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Rhinology

Effects of creating a non-specific, virus-hostile environment in the nasopharynx on symptoms and duration of Common Cold

Effetti di un ambiente inibente non virus-specifico nel rinofaringe sui sintomi e la durata del raffreddore comune

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SUMMARY

The Common Cold remains the most frequent symptomatic viral infection in man. Current best therapies are all symptomatic. New pharmacological therapies are likely to be prescription-bound, and as most Common Cold infections are successfully treated without the intervention of a Physician, there is a need for effective non-prescription therapy options. Aim of this study is to propose a new type of approach, based on the concept of making a hostile biological environment for virus survival and spreading at the point of infection, the nasopharynx. The hypothesis was advanced that infections could be controlled using a physical biological approach to create an environment at the point of infection, that is inhibitory to the survival, and persistence of infecting virus, and of viruses newly released from infected mucosal epithelial cells. A nasal irrigation spray, designed to deliver a low pH gel to the nasal cavity, was developed and tested in this study. The study was a randomised, parallel, double-blind, placebo-controlled evaluation of three formulations of irrigation nasal spray in 441 subjects. The objective was to test whether the formulations reduced Cold severity and Cold duration compared to a placebo nasal spray. Subjects were recruited, and supplied with the product when healthy, and were instructed to begin treating and recording symptom severity once they experienced the "first signs" of a Common Cold. To qualify, subjects had to volunteer that they had at least one of the symptoms: sore/scratchy throat, runny nose or congested nose. The product was used 4 times daily, with at least 4 hours separating each dose, for a maximum of 7 days. Efficacy was assessed by an Interactive Voice Recall System whereby subjects were required to contact the investigation site, by telephone, twice daily when they were asked to assess the severity of their symptoms using a four point ordinal scale where 0 = "absent", and 3 = "severe". The symptoms assessed were sore throat, runny nose, blocked nose, cough and tired/run-down feeling. Two formulations demonstrated significant effects. A hydroxy methyl propyl cellulose based formulation reduced symptom severity compared with placebo by 17% and a Poloxamer based formulation reduced severity by 21%. Duration of illness was reduced with a hydroxy methyl propyl cellulose based formulation by 1.5 days to 2.4 days (according to the dose) and by a Poloxamer based formulation by 2.5 days. Results of this study suggest that the creation of a non virus-specific, inhibitory environment in the nasopharynx holds promise as an effective method of controlling the severity and duration of the Common Cold.

KEY WORDS: Nose • Common cold • Therapy

RIASSUNTO

Il raffreddore comune è la più frequente infezione virale dell'uomo. Tutte le terapie, anche le più recenti, sono sintomatiche. Le nuove terapie farmacologiche sono generalmente legate a prescrizione medica ma, poiché la maggior parte dei pazienti affetti da raffreddore comune non ricorrono all'intervento del medico, vi è necessità di efficaci opzioni terapeutiche non soggette all'obbligatorietà di prescrizione medica. Nel presente studio proponiamo un approccio innovativo basato sulla possibilità di rendere il sito d'infezione, il rinofaringe, ambiente biologico ostile per la sopravvivenza e la diffusione del virus. Abbiamo ipotizzato che le infezioni possano essere prevenute utilizzando un approccio fisico-biologico atto a creare, nel sito d'infezione, condizioni in grado di inibire la sopravvivenza e la persistenza del virus infettante e dei virus rilasciati dalle cellule epiteliali infettate. Per il presente studio è stato sviluppato e testato uno spray per irrigazioni nasali, in grado di rilasciare un gel a basso pH. Lo studio randomizzato in doppio cieco verso placebo ha valutato in parallelo tre formulazioni per spray nasale in 441 soggetti con l'obiettivo di valutare se tali formulazioni erano in grado di ridurre la severità e la durata del raffreddore rispetto ad uno spray placebo. Ai soggetti reclutati, tutti volontari, il prodotto è stato fornito quando ancora privi di sintomi istruendoli ad iniziare il trattamento non appena avessero riconosciuto i primi segni di un incipiente raffreddore; essi dovevano percepire almeno uno dei seguenti sintomi: bruciore o prurito in gola/naso chiuso o secrezione nasale siero-mucosa. Il prodotto è stato somministrato quattro volte al giorno con almeno 4 ore d'intervallo fra una somministrazione e l'altra per 7 giorni. L'efficacia è stata valutata per mezzo di un Sistema Interattivo di chiamata vocale (IVRS) secondo il quale ai soggetti è stato richiesto di contattare per telefono il centro di riferimento due volte al giorno e riferire la severità dei sintomi in base ad un punteggio da 0 a 3 dove 0 corrispondeva ad "assenza del sintomo" e 3 a "sintomo severo". I sintomi valutati sono stati: bruciore di gola,

secrezione nasale siero-mucosa, ostruzione nasale, tosse e sensazione di prostrazione. Due formulazioni hanno dimostrato efficacia significativa. La formulazione a base di idrossi-metil-propil cellulosa ha ridotto la severità dei sintomi nei confronti della formulazione placebo del 17%, la formulazione a base di Poloxamer del 21%. La durata della malattia si è ridotta con la formulazione a base di idrossi-metil-propil cellulosa di 1,5 e 2,4 giorni (in base al dosaggio utilizzato) e di 2,5 giorni con la formulazione a base di Poloxamer. I risultati del presente studio suggeriscono che il favorire un ambiente inibente non virus specifico nel rinofaringe si presenta come un efficace e promettente metodo per ridurre la severità e la durata del raffreddore comune.

PAROLE CHIAVE: *Naso • Raffreddore comune • Terapia*

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Introduction

Upper Respiratory Tract Infections (URTIs) of viral aetiology, commonly described as "Common Cold" and "Flu", remain the most common of human illnesses [1 2]. The rate of symptomatic infection is estimated to be 2-5 per person, per year, with school-age children suffering between 7-10 symptomatic infections per year [3]. As such, URTIs represent a considerable morbidity and economic burden to society. In the United States alone, it is estimated that $ 25 billion is lost due to the Common Cold (excluding influenza-related URTIs), of which $ 16 billion is on-the-job productivity loss, $ 8 billion is due to absenteeism and $ 230 million due to caregiver absenteeism [4].

Several virus classes are recognised as responsible for the Common Cold. It has been estimated that the Rhinoviruses cause 30-50%, Corona viruses 10-15% and Respiratory Syncytical Virus, Parainfluenza and Adenovirus each causing approximately 5% of symptomatic infections [5].

There is no effective prevention or treatment option available to patients for the infection/illness itself. All current best therapies are symptomatic, addressing particular symptoms or groups of symptoms. Developmental drugs such as the anti-picornaviral, Pleconaril [6] and the anti I-CAM agent, Tremacamra [7] show promise in reducing symptom load and the duration of illness, but will likely be available only as prescription medications. As most patients suffering from uncomplicated Common Cold do not consult a Physician but rely on self-medication, there remains a place in the armamentarium for an effective non-prescription therapy option.

Recently, it has been suggested that "Given the multiagent nature of the causes of the common cold, future research efforts should focus on non virus-specific compounds" [8]. Following this innovative idea, we proposed, in this study, a new type of approach, based on the concept of creating a hostile biological environment for virus survival and spreading, at the point of infection, the nasopharynx [9].

This environment was achieved by means of a nasal irrigation spray that created a temporary lowering of nasal pH to inactivate virus, trapped virions by means of a gel allowing natural disposal via the mucociliary clearance system, and, in addition, encouraged physical removal of virus by flushing of the nasal cavity by inducing a transient rhinorrhoeal effect in the nose [10].

It was hypothesised that, when used at the first symptoms/signs of a symptomatic Cold, this simple device would lead to a reduction in symptom severity and in duration of infection.

Methods

Formulations

The primary comparison in this study was between placebo and two distinct formulations of the nasal irrigation spray: an early prototype formulation, based on carbopol 980 at 1% w/w (Formulation M), which had shown efficacy in Induced Colds studies, and a test formulation based on hydroxy propyl methyl cellulose at 1% w/w (Formulation HPMC). All were buffered to pH 3.5 with L-pyroglutamic acid, succinic acid and disodium succinate. Formulation HPMC was tested at two different spray volumes: 100 μL (designated HPMC 100) and 130 μL (designated HPMC 130). Furthermore, an additional formulation, approved for human testing and based on a Poloxamer gel agent (designated Formulation P), was also included in this study.

The placebo formulation was a physiological saline spray containing the same mixture of sensate ingredients as the test formulations. A small pre-study test provided no evidence that the placebo formulation was more likely to be perceived as a placebo than the test formulations.

Test formulations were prepared by Procter & Gamble, Health Sciences Institute, Rusham Park, Egham, Surrey, UK.

Study design

The study was a randomised, parallel, double-blind, placebo-controlled trial conducted at 12 centres in the United States in the period January-March 2003. The study was managed by a Research Agency (Delve,1355 North Highway Drive, Fenton, St. Louis County, MO 63099, USA).

The study recruited healthy subjects, provided them with medication ahead of an anticipated natural Common Cold infection period and requested them to begin treatment when they first experienced signs/symptoms of a Common Cold. Qualification for the study required subjects to be healthy males and females between the ages of 18 and 65 years. Subjects were excluded if they were experiencing any of the symptoms of a Common Cold at the time of recruitment. Females who were pregnant, trying to become pregnant, or nursing were also excluded. Additionally, subjects were excluded if they reported any of the following: a history of hypersensitivity to zinc or any component of the nasal test formulations, currently suffering from a chronic medical condition requiring medication, taking any medication, with the exception of birth control pills and hormone replacement products, on a regular basis (3 or more times per week), frequent infections in the nose, lung or ear, problems related to upper or lower respiratory tract (e.g. nose bleeds, breathing difficulties or throat sensitivity), a history of frequent head-

aches/migraine, having been exposed to any investigational drug within 1 month prior to the start of the study, or if the subject planed to participate in any other investigational drug study while in this trial, was currently suffering, or was prone to experiencing, the symptoms of respiratory allergy (rhinitis), was currently using decongestants, oral antihistamines or oral zinc products, or had experienced problems using nasal sprays. Full Informed Consent was obtained from all participants at the time of enrolment into the study.

Equal numbers of qualified subjects were randomised to receive either Formulation M dosed at 100 μL per spray, Formulation HPMC dosed at 100 μL per spray, Formulation HPMC dosed at 130 μL per spray, Formulation P dosed at 100μL per spray or placebo dosed at 100 μL per spray. Subje cts were supplied with their assigned study product and sent home with instructions to call into an Interactive Voice Recall System (IVRS) when they experienced the first signs of a Cold.

Subjects were prompted to enter the severity of their Cold symptoms and whether or not their Cold was bothersome when they called into the IVRS for the first time. Those who reported the presence of either, a sore/scratchy throat, runny nose, or congested nose were then instructed to immediately take their first dose of the test product.

Subjects dosed with their study product 4 times per day for a period of 7 days, leaving a minimum of 4 hours between doses. Each dose consisted of a single spray in each nostril. Subjects called into the IVRS to record the severity of their Cold symptoms and whether or not their Cold was bothersome twice per day (at 09.00 and 21.00) for a period of 14 days. Subjects rated the severity of their symptoms (sore throat, runny nose, blocked nose, cough and tired/run down feeling) using a 4 point scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe).

Efficacy Endpoints

Time to Resolution of Symptoms was the number of days from the first call into the IVRS (prior to the first dose) to the first of four consecutive calls where all symptoms were entered as absent.

Time to Alleviation of Symptoms and No Rhinorrhoea was the number of days from the first call into the IVRS (prior to the first dose) to the first of four consecutive calls where rhinorrhoea was entered as absent and all other symptoms were entered as either mild or absent.

Time to Alleviation of Symptoms was the number of days from the first call into the IVRS (prior to the first dose) to the first of four consecutive calls where all symptoms were entered as either mild or absent.

Time to Response of No to Bothersome Cold Question was the number of days from the first call into the IVRS (prior to the first dose) to the first of four consecutive calls where the Cold was entered as not bothersome.

In addition, a single modification of *Time to Resolution of Symptoms* was analysed on the basis that all symptoms absent for four consecutive calls was considered to be an overly stringent criterion for signalling the resolution of a Cold. *Modified Time to Resolution of Symptoms* was the number of days from the first call into the IVRS (prior to the first dose) to the first of four consecutive calls where either: 1) all symptoms were entered as absent or, 2) one symptom was entered as mild and all others as absent.

Cold Severity for the 7 Days of Dosing was the mean of: 1) average of total symptom severity scores for the 09.00 calls into the IVRS across the 7 days of dosing, and 2) average of the total symptom severity score for the 21.00 calls into the IVRS across the 7 days of dosing. The Total Symptom Severity Score (TSSS) was calculated for each call into the IVRS by summing the severity scores across all symptoms.

Statistical Methods

Test formulations were compared to placebo for each duration and severity parameter. For *Cold Severity for the 7 Days of Dosing,* these comparisons were made using the Wilcoxon Rank Sum test. The Logrank test was used to make these comparisons for each of the duration parameters. Treatment differences were expressed as means for Cold Severity for the 7 Days of Dosing and medians for the duration parameters (pooled from the Kaplan Meier estimates of the survivor functions). Due to the exploratory nature of this study, all comparisons were made on a one-sided basis at a type I error rate of 10%.

Results

Subject Populations Analysed

One thousand subjects were randomized to study product (200 subjects per group). Four hundred and forty one (441) experienced the first signs of a Cold, qualified to begin dosing, and took at least 1 dose of their study product (85 on placebo, 82 on Formulation M, 86 on Formulation HPMC 100, 91 on Formulation HPMC 130, and 97 on Formulation P). Of these subjects, 7% were excluded from the analyses of the duration parameters, and 32% were excluded from the analysis of *Cold Severity for the 7 Days of Dosing*. The percents of excluded subjects were generally equally distributed across the treatment groups. The majority of exclusions from analysis of *Cold Severity for the 7 Days of Dosing* were due to consecutive missing data.

Demographic and Baseline Characteristics

Treatment groups were well balanced in terms of age with averages of the treatment groups ranging from 39 to 42 years and an overall average age of 41 years (range 18-65 years). Approximately 75% of subjects entering the study were female, with only a slight variation between treatment groups (ranging from 71% for Formulation HPMC 130 to 78% for Formulation P). The excess of female subjects is a common finding in studies recruiting for Common Cold from the general population and is not expected to influence the results, particularly as they are balanced between the two treatment groups.

Baseline symptom severity scores were well balanced across treatment groups with individual symptom severity scores averaged across all treatment groups ranging from 0.8 to 1.4 (i.e., mild symptoms). Cough was generally less severe than other symptoms at baseline (0.8), whilst tired/run down feeling scored highest on average (1.4).

Overall, 77% of subjects entering the study reported their Cold as bothersome at baseline. There was some variation between treatment groups (ranging from 67% for Formulation P to 87% for the placebo group).

Cold Severity for the 7 Days of Dosing

All test formulations exhibited directionally lower mean responses *vs.* placebo for *Cold Severity for the 7 Days of Dosing* (Table I). Statistically significant reductions related to placebo were observed for Formulation P (0.18 units; p = 0.0077) and Formulation HPMC 130 (0.14 units; p = 0.0224).

Cold Duration

Formulations P and HPMC 130 exhibited directionally lower responses *vs.* placebo for all five measures of Cold duration. Formulations HPMC 100 and M exhibited directionally lower responses *vs.* placebo for three of the five measures (Table II). Statistically significant reductions were observed for Formulation P for *Time to Resolution of Symptoms* (2.2 days; p = 0.0881), *Modified Time to Resolution of Symptoms* (2.5 days; p = 0.0757), and *Time to Alleviation of Symptoms and No Rhinorrhoea* (1.5 days; p = 0.0945). Statistically significant reductions were also observed for Formulation HPMC 100 (1.5 days; p = 0.0388) and Formulation HPMC 130 (2.4 days; p = 0.0171) for *Modified Time to Resolution of Symptoms*.

Table I. Cold severity for the 7 days of dosing.

Treatment	Mean (SD)	p[a]
Placebo	0.84 (0.47)	
Formulation P	0.66 (0.42)	0.0077
HPMC 100	0.78 (0.38)	0.2577
HPMC 130	0.70 (0.47)	0.0224
Formulation M	0.80 (0.48)	0.3109

[a] One-sided p value for comparison *vs.* placebo.

Discussion

The basic aim of this study was to investigate a new therapeutic approach to the treatment of Common Cold, achieved by creating an intranasal environment hostile to virus survival and spreading, thus affecting the severity and duration of naturally acquired, symptomatic Common Cold infections. The proposed approach was to control the natural process of virus infection and spread by using nasal irrigation sprays, able to trap, inactivate at low pH and flush infectious viruses. *In vitro* data on a series of formulations using this approach indicated that each of these methods individually, was capable of reducing virus infectivity in cultured cells [10]. On the basis of these findings, it was hypothesised that the combination of these physical, non-specific activities would

Table II. Cold duration parameters.

Cold duration parameter	Treatment	Median[a]	p[b]
Time to resolution of symptoms	Placebo	10.1	
	Formulation P	7.9	0.0881
	HPMC 100	8.5	0.2508
	HPMC 130	9.4	0.3290
	Formulation M	9.7	0.3067
Modified	Placebo	7.8	
time to resolution of symptoms	Formulation P	5.3	0.0757
	HPMC 100	6.3	0.0388
	HPMC 130	5.3	0.0171
	Formulation M	7.2	0.1496
Time to alleviation of symptoms	Placebo	2.9	
	Formulation P	2.7	0.2989
	HPMC 100	3.3	0.5629
	HPMC 130	2.7	0.2266
	Formulation M	3.4	0.5439
Time to alleviation of symptoms	Placebo	6.3	
and no rhinorrhoea	Formulation P	4.8	0.0945
	HPMC 100	5.3	0.3160
	HPMC 130	5.2	0.2985
	Formulation M	5.7	0.1651
Time to response of "No"	Placebo	4.1	
to bothersome cold question	Formulation P	3.4	0.3280
	HPMC 100	4.4	0.7503
	HPMC 130	3.8	0.6838
	Formulation M	4.2	0.6610

[a] Median from Kaplan-Meier curve; [b] One-sided p value for comparison vs. placebo.

have a clinically useful, inhibitory effect on naturally acquired, symptomatic infection.

The efficacy of this approach is believed to be dependent upon initiating treatment at a very early stage of the infection process, ideally as close as possible to the time when virus replication begins. Maximum efficacy is expected when the spray is used from the first symptoms of a Cold, for example mild sore throat or congested nose. The products tested here are not expected to have any intra-cellular activity. Efficacy is achieved by entirely topical, extra-cellular mechanisms. It is proposed that creating a hostile, extra-cellular environment in the nasal passages and at the nasopharynx inactivates virus released from infected cells, thus preventing re-infection and progression of the illness.

Previous pilot studies with induced Colds, indicated that the concept of treating URTIs with a product that intervenes in the early stages of illness was acceptable to patients and that the formulations had the potential for measurable efficacy. The concept of early intervention, rather than prevention (using when healthy to avoid infection) or treatment (use of a product when illness is established) is to the knowledge of the Authors, a new approach to non-prescription Common Cold therapy. It relies on the fact that most patients can easily recognise the very early signs of illness and to treat them as they begin to get ill in the expectation of reducing overall morbidity.

Our findings support the efficacy of this new approach in the treatment of the Common Cold and also indicate that formulations with different gel agents can give different results. The comparison between the two formulations based on carbopol and HPMC showed that HPMC gave better results. The further comparison between the amount of spray delivered to the nose indicated that, while 100 μl was effective, a larger volume improved the final clinical result. The last finding was that the new formulation (Formulation P) may further improve efficacy of this approach to treatment of Common Cold.

To summarise, the results of this study suggest that the creation of a non virus-specific inhibitory environment in the nasopharynx holds promise as an effective method of controlling the severity and duration of naturally acquired Common Cold infections. This technology is a promising addition to the armamentarium of Common Cold therapies.

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