Investigation of Reasons for Discontinuance of Kampo Medicines (Japanese traditional herbal medicines) and Improvement of Continuance through Better Instructions to Patients

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Recently, Kampo medicines (Japanese traditional herbal medicines) have been contributing greatly to patient treatment but there have been cases in which the patient’s symptoms deteriorated during treatment and they had to discontinue the Kampo medicines. We investigated the reasons for discontinuing Kampo medicines at our institute, and discussed the improvement of continuance through giving patients better instructions. The most frequent reason for discontinuation was aggravation of symptoms by the medicines and we determined this by making a classification of the reasons for discontinuation. Next, we examined these symptoms to see if they were related to the adverse effects of Kampo medicines.

Based on the results of our investigation, we devised measures for improving continuance for Kampo medicines. In 2004, when these measures were implemented, the annual number of cases of discontinuation decreased from 96 to 78. This resulted from the clarification of the reasons for discontinuance of Kampo medicines, and the improvement of pharmacists’ instructions to patients.

Key words —— Kampo medicines, discontinuance, adverse effect, patient instruction

Introduction

Based on Kampo theory, Kampo therapy emphasizes concern for specific patient complaints and physical symptoms rather than the name of diseases in treatment. Patients who wish for not only Western medicine but also Kampo Medicine are increasing. In modern medicine the expectation for Kampo Medicine is getting higher and higher1-3. And it is becoming more common for pharmacists to dispense Kampo medicines4.

Kampo medicines are used for many diseases and have contributed greatly to patient treatment. However, there also exist cases in which the patients’ symptoms deteriorate during Kampo medicines treatment and the treatment has to be discontinued. To investigate the reasons for discontinuance of Kampo medicines and to discuss the relationship between Kampo medicines and the reasons for their discontinuance are critical steps in aiding pharmacists to give proper patient instructions regarding Kampo medicines. After receiving permission from our institute’s ethics committee, we investigated the cases in which Kampo medicines were discontinued at our institute. Based on the results of this investigation, we examined how to improve continuance of Kampo medicines through improving pharmacist’s patient instructions.

Methods

1. Period and Subject of Investigation
We investigated the cases in which prescribed Kampo medicines were discontinued by doctors at the outpatient Kampo clinic of Oriental Medicine Research Center of the Kitasato Institute, during the period from May 2000 to December 2003 (44 months).

2. Classification of Reasons for Discontinuance
We classified the reasons for discontinuance of Kampo
medicines into three categories: symptoms found after taking Kampo medicines, the tastes and smell of Kampo medicines, and others. We also classified the symptoms found after taking Kampo medicines into cases in which the main complaint was aggravated and diseases other than the main complaint. Furthermore, we classified the main complaint and other diseases into categories according to the symptoms. For symptom classification, when a fever was accompanied with cough or dyspnea, we classified it as respiratory organs symptoms, and when there was no respiratory organs symptom we classified it as others.

3. The Prescriptions Related to the Discontinuance and the Source Herbal Medicine

Among the prescriptions used in the cases in which Kampo medicines were discontinued, we looked over prescriptions that appeared in two or more such cases and the herbal medicines considered as the reason for adverse effects. Furthermore, we analyzed prescriptions including the crude drugs, which were considered to cause adverse effect among discontinued Kampo medicines, and calculated the incidence rate of adverse effect caused by crude drugs in the occurrence of symptoms after taking Kampo medicines. We also examined their relation with the reasons for discontinuance of the Kampo medicines. The Japanese Traditional Drug’s Name (JTDM) was used for the name of the prescription.

4. Prevention Measures Based on the Investigation Results

Based on our investigation results, we examined the necessary countermeasures for pharmacists’ patient instructions to prevent the discontinuance of Kampo medicines.

Results

1. The Number of Cases of Discontinuance of Kampo Medicines

Among 119,000 outpatients from May 2000 to December 2003, the number of cases in which Kampo medicines were discontinued was 351, and accounts for 0.29% of all cases. In this investigation, no relation was found between treatment periods and discontinuance.

2. The Reasons for Discontinuance of Kampo Medicines

Among the 351 cases of discontinuance of Kampo medicines, the most frequent reason for discontinuance was because of the occurrence of symptoms after taking the medicines (265 cases). The second reason given was taste and/or smell (37 cases). There were 49 cases categorized as “others” (Fig. 1).

In cases of discontinuance because of the taste and/or smell of Kampo medicines, most complaints were “could not drink because it smelled of cinnamon,” “could not drink because it was too bitter,” “could not drink because it smelled like medicine,” and etc. Related to the smell of cinnamon, there were 10 cases in which the prescriptions included Cinnamomi Cortex. There were 6 cases in which the prescriptions included Coptidis Rhizoma, which is very bitter. However, there were 21 cases not related to Cinnamomi Cortex and Coptidis Rhizoma in which the reason for discontinuance was the complex taste of the Kampo medicines, and not the taste of a specific ingredient.

Other reasons for discontinuance included cases in which the patients overreacted on information regarding adverse effects; cases in which the patients preferred their previous prescriptions to the new ones; and cases in which Kampo
medicines were discontinued because of pregnancy or death.

In cases of discontinuance due to the occurrence of symptoms after taking the medicines, there were 109 cases in which the main complaint was aggravated. There were 72 cases of upper digestive track symptoms, 54 cases of lower digestive track symptoms, 44 cases of skin symptoms, 44 cases of psychological nervous system symptoms, 27 cases of respiratory organs symptoms, and 79 cases of others.

We classified the main disease and other diseases into categories according to the symptoms (Fig. 2).

A. Among the 109 cases of main complaint aggravation, 66 cases were because of skin symptoms such as rash and/or itch, 17 cases were because of lower digestive track symptoms such as diarrhea and/or abdominal pain, and 6 cases were because of sleeplessness.

Classification of cases of diseases other than main complaint aggravation is as follows:

B. Among 72 cases of upper digestive track symptoms, there were 28 cases of nausea and/or vomiting, 14 cases of stomachache, and 14 cases of epigastic distress.

C. Among 54 cases of lower digestive track symptoms, there were 33 cases of diarrhea, 9 cases of abdominal pain, and 6 cases of constipation.

D. Among 44 cases of skin symptoms, there were 28 cases of rash, and 9 cases of itch.

E. Among 44 cases of psychological nervous system symptoms, there were 8 cases of headache and/or sluggishness, 7 cases of sleeplessness, and 6 cases of dizziness.

F. Among 27 cases of respiratory organs symptoms, there were 10 cases of cough and/or phlegm, 7 cases of dyspnea, 6 cases of fever.

G. There were 79 cases that do not fit in any of the above categories, including 15 cases of edema, 14 cases of liver dysfunction, 14 cases of fever, 11 cases of labial paralysis, 6 cases of stiff neck, 6 cases of paralysis of hand and/or feet, and 6 cases of body ache.

We found that skin symptoms in main complaint aggravation, diarrhea in lower digestive track symptoms, and rash in skin symptoms accounted for over 60% of incidents. On the other hand, in the group of psychological nervous system symptoms...
symptoms, the “others” had a high rate of 52%, and included uneasiness, flush, lassitude, and irregular heartbeat etc.

3. The Prescriptions Related to the Discontinuance and the Source Herbal Medicines

We investigated prescriptions and herbal medicines that were reported to have adverse effects\(^6\).

Furthermore, in this investigation we determined the adverse effects of herbal medicines and their rate of occurrence (Table 1). Based on this adverse effect report, we examined the prescriptions related to the discontinuance and the source herbal medicines. For each symptoms (except E: psychological nervous system symptoms), we investigated the ingredient herb medicines that were included in two or more prescriptions used in discontinuance cases, examined the herbal medicines related to adverse effects and prescriptions that have these herbal medicines, and the relations to other adverse effects (Table 2).

A. Rash, Itch, and Diarrhea as Main Complaint

For rash and/or itch, there were 4 cases of Orengedokuto (JTDN) added to Jumihaidokuto (JTDN), 3 cases of Unseiin (JTDN), 3 cases of Keishikaogito (JTDN), 3 cases of Saikokeishito (JTDN), 3 cases of Juzentaihoto (JTDN), and 2 cases of Orengedokuto (JTDN) added to Yokukansan (JTDN). Among these prescriptions, the herbal medicines that were reported to be responsible for the adverse effect of rash and/or itch were Cinnamoni Cortex and Ginseng Radix. There is Cinnamoni Cortex in Keishikaogito (JTDN), and both Cinnamoni Cortex and Ginseng Radix in Saikokeishito (JTDN) and Juzentaihoto (JTDN). There are no herbal medicines that causes rash and itch in Orengedokuto (JTDN) added to Jumihaidokuto (JTDN), but Schizonepetae Spica, Bupleuri Radix, Cnidii Rhizoma, Araliae Cordatae Rhizoma and Saposhnikoviae Radix in Jumihaidokuto (JTDN) are considered to have an emission action for skin (to excrete an
### Table 1. Adverse Effects of Herbal Medicines.

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Herbal Medicines</th>
<th>Number of the adverse effect (incidence rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure rise, Edema, Lassitude, General fatigue, Paralysis</td>
<td>Glycyrrhizae Radix</td>
<td>10 (3.8%)</td>
</tr>
<tr>
<td>Rash</td>
<td>Cinnamomi Cortex, Ginseng Radix</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Ginseng Radix</td>
<td>0</td>
</tr>
<tr>
<td>Skin red, Itch</td>
<td>Cinnamoni Cortex</td>
<td>14 (5.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Rehmanniae Radix, Cnidii Rhizoma, Angelicae Radix, Aconiti Tuber, Ephedrae Herba</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Rehmanniae Radix, Ephedrae Herba</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Gardeniae Fructus, Zizyphi Spinosi Semen, Rehmanniae Radix, Gypsum Fibrosum, Cnidii Rhizoma, Rhei Rhizoma, Angelicae Radix, Ephedrae Herba</td>
<td>0</td>
</tr>
<tr>
<td>Epigastric distress</td>
<td>Gardeniae Fructus, Rehmanniae Radix, Gypsum Fibrosum, Cnidii Rhizoma, Angelicae Radix, Ephedrae Herba</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Zizyphi Spinosi Semen, Rhei Rhizoma, Natrium Sulfuricum</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Gardeniae Fructus, Zizyphi Spinosi Semen, Rehmanniae Radix, Gypsum Fibrosum, Cnidii Rhizoma, Rhei Rhizoma, Angelicae Radix, Natrium Sulfuricum</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td>Labial paralysis, Palpitation, Flush</td>
<td>Aconiti Tuber</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Sleeplessness, Excessive sweat, Pollakisuria, Palpitation, General fatigue, Excitement, Urination disorder</td>
<td>Ephedrae Herba</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 2. Relation to the Adverse Effects of Herbal Medicines and their Composition.

<table>
<thead>
<tr>
<th>Disease(n)</th>
<th>Symptom(n)</th>
<th>Prescription(n)</th>
<th>Cause of Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Primary complaint (106)</td>
<td>Skin symptoms (66)</td>
<td>Rash and/or Itch (66)</td>
<td>Orenegokudotto added to Jumihaidokuto (4), Unsein (3), Keishiikagito (3), Saikokeishithito (3), Juzentaihoto (3), Orenegokudotto added to Yokukamsan (2)</td>
</tr>
<tr>
<td></td>
<td>Digestive Symptoms (17)</td>
<td>Diarrhea (8)</td>
<td>Kamishoyosan added to Kososan (2)</td>
</tr>
<tr>
<td>B. Upper digestive track symptoms (72)</td>
<td>Nausea and/or Vomiting (28)</td>
<td>Kamikihito (2), Hocysukkito (2)</td>
<td>Angelicae Radix</td>
</tr>
<tr>
<td>C. Lower digestive track symptoms (54)</td>
<td>Diarrhea (33)</td>
<td>Keishibakuryogun (5), Tokakukajkito (3), Juzentaihoto (2)</td>
<td>Rehmanniae Radix, Rhei Rhizoma, Angelicae Radix, Persicariae Semen, Natrium Sulfuricum, Moutan Cortex</td>
</tr>
<tr>
<td>D. Skin symptoms (44)</td>
<td>Rash (28)</td>
<td>Keishibakuryogun (2)</td>
<td>Cinnamomi Cortex</td>
</tr>
<tr>
<td>F. Respiratory organs symptoms (27)</td>
<td>Dyspnea (7)</td>
<td>Orenegokudotto (2)</td>
<td>Interstitial pneumonia</td>
</tr>
<tr>
<td>G. Others (65)</td>
<td>Edema (15)</td>
<td>Keishikuyosakukyukato (1), Kososan (1), Syakuyakukanzuto (1), Jumihaidokuto (1), Shousaijito (1), Shokunenkoto (1), Seishinrenshin (1), Tokukuncho (1), Bofutsushosan (1), Hochuikikito (1)</td>
<td>Glycyrrhizae Radix</td>
</tr>
<tr>
<td></td>
<td>Liver Dysfunction (4)</td>
<td>Saikokeishikakgyukoto (1), Saikokeishikakgyukoto (1), Saikogakuto (2), Saireito (1), Shousaijito (1), Daisaijito (1)</td>
<td>Saiko-zai (the name of prescription that has Bupleuri Radix (5-7g))</td>
</tr>
<tr>
<td></td>
<td>Fever (13)</td>
<td>Orenegokudotto (3), Saikokeishikakgyukoto (2), Seihakito (2)</td>
<td>Interstitial pneumonia</td>
</tr>
<tr>
<td></td>
<td>Labial paralysis (11)</td>
<td>Juzentaihoto added to Aconiti tuber (1), Hackuminjogun (1), Bukuhrongyukato (1)</td>
<td>Aconiti Tuber</td>
</tr>
</tbody>
</table>
etiology material out of the skin) according to Kampo Medicine theory\(^7\). It is possible that such an action on the part of these herbal medicines caused a rash and itch. For diarrhea, there were 2 cases of Kamishoyosan (JTDN) added to Kososan (JTDN). Gardeniae Fructus and Angelicae Radix in Kamishoyosan (JTDN) were reported to have the adverse effect of diarrhea.

B. Upper digestive track

For nausea and/or vomiting, there were 3 cases of Saiko-keishito (JTDN), 2 cases of Kamikihito (JTDN), and 2 cases of Hochuekkito (JTDN). Angelicae Radix in Kamikihito and Hochuekkito (JTDN) was reported to have the side effect of nausea.

C. Lower digestive track

For diarrhea, there were 5 cases of Keishibukuryogan (JTDN), 3 cases of Tokakujokito (JTDN), and 2 cases of Juzentaihoto (JTDN). Rhei Rhizoma and Natrium Sulphuricum in Tokakujokito (JTDN), and Rehmaniae Radix and Angelicae Radix in Juzentaihoto (JTDN) were reported to have the adverse effect of diarrhea. Also, according to Kampo Medicine theory, if Ku-oketsu-zai (herbal medicines that accelerate blood circulation, and improve pain, paralysis, and irritation), such as Persicae Semen and Moutan Cortex, are given to patients with weak stomachs, diarrhea may result\(^6\). Diarrhea was indeed found in cases in which Keishibukuryogan (JTDN), which has 4 g, each of Persicae Semen and Moutan Cortex, was used.

D. Skin

For rash, there were 2 cases of Keishibukuryogan (JTDN), in which Cinnamomi Cortex was reported to have the adverse effect of rash.

F. Respiratory organs

For dyspnea, there were 2 cases of Orengedokuto (JTDN), which was reported to have the adverse effect of dyspnea from interstitial pneumonia.

G. Others

Among the prescriptions in which edema appeared, 10 had Glycyrrhiza Radix. It was reported that Glycyrrhiza Radix has the adverse effect of edema. Among the 14 prescriptions in which liver dysfunction occurred, 8 were reported to have the adverse effect of liver dysfunction aggravation, and 7 contained Saiko-zai (the name of prescription that has Bupleuri Radix (5-7 g)). It was reported that the prescriptions in which fever occurred had the adverse effect of interstitial pneumonia. Also, in 3 of the prescriptions in which fever occurred, liver dysfunction occurred too. For labial paralysis, there were 3 prescriptions that had Aconiti Tuber. It was reported that Aconiti Tuber had the adverse effect of labial paralysis.

4. Prevention Measures Based on the Investigation Results

1) When a doctor decided to discontinue Kampo medicines due to the occurrence of symptoms after medicines were taken, the reasons for discontinuance were recorded in the clinical record. However, in some cases, if one only depends on the clinical record, it is hard to understand the relationship between the reasons for discontinuance and the Kampo medicines. Therefore, in addition to the clinical record, we required that the reasons for discontinuance be recorded on a "Discontinuance Sheet" maintained by the pharmacists (Fig. 3). The original "discontinuance sheet" recorded by the doctor is attached to the clinical record, and a copy of it is distributed to the pharmacy so the necessary information is recorded in the patients’ pharmaceutical history. This made it possible for pharmacists to understand the reasons for discontinuance in detail.

2) When the reasons for discontinuance are related to Kampo medicines and herbal medicines, the related medicines should be recorded at the "forbidden/allergy" column in both the clinical record and the pharmaceutical history. Furthermore, red marks are made on the right corner of both sides of the pharmaceutical history to distinguish it from other pharmaceutical histories. In this way, we have prevented the Kampo medicines or herbal medicines that were the reason for discontinuance from being prescribed again.

3) We required distribution of the medical history questionnaire filled in by new patients before their examination. Referring to the questionnaire, pharmacists are able to understand the current medical history of new patients when they dispense Kampo medicines or give patient instructions, pharmacists can also check if there is a potential problem when using Kampo medicines in conjunction with Western medicines or supplements. We also required checking for patients who are allergic to foods such as cinnamon, if herbal medicines containing such ingredients were included in the prescribed Kampo medicines.

4) When pharmacists give patients instructions, we require them to understand the tastes of prescribed Kampo medicines, and to make sure to explain the tastes to new patients or patients who had a new prescription.

Discussion

In this investigation, the rate of discontinuance of Kampo medicines because of adverse effects or other reasons was 0.29%. This is very low compared to other institutes\(^5,10\). According to "A Classification Standard by Degrees of Seriousness for Side Effects Caused by Medical Supplies," the symptoms that occurred were very light, equal to grade 1\(^11\). Serious side effects found in general hospitals' report (grade 3) were not found\(^12\).

As for the reasons for discontinuance, cases in which symptoms occurred after taking Kampo medicines accounted 75% of the total. The rate of skin symptom aggravation as the main complaint was especially high. This is probably because most of the outpatients of our institute had skin diseases\(^13\). Also, skin can be more sensitive to medicines. This is probably why there were more cases of discontinuance because of skin symptoms.

The next most common reason for discontinuance was digestive track symptoms: diarrhea was first, nausea and vomiting second. This is probably because many Kampo medi-
Cines are liquid oral medicines. Reactions found a short time after the medicines were taken were mostly digestive track symptoms. Also, the prescriptions used in cases of nausea and vomiting were less bitter and comparatively easy to drink. Patients complained that they felt ill after taking the medicines. Generally, Kampo medicines with stronger bitterness are considered hard to drink. However, for some patients it is possible that the smell of Angelicae Radix or the sweetness of Glycyrrhizae Radix and Ginseng Radix caused nausea and vomiting.

Among the cases of respiratory organ symptoms or fever after taking Kampo medicines, some cases involved prescriptions previously reported as being related to interstitial pneumonia. On the other hand, when Kampo medicines thought to have a causal relationship with interstitial pneumonia were prescribed, a note of “in some rare cases, symptoms such as fever, dry cough, or dyspnea were reported after these medicines were taken” was printed on the medicine bag. Therefore, patients may have feared these kinds of adverse effects. There were cases in which fever caused by a cold or influenza was mistakenly attributed to a adverse effect of Kampo medicines. Regarding adverse effects, we believe that it is necessary to not only offer written information, but also to explain the meaning to patients in person. Among the cases of liver dysfunction, 8 cases out of 14 used prescriptions that were reported to have the adverse effect of liver dysfunction. This suggests that taking Kampo medicines caused the liver dysfunction.

11% of discontinuation cases were because of the taste and/or smell of Kampo medicines. Kampo medicines have a complex taste—a mix of bitterness and sweetness—since Kampo medicines include multiple herbal medicines that have different tastes. Although patients can get used to Kampo medicines that fit their predisposition, there are many cases in which they cannot take Kampo medicines that do not fit their predisposition. If patients force themselves to take Kampo medicines that do not fit them, it may cause nausea and vomiting. When giving patients instructions, it is necessary for pharmacists to explain the taste and smell of Kampo medicines in addition to how to take the medicines and their possible side effects. In addition, there are many patients who have food allergies. It is important to check if there is any ingredient that may trigger a food allergy in the Kampo medicines. Therefore, pharmacists must know about the taste and/or smell of, and the possible food allergies related to, Kampo medicines and make such information clear in patient instructions.

Based on the investigation results, we examined methods to improve continuance of Kampo medicines. To help pharmacists understand the reasons for discontinuance, a “Discontinuance Sheet” was made which revealed the reasons for discontinuance. It also helps prevent re-prescribing the same
prescription when Kampo medicines were related to the discontinuance. Furthermore, we required an explanation of the tastes, possible food allergies, and the side effects of Kampo medicines to patients, and improved pharmacists’ patient instructions by helping them to understand information gathered from the patients. In 2004, when we practiced these countermeasures, the discontinuance cases were 78 among 31655. The number of discontinuance cases in a year dropped from 96 to 78. Especially, the rate of discontinuance caused by taste and/or smell dropped from 11% to 4%.

We clarified the reasons for discontinuance of Kampo medicines, and improved pharmacists’ patient instructions. By doing so, we were able to decrease the number of discontinuance cases. This report is meaningful in a way that reflects the role of pharmacists as part of the medical team for proper treatment of Kampo medicines.

References