Clinical Report 3 (Japan)

Maoto Demonstrated as Highly Effective for the Treatment of Influenza (B)

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Introduction

Recently avian influenza has received a good deal of attention in the media. Currently, secondary infection among people does not seem to occur. If such a pathogenecity would be acquired, the disease would be associated with considerable mortality because the human race does not have antibodies to use against it.

In western medicine the drug Oseltamivir (brand name: Tamiflu) seems to be highly effective, so that stockpiling of the drug by the individual nations has been recommended. Yet, it must be noted that upon indiscriminate administration, side effects cannot be disregarded. Moreover, in order for the drug to be effective, it needs to be administered within 48 hours after onset and its administration has to be continued over a period of 5 days[2].

The author has 20 years of experience having treated over 1,000 patients with influenza. This has been done solely with Kampo medicine in his clinic which specializes in Kampo treatment. In January last year, the author had a chance to use Oseltamivir, providing the opportunity to compare it with Kampo preparations. His experience is presented below.

One patient with influenza who was successfully treated with Kampo is presented below.

Patient: age 32, male, employed.
Chief complaint: chills, fever, generalized arthralgia.
Family history, past history: n.p.
Description of occurrence of illness:

On January 1, 2005 the patients went to work at 9:00am, but suddenly felt chills over his back. This was followed by shaking of the entire body which the patient could not stop intentionally (shaking chills). After a short period, he started to feel feverish, developed a headache and joints and muscles throughout the body started aching. At the same time he felt drained of energy. The patient visited our clinic at 5:00pm of that same day.

Initial Observation

Inspection: pale face and appeared generally exhausted
Listening: voice was rather loud.
Reasoning: clear
History: Loss of appetite, bowel movements and micturition remained normal. Influenza seemed to be prevalent in his environment with many people being absent from work. He claimed to have a lot of work to do and thus needed to recover as quickly as possible.
Palpation (physical findings):

Physical build and nutritional status were good. Examination of the pulse showed a rate of 100/min, regular floating, tense, fast. Blood pressure was 120/78 mmHg. The throat was slightly inflammed. Auscultation of the heart and lungs did not reveal any anomalies. Abdominal examination showed intermediate abdominal tension and mild tenderness in the right hypochondrial region (these abdominal findings would be designated "fullness, tenderness or discomfort of the hypochondrium). Body temperature was 38.3°C. There was no perspiration.

Diagnosis

Western medical: quick diagnostic kit identifies type B influenza.
Kampo medical: according to the "Shang Han Lun" the condition is considered to be a cold injury excess disorder of the greater yang type.

Prescribed Course

Maoto made by Tsumura (a 7.5-g portion of the drug contains the following amount of dried crude drug extract 1.75 g (Ephedra 5.0 g, Apricot Seed 5.0 g, Cassia Bark 4.0 g and Licorice Root 1.5 g) was given in packages of 2.5 g each taken with warm water at intervals of 4 hours. The patient was instructed to cover the body until the body warmed and he started perspiring. The patient called, reporting that after taking three packages, the body temperature conversely had risen above 39°C, but he was still not perspiring. Therefore I instructed the patient to continue the medication.

On the next morning, the patient called again, reporting that 30 minutes after taking another package he started to sweat profusely over the entire body, which in turn caused a fall in his temperature and the alleviation of the joint and muscle aches. At the time he was calling, he said he was feeling refreshed. After that I instructed the patient to discontinue the medication and take a day off to rest quietly. Four days after the initial onset, he returned to work without any recurrences.

Discussion

This patient followed a typical course of patients treated during the early phase of influenza with *maoto*. The author has treated over 1,000 patients with influenza, and found that during the initial phase 90% of the patients recovered within 2-3 days following treatment with *maoto* after perspiration and defervescence. When the fever continued, even after the administration of 9 packages without perspiration, and in the presence of feverish restlessness or dry mouth, switching to the preparation *daiseiryuto* usually resulted in the onset of perspiration, defervescence and recovery within 24 hours.

In case of influenza, patients usually can tell rather precisely on "what day and at what hour" the sudden onset of chills, fever, arthralgia, general malaise, loss of appetite or the development of cough occurred approximately 1 or 2 days after the infection. This condition had in the latter half of the second century AD been described in the "Shang Han Lun" edited by Zhang Zhong Jing of the later Han period in China. In the chapter on greater yang diseases it states: "During greater yang disease, fever develops, or if it has not yet developed chills set in, the body starts aching, there will be vomiting and both yin and yang pulses will be tense." The description in this text coincides with the "Shang Han" (Shokan) pathology.

For this Shokan condition the text states *maoto* governs the greater yang condition characterized by headache, fever, body pain, low back pain, pain in the bones and joints, chills and a lack of perspiration[3]. Thus, following the instructions in the text, and taking *maoto* warm, the drug results in perspiration and defervescence and is characterized in that it simultaneously improves all the other symptoms, eventually leading to a complete cure without any complications or sequelae. Yet, *maoto* is only effective for the early phase of influenza. This means the condition described in the "Shang Han Lun" as the greater yang disease phase when it is used for the aforementioned symptoms. This resembles the provision that Oseltamivir should be administered within 48 hours after onset.

As described above, Oseltamivir should be administered within 48 hours after onset and then continued over a period of 5 days[2]. Definitely the author achieved defervescence in all 10 patients who were treated within 48 hours after onset, but in 2 out of 5 patients who discontinued the medication after 3 days a recurrence of fever and cough was observed 2-3 days later. The condition here had to be viewed in Kampo medical terms as a lesser yang condition that then required treatment with *shosaikoto*.

When *maoto* is administered for its indicated symptoms, defervescence can be achieved in most patients within a period of 24 to 48 hours. When perspiration is not observed within a period of 48 hours and the patient develops signs of (feverish) restlessness, the author prescribed *daiseiryuto*. Application of both these preparations led in almost 100% of the patients the onset of perspiration and defervescence within 72 hours. Subsequently, the course was favorable and without recurrences.

Considering financial aspects shows that 2 capsules of Oseltamivir per day for 5 days would amount to, according to the Japanese drug price in the National Health Insurance scheme, 3,780 Yen (USD31.50). The price for a 3-day dose of *maoto* is only 210 Yen per day (USD1.75). Conversely, since the *daiseiryuto* is not a ready-made extract preparation, it is prepared from two available extract preparations. When preparing it using Tsumura's extracts, the author used 7.5 g of *maoto* and 7.5 g of *eppikajutsuto* per day. In this case, the price for two days is 340 Yen (USD2.80). Applied for suitable indications, Kampo preparations are not only highly effective for the treatment of influenza, but also economically superior.

Conclusion

* One case was reported where the greater yang condition described in the "Shang Han Lun" can be viewed as a cold injury and the treatment with 7.5 g of *maoto* made by Tsumura per day and proved to be markedly effective within 2 days.
* Oseltamivir is definitively effective, but Kampo medicine, in particular *maoto* and *daiseiryuto*, when administered based on a suitable pattern identification, appear to have equivalent effects.
* Considering cost factors, *maoto* and *daiseiryuto* (combination of *maoto* and *eppikajutsuto*) seem to be economical.

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Clinical Report 3 (Japan) - continued

Efficacy of Kampo Medicine for Influenza – with Particular Focus on Maoto

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History records reveal that approximately 1800 years ago there was an epidemic of a condition called "Shang han (cold injury)" in China, that closely resembled what we today call influenza. Descriptions of therapies for this disease found in the book "Shang Han Lun" are actually highly effective for the treatment of influenza. In fact, more than half of the Kampo prescriptions currently used in Japan are derived from either this "Shang Han Lun (Treatise on cold-induced diseases)" or else the "Jin Kui Yao Lue (Synopsis of the Golden Chamber)". For this reason Kampo medicines are frequently used in Japan for the treatment of influenza. In particular, the early phase after the onset is often an indication for the use of prescriptions containing Ephedra like *maoto* or *daiseiryuto*.

Clinical research

Signs considered to be indications for *maoto* include chills, fever, headache, arthralgia, muscle aches, a tendency towards perspiration etc.; closely resembling the symptoms observed during the early phase of influenza. For this reason *maoto* is often used for the treatment of this condition.

Abe published detailed reports on the treatment of influenza with Kampo medicine before the introduction of antiviral agents. In these reports, he indicated that for symptomatic treatment, Kampo medicines are superior to western medications[1]. Later research comparing the antipyretic effects of amantadine and *maoto* revealed almost equivalent effects.[2]

In recent years, Oseltamivir has come into use, and thus many studies have been conducted examining the effects of a combination therapy with *maoto*. The combination of inhibition of the virus proliferation by Oseltamivir, and improvement of the body defences facilitated by *maoto,* is considered to provide an ideal therapy form. Below are several clinical studies that investigated these questions.

Kubo et al. treated a total if 49 patients (male:female = 24:25) with an age ranging from 5 months and 13 years with influenza symptoms including high fever of over 38°C. These were divided into a group of 18 patients treated with Oseltamivir, a group of 14 patients treated with a combination therapy of Oseltamivir and *maoto* and a group of 17 patients treated with *maoto*[3].

Among these patients those over one year of age were diagnosed using a quick diagnostic kit for influenza and subsequently randomly assigned into (1) a Oseltamivir (brand name: Tamiflu) group treated with 4 mg/kg for 2 days and (2) a *maoto* made by Tsumura 0.18 g/kg for 3 days) and (3) a combination therapy of Oseltamivir and *maoto*. Patients under one year, not suitable for treatment with Oseltamivir and patients in whom the influenza quick diagnostic test was negative, were treated only with *maoto* (independent therapy). Guardians were requested to supervise the actual application of the drug and record measurements of body temperature. The study then compared the differences between the individual groups until defervescence (down to 37.2°C) had been achieved. Differences in background factors like average age at the initiation of the treatment, male-female ratio, duration of the fever prior to treatment begin, degree of the fever, history of vaccinations etc. were not observed.

Regarding the time from beginning treatment until defervescence in all three groups was in the Oseltamivir treatment group, on the average 31.9 hours; in the *maoto* – Oseltamivir combination therapy group 21.9 hours; and in the *maoto* group 17.7 hours. Side effects or adverse events were observed in none of the groups.

Similar studies have also been conducted by Kuroki, Fukutomi et al. and Kimoto et al. Kuroki investigated the effects of a *maoto* – Oseltamivir combination therapy for the treatment of influenza over the three seasons from 2003 to 2005 and obtained results similar to those reported by Kubo. In the combination therapy group, improvement in clinical symptoms was reportedly superior[4].

Fukutomi et al. divided 24 patients diagnosed with influenza using the quick diagnostic kit from winter 2003 until spring 2004 into two groups and treated them with a regimen similar to that described above. The results showed that the duration of headache in days and the number of days general malaise continued was shorter with a combination therapy of Oseltamivir and *maoto* than in the group treated only with Oseltamivir (significant difference) [5].

Kimoto et al. treated patients diagnosed with influenza using the quick diagnostic kit during the period from January to March 2004 with Oseltamivir and then compared the clinical course with patients treated either with *maoto* or else ordinary western medications. Defervescence occurred in the group treated with a *maoto* combination therapy approximately 12 hours earlier than in the group

treated with a combination therapy with western drugs. They also reported a tendency toward an early recovery from fatigue, dizziness and loss of appetite. In the group treated with combination therapy with western drugs a rise in CRP was observed in 3 patients, but in the group treated with a *maoto* combination therapy this was not observed[6].

Similar to the case reports published by Oribe, symptoms were often relieved early in many patients treated with *maoto* only. Therefore specialists of Kampo medicine hold the view that Oseltamivir may not necessarily be required. In Japan, generally the diagnosis of influenza is confirmed with the quick diagnostic kit first and patients are then treated with Oseltamivir. For this purpose, case-control studies are mainly reports of combination therapies with *maoto*. Yet, the accuracy of the quick diagnostic kit in establishing a definite diagnosis is not 100%. Immediately after onset in many cases positive results are not obtained.

The Kampo preparation used predominantly during the early phase is *maoto* followed by *daiseiryuto*. It would be easy, if *daiseiryuto* were a decoction, but since there are no extract preparations, this formula needs to be prepared by combining two available extract preparations. Mitani reported obtaining good results in treating patients with influenza associated with high fever by using combinations of either *keishito + makyokansekito* or else *maoto + eppikajutsuto*[7]. These combinations contain in the first case, an excessive amount of Paeonia and in the second case Atractylodes rhizome, but reportedly were clinically effective. In the latter case, the increase in the amount of Ephedra needs to be carefully considered.

Other preparations beside *maoto* or *daiseiryuto* are also used for the treatment of this disease. Patients do not necessarily visit clinics during the early phase following onset, or else because of factors like age or due to a preexisting disposition. *Maoto* may not always be suitable. In these cases, a wide variety of other preparations are used. Kimoto et al. are conducting research on this topic.

Kimoto et al. divided 155 patients diagnosed with influenza, using the quick diagnostic kit, into an Oseltamivir or amantadine treatment group, a Kampo medicine treatment group, and a third group treated with a combination therapy. The results showed that the number of days the drugs were administered were fewer in the combination therapy group. The total of 11 drugs used here included for adults *kakkonto*, *maoto*, *keishimaokakuhanto*, *shosaikoto* and others, while for children four prescriptions including *maoto* were used[8].

Costs versus effects

Oribe pointed out that regardless of whether it is *maoto* or *daiseiryuto*, these drugs when compared to Oseltamivir are inexpensive. Regarding the cost-effect ratio, these drugs cannot compare with Oseltamivir. In Japan, seven pharmaceutical companies produce and sell *maoto*. The drug price in the NHI scheme for each of these products is around 70 Yen/day. The drug price for Oseltamivir is 756 Yen/day. That results in a price difference between the two drugs of more than 10-fold.

Since the research conducted so far appears to reveal that these two drugs (*maoto* and Oseltamivir) have approximately equivalent effects, the cheaper Kampo preparations should be made the drug of first choice. Yet, for this decision, more research is called for.

Basic research

There is basic research about the most important effective ingredient in the preparation used for the treatment of influenza, namely Ephedra.

Mantani et al. noticed that for the growth of influenza viri, an acid milieu is required within the vacuoles during the threshing process and thus performed the following experiments. They used MEM containing medium to cultivate Madin-Darby canine kidney (MDCK) cells and then infected those with the influenza strain A/PR/8/34 (H1N1 subtype) to investigate the inhibitory action of Ephedra on the proliferation of the viri. The results showed that an extract of Ephedra in dose-dependent manner, inhibited the acidification of the vacuolar fluid. Moreover, regarding the viral growth, Ephedra induced immediately after the infection during a loading period of 10 minutes a less than 50% inhibition. This suggests that Ephedra inhibits the growth of influenza viri during the early phase[9].

Ochiai conducted several other studies differing from the study of Mantani et al. described above and verified the inhibitory action of Ephedra on the growth of influenza viri[10].

Avian influenza and new influenza types

In Japan so far, no people have been infected by, or developed, avian influenza. Accordingly, we haven't had the opportunity to treat this disease and thus cannot give definitive comments. However, China had the opportunity to treat patients with this disease and the governmental Department of Hygiene has classified the

disease into four types (four stages), suggesting therapies for these respective stages (including prescriptions). According to that information, avian influenza falls under the classification of "Wen Bing (warm diseases)" and not the "Shang han (cold injuries)"[11].

Conversely, for types of avian influenza with a potential man-to-man infectivity, meaning new influenza types, it remains obscure as to what type of clinical picture will be presented. In the past, influenza usually was classified as "cold injury", but that may not necessarily hold true for the future.

The great pandemic that occurred in 1918, and claimed many victims during the Spanish flu epidemic, has been classified based on the experience of the physician specializing in Kampo medicine (Dr. Mori) into three types. The type marked mainly by pathologic changes of the gastrointestinal tract was treated with *kososan* with added Indian Bread Exodermis, Atractylodes Rhizome and Pinellia Tuber; the type with predominantly pulmonary lesions with *shoseiryuto* plus added Apricot Seed and Gypsum; while the type associated with encephalopathies was treated with *shomakakkonto* with added Angelica Dahurica Root, Cnidium Rhizoma and Asiasarum Root. These therapies produced excellent results[12].

If new types of viri should evolve in this century, we would like to prepare as many means as possible to keep casualties among a human race without immunologic protection at a minimum. The development of vaccines against new strains will require at least 6 months, so that the number of effective antiviral drugs during that period is unknown. Under these circumstances, the experiences of Mori might prove helpful for the treatment of new forms of influenza.

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