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Ambroxol for the prevention of acute upper respiratory disease

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Abstract Although acute upper respiratory diseases (AURDs) such as common cold and influenza are common, few interventions have been proven to be effective in their prevention and treatment. The aim of this study was to assess the efficacy of ambroxol for preventing AURD. Fifty-four patients were randomly divided into 3 groups: a rebamipide (non-mucoactive drug) group (300 mg/day), carbocisteine group (1500 mg/day) and ambroxol group (45 mg/day). The study was divided into 2 terms, the first half-year (summer season) and the second half-year (winter season). In the preceding winter, only 19.5% of the patients had been vaccinated against influenza viruses (flu). The primary goal of this study was to evaluate the effectiveness of mucoactive drugs in decreasing the frequency of AURD. Treatment with ambroxol, but not carbocisteine, significantly reduced the median number of AURD episodes (P=0.0049 *vs.* rebamipide). Thirty-three patients without vaccination against flu were assessed especially during the second half-year. Treatment with ambroxol also significantly reduced the median number of AURD episodes in this assessment (P=0.0028 *vs.* rebamipide in the second half-year). In conclusion, ambroxol may be useful for preventing AURD.

Key words Ambroxol • Prevention • Acute upper respiratory disease • Common cold • Influenza

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Introduction

Although acute upper respiratory diseases (AURDs) such as common cold and influenza are common, few interventions have been proven to be effective in preventing them. The risk of infection can be reduced by clearing the bronchial tree [1]. Ambroxol is thought to be useful for this purpose. Clinical studies of this drug have shown that it significantly improves the coughing and sputum production of patients with chronic bronchitis [1, 2]. Mucoactive drugs such as ambroxol and carbocisteine have numerous pharmacological activities that inhibit bronchial secretion, including direct mucoregulatory effects on gland cells and mucociliary clearance, which are responsible for their clinical efficacy. Ambroxol in particular enhances production of pulmonary surfactant [3, 4].

On the basis of these reports, we hypothesised that ambroxol might be useful in preventing AURD by enhancing production of surfactant. The aim of this study was to assess the efficacy of ambroxol in preventing AURD.

Methods

Patient selection

We conducted this study in the mountain village of Kamitaira. There was only one clinic in the village, and only one doctor for

the period of one year. It is difficult for the village's senior citizens to consult other clinics or hospitals, because large towns can only be reached by car. Because of their difficulty consulting other medical facilities, we were able to follow them whenever they suffered AURDs. This study was approved by the local ethics committee of our institution. We were thus able to correctly determine the frequency of AURD in the village during this study period.

Fifty-four patients aged 65 years or older (76.0±7.4) were registered in this study (7 males and 47 females). All of the 7 males had a history of smoking, while none of the 47 females did. They suffered from hypertension, hyperlipidaemia, diabetes mellitus and other related conditions, which were mild and well controlled with medication. The patients were diagnosed as free of respiratory diseases (bronchial asthma, pulmonary emphysema, chronic bronchitis, etc.) based on their clinical histories, symptoms, results of physical examination and chest X-ray examination. Diagnostic criteria for AURD were chest X-ray without abnormal shadows and respiratory symptoms characterised by a rapid increase in rhinorrhoea, coughing or sputum, with fever (>37°C) and with or without dyspnoea or sore throat. The causes of AURD appeared to be viral infections, including those due to influenza viruses (flu). Because allergy is not accompanied by fever, fever was a key criterion in distinguishing AURD from allergy. An influenza quick kit was used for diagnosis of flu. High fever (>38.5°C) was also useful for diagnosing flu during the winter season. Even if the quick kit result was negative, high fever was considered key evidence that a patient had developed flu. Pneumonia was excluded by chest X-ray examination. The criteria for recovery from AURD were complete disappearance of respiratory symptoms and a symptom-free period lasting for more than a few weeks until a new AURD was observed, as it is known that a single AURD episode may last days or weeks with intensity of symptoms ranging from nasal obstruction to severe rhinosinusitis. Recovery of AURD was judged to have occurred when we confirmed the above in the clinic. All patients gave informed consent to participate in this prospective study and were evaluated between 2 April 2001 and 3 March 2002.

Study design

The primary goal of this study was to evaluate the effectiveness of mucoactive drugs in decreasing the number of AURD episodes. The patients were randomly divided into 3 groups: a rebamipide group (non-mucoactive drug), carbocisteine group and ambroxol group. Each group was given the usual dose of oral drug: rebamipide at a dose of 300 mg/day, carbocisteine at 1500 mg/day or ambroxol at 45 mg/day. Drugs were randomly allocated in the run-in period, and patients continued to take the allocated drug for 1 year. The study was divided into 2 terms: the first half-year (summer season: from April to September) and the second half-year (winter season: from October to March). Finally, patients who could continue to receive each drug until the end of the study were evaluated.

Patients were always checked for their condition when they consulted our clinic. When they suffered from AURD, if needed, non-steroidal anti-inflammatory drugs and/or antibiotics were prescribed. All patients visited our clinic at regular intervals even if they did not suffer from AURD, in order to be checked for chronic diseases and conditions (hypertension, hyperlipidaemia, diabetes mellitus, etc). As it was difficult for them to consult other clinics or hospitals because other medical facilities were far from the village, we were able to correctly determine the number of AURD episodes.

In the preceding winter, villagers were advised to receive a flu vaccine, though almost all of the patients did not request it. Only 19.5% of the patients had been vaccinated against flu (Table 1). Whether or not antiviral vaccination was given, test drugs were continued during the period of the study.

Table 1 Characteristics of patients. Data are mean+SD if not otherwise indicated

	Rebamipide	Carbocisteine	Ambroxol	Total
Subjects, *n*	16	13	12	41
Female-male ratio	14:2	11:2	9:3	34:7
Mean age, years	78.0±8.2	75.0±6.3	76.9±6.6	76.7±7.1
Smoking (pack-year)	6.1±16.6	8.3±20.4	15.2±27.4	9.4±21.2
Mean number of common colds during the first half year	1.6±1.1	1.4±1.6	0.2±0.4***#	1.1±1.3
Mean number of common colds during the second half year	1.4±0.6	1.0±1.2	0.6±1.1*	1.0±1.0
Mean number of common colds during the year	3.0±1.2	2.4±2.4	0.8±1.2***#	2.1±1.9
Vaccination against flu ratio (+/–)	2:14	3:10	3:9	8:33
Complications				
Hypertension, *n*	9	9	9	27
Hyperlipidaemia, *n*	4	4	5	13
Diabetes mellitus, *n*	1	1	1	3
FEV1	1.53±0.60	1.59±0.41	1.50±0.24	1.54±0.45
FVC	1.81±0.90	1.88±0.67	1.70±0.27	1.80±0.68
FEV1/FVC	87.2±10.8	86.7±8.7	98.7±9.5	87.4±9.6

Forty-one patients completed the present one-year study: 16 patients with rebamipide, 13 carbocisteine and 12 ambroxol. The treatment with ambroxol significantly reduced the probability of catching a common cold (P=0.0012 *vs.* rebamipide). No significant differences were found in all data except the number of common colds between ambroxol, carbocisteine and rebamipide groups. 19.5% of the patients who completed the study received vaccination against the influenza virus (flu) before the winter season in the study period.
*P<0.05, ***P<0.005 *vs*. rebamipide group, #P<0.05 *vs*. carbocisteine group.

Statistical analysis

Analysis was performed with the Kruskal-Wallis non-parametric analysis of variance (ANOVA) with comparison of the median. All data were presented as median values. *P* values of 0.05 or less were considered significant.

Results

Of the 54 patients included in this trial (17 given ambroxol, 17 carbocisteine and 20 rebamipide), 41 completed this one-year trial (12 patients with ambroxol, 13 with carbocisteine and 16 with rebamipide). Numbers of AURD episodes are shown in Table 1 and Figure 1. The median number of AURD episodes was 3.0 (range: 2–6) in the rebamipide group, 2.0 (range: 0–9) in the carbocisteine group and 0.0 (range: 0–3) in the ambroxol group during the one-year study period (Fig. 1). Treatment with ambroxol significantly reduced the median number of episodes (*P*=0.0049 *vs.* rebamipide). In Figure 1, results are shown separately for the first half-year and second half-year. The median number of AURD episodes during the first half-year was 2.0 (range: 0–4) in the rebamipide group, 1.0 (range: 0–5) in the carbocisteine group and 0.0 (range: 0–1) in the ambroxol group. Median numbers during the second half-year were 1.0 (range: 0–2) in the rebamipide group, 1.0 (range: 0–4) in the carbocisteine group and 0.0 (range: 0–3) in the ambroxol group. Treatment with ambroxol significantly reduced the median number of episodes compared with rebamipide in both the first half-year and the entire one-year period (*P*=0.0081; 0.0049), and compared with carbocisteine during the first half-year (*P*=0.0408).

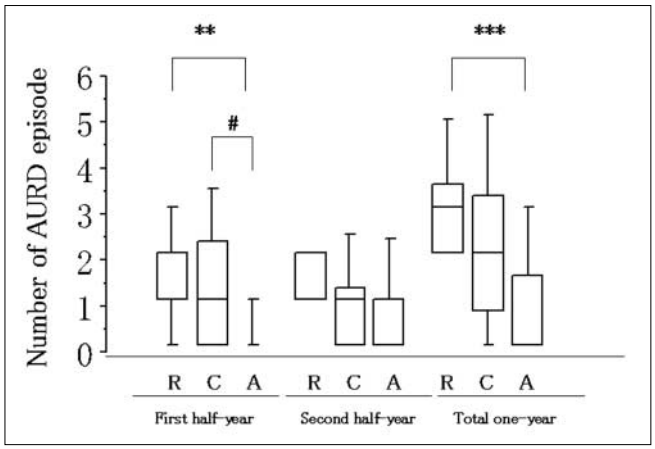

Fig. 1 Effect of long-term treatment with rebamipide, carbocisteine and ambroxol on the number of acute upper respiratory disease (AURD) events during the first and second half-years. The median number of AURD episodes during the first half-year was 2.0 in the rebamipide group (*R*), 1.0 in the carbocisteine group (*C*) and 0.0 in the ambroxol group (*A*). The median number of AURD episodes during the second half-year was 1.0 in the rebamipide group (*R*), 1.0 in the carbocisteine group (*C*) and 0.0 in the ambroxol group (*A*). Treatment with ambroxol significantly reduced the median number of AURD episodes compared with rebamipide in both the first half-year and the entire one-year period, and compared with carbocisteine during the first half-year. $^{**}P<0.01$; $^{***}P<0.005$ *vs.* rebamipide group; $^{\#}P<0.05$ *vs.* carbocisteine group

To exclude possible effects of vaccination against flu, 33 patients without vaccination against flu were re-assessed (9 given ambroxol, 10 carbocisteine and 14 rebamipide). The median number of AURD episodes during the one-year study period was 3.0 (range: 2–7) in the rebamipide group, 2.0 (range: 0–9) in the carbocisteine group and 0.0 (range: 0–4) in the ambroxol group. The median number was significantly less in the ambroxol group than in the rebamipide group (*P*=0.0017) and the carbocisteine group (*P*=0.0308). The median number of AURD episodes in the second half-year was also significantly (*P*=0.0028) smaller in the ambroxol group (median: 0.0) than in the rebamipide group (median: 1.5).

As noted above, all of the male patients had a history of smoking (mean Brinkmann Index: 1105.7±126.3). For males, no correlation was found between Brinkmann Index and number of AURD episodes.

No patients in the study developed pneumonia or severe bronchitis during the study period. No adverse effects of treatment were observed in any of the patients who completed the study, though some of the patients who dropped out of the study experienced side effects, as shown in Table 2 (6 patients). Seven patients who dropped out of the study did not have physical side effects, but wished to discontinue taking drugs because of problems paying for them. Altogether, side effects were noted in

Table 2 Patients withdrawn from the study

	Rebamipide	Carbocisteine	Ambroxol	Total
Subjects, *n*	2	2	2	6
Constipation, *n*	2	0	0	2
Diarrhoea, *n*	0	1	1	2
Nausea, *n*	0	1	1	2

Adverse effects were not recognised in the patients who completed the study, but patients who had some side effects dropped out from the study. The total prevalence of side effects was noticed in 10.0% in the rebamipide group, 11.8% in the carbocisteine group and 11.8% in the ambroxol group. All of the side effects were slight and subsided immediately after stopping the administration of each test drug.

10.0% of patients in the rebamipide group, 11.8% of those in the carbocisteine group and 11.8% of those in the ambroxol group. All of the side effects were mild, and disappeared after drug use was discontinued. Many of the patients who suffered no episodes of AURD experienced no severe side effects during the study period.

Discussion

Rebamipide is a non-mucoactive agent that increases mucin secretion in the stomach and eyes [5], suggesting that it may have similar effects in the airways. However, we found that ambroxol prevented AURD more strongly than rebamipide did. To our knowledge, this is the first study to demonstrate a preventive effect of long-term ambroxol therapy against AURD in elderly patients without respiratory disease. Most of the subjects in this study were female elderly subjects, and thus not representative of the general population. However, it is particularly noteworthy that, as the patients examined in this study had difficulty consulting other clinics or hospitals, we were able to follow them whenever they suffered AURD, and were thus able to correctly determine the frequency of AURD during the study period.

Recent studies have indicated that pulmonary surfactant and its apoprotein play important roles in the host defence system in the lung, by increasing phagocytosis by mononuclear phagocytes [6] and uptake of liposomes by alveolar macrophages [7]. Kido et al. [8] found that pulmonary surfactant purified from rat bronchoalveolar lavage fluid inhibits the proteolytic activation of Sendai virus and influenza A virus.

Ambroxol, a mucolytic agent, has been used for the treatment of chronic bronchitis and neonatal respiratory distress syndrome [9]. The pharmacological activities of ambroxol have been reported to include mucoregulation of gland cells and enhancement of the production of pulmonary surfactant [10]. Tashiro et al. [11] reported that intranasal administration of pulmonary surfactant suppressed activation of virus and pathological changes in the lungs in infected rats, suggesting the possibility of therapeutic use of pulmonary surfactant for the treatment of respiratory viral infection. Recently, it has been shown that ambroxol has antioxidant [12] and anti-inflammatory properties, and reduces release of inflammatory cytokines from bronchoalveolar macrophages, monocytes and granulocytes [13, 14]. Yang et al. [15] found that ambroxol has antioxidant properties and stimulates the release of pulmonary surfactant, which prevents proliferation of influenza viruses in the airways in mice. Gillissen et al. [16] found that ambroxol might be a useful alternative in antioxidant augmentation therapy, particularly for pulmonary diseases characterised by excessive toxic oxygen metabolites, as it suppressed toxic oxygen production by polymorphonuclear and mononuclear cells isolated from the blood of healthy volunteers.

In the present study, the number of patients vaccinated against flu was small (8 of 41 patients, 19.5%). Ambroxol was also effective in patients not vaccinated against flu. Our findings suggest that long-term oral ambroxol therapy may be effective in preventing viral infections such as influenza. As vaccination against flu is very useful in combating influenza, but not viruses other than those causing influenza, it might be of considerable importance that ambroxol therapy is effective for non-specific viral infections. The pharmacological activities of ambroxol that increase surfactant protein A, mucus protease inhibitor, immunoglobulin A and immunoglobulin G, and suppress the release of inflammatory cytokines in the airway [15], may play roles in the mechanism by which ambroxol prevents AURD. Further studies are needed to investigate whether ambroxol exerts effects at not only the alveolar level but also the upper respiratory tract level, in attempting to determine the mechanism of its effects.

Although in total adverse effects were noted in 11.8% of participants taking ambroxol, all such effects were mild and disappeared immediately after discontinuation of the drug. These adverse effects thus did not compromise the usefulness of ambroxol.

In conclusion, our findings suggest that long-term oral ambroxol therapy may be useful for preventing AURD. Further studies are needed to test this hypothesis, as neither viral titration nor bacteriological examinations were performed in our study. Our findings suggest that oral ambroxol therapy is important not only in preventing AURD, but also in introducing a new chapter in improvement of the quality of life.

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