

Kampo Medicine - Current Research

Use of Kampo Medicine in Treatment of Influenza

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1. Introduction

Influenza is one of the most common conditions encountered in a clinical setting. The disease is widespread during the winter months, sometimes reaching pandemic proportions. Vaccination against influenza has become commonplace in the developed nations in recent years, which has led to a reduction in flu epidemics. With the development of medications such as oseltamivir phosphate (Tamiflu®) that are particularly effective against the influenza virus, the period required for recovery from influenza infection can be considerably shortened. Nevertheless, an influenza infection can be quite serious for the afflicted patients, frequently requiring several days' absence from work or school.

It is also possible that a particularly virulent form of influenza causing a cytokine storm, such as the Spanish Flu in 1918, could again reach pandemic proportions and cause worldwide panic. In fact, that probability is actually quite high. If we are ever faced with such a pandemic, Kampo should prove to be particularly useful because of its long history as an effective intervention for the treatment of influenza even during major epidemics.

Here we introduce the use of Kampo medicine in the treatment of ordinary influenza, and discuss responses to a new and potentially more virulent influenza epidemic.

2. The Disease-Causing Elements of Influenza

The textbook description of influenza symptoms generally includes high fever, accompanying severe chills, headache, and joint pain, along with sore throat, pharyngeal erythema, and sometimes a severe cough. From a Kampo perspective, the symptoms of chills, fever, headache, and joint pain are the result of an intense battle between disease-causing elements and

the vital principle, occurring because of the invasion of wind-cold with predominance of cold.

The sore throat accompanied by pharyngeal erythema is the result of heating within the body caused by wind-cold. Regardless of whether or not internal heat is present, this heating is assumed to be intrinsic within the disease-causing element itself. When there is a cough beginning in the early stages of illness, that cough is judged to be a manifestation of the characteristics originally present in this element.

That is to say, the element that causes influenza should not be considered as a simple cold element, but instead as an influenza-specific element that characteristically generates heat as soon as it enters the body and directly invades the lungs. Although this element has the intensified characteristics of cold, it can be considered a type of "epidemic pathogen", an element of infectious disease similar to the pestilence.

3. Are "Cold Damage" and Influenza the same condition?

Kampo treatment for influenza very commonly utilizes "*Shang Han Lun (Treatise on Cold Damage Diseases)*" formulations. These formulations are effective in most cases. However, the conditions of "cold injury" and influenza, although similar, are not identical. "Cold injury" is not fundamentally associated with sore throat, and is not necessarily accompanied by coughing. Other symptoms are very similar to those for influenza, so "cold injury" is presumed to be a special form of influenza.

The preface to *Shang Han Lun (On Cold Damage)* notes, "I had a very large family, over 200 people. However, within 10 years after the start of the Jian'an Era (196 AD), two-thirds of them had died, and seven out of 10 of those deaths were due to 'cold damage'." In other words, during a ten-year period about 100 people in that family died from "cold damage". That would mean about 10 deaths per year would be ordinary. However, if there were 50 deaths per year for two years, that would be a pandemic.

The same virus can manifest with different

symptoms depending on the area and season of contagion. It is also unlikely that antigenicity will be absolutely the same in different locations and during different seasons. In Japan in 1918, the "Spanish flu" generally started out with "chills and shivering, followed quickly by fever, with the simultaneous development of localized symptoms such as pharyngeal erythema, pain, and cough." [1] At the same time, Keegan (JAMA, Vol. 71, No. 8) states that the early-stage pharyngeal symptoms may be omitted, with the patient simply showing a fever and general symptoms, and that this is considered characteristic of influenza in the United States [1], indicating that when viewed on a worldwide scale influenza manifests with a wide diversity of symptoms. The contents of Keegan's report are very similar to descriptions in the "*Shang Han Lun*". As will be discussed later, formulations that are used for "cold injury" are also extremely effective against influenza.

A useful book for reference in this area is John Barry's "*The Great Influenza*", which details the stories of patients during the Spanish flu epidemic of 1918. "Patients cried from joint pain. They suffered from high fever and chills, shaking under their blankets. They complained of abdominal pain, and vomited repeatedly." (From the Japanese translation, retranslated into English) [2].

This description is very similar to the "*Shang Han Lun*", which states that "Greater Yang Disease, with or without fever, but always with chills, complaints of pain in areas such as the joints, vomiting, and tense pulse, is termed 'cold injury'". Given this, it seems likely that the "cold injury" described by Zhang Zhong-jing in the preface to the "*Shang Han Lun*" was a variation of influenza.

4. Research into the Treatment of Influenza with Kampo Medicine

Experientially, influenza responds well to Kampo therapy, and considerable clinical research is currently underway or has been completed. Some typical examples are described below.

Research by Kawamura [3]

Kawamura selected 129 patients (0.5 to 14.6 years of age) who tested positive with the influenza rapid diagnosis kit between February 22 and June 13, 2007. These patients were divided into four groups for treatment: type A-flu oseltamivir group, the type A-flu *maoto* group, type B-flu oseltamivir group, and type B-flu *maoto* group. Kawamura's results showed *maoto* to be as effective as oseltamivir, and to be particularly effective against type B influenza.

Research by Kubo and colleagues [4]

Kubo and colleagues treated 49 patients five months to 13 years of age (24 boys and 25 girls) who had influenza-like symptoms including fever of 38°C or above, divided into an oseltamivir monotherapy group (18 patients), a *maoto* + oseltamivir concomitant use group (14 patients) and a *maoto* monotherapy group (17 patients), and investigated the effects of treatment in each group. Of these patients, those one year of age or older who had been diagnosed with influenza using a means such as the rapid diagnosis kit, were randomly allocated between: (1) the oseltamivir (trade name Tamiflu) group (4 mg/kg/day, divided into two daily doses), (2) *maoto* (Tsumura & Co., Ltd., Tokyo, Japan) 0.18g/kg/day, divided into three daily doses) + oseltamivir concomitant use group. Patients less than 1 year old, for whom oseltamivir is not indicated, and patients who tested negative for influenza with the rapid diagnosis kit, were placed in, (3) *maoto* monotherapy group. The parent or other caregiver was asked to provide information about any medications being used and records of body temperature, and the time from the start of treatment until the fever was resolved (body temperature of 37.2°C or below) was compared among these groups. There were no differences among the groups with regard to patient characteristics such as mean age at the start of treatment, male/female ratio, duration of fever before first treatment, degree of fever, or history of preventative inoculation. Meantime, resolution of fever was 31.9 hours in the oseltamivir monotherapy group, 21.9 hours in *maoto* + oseltamivir group, and

17.7 hours in *maoto* monotherapy group. No adverse drug reactions or other adverse events were observed in any of the groups treated.

Research by Kuroki [5]

Kuroki investigated the effects of concomitant use of oseltamivir and *maoto* in the treatment of influenza during three influenza seasons from 2003 through 2005. Results showed excellent improvement in clinical symptoms in the concomitant therapy group, but the change in the amount of time required to relieve fever was not as significant.

Research by Fukutomi and colleagues [6]

Fukutomi and colleagues enrolled 24 patients who were diagnosed with influenza based on findings from the rapid diagnosis kit. Those patients were divided into two groups and treated as described above. Their results showed a significant reduction in the number of days of persistent headache and general malaise in the group treated with oseltamivir + *maoto* in comparison to the group treated with oseltamivir only.

Research by Kimoto and colleagues [7]

From January through March of 2004, Kimoto and colleagues administered oseltamivir to patients who were diagnosed with influenza on the basis of findings from the rapid diagnosis kit, and compared the clinical course for those patients receiving concomitant treatment with *maoto* in comparison to patients receiving ordinary concomitant therapy in the context of Western medicine. Fever was resolved approximately 12 hours sooner in the *maoto* concomitant use group than in the Western medicine concomitant use group, and fatigue, dizziness, lightheadedness, and anorexia also tended to be improved more rapidly in the *maoto* group. Elevated CRP was noted in three patients in the Western medicine concomitant use group. There were no such adverse events in the *maoto* concomitant use group.

These studies show that *maoto*, although its mechanism of action is completely different from that of oseltamivir phosphate, provides a very similar level of clinical effectiveness, and that the effectiveness of treatment is further potentiated by concomitant

administration of both agents. The research by Kubo and colleagues, which found *maoto* monotherapy to be more effective than treatment either with oseltamivir alone or oseltamivir + *maoto*, also showed that the effectiveness of such treatment was increased if the agent was administered very early in the course of illness. *Maoto* was used in these studies because the majority of researchers performing the studies were pediatricians.

Maoto is more commonly indicated for use in children than in adults. As can be seen from the research reported here, *maoto* does not require careful selection of patient conditions, and is safe for use as long as it is administered as instructed. *Maoto* is a typical agent that resolves fever by warming the body. Its primary ingredient is *Ephedra* Herba, which contains ephedrine. *maoto* is used in the treatment of chills, fever, headache, arthralgia, and myalgia in cases where the patient shows no spontaneous sweating and has a floating and tense pulse. The method of administration is in accordance with the chapter on *maoto* in the “*Shang Han Lun*”. After administration, the patient should be covered and kept warm. Treatment is generally repeated every two hours until sweating begins, but is usually effective even if given only every three to four hours. After administration there will be a transient rise in body temperature, and the patient should be monitored closely for the development of febrile seizures and impaired consciousness. Administration should be discontinued as soon as the patient begins to sweat. This is because sustained sweating can lead to dehydration.

The ordinary course of treatment is as described above. In most cases, children show the diagnostic criteria of *maoto* chapter when they first develop influenza. However, caution is advised because there are rare instances of lesser yin disease, in which there is no chilling, and also influenza can develop with many elements of warm disease, so *maoto* monotherapy is not always the optimal choice for treatment.

Adults tend to show a wider variety of influenza types than seen in children. Symptoms may be more severe than in children, the condition may be accompanied by a sore throat and severe cough, and patients who cannot be cured early may lose appetite and waste away. Mori and Miyazaki conducted research in adult patients who were allocated into treatment groups depending on Sho diagnosis.

Research by Mori and Miyazaki [8]

Mori and Miyazaki enrolled influenza patients who came for treatment between January and April 2005, allocated those patients into three groups (Groups I, II, and III) for treatment, and determined the number of days until recovery occurred in each patient. The results were as follows.

Group I (oseltamivir + Kampo concomitant use group, 20 patients). Time to recovery: 3.4 days

Group II (oseltamivir + Kampo, escalated dose/frequency of administration group, 25 patients). Time to recovery: 2.0 days

Group III (oseltamivir monotherapy + concomitant Western medical treatment group, 29 patients). Time to recovery: 6.3 days

In adults, *shoseiryuto* is generally indicated for the early stages of influenza. Agents that may be prescribed other than *maoto* and *daiseiryuto* include *keishimaoukakuanto*, *keishinimaoichito*, *keishinieppiichito*, *maobushisaishinto*. For cases transitioning into lesser yang disease, agents such as *saikokeishito* and *shosaikoto* may be considered. If the condition transitions to yang brightness disease, *byakkoto* chapter may develop. In cases of severe cough, *makyokansekito* or *chikujountanto* should be considered. Deficiencies in both qi and yin frequently develop during the recovery period, so the use of *bakumondoto* and *shakanzoto*, which are beneficial for the lung, may be useful. Since very few Western treatment modalities address this stage in the recovery process, these Kampo formulations can provide a valuable contribution to patient healing. If warm disease develops, the patient should be treated

with *gingyosan* or a similar agent to cool fever and eliminate surface elements of disease. *gingyosan* is not available in extract formula of ethical use, but nearly the same effects can be obtained by substituting *seijobofuto* or *keigairengyoto*.

According to announcements and releases available to date, Japanese influenza tends in most cases to be of the wind-cold type, and wind-heat variations are rare. However, there have been some reports of influenza of the warm-disease type.

5. Closing Remarks

This article has viewed influenza from a number of angles based on a Kampo medicine perspective. A variety of medical procedures are available for the prevention and treatment of influenza, from basic preventative measures such as wearing face masks and gargling to vaccination and the administration of antiviral agents such as oseltamivir. We feel that Kampo medicine offers unique advantages in this context, and that its inclusion among the medical treatment options will provide additional security in the treatment of influenza, particularly in the event of a pandemic.

References

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