Efficacy of Coadministration of Maoto and Shosaikoto, a Japanese Traditional Herbal Medicine (Kampo Medicine), for the Treatment of Influenza A Infection, in Comparison to Oseltamivir

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[ABSTRACT]
14 Japanese patients ≥18 years old who were diagnosed to have influenza A by an influenza antigen detection kit test were randomized to two groups and received either Maoto and Shosaikoto (MS; n=6) or Oseltamivir (O; n=8). The MS group received 7.5 g/day Maoto extract granules and the same dose of Shosaikoto for 3 days. The O group received 150 mg/day Oseltamivir for 5 days. No significant differences were observed between the MS and the O group in regards to the duration of fever after treatment (2.3±1.0 vs. 2.0±0.6 days).

[Key words]
Maoto, Shosaikoto, influenza

INTRODUCTION

Influenza epidemics have a huge impact on individuals and society1). The neuraminidase inhibitors, Oseltamivir and Zanamivir, are used for the treatment and prevention of influenza. However, recent studies have noted the emergence of viruses resistant to neuraminidase inhibitors2,3). In addition, neuraminidase inhibitors can possibly cause abnormal behavior in children with influenza infection4). Therefore the value of the Japanese traditional medicine (Kampo medicine) Maoto has been reconsidered, and sales of Maoto, which is used for the treatment of influenza in Japan, have recently increased. Shosaikoto has also been used for the treatment of acute febrile diseases including influenza5). The coadministration of Maoto and Shosaikoto is not contraindicated, but there are no reports addressing the coadministration of Maoto and Shosaikoto for the treatment of influenza. The present study compared the efficacy of Maoto and Shosaikoto coadministration with the administration of Oseltamivir in adults with influenza A.

SUBJECTS, MATERIALS AND METHODS

Patients enrolled in this study were individuals ≥18 years old who visited our clinic from December 2007 to March 2008 and had influenza-like symptoms, such as body temperature above 37.5°C, upper respiratory tract symptoms or systemic symptoms within 48 hours of onset of fever. 22 Japanese patients tested positive for influenza A with an influenza
antigen detection kit test (RapidTesta® FLU Stick, Sekisui Medical Co. LTD., Tokyo, Japan). 14 patients were selected for this study and were classified into two groups, based on the administration of either Maoto and Shosaikoto (MS group) or Oseltamivir (O group), in order to make a diagnosis. The MS group included four males and two females; 2.5 g of Maoto extract granules and the same dose of Shosaikoto extract granules (Tsumura & Co., Tokyo, Japan) were administered orally at the same time three times per day for 3 days. One daily dose of Maoto contains 1.75 g of spray-dried powdered extract from Ephedra Herb (Mao) 5.0 g, Cinnamon Bark (Keihi) 4.0 g, Apricot Kernel (Kyomin) 5.0 g and Glycyrrhiza Root (Kanzo) 1.5 g. One daily dose of Shosaikoto contains 4.5 g of spray-dried powdered extract from Bupleurum Root (Saiko) 7.0 g, Pinellia Tuber (Hange) 5.0 g, Scutellaria Root (Ogon) 3.0 g, Jujube Fruit (Taiso) 3.0 g, Ginseng Root (Ninjin) 3.0 g, Glycyrrhiza Root (Kanzo) 2.0 g and Ginger Rhizome (Shokyo) 1.0 g. The O group included five males and three females, and 75 mg of Oseltamivir (Tamiflu®) was administered orally twice per day for 5 days. Acetaminophen (400 mg) for headache or arthralgia, and Clofedanol Hydrochloride (25 mg) or Cloperastine Hydrochloride (20 mg) for cough was allowed for use on demand. The date and time of onset and resolution of fever, highest body temperature, and number of doses of antipyretics and cough medicines during the course of the disease were recorded for all patients. Patients measured their body temperature as needed; the time at which a body temperature of 37.0°C was attained was defined as the time when the patient became afebrile. The study protocol was approved by the institutional ethics committee of Matsumoto Kyoritsu Hospital, and all patients were informed about the aim and procedure of this study and consent was obtained in writing. There is no conflict of interest with regard to this study.

RESULTS

The demographic findings of the patients in the MS group (n=6) and the O group (n=8) are summarized in Table 1. There were no significant differences in age, BMI, gender, comorbidities or smoking between the MS group and the O group.

There were also no significant differences between the MS group and the O group for the duration of fever after onset and after treatment, the period from onset of fever to making a diagnosis of influenza, the highest body temperature recorded, and the number of doses of antipyretics and cough medicines administered during the course of the disease (Table 2).

No adverse effects related to the administration of Maoto, Shosaikoto or Oseltamivir were observed.

DISCUSSION

This study suggested that the coadministration of Maoto and Shosaikoto extract granules might be comparable to treatment with Oseltamivir for reducing the duration of fever in adults with influenza A.

Maoto is a Kampo medicine for influenza- or typhoid-like acute febrile illnesses, and use of Maoto extract granules is acceptable by the Japanese medical insurance administration.
for patients with influenza. Maoto is used in the Tai yang stage of an acute disease according to Shokanron, a classic Kampo textbook. A neuraminidase inhibitor like Oseltamivir is used for the treatment of early stages of influenza infection, but the emergence of viruses resistant to Oseltamivir\textsuperscript{2,3} and the possibility of causing abnormal behavior in children with influenza infection are becoming problematic\textsuperscript{4}. Maoto is effective in comparison to treatment with Oseltamivir in the control of fever in children with influenza A infection\textsuperscript{6}. There is no evidence that taking Kampo medicine causes abnormal behavior in influenza patients.

Shosaikoto is also a Kampo medicine for acute febrile diseases, and is used in the Shao yang stage of the disease. The Shao yang stage usually comes after the Tai yang stage, so Shosaikoto should be used subsequent to Maoto treatment. However, it is not easy to confirm the shift from the Tai yang to the Shao yang stage in outpatients and thus switch from Maoto to Shosaikoto. Shosaikoto has a harmonizing action and the use of Shosaikoto extract granules is considered acceptable by the Japanese national health insurance system for patients with chronic gastrointestinal disorders. However, the Ephedra herb contained in Maoto can sometimes cause loss of appetite, nausea and digestive system discomfort. The combined use of Shosaikoto with Maoto might reduce the side effects associated with the Ephedra herb in Maoto. In this study, no adverse effects due to the coadministration of Maoto and Shosaikoto occurred, and therefore it appears that Maoto and Shosaikoto can be used simultaneously in the early stage of influenza.

The drug costs of Maoto and Shosaikoto extract granules of Tsumura & Co. during the course of influenza were 954 yen over three days (Maoto extract granules 65.25 yen/day, and Shosaikoto extract granules 252.75 yen/day) whereas that of Oseltamivir was 3091 yen over five days (Tamiflu\textsuperscript{®} 75 mg capsules 618.2 yen/day). The coadministration of Maoto and Shosaikoto extract granules may thus yield similar clinical effects for about a one-third the cost of Oseltamivir; thus Kampo medicine treatment of influenza possesses superior cost effectiveness compared to this particular neuraminidase inhibitor.

**CONCLUSIONS**

These results suggest that Maoto/Shosaikoto coadministration had comparable effectiveness to Oseltamivir for the treatment of influenza A infection in Japanese adults. In addition, Maoto and Shosaikoto extract granules cost less than Oseltamivir. In short, Kampo treatment possesses superior cost effectiveness.

**GRANT**

None

**REFERENCES**

要旨

オセルタミビルと比較した A 型インフルエンザに対する麻黄湯・小柴胡湯併用療法の有効性について

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発熱後 48 時間以内に A 型インフルエンザと診断した 18 歳以上の患者 14 名を、麻黄湯・小柴胡湯（6 名：麻黄湯エキス粉末 7.5 g・小柴胡湯エキス粉末 7.5 g/日、3 日間内服）と、オセルタミビル（8 名：150 mg/日、5 日間内服）にて治療した。各群の治療開始から解熱までの期間に有意差を認めなかった。

キーワード：麻黄湯、小柴胡湯、インフルエンザ