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Stability of cough reflex sensitivity during viral upper respiratory tract infection (common cold)☆

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ABSTRACT

Cough is among the symptoms most commonly associated with an acute, viral upper respiratory tract infection (URI), such as the common cold. Two previous studies incorporating capsaicin cough challenge methodology have demonstrated that cough reflex sensitivity is transiently enhanced during URI. These studies used single measurements of cough reflex sensitivity during the URI period. To our knowledge, no previous studies have included multiple measurements of cough reflex sensitivity to capsaicin during a URI to evaluate the stability of this measure during the acute viral illness.

In the current methodological investigation, we performed capsaicin cough challenges in 42 subjects with URI who were otherwise healthy, adult, nonsmokers (25 female). Subjects were enrolled within 72 h of onset of illness and randomly assigned to 3 groups ($n = 14$ each) that underwent cough reflex sensitivity measurement (C_2 and C_5) at days 0 and 1 for group 1; days 2 and 3 for group 2; or days 4 and 5 for group 3. Each subject returned 4–8 weeks post-viral infection to establish a healthy baseline measurement (recovery).

Our results support that cough reflex sensitivity to capsaicin, as measured by C_5, is a sensitive measure that remains stable during 6 days of a URI. These results suggest that cough reflex sensitivity measures in the presence of a URI provide a sensitive and reproducible approach that could be used in future investigations seeking to test experimental antitussive therapies.

1. Introduction

Cough is among the most common symptoms associated with an acute, viral upper respiratory tract infection (URI), otherwise known as the common cold or flu. Traditionally, efficacy of an antitussive therapy has relied on objective cough counting in a natural cold population. However, given the highly variable nature of cough in this context, identification of new treatments of acute cough in the natural setting remains a challenge. Consequently, the search for additional safe and effective therapeutic agents remains an area of active investigation [1,2] as does the search for alternative methods for assessing their activity. In 1996, O'Connell and colleagues demonstrated that cough reflex sensitivity to inhaled capsaicin is transiently increased during URI in otherwise healthy persons, compared to their pre-illness baseline and post-recovery [3]. These observations were recently confirmed in a study of otherwise healthy, adult, non-smokers who underwent capsaicin cough challenge testing during acute URI and 4–8 weeks subsequently (post recovery) [4]. Both of these studies measured cough reflex sensitivity at a single time-point during the acute viral illness. To our knowledge, no one has previously performed multiple measurements of cough reflex sensitivity over the early days of a URI to evaluate the utility of such a model. The goal of this research was to determine if cough reflex sensitivity, as measured by C_2 (concentration of capsaicin inducing 2 or more coughs) and C_5 (concentration of capsaicin inducing 5 or more coughs), remains stable over 6 days of a URI, when subjects were enrolled within the first 3 days of the illness. If cough reflex sensitivity is stable over

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time, this methodology may provide a sensitive and reproducible measure for examining the effect of purported antitussive therapies in the setting of a URI.

2. Methods

2.1. Subjects

Forty-two (42) otherwise healthy, adult, non-smokers developing symptoms consistent with acute viral URI (common cold) were recruited and enrolled within 3 days of symptom onset. An acute URI was defined as an illness of acute onset typical of previous episodes of common cold for that subject, including some, but not necessarily all, of the standard symptoms of cough, sore throat, rhinorrhea, nasal/sinus congestion, and sneezing. Subjects with a history of allergic rhinitis in whom symptoms may not have been attributable to viral URI were excluded. Subjects with symptoms suggestive of possible bacterial infection, such as fever associated with sinus pain and/or purulent nasal discharge were excluded, as were individuals who had taken medication for their illness that could affect cough reflex sensitivity (antihistamines, decongestants, and cough suppressants including dextromethorphan, codeine, hydrocodone). All subjects provided written informed consent for this study, which was approved by the Institutional Review Board of Montefiore Medical Center, Bronx, NY, USA.

2.2. Study protocol

This study was conducted under the Principal Investigator's Investigational New Drug (IND) application for administration of capsaicin in human subjects. Under this protocol, subjects can undergo upto 3 separate capsaicin cough challenge studies. Based on this criterion, subjects could not be studied daily over the entire week of the URI. Instead, upon enrollment (day 0), subjects were randomly assigned to one of three groups, thereby undergoing capsaicin cough challenge testing on day 0 and day 1 (Group 1); day 2 and day 3 (Group 2); or, day 4 and day 5 (Group 3). In addition, all subjects underwent their third capsaicin cough challenge test 4–8 weeks after recovery from their URI.

2.3. Capsaicin cough challenge

Subjects underwent capsaicin cough challenge testing as previously described [5,6]. Briefly, subjects inhaled single, vital-capacity breaths of capsaicin aerosol administered in ascending doubling concentrations (range 0.49 μM–1000 μM) via a compressed air-driven nebulizer controlled by a dosimeter (KoKo DigiDoser, nSpire Health, Louisville, CO, USA), until the concentrations of capsaicin inducing 2 or more (C_2) and 5 or more coughs (C_5) were determined. Only coughs occurring within 15 s of each inhalation were counted. Placebo breaths of physiologic saline aerosol were randomly interspersed to maintain challenge blindness. Subjects were instructed not to suppress cough and were unaware that the induction of a specific number of coughs constituted the end point of the study.

2.4. Statistical analysis

The primary objective of the study was to determine if cough reflex sensitivity is stable over 6 days of an acute, viral URI in subjects enrolled within 3 days of onset of illness. A secondary objective was to evaluate changes in cough reflex sensitivity during acute, viral URI in relation to the healthy (post-recovery) state.

Demographic characteristics of the individual subgroups were evaluated with two-sided *p*-value for comparing groups using the chi-square test statistic for sex and the Kruskal–Wallis test for all other variables (age, number of days ill at time of enrollment, and post-recovery C_2 and C_5 values). A mixed linear model was used to analyze each C_2 and C_5 concentration determined during the illness phase on the base 10 logarithmic scale. The model included fixed effects for group, time, time-by-group interaction, and subject as a random effect. In addition, the corresponding concentration determined during the recovery phase was modeled as a continuous covariate. The above mixed linear model was repeated but instead of analyzing C_2 and C_5 concentration, change from recovery in C_2 and C_5 concentration was modeled as the response.

Sample size was determined based on data from a previous study by the Investigator [7]. Based on these data, the within-subject standard deviation is estimated to be 0.175 for log C_5.

Table 1
Demographics and recovery characteristics descriptive statistics[a].

Characteristic	Descriptive statistic[b]	Group 1[c]	Group 2[c]	Group 3[c]	Two-sided *P*-value[d]
Age	*N*	14	14	12	0.5809
(Years)	Mean (SD)	34.0 (6.9)	32.1 (6.0)	35.7 (7.7)	
	Median	32.0	30.5	36.0	
	Minimum–Maximum	25–50	25–41	25–48	
Sex	*N*	14	14	12	0.5196
	Female	57.1%	71.4%	50.0%	
	Male	42.9%	28.6%	50.0%	
Number of days sick at screening	*N*	14	14	12	0.2056
	Mean (SD)	2.07 (0.83)	1.71 (0.91)	2.33 (0.89)	
	1 Day	28.6%	57.1%	25.0%	
	2 Day	35.7%	14.3%	16.7%	
	3 Day	35.7%	28.6%	58.3%	
Log capsaicin concentration inducing	*N*	14	14	12	0.0718
2 coughs during recovery phase (μM)	Mean (SD)	0.24 (0.32)	0.19 (0.30)	0.53 (0.51)	
	Median	0.30	0.15	0.30	
	Minimum–Maximum	−0.30–0.90	−0.30–0.90	0.00–1.50	
Log capsaicin concentration inducing	*N*	14	14	12	0.0876
5 coughs during recovery phase (μM)	Mean (SD)	0.73 (0.40)	0.73 (0.56)	1.10 (0.43)	
	Median	0.90	0.60	1.05	
	Minimum–Maximum	0.00–1.50	0.00–2.10	0.30–1.80	

[a] Descriptive statistics were used to summarize each capsaicin concentration determined during the recovery phase on the base 10 logarithm scale. All other characteristics were summarized on the original scale.
[b] *N* = number of subjects and SD = standard deviation.
[c] Subjects received challenges on Days 0 and 1 in Group 1, Days 2 and 3 in Group 2, and Days 4 and 5 in Group 3.
[d] Two-sided *p*-value for comparing groups using the chi-square test statistic for sex and the Kruskal–Wallis test for all other variables.

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