Comparison between Bakumondo-to (Mai men dong tang) and Dextromethorphan Hydrobromide in Terms of Effect on Postinfectious Cough: A Pilot Study

Katsuya FUJIMORI1) Eiichi SUZUKI2) Fumitake GEJYO2)

1) M.D., Department of Internal Medicine, Niigata Prefectural Shibata Hospital, Ohte-machi 4-5-48, Shibata, Niigata 957-8588, Japan
2) M.D.s, Department of Medicine (Ⅱ), Niigata University School of Medicine, Asahi-machi-dori 1, Niigata 951-8510, Japan

Abstract  Objective: Bakumondo-to (Mai men dong tang, B), a traditional Chinese blended medicine, has notable antitussive activity in bronchitic guinea-pigs. In this study, we examined whether or not B was effective in treating postinfectious cough.

Methodology: Consenting, non-smoking patients who met the following diagnostic criteria were selected as subjects: (1) those who had been coughing continuously for more than two weeks postinfectiously; (2) who did not use angiotensin-converting enzyme (ACE) inhibitors orally; (3) who had no history of nasal and/or paranasal disease, chronic pulmonary disease, atopy or gastroesophageal reflux disease; and (4) who had normal chest X-rays, respiratory function, peripheral eosinophil counts, levels of C-reactive protein, and serum IgE concentrations. Subjects were randomized into two groups: those given a daily dose of 9 g of B extract granules orally for one week, and those given a daily dose of 60mg dextromethorphan hydrobromide (D) orally for one week. Using a cough diary (in which cough was scored from 0 to 9 points), we compared and studied the antitussive effects between the two groups.

Results: Group B was comprised of thirteen patients, and Group D, twelve. There were no significant differences between the two groups with respect to age, sex, cough scores at the time of hospital visits, duration of continuous coughing, and test results. Significant antitussive effects were seen in both groups. However, cough scores decreased significantly from the second day for the B group, and on the third, sixth and seventh day for the D group. Compared with the D group subjects, those in the B group showed higher antitussive
INTRODUCTION

Cough is a problem in that physicians frequently encounter in clinical situations. It is treated by identifying the cause and administering appropriate medicine. Major causes of chronic, persistent coughing that continues for more than three weeks despite normal chest X-ray (CXR) and respiratory functions are postnasal drip, cough-variant asthma, and gastroesophageal reflux induced cough. Postinfectious (persistent) cough is also reported to be one of the causes. There is an increasing usage of Chinese traditional medicines in hospitals, because such medicines tend to have minor side effects coupled with at times, a remarkable efficacy. Fuchikami et al. reported that Bakumondo-to (Mai men long tang), a traditional Chinese blended medicine had notable antitussive activity produced by a peripheral mechanism of action on the cough associated with bronchitic guinea-pigs. We have reported earlier that Bakumondo-to was effective in treating postinfectious persistent cough. In a comparative study of cough disappearance rates one week after the administration of a variety of drugs, we found that the rates were 0% for the nine patients given only dextromethorphan hydrobromide (a central non-narcotic antitussives), 18% for the eleven patients given a combination of dextromethorphan and oxatomide, a H1 receptor antagonist, and 50% for the eighteen patients given those two drugs plus Bakumondo-to. These findings showed that, for patients with postinfectious persistent cough, the cough-disappearance rate was highest in the group receiving a combination of three drugs including Bakumondo-to. For this study, we compared the antitussive effects of Bakumondo-to and dextromethorphan on postinfectious cough.

MATERIALS AND METHODS

Definition of postinfectious cough

Postinfectious cough was defined as a symptom meeting the following five requirements: (1) cough (primarily dry cough) which follows cold-like symptoms, including nasal secretion, sneezing, nasal obstruction, fever, epiphora, sore throat, and hoarseness; (2) this cough persists for more than two weeks; (3) the patient has no history of nasal and/or paranasal disease and chronic pulmonary disease which may cause cough; (4) the patient has no history of atopy, does not use angiotensin-converting enzyme (ACE) inhibitors orally, and does not have bronchial asthma, gastroesophageal reflux, postnasal drip, chronic obstructive pulmonary disease, or pneumonia; and (5) the patient has normal CXR and respiratory function.

Subjects

Non-smoking patients were enrolled in the study if they had visited Niigata Prefectural Shibata Hospital’s Department of Internal Medicine between January to December 1997 primarily for cough which persisted for two weeks or more, and who met the
five criteria of postinfectious cough as stated above, and who had normal peripheral leukocyte counts, peripheral eosinophil counts, levels of C-reactive protein (CRP) and serum IgE concentrations. Before conducting tests and treatments, we explained the procedure to the subjects and obtained their informed consent.

Methods

Protocol

We interviewed the subjects and confirmed that they did not take ACE inhibitors orally, did not smoke, and had no history of nasal and/or paranasal disease, chronic pulmonary disease or gastroesophageal reflux disease. Moreover, we conducted physical examinations to confirm that they had no postnasal drip and that there were no abnormal findings on chest auscultation. We then conducted CXR and pulmonary function tests to confirm that there were no abnormalities. We also checked to see if there were no abnormalities in peripheral leukocyte counts, peripheral eosinophil counts, CRP concentrations, and serum IgE concentrations. Furthermore, only those patients who were able to maintain a cough diary were considered competent subjects. Subjects were divided randomly into two groups: those given a daily dose of 9 g of Bakumondo-to extract granules (Tsumura Corp; Tokyo, Japan) orally, and those given a daily dose of 60 mg of dextromethorphan orally. Patients in both groups took the drugs orally for one week. Using a cough diary, we compared and studied the antitussive effects between the two groups. Specifically, we compared and studied the cough scores for the day immediately before therapy, the day of therapy (the first day), the second, third, fourth, fifth, sixth, and seventh days of therapy, respectively.

Assessment of cough (cough diary)

The degree of cough (frequency and intensity) was divided into four levels: zero for no cough, 1 for mild coughing, 2 for strong coughing, and 3 for extremely strong coughing. We also divided the day into the following three time zones: morning to afternoon (6:00 a.m. to 2:00 p.m.), afternoon to night (2:00 p.m. to 10:00 p.m.), and during sleep (10:00 p.m. to 6:00 a.m.). Subjects were asked to assess the degree of cough in each time zone by themselves and record the scores. Thus, a daily total cough score ranged from 0 to 9 points.

Assessment of adverse reactions

During examination one week after administration, we asked the patients about adverse reactions.

Statistical processing

Mann-Whitney U-test (Table 1), one-way repeated-measures ANOVA (Fig. 1 and 2) and two-way repeated-measures ANOVA (Fig. 3) were used to test for statistical significance, with P < 0.05 deemed to be significant. In addition, 7 tests (1 test for each day) were carried out for each group, the significance level was corrected with the Bonferroni inequality method. Thus, when the probability was smaller than the significance level of α/7, we expressed it as P < α, by setting α = 0.05.

RESULTS

Interim analysis was made after thirteen patients each were registered in both groups. These 26 patients all met the diagnostic criteria for postinfectious cough, and had their peripheral leukocyte/eosinophil counts, CRP concentrations, and serum IgE concentrations within the normal range.

One dextromethorphan group patient dropped out because of failure to bring a cough diary when visiting the hospital. Other patients kept their cough diaries on a regular basis. Table 1 shows the comparison of background factors between the thirteen patients in the Bakumondo-to group (one male and twelve females) and the twelve patients in the dextromethorphan group (one male and eleven females). There were no significant differences between the two groups in terms of age, sex, cough duration, test findings, and cough scores one day before treatment.

Fig. 1 shows the changes in cough scores of
Bakumondo-to group patients. Their cough score one day before treatment was 5.4 ± 1.7, which fell significantly to 1.5 ± 1.3 on the seventh day (P < 0.005). In addition, cough scores dropped significantly from the second day. There were no serious adverse reactions.

Fig. 2 shows the changes in cough scores of dextromethorphan group patients. Their cough score one day before treatment was 4.1 ± 2.0, which fell significantly to 1.8 ± 1.3 on the seventh day (P < 0.01). Moreover, cough scores fell significantly on the third, sixth and seventh day. There were no serious adverse reactions.

Fig. 3 shows the changes in post-treatment % cough scores for both groups, with the cough scores of the day immediately before treatment assigned a
Fig. 2 Cough scores (means±SD) before and after treatment with dextromethorphan in patients with postinfectious cough. From trial day 3, 6 and 7, cough scores decreased significantly after the start of treatment with dextromethorphan.

*P<0.05, **P<0.01, ***P<0.005

Fig. 3 Comparative results of % cough score before and after treatment with Bakumondo-to (closed circle) and dextromethorphan (open circle). % cough score was calculated by (cough score in trial day) / (cough score before treatment)×100 (%). In trial day 2, % cough score was significantly lower with Bakumondo-to than with dextromethorphan (P<0.05).
value of 100%. Percentage cough scores were calculated by using the pre-treatment cough scores for the denominator, and the post-treatment cough scores for the numerator. In comparing the two groups, Bakumondo-to group had significantly lower % cough scores on the second days, demonstrating its high antitussive effects (P<0.05).

This trial was stopped because of significant differences between the two groups in the interim analysis.

DISCUSSION

Poe et al. have stated that postinfectious cough accounted for 11 to 25% of the causes of chronic cough that persists for three weeks or more. We have studied the causes of chronic cough in 43 patients who had no abnormal findings in their CXR and respiratory functions, had no postnasal drip, and whose symptoms had persisted for three weeks or longer. Of these, 22 patients had postinfectious persistent cough, eight had cough in which eosinophils contained in sputum had increased (cough-variant asthma and eosinophilic bronchitis without asthma), seven had cough caused by ACE inhibitors, and six had cough caused by gastroesophageal reflux. Postinfectious persistent cough is a frequently-occurring disease and a trigger of chronic cough in Japan. For this study, we investigated patients suffering from cough that persisted for two weeks or more postinfectiously.

A variety of methods have been reported to treat postinfectious cough, including oral steroids, inhalational steroids, and inhalational ipratropium bromide. Many non-narcotic antitussives have been used clinically. Dextromethorphan, an agent that may increase the latency or threshold of cough reflex through action on the cough center, was effective in patients with bronchitis. In this study, we conducted an open comparative test on the antitussive effects of Bakumondo-to, an herbal drug, and dextromethorphan hydrobromide, a useful and a central antitussive, for postinfectious cough. As a result, compared with dextromethorphan, Bakumondo-to was thought to demonstrate a significant prompt antitussive action, beginning on the second days after oral dosing. The drug did not induce serious adverse reactions.

Bakumondo-to contains six types of basic drugs: Bakumondo (Ophiopogonis Tuber), Hange (Pinelliae Tuber), Kanzo (Glycyrrhizae Radix), Taiso (Zizyphi Fructus), Ninjin (Ginseng Radix), and Kobei (Oryzae Semen). Miyata et al. studied the antitussive effects of mechanical stimulation on the bronchial mucous membrane in bronchitic guinea-pigs, and found that Bakumondo-to, Bakumondo, Hange, and Kanzo had significant antitussive effects. Moreover, they used guinea-pigs which had become bronchitic after inhaling sulfur dioxide gas, and reported that: (1) Bakumondo-to suppressed the cough which had increased after inhaling substance P and phosphoramidon (neutral endopeptidase inhibitor), and (2) it suppressed the reduction of neutral endopeptidase levels in the trachea and bronchus. In other words, they reported that Bakumondo-to was effective in treating cough induced by chemical mediators such as substance P, neurokinin, and bradykinin. On the other hand, Jacoby et al. reported that influenza infection decreases neutral endopeptidase levels. And Chung et al. proposed a mechanism for the development of postinfectious cough as follows: irritants may penetrate more readily through the damaged epithelium, and endogenous peptidases (neutral endopeptidase) may be reduced allowing a greater concentration of endogenous tachykinins (substance P) to stimulate hypersensitive cough receptors. Theoretically, Bakumondo-to is thought to exert antitussive effects via peripheral actions which in contrast to the action of dextromethorphan and other central antitussives. Because of this, it may very well be effective in treating postinfectious cough, which is thought to be caused by peripheral mechanisms. Our present findings have shown the possibility that Bakumondo-to, a peripheral antitussant, is effective in treating...
postinfectious cough. We feel it is now necessary to conduct double-blind comparative tests to see if Bakumondo-to is indeed effective or not.

All patients’ cough ultimately resolves within four weeks. No patient had recurrence of a cough. Therefore we made a final diagnosis of postinfectious cough. In all patients a specific cause of cough such as gastroesophageal reflux and mass lung lesion were excluded by history, appropriate investigation, or both. No patients had underlying asthma. All patients complained of cough only after a respiratory tract infection and had normal chest radiographs and lung functions.

Until now, no standard method has been established to evaluate cough. A variety of methods are currently being tested, such as using cough diaries as a subjective assessment method, and inducing cough by inhaling distilled water, capsaicin and tartaric acid, as an objective method. For this study, we utilized a subjective assessment method using cough diaries.

Cough is one of the five symptoms of which outpatients complain the most frequently. Establishment of a standard method to assess cough, and a standard method to treat postinfectious cough is strongly called for.

In conclusion, we studied the antitussive effects of Bakumondo-to and dextromethorphan hydrobromide for postinfectious cough, using cough diaries. Significant antitussive effects were seen in both groups. But cough scores dropped significantly from the second day for Bakumondo-to, and on the third, sixth and seventh day for dextromethorphan. Bakumondo-to was thought to demonstrate antitussive effects more rapidly after administration compared to dextromethorphan. We hope to undertake a cooperative randomized double blind trial in patients with postinfectious cough to further evaluate the efficacy of Bakumondo-to compared to oral or inhaled steroids, or inhaled ipratropium.

REFERENCES
10) Fujimori K., et al.: Clinical features of Japanese patients with chronic cough induced by gastroe-
要旨　麦門冬湯（B）は漢方薬で、気管支炎モデルの咳嗽を抑制することが知られている。かぜ症候群後咳嗽に麦門冬湯が有効か否か検討した。非喫煙者で、かぜ症候群後2週間以上咳嗽が続、ACE阻害薬を内服しておらず、鼻・副鼻腔疾患、慢性呼吸器疾患、アトピー歴、胃食道逆流症がなく、胸部単純X線、呼吸機能、末梢血好酸球数、CRP、血清IgE値に異常のない症例を対象症例とした。対照例を、無作為にBエキス顆粒9g/日と並行治験酸デキストロメトルファン（D）60mg/日の1週間内服群に分け、咳日記（咳点数0 - 9 点に分布）を用いて、2群間の咳嗽抑制効果を比較検討した。B13例、D12例で検討した。両群で、年齢、性、来院時咳点数、咳嗽持続期間、検査成績に有意差はなかった。B、D両群で有意の咳嗽抑制効果が認められたが、Bでは2日目より、Dでは3・6・7日目に、有意に咳点数が低下した。BはDに比し、2日目で咳嗽抑制効果が強かった（P<0.05）。両群に重篤な副作用を認めなかった。以上より、麦門冬湯は、非喫煙者のかぜ症状群後咳嗽有用で、内服後すみやかに咳嗽抑制効果を現すと考えられた。

キーワード：麦門冬湯、持続性咳嗽、臭化水素酸デキストロメトルファン、かぜ症候群後咳嗽