J. Pharm. Pharmacol. 1995, 47: 990–993
Received June 1, 1995
Accepted July 6, 1995

A Clinical Study to Evaluate the Efficacy of the Antihistamine Doxylamine Succinate in the Relief of Runny Nose and Sneezing Associated with Upper Respiratory Tract Infection

R. ECCLES, P. VAN CAUWENBERGE*, W. TETZLOFF† AND P. BORUM‡

*Common Cold and Nasal Research Centre, University of Wales, Cardiff, UK, *Neus, Keel en Oorkliniek, Universitair Ziekenhuis, Gent, Belgium, †IPHAR Institut Fur Klinische Pharmakologie, GmbH, Germany, and ‡Otorhinological Laboratory, Glostrup Hospital, Denmark*

Abstract

Antihistamines are widely used in common cold medications, although the role of histamine in the development of common cold symptoms is unclear and the use of antihistamines for the treatment of common cold is controversial. It is clear that antihistamines do not offer a cure for common cold but they may alleviate symptoms of sneezing and runny nose. The present study was designed to investigate the efficacy of an antihistamine, doxylamine, on the symptoms of runny nose and sneezing associated with common cold.

We conducted a randomized double-blind study in cold sufferers. One thousand and one volunteers with cold symptoms were screened in four centres (UK, Denmark, Belgium, Germany) and 688 satisfied the entry criteria of the study. The main reasons for excluding subjects were a low nasal secretion weight (secretion weight $< 0{\cdot}2$ g, 72%) and a low subjective rhinorrhoea score (24%). Volunteers were randomized to receive either doxylamine succinate 7·5 mg by mouth four times a day up to nine doses ($n = 345$) or placebo ($n = 343$). The principal measurements were prospectively defined as runny nose and sneezing symptom scores. Data were analysed on an intention-to-treat basis, using Cochran-Mantel-Haenszel statistics controlling for baseline symptom scores.

A between-group comparison showed that doxylamine-treated volunteers benefited from a significantly greater reduction in runny nose scores ($P < 0{\cdot}01$) and sneezing scores ($P < 0{\cdot}001$), than those volunteers in the placebo group. Doxylamine therapy was well tolerated; the incidence of unexpected side-effects was comparable with placebo. Of the expected side-effects, 13·3% of doxylamine-treated patients reported drowsiness. The incidence of sedative effects was lower than has been reported for other commonly used first-generation antihistamines.

Infections of the upper respiratory tract are the most common of human diseases. The common cold is a part of our normal life, with most adults having 2–3 symptomatic infections each year and children in their early lives having a much greater incidence with little respite from infection. There are over 200 viruses which infect the upper airway and cause symptoms of common cold, and modern cities with crowded work places and transport systems provide an ideal environment for viral transmission (Sperber 1994).

Although the common cold is usually associated with a relatively mild and acute illness of no great consequence to the majority of patients, common cold is a leading cause of visits to the physician and a primary cause of absenteeism from school or work. The symptoms of common cold include sneezing, runny nose, sore throat, headache, nasal and sinus congestion, and cough. The infection is commonly caused by rhinovirus which infect the upper respiratory tract and give rise to the common cold syndrome. There is current scientific consensus on the futility of attempting a cure by vaccination or other means of combating the virus (Sperber 1994). Instead, symptomatic treatment is recommended as a more practical approach to providing subjective relief during the short course of the infection (Welliver 1990; Grimm 1991).

Correspondence: R. Eccles, Common Cold and Nasal Research Centre, 56 Park Place, University of Wales College of Cardiff, Cardiff CF1 3AT, UK.

Antihistamines are widely used in common cold medications, although the role of histamine in the development of common cold symptoms is unclear and the use of antihistamines for the treatment of common cold is controversial (Fabricant 1950; Welliver 1990; Hendeles 1993). It is clear that antihistamines do not offer a cure for common cold but they may alleviate symptoms of sneezing and runny nose by an anticholinergic action (Woodward 1990). The present study was designed to investigate the efficacy of an antihistamine, doxylamine, on the symptoms of runny nose and sneezing associated with common cold. A preliminary communication of this study was made to the American Thoracic Society (Borum et al 1994).

Materials and Methods

Study procedure

The study was a multicentre randomized, double-blind, parallel-group design with sites in the United Kingdom, Germany, Denmark and Belgium. Otherwise healthy

patients with runny nose associated with a history of common cold of less than 72 h were recruited by local advertisement at each centre. Patients with a history of perennial allergic rhinitis or an acute exacerbation of seasonal allergic rhinitis or any systemic disease which may have compromised respiratory function were excluded from the study.

To establish that the patients were suffering from rhinorrhoea associated with common cold, patients were screened using a subjective symptom score and by weighing expelled nasal secretions.

As part of the entry criteria for the study, patients were asked to score symptoms of sneezing, runny nose, blocked nose, sore throat, cough and headache on a five-point box scale with symptoms labelled: 0 = not present, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. To enter the trial, patients had to score 2 or greater for runny nose and 1 or greater for at least one other cold symptom.

To obtain an objective measure of nasal secretions patients were first asked to clear their nose by blowing into a paper handkerchief and then to refrain from sniffing or clearing their nose for 15 min. Patients were then asked to blow their nasal secretions into a preweighed paper handkerchief which was then weighed on an electronic balance. To enter the study patients had to provide a minimum weight of 0·2 g nasal secretion.

After satisfying the subjective and objective entry criteria for assessment of common cold symptoms, patients were randomly allocated treatment with either doxylamine succinate (7·5 mg/10 mL syrup) at a dose of 7·5 mg, four times a day or an identical placebo syrup vehicle. Patients were asked to take a single dose of their medication at 2030 h on day one, and at 0830, 1230, 1630 and 2030 h on days two and three. Patients were asked to score symptoms of runny nose and sneezing in a diary, using the five-point box scale described above, 90 min after taking the second and fourth doses of medication (i.e. at 1400 and 2200 h).

The allocation of treatment was stratified: firstly according to the baseline severity of symptoms as rated by the subjective runny nose score; and secondly according to the time since the cold symptoms became apparent to the volunteer (6–48 and 49–72 h).

The study protocol was approved by the local research ethics committee at each site.

Statistical analysis

All patients receiving medication were included in summaries of demographic data, baseline data and all safety data. The variables of principal interest with regard to efficacy were stated in the protocol as the day two median subjective symptom scores for runny nose and sneezing. Between-group comparisons of these variables were made with reference to Cochran-Mantel-Haenszel statistics with adjustments for baseline symptom scores. These statistics were based on modified Ridit scores (Lehman 1975).

Results

The study was run over the period October 1992–March 1993 and a total of 1001 patients was screened for entry, with 688 qualified patients entered onto medication. The main reasons for subject exclusion were low nasal secretion weight (72%) and low subjective runny nose scores (24%). The study population consisted of 359 female and 329 male patients with a mean age of 25 years.

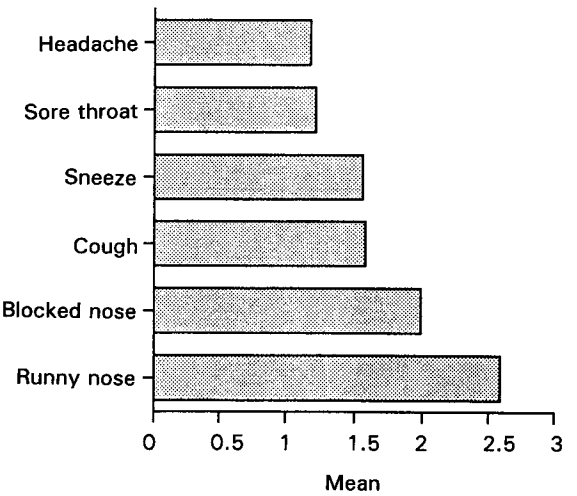

FIG. 1. Mean baseline symptom scores for all volunteers on entry to the study (n = 688). Patients were asked to score symptoms of sneezing, runny nose, blocked nose, sore throat, cough and headache on a five-point box scale with symptoms labelled: 0 = not present, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe.

On entry into the study all patients provided subjective scores for the common cold symptoms on a five-box symptom severity scale. The mean symptom scores for all 688 qualified patients are illustrated in Fig. 1. Since the entry criteria of the study selected patients with runny nose, it is to be expected that this symptom had the highest mean score but it is interesting to note the relative scores for the other symptoms. Symptoms of blocked nose had the next highest mean symptom score followed by cough, sneeze, sore throat and headache.

After fulfilling the entry criteria patients were randomly allocated treatment with vehicle or doxylamine syrup. The two treatment groups were well-balanced with 343 patients allocated to the vehicle group and 345 to the doxylamine group.

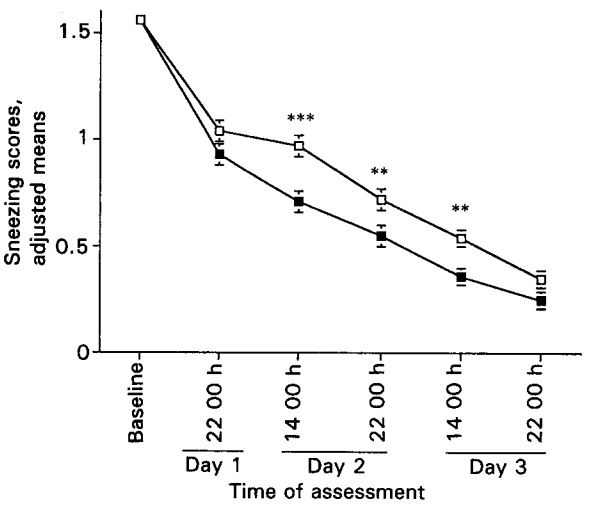

FIG. 2. Mean sneezing scores for patients treated with doxylamine (■, n = 345) and vehicle (□, n = 343). The mean values (± s.e.) represent least-squares means, calculated through controlling for site and baseline. $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$.

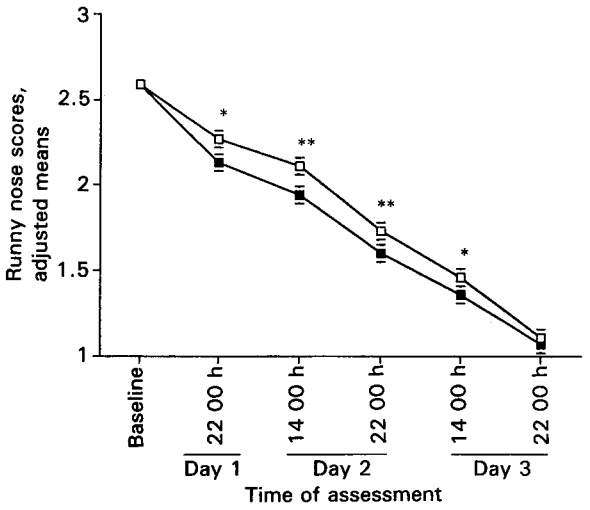

FIG. 3. Mean runny nose scores for patients treated with doxylamine (■, n = 345) and vehicle (□, n = 343). The mean values (± s.e.) represent least-squares means, calculated through controlling for site and baseline. $*P < 0.05$, $**P < 0.01$.

The two groups were well balanced for gender and age and no significant interactive variation between the four recruiting sites was found.

There was a wide variation in the objective measurement of nasal secretions at baseline with a range of 0·2–8·0 g secretion obtained on nose blowing. However, the two treatment groups were well balanced with a mean secretion weight (± s.d.) of 0·78 ± 0·85 g in the vehicle group and 0·88 ± 0·77 g in the doxylamine group.

On entry into the study patients were instructed to score the severity of symptoms of runny nose and sneezing on the evening of the first day after a single dose of medication and then at 1400 and 2200 h each day for the next two days. The changes in symptom scores over the course of the study and between treatment groups are illustrated in Fig. 2 for sneezing scores, and Fig. 3 for runny nose scores. The figures plot the least-squares means for the two symptom scores for ease of illustration, but all the statistical analysis was based on the ordinal nature of the data. The figures show a rapid decline in symptom severity over the course of the study for both sneezing and runny nose symptoms in both the treatment groups. The baseline scores for sneezing and runny nose were adjusted as part of the statistical analysis and it is the differences between the treatment groups after baseline that are relevant in Figs 2 and 3. Fig. 2 illustrates that on both time periods of assessment on day two of treatment and on the first assessment on day three there was a significant difference in symptom scores for sneezing between the two treatment groups. Similarly, Fig. 3 illustrates that there was a significant difference in symptom scores for runny nose between the two treatment groups at four separate time points.

The protocol for this study defined the main outcome variable of interest as the difference between the two treatment groups in day 2 median symptom scores for sneezing and runny nose. The mean day 2 median score for sneezing (hereafter referred to as day 2 symptom score) in the vehicle treatment group was 0·843, which was significantly greater than the day 2 symptom score of 0·627 for the doxylamine-treated group ($P < 0.001$). Similarly, the day 2 symptom score for runny nose in the vehicle treatment group was 1·918, which was significantly greater than the day 2 symptom score of 1·768 for the doxylamine-treated group ($P < 0.01$).

Adverse events

A total of 14 unexpected adverse events were reported from the 688 patients entered on medication, with five in the doxylamine group and nine in the vehicle group. The reported unexpected adverse events consisted of nausea, vomiting, diarrhoea, nose bleed, skin rashes and severe dysmenorrhoea. Three patients withdrew from the study with skin rash, severe dysmenorrhoea and progression of cold or fever. The investigators did not assess causality but it is considered unlikely that these adverse effects were related to treatment with doxylamine or the vehicle control.

A number of patients experienced drowsiness as an expected adverse event; 46 patients (13·3%) given doxylamine and 18 patients (5%) given vehicle reported drowsiness.

Discussion

When antihistamines were first introduced into clinical medicine in the 1940s, their effectiveness on allergic diseases was immediately apparent and claims were also made that they could prevent, cure and abort a common cold infection. These claims were made on the basis that an allergic reaction was responsible for the symptoms of the common cold. The extravagant claims made for antihistamine therapy of the common cold were quickly counteracted by the results of several clinical trials which clearly demonstrated that antihistamines did not prevent, abort or cure an infection (Fabricant 1950). Subsequent clinical trials on the efficacy of antihistamines such as chlorpheniramine in providing relief from the symptoms of common cold have provided conflicting results. This is partly because in many of the trials the statistical analysis was underpowered, especially in those involving rhinovirus challenge where treatment groups were very small (Gaffey et al 1987), and partly because again expectations have been raised that antihistamines are effective against all the symptoms of common cold.

However, it is unreasonable to expect antihistamines to provide relief from all common cold symptoms and the present study focused on the symptoms of runny nose and sneezing, as these symptoms have been previously shown to be susceptible to treatment with antihistamines (Howard et al 1979; Doyle et al 1988). The baseline scores for nasal congestion, sore throat, headache and cough show that these symptoms were also present in many of the patients.

Clinical trials on medications for the symptomatic treatment of acute upper respiratory tract infection are difficult because of the acute nature of the illness and the difficulty in recruiting a sufficient number of qualified patients. The natural course of an upper respiratory tract infection is normally a rapid decline in symptom severity over a period of 2–3 days. The results of this study support this generally accepted natural history, as there was a rapid decline in the scores for sneezing and runny nose in both treatment groups over the three days duration of treatment.

The results of the present study demonstrate that doxylamine is more effective than a control vehicle medication in alleviating the symptoms of runny nose and sneezing associated with common cold. The difference in symptom severity scores between the vehicle- and doxylamine-treated groups for runny nose and sneezing was small and it could be argued that this is not a clinically significant difference despite the highly significant statistical difference between the two treatment groups. However, the patients with common cold symptoms recruited into this study clearly felt there was a difference as the outcome measures for the study were based on subjective scores.

Treatment with doxylamine was well tolerated and the incidence of unexpected side-effects in the doxylamine group was comparable with that observed in the vehicle control group. Of the expected side-effects, the incidence of sedative effects of treatment was lower than has been reported for other commonly used first-generation antihistamines (Fastner 1980).

In summary, in contrast to many other published studies evaluating antihistamines for the symptomatic treatment of upper respiratory tract infection, this study was deliberately designed, statistically powered and focused to test the hypothesis that doxylamine effectively ameliorates symptoms of sneezing and runny nose when used in a standard over-the-counter medicine treatment regimen. The results demonstrate that doxylamine is an effective medication for the treatment of sneezing and runny nose symptoms associated with common cold.

Acknowledgement

We would like to thank Chris Hannigan for conducting the statistical analyses on the trial data.

References

Borum, P., Eccles, R., Tetzloff, W., Van Cauwenberge, P. (1994) Can antihistamines relieve symptoms of common cold? Am. J. Respir. Crit. Care Med. 149: A602

Doyle, W. J., McBride, T. P., Skoner, D. P., Maddern, B. R., Gwaltney, J. M., Uhrin, M. (1988) A double-blind, placebo-controlled clinical trial of the effect of chlorpheniramine on the response of the nasal airway, middle ear and eustachian tube to provocative rhinovirus challenge. Pediatr. Infect. Dis. J. 7: 229–238

Fabricant, N. D. (1950) Critical evaluation of antihistaminic drugs in the common cold. Arch. Otolaryngol. Head Neck Surg. 52: 888–899

Fastner, Z. (1980) Antihistamines. In: Griffin, J. P. (ed.) Meyler's Side Effects of Drugs. Excerpta Medica, Amsterdam, pp 265–268

Gaffey, M. J., Gwaltney, J. M. J., Sastre, A., Dressler, W. E., Sorrentino, J. V., Hayden, F. G. (1987) Intranasally and orally administered antihistamine treatment of experimental rhinovirus colds. Am. Rev. Respir. Dis. 136: 556–560

Grimm, A. M. (1991) Review of the common cold. Am. Druggist 203: 63–72

Hendeles, L. (1993) Efficacy and safety of antihistamines and expectorants in non prescription cough and cold preparations. Pharmacotherapy 13: 154–158

Howard, J. C., Kantner, T. R., Lillenfield, L. S., Princiotto, J. V., Krum, R. E., Crutcher, J. E., Belman, M. A., Danzig, M. R. (1979) Effectiveness of antihistamines in the symptomatic management of the common cold. J. Am. Med. Assoc. 242: 2414–2417

Lehman, E. L. (1975) Nonparametrics: Statistical Methods Based on Ranks. Holden-Day, San Francisco

Sperber, S. J. (1994) The common cold. Infect. Med. 11: 235–242

Welliver, R. C. (1990) The role of antihistamines in upper respiratory tract infections. J. Allergy Clin. Immunol. 86: 633–637

Woodward, J. K. (1990) Pharmacology of antihistamines. J. Allergy Clin. Immunol. 86: 606–612