



## ANTITUSSIVE EFFECT OF A DIPHENHYDRAMINE-CONTAINING MULTICOMPONENT COUGH SYRUP IN ACUTE VIRAL COUGH

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### INTRODUCTION

Cough is among the most common complaints for which patients seek medical attention. Currently available over-the-counter cough remedies historically have been criticized for lack of scientific evidence supporting their efficacy. Although the first-generation antihistamine diphenhydramine is classified as an antitussive by the US Food and Drug Administration,<sup>1</sup> to the authors' knowledge it has never been shown to inhibit cough reflex sensitivity in subjects with pathological cough.

Capsaicin cough challenge is an established method of measuring cough reflex sensitivity. The test involves inhalation of single, vital-capacity breaths of capsaicin aerosol delivered in ascending, doubling concentrations via a nebulizer controlled by a dosimeter.<sup>2</sup> The standard end point is  $C_5$ , the concentration of capsaicin inducing 5 or more coughs. Studies have shown this end point to be highly reproducible.<sup>2</sup>

Cough reflex sensitivity is transiently enhanced during acute viral upper respiratory tract infection (URI),<sup>3</sup> but remains stable during the first week of URI,<sup>4</sup> thus allowing assessment of the effect of potential antitussives during this period.

### REFERENCES

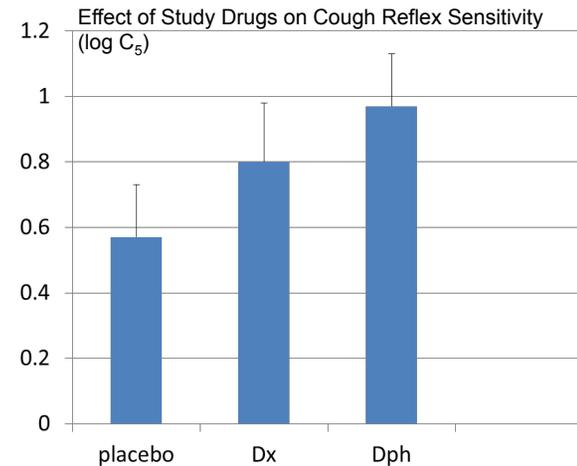
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### METHODS

22 otherwise healthy adult nonsmokers with acute URI (common cold) underwent cough reflex sensitivity measurement employing capsaicin challenge on 3 separate days, 2 hours after ingesting a single dose of study drug (to coincide with peak blood levels) that was administered in a randomized, double-blind manner: a multicomponent syrup containing diphenhydramine (25 mg), phenylephrine (10 mg), in a natural cocoa formulation (Dr. Cocoa, Infirst Healthcare, Inc., USA); dextromethorphan (Dx) (30 mg) syrup; and, placebo syrup. The standard endpoint of cough challenge was used: the concentration of capsaicin inducing  $\geq 5$  coughs ( $C_5$ ).

### RESULTS

Differences in  $\log C_5$  responses were analyzed by 1-way ANOVA for dependent samples combined with Tukey's HSD test for pairwise comparisons. A significant difference ( $p=0.0024$ ) was established among the groups, with pairwise analysis revealing a significant increase in mean  $\log C_5$  ( $0.4 \pm 0.12$ (SEM);  $p < 0.01$ ) for the diphenhydramine-containing medication (Dph), but not for the other groups (see figure).



### DISCUSSION

In the USA, the majority of OTC cough preparations contain dextromethorphan or diphenhydramine as the active component. Significant criticism has been directed at the OTC cough and cold market due to lack of adequately performed clinical trials demonstrating these agents to be effective antitussives. To the authors' knowledge, this is the first demonstration of the ability of diphenhydramine to suppress cough reflex sensitivity in subjects with acute URI. Although both the Dph-containing and Dx formulations suppressed cough reflex sensitivity relative to placebo, only the degree of inhibition attained by Dph achieved statistical significance. Further clinical trials are needed to adequately evaluate this and other OTC cough and cold products, so as to allow physicians and consumers alike to make informed treatment decisions based on proper scientific data.

# Antitussive effect of a diphenhydramine-containing multicomponent cough syrup in acute viral cough

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## Background

Cough is among the most common complaints for which patients seek medical attention. Currently available over-the-counter cough remedies historically have been criticized for lack of scientific evidence supporting their efficacy. Although the first-generation antihistamine diphenhydramine is classified as an antitussive by the US Food and Drug Administration (Fed Regist 1994;59:29172-4), to the authors' knowledge it has never been shown to inhibit cough reflex sensitivity in subjects with pathological cough.

## Methods

22 subjects with acute viral respiratory tract infection (common cold) underwent cough reflex sensitivity measurement employing capsaicin challenge on 3 separate days, 2 hours after ingesting a single dose of study drug (to coincide with peak blood levels) that was administered in a randomized, double-blind manner: a multicomponent syrup containing diphenhydramine (25 mg), phenylephrine (10 mg), in a natural cocoa formulation (Dr. Cocoa, Infirst Healthcare, UK); dextromethorphan (30 mg) syrup; and, placebo syrup. The standard endpoint of cough challenge was used: the concentration of capsaicin inducing  $\geq 5$  coughs (C5).

## Results

Differences in log C5 responses were analyzed by 1-way ANOVA for dependent samples combined with Tukey's HSD test for pairwise comparisons. A significant difference ( $p=0.0024$ ) was established among the groups, with pairwise analysis revealing a significant increase in mean log C5 ( $0.4 \pm 0.12$ (SEM);  $p < 0.01$ ) for the diphenhydramine-containing medication, but not for the other groups.

## Conclusion

Our results provide the initial evidence of the ability of diphenhydramine to inhibit cough reflex sensitivity in subjects with acute pathological cough.