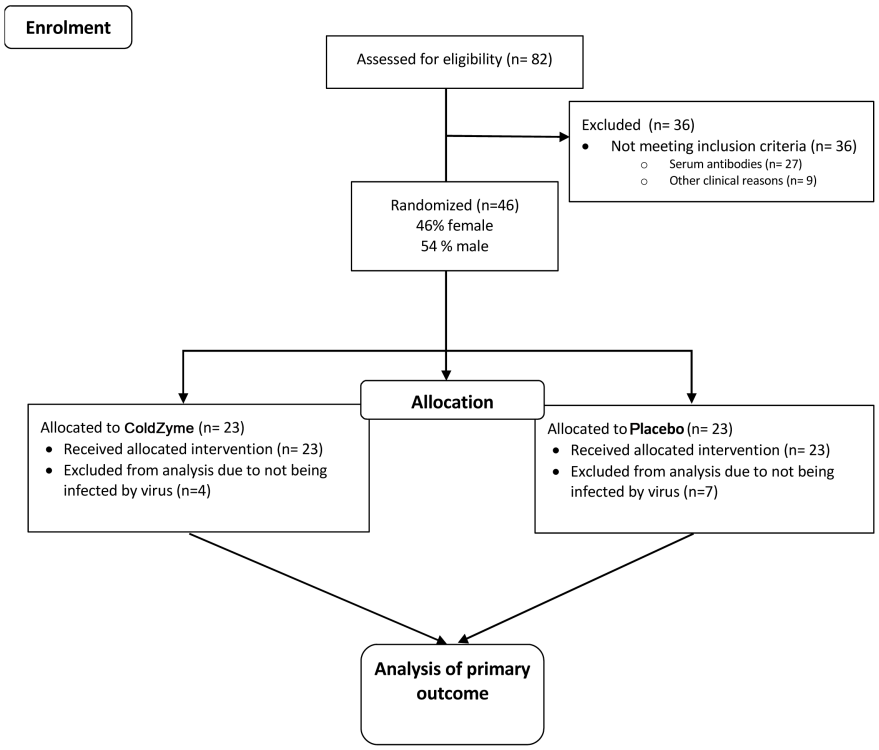

Figure 1. Flow scheme for study participants.

oropharynx. Inoculations were performed using a disposable intranasal mucosal atomization device. Subjects visited the clinic on 8 occasions including screening. Inoculation was performed during visit 3. Oropharyngeal and nasal samples were taken on visits 3 - 8 (see **Figure 2**).

2.3. Outcomes

The primary outcome of the trial was defined as a reduction in viral load in the upper respiratory tract, after challenge with rhinovirus, in relation to placebo and determined by the quantitative measure (number of RNA copies per standardized sample) of rhinovirus replication (viral load) in oropharyngeal samples using RT-qPCR. The exploratory primary outcome measure was total viral load (area under the curve (AUC)) for days 3 - 10 in oropharyngeal samples. This analysis was performed on subjects who experienced an infection, defined as subjects with a value of viral load above 0 in an oropharyngeal or nasal sample at any time during the study period. Subjects who did not have a detectable amount of virus in any sample were excluded (*i.e.*, subjects: 4, 5, 6, 12, 13, 20, 22, 35, 38, 44, 46).

The secondary outcome was defined as a reduction in the number of days with a symptomatic cold. Symptoms assessed were sneezing, rhinorrhea, nasal obstruction, sore/scratchy throat, cough, headache, malaise, hoarseness and chills, with their severity rated from 0 (absent) to 4 (very severe). The subjects made daily self-assessments in their personal study diaries, using a 5-graded Jackson scale [8]. A symptomatic cold was defined as having total symptom se-

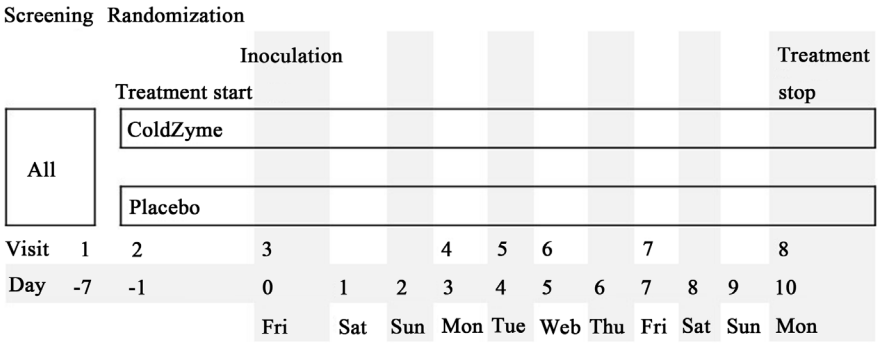

Figure 2. Study scheme.

verity score > 5 any time during the study period. Subjects having no symptomatic colds were excluded from this exploratory analysis (*i.e.*, subjects: 4, 13, 20, 21, 24, 25, 38, 40, 44). Not all analyses are presented in this report, but all pre-defined analyses can be found at NCT02522949.

2.4. Study Products and Dosing

ColdZyme® Mouth Spray (Enzymatica AB, Lund, Sweden) is a medical device used to prevent the common cold. It is designed to deposit a viscous solution containing primarily glycerol and cod trypsin onto the throat. The ColdZyme solution contained cod trypsin, glycerol, water, Tris-HCl pH 8.0, $CaCl_2$ and menthol. The placebo spray matched ColdZyme in taste and contained water, phosphate buffer, sucralose, propylparaben and menthol. Subjects received 6 doses as a pretreatment on the day prior to inoculation and thereafter 6 doses of spray daily, evenly spaced during waking hours, for 10 days.

2.5. Oropharyngeal Samples

Oropharyngeal samples were taken from the tonsils and posterior pharyngeal area using nylon-flocked swabs at visits 3 - 8. A tongue depressor was used during the procedure and care was taken to avoid touching the tongue with the swabs. After swabbing, the tip was placed in a tube with saline solution and vigorously vortexed for 5 minutes. Five hundred microliters was aliquoted to a cluster tube and stored at −80˚C until subsequent processing for analysis by RT-qPCR (Quantitative real-time PCR).

2.6. Nasal Samples

A nasal pool device was used for saline nasal lavages at visits 3 - 8. The nasal pool device is a compressible plastic container equipped with a nasal adapter [9]. The adapter is inserted into one of the nostrils, and the container is compressed while the patient is leaning forward in a 60˚ flexed-neck position. Thus, the nasal pool fluid is instilled into one of the nasal cavities and remains in contact with a large area of the mucosal surface for five minutes. The subjects themselves instilled the nasal pool fluid. When the pressure on the device is released, the fluid returns to the container. In the present study, the volume of the nasal pool fluid

was 15 mL. The solution was transferred to a 15-mL sample tube and vigorously vortexed for 5 minutes. 500 µL was aliquoted to a cluster tube designated for RT-qPCR analysis and stored at −80˚C.

2.7. RT-qPCR Assay

Rhinovirus 16 quantification was conducted in the nasal lavage and oropharyngeal swab samples. All analyses were performed and analyzed at the Dept. of Clinical Sciences, CRC, Skåne University Hospital, Malmö, Sweden.

Preparation of RNA from nasal lavage and pharyngeal swab samples

The samples were immediately transferred onto ice from −80˚C, thawed on ice and then instantly processed for viral RNA preparation. MagMAX-96 Viral RNA Isolation kits (AM1836, Life Technology) were used in all the samples for isolation of viral RNA. The kit is designed for rapid high-throughput purification of viral RNA from biofluid samples. The reagent preparation and RNA isolation procedures were performed as written in the instruction manual provided with the kit (P/N 1836 M Revision F). The RNA extraction internal control was spiked into the lysis buffer (4 µl/sample) provided from the human rhinovirus 16 OneStep RT-qPCR kit, PrimerDesign, UK, and prepared according to their instructions. Nucleic acids were eluted and stored at −20˚C until RT-qPCR analysis.

RT-PCR for quantification of rhinovirus 16 genomes

Quantitative real-time RT-PCR (RT-qPCR) of human rhinovirus 16 was assessed using Precision OneStep RT-qPCR Mastermix (One Step150-LR) and PCR detection kit for HRV16 (Path-HRV16) both from PrimerDesign, UK. All samples were run as duplicates in the RT-qPCR assay. Rhinovirus 16 and the extraction control RNA were detected in different channels, FAM and VIC, respectively, allowing simultaneous/same sample measurements in the Viaa7 real-time PCR system, Life Technologies. Extraction control RNA was used to ensure efficient RNA extraction. The viral rhinovirus 16 quantifications, copy/mL in the original sample, were calculated from the copies/mL RT-PCR reaction generated from the standard curve in the Viaa7 software. For statistical analysis, the mean of each duplicate pair was used.

2.8. Statistical Analysis

Statistical hypotheses for the exploratory analysis were analyzed using two-sided tests with a significance level of 5%. As data over virus load was not normally distributed (Shapiro–Wilk normality test, $p < 0.1$) and data on days with cold was ordinal, Exact Wilcoxon Rank Sum Test was used for hypothesis testing. All statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC, USA). Data management and statistical analyses were conducted by Norma, Lund, Sweden.

3. Results

All 46 enrolled subjects completed the study, 46% of whom were female and 54%

were male. Mean age was 24 (range: 20 - 49). The mean age was similar between the two groups, 24 years (range 20 - 39) in the ColdZyme group and 23 years (range: 20 - 37) in the placebo group. Further baseline characteristics and demographics were similar between the ColdZyme and placebo group (mean height (cm); 176.8 vs. 176.0, mean weight (Kg); 71.1 vs. 71.9). The infection rate, based on detection of rhinovirus 16 in either pharyngeal swabs or nasal lavage was 76% for the whole study population. Sixteen out of 23 subjects in the placebo group and 19 out of 23 subjects in the ColdZyme group were successfully infected (*i.e.*, they had a detectable amount of rhinovirus 16).

3.1. Primary Outcome

The objective was to evaluate the effect of ColdZyme on viral loads in the oropharynx. The a priori intended-to-treat analysis using peak viral load was found to be an unreliable outcome parameter due to the high rate of unsuccessful inoculation and the different appearance of viral load graphs in both the active and placebo groups. Total viral load (*i.e.*, area under the curve (AUC)) for days 3 - 10 in successfully inoculated subjects was found to be a more reliable outcome parameter. A significantly lower total viral load in oropharyngeal samples was seen in the ColdZyme group (median of 3.87 log copies/mL) compared to the placebo group (11.8 log copies/mL; $p = 0.023$) as shown in Figure 3.

3.2. Secondary Outcome

The objective was to evaluate the effect of ColdZyme on the reduction in the number of days with a symptomatic cold in subjects who experienced a symptomatic cold. The ColdZyme group experienced a significantly shorter duration of the period with manifested common cold symptoms (having a total symptom score > 5), with a median of 3.0 days compared to 6.5 days in the placebo group ($p = 0.014$, see Figure 4).

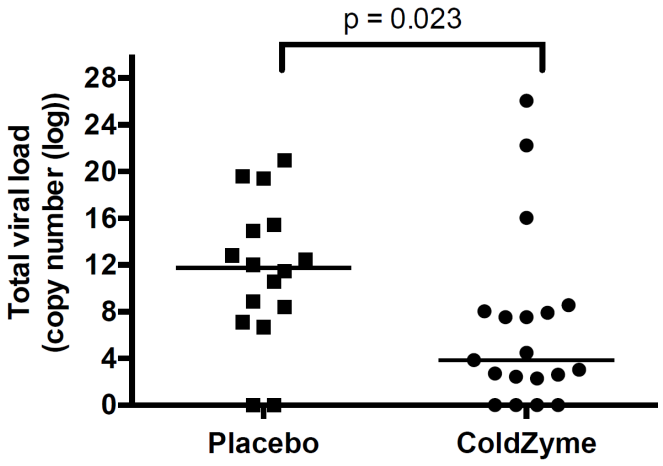

Figure 3. Total oropharyngeal viral load. The total viral load in oropharyngeal samples was determined as the area under the curve for the concentration of virus on days 3 to 10.

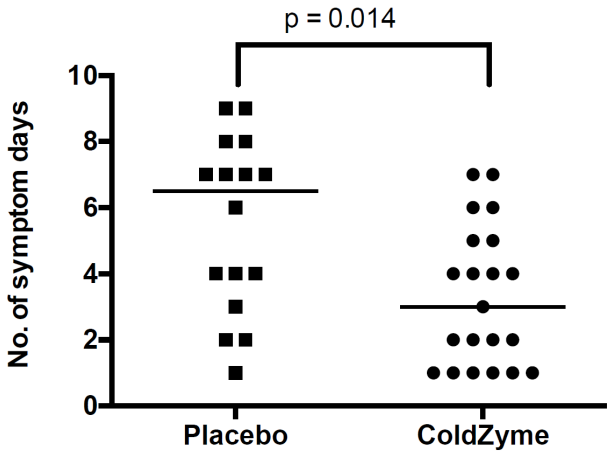

Figure 4. Number of days with common cold symptoms. The median number of days was 3.0 days with common cold symptoms for ColdZyme and for placebo 6.5 days.

3.3. Adverse Events

There were 11 adverse events reported by 7 subjects. In the ColdZyme group, 3 (13%) subjects reported at least one adverse event: menstrual pain, herpes simplex on lip and urticaria. The corresponding number for the placebo group was 4 (17%) subjects who reported at least one adverse event: fever (2 subjects), swollen uvula, urinary infection and heartburn. None of the events were reported as severe; 6 were reported as mild and 5 were reported as moderate. None of the above adverse events were considered to be connected to the study treatment. All adverse events were resolved by the end of the study period and no special treatments were necessary. No device-related adverse events were reported.

4. Discussion

This was the first randomized, double-blind study to test ColdZyme, a glycerol and cod trypsin based mouth spray, against common cold in an experimental rhinovirus challenge model where healthy volunteers were infected via nasal inoculation. Previous experience using experimental models for the evaluation of conventional antiviral therapies and treatments for symptoms of the common cold has demonstrated that experimental models accurately predict the effectiveness of treatments in a natural setting [10]. Rhinovirus was inoculated in the nasal cavity and ColdZyme or placebo was administered via the oral cavity using a mouth spray device. In this study, we chose to separate the inoculation site from the treatment site to increase the probability of infection and to inoculate subjects using a low dose of rhinovirus to resemble a natural common cold infection. It was estimated that the viral titers should peak after approximately 3 days.

In this study, viral load was defined as the quantitative measurement of virus by RT-qPCR. The viral load is a direct manifestation of the infection: the more cells that are infected, the higher the viral load, and the viral load is of importance as there is a dose-response function between exposed rhinovirus dose and

the probability of infection [11]. The pre-defined primary endpoint (peak viral load) was concluded to be unreliable, whereas total viral load during infection, measured as the area under the curve, appeared to be a better outcome measure. Further, quantification of viral load by RT-qPCR surprisingly showed that only 35 subjects out of 46 had detectable levels of virus in either oropharyngeal or nasal lavage samples at any time in the study and were thus confirmed to be infected. These findings should provide guidance for better study design in future studies on experimentally induced common cold.

It is known that viruses replicate in nasal epithelial cells and that a proportion of those viruses that do not infect new nasal epithelial cells are transported by the mucociliary transport mechanism [12], to the oropharynx. In the group of subjects using ColdZyme, the infection of oropharyngeal epithelial cells was largely prevented, which is evident from the fact that oropharyngeal viral load was significantly lower (by a factor of 10^8) in the ColdZyme group compared to the placebo group. In conclusion, it appears that ColdZyme had a significant protective effect towards rhinovirus infection of cells in the applied area (*i.e.*, the oropharynx) despite subjects simultaneously having significant viral shedding in the nasal cavity. In subjects who experienced a symptomatic cold, the ColdZyme group also experienced a significantly shorter duration of the period with manifested common cold symptoms (from 6.5 to 3.0 days) in comparison to placebo. Targeting the oropharynx instead of the nasal cavity may reduce the viral load without compromising the host immune response towards common cold viruses. Rhinoviruses not only are the major cause of the common cold but also trigger acute exacerbations in asthma [13]. Rhinoviruses and other common cold viruses also play an important role in lower airway infections (e.g., bronchiolitis and pneumonia) [14] [15] [16]. We suggest that depositing a glycerol and cod trypsin-based barrier to the oropharynx using a mouth spray device such as ColdZyme may act to enhance the oropharyngeal mucosal barrier, which aids in host defense and protects against disease progression.

5. Conclusion

The present pilot study assessed the treatment of common cold by topical application of ColdZyme, a glycerol and cod trypsin-based barrier, to the oropharyngeal area in subjects inoculated with rhinovirus and highlights the possible importance of the oropharynx in common cold pathogenesis. ColdZyme reduced virus infection in the oropharynx and reduced the number of days with common cold symptoms from 6.5 to 3.0 days. Observations in this pilot study also provide information for the design of future studies on ColdZyme against common cold in experimental rhinovirus models.

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