Research Review

Adverse Effects of Kampo Medicine

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In the past in Japan, when unexpected incidents occurred by the administration of Kampo prescriptions, those are not recognized as adverse effects but the drugs used are prescribed under incorrect diagnosis in the patient's symptom or the essential worse reaction to make a full recovery. However, now the adverse effect of Kampo prescriptions are well recognized, and when it happens, the medication should be stopped and suitable treatment is needed. The most frequent adverse effect occurred by Kampo prescriptions is gastrointestinal disorders, and rehmanniae radix, gypsum, ephedrae herba, and angelicae radix sometime cause. In addition, drug eruption and cystitis due to allergy sinetunes occur with several kinds of crude drugs. Furthermore, various symptoms caused by the sympathetic stimulation of ephedrine contained in ephedrae herba, pseudoaldosteronism caused by glycyrrhizae radix, aconitine poisoning caused by aconiti radix processa, interstitial pneumonia and drug-induced liver injury caused by scutellariae radix, mesenteric phlebosclerosis caused by gardeniae fructus has been reported.

Keywords: Kampo prescriptions, adverse effects, drug allergy, pseudoaldosteronism, interstitial pneumonia, drug-induced liver injury, mesenteric phlebosclerosis

Japan has a centralized medical system centered on Western medicine, and Japanese traditional Kampo medicine is also used in this system. In recent years, with the spread of Kampo medicines, it has been found that Kampo prescriptions also have considerable side effects [1]。 In the past, when unexpected incidents occurred by the administration of Kampo medicine, those are not recognized as adverse effects but the drugs used are prescribed under incorrect diagnosis in the patient's symptom or the essential worse reaction to make a full recovery. However, now the adverse effect of Kampo medicines are well recognized, and when it happens, the medication should be stopped and suitable treatment is needed.

Kampo formula is a mixture of several crude drugs, and their adverse effects can be explained by the crude drugs contained therein. The side effects that can be caused by each crude drug are described below.

1. Gastrointestinal disorders

The most frequent side effects of Kampo medicines are gastrointestinal disorders. Typical crude drugs that induce gastrointestinal disorders include ground rehmanniae radix, gypsum, ephedrae herba, angelicae radix, cnidii rhizoma, and zizyphi spinosi semen. Among them, rehmanniae radix often causes anorexia, epigastric discomfort, epigastric pain, diarrhea, etc. Ephedrae Herba also causes anorexia and epigastric pain.

Most of these symptoms usually relieve if the drugs are stopped. Kampo prescriptions are basically administered before meals, but administration after meals may avoid to cause such symptoms.

2. Drug allergy

It is known that some crude drugs easily cause allergic reactions to the living body. The most common symptom is on the skin (drug eruption). Rash or pruritus is sometimes caused by cinnamomi cortex, ginseng radix, astragali radix, rehmanniae radix, tritici fructus, oryzae fructus, dioscoreae rhizoma, and perillae herba [2; 3]. In addition to these crude drugs, there are reports on crude drugs

and prescriptions that caused a rash upon taking drugs. Drug allergies occur not only in crude drugs but also in Western drugs at a certain rate, so it is necessary to pay close attention to the patient's medical history in order to prevent the occurrence.

<Case report>

The patient is a 56-year-old man. A few years ago, renal function was pointed out, but a doctor at a visiting hospital told him that his serum creatinine level was so high that hemodialysis would be needed soon. Then, he visited my clinic on May 6, 20XX. The serum creatinine level was 5.78 mg/dl. I prescribed him for yojinkodakuto. Astragali radix was 20 g. Creatinine continued to fall as expected, reaching 2.16 mg/dl on July 31. However, at this point, a strong pruritic rash appeared on his entire body, and I was forced to discontinue the prescription. His serum creatinine level began to rise gradually, reaching 3.85 mg/dl on November 28, but when I administered the same prescription instead of astragali radix, the rash appeared two weeks later, serum creatinine dropped to 3.21 mg/dl.

In addition, drug-induced cystitis has been reported for saireito, shosaikoto, saibokuto, saikokeishito, seijobofuto, and unseiin. It has been reported that the administration of these Kampo prescriptions caused cystitis-like symptoms, such as dysuria, dysuria, pollakiuria, pusuria, and hematuria [2; 3]. The pathological condition is drug-induced cystitis, *i.e.*, eosinophilic cystitis with eosinophil infiltration. Some allergic mechanism has been speculated. As of 2011, 90 cases of cystitis were reported due to Kampo prescriptions in Japan, and among these prescriptions, 80 cases are using prescriptions including scutellariae radix [4]. These are rare side effects, and withdrawal of the drug often improves the symptoms promptly, but care must be taken.

3. Licorice-induced pseudoaldosteronism

Glycyrrhizae radix is the dried root and stolon, with (unpeeled) or without (peeled) the periderm, of *Glycyrrhiza uralensis* Fischer or *Glycyrrhiza glabra* Linné (Leguminosae), and it is commonly called as licorice root. This causes pseudoaldosteronism with some frequency. Therefore, it is necessary to pay attention to physical findings (edema, increased blood pressure) during the administration and to measure potassium in the blood regularly. In Europe, where licorice is used as a food additive sweetener, this side effect has long been reported [5-8]. In Japan, the incidence of pseudoaldosteronism due to Kampo prescriptions was said to be higher rate among elderly women. However, this is not true, and although there are large individual differences in the onset, it occurs in all generations regardless of gender at a fixed rate [9]. The onset of pseudoaldosteronism depends to some extent on the amount of licorice intake, and when using Kampo prescriptions containing 2.5 g or more of licorice per day, be sure to pay attention to the onset of this side effect. In addition, licorice is the most commonly prescribed crude drug in Japanese Kampo prescriptions. There is a possibility that the combination of Kampo prescriptions may not be noticed, or exceed amount when combined with the use of licorice as a food additive.

Symptoms of pseudoaldosteronism include hypokalemia, increased blood pressure, sodium/body fluid retention, edema, and weight gain. In severe cases, it causes myopathy and rhabdomyolysis. Therefore, attention should also be paid to weakness, muscle pain, limb spasms and paralysis, CK (CPK), etc. When licorice is used, serum potassium levels should be measured sufficiently. If abnormalities are observed, the administration should be discontinued, and appropriate treatments such as the administration of potassium agents should be taken as necessary. It also improves when used in combination with aldosterone antagonists such as eplerenone [10].

The component that causes pseudoaldosteronism caused by licorice is glycyrrhetinic acid (GA), a metabolite of glycyrrhizin contained in licorice by intestinal bacteria. GA inhibits type 11*β*-hydroxysteroid dehydrogenase (11*β*-HSD) 2 present in renal tubular epithelial cells, and the accumulated cortisol activates mineralocorticoid receptors, thereby excreting potassium to promote reabsorption of sodium and sodium, resulting in hypokalemia [7; 8]. However, since GA appears as a metabolite in the blood of all patients who take licorice, it cannot explain the individual differences in the occurrence of pseudoaldosteronism, so a search for a true causative substance instead of GA was conducted, At present, glycyrrhetinic acid-3-*O*-sulfate, another metabolite of glycyrrhizin, is estimated to be the causative substance [11], and hypoalbuminemia is considered as one of the risk factor to cause pseudoaldsteronism [12].

4. Palpitations, tachycardia caused by Ephedrae Herba

Ephedrae herba is the dried terrestrial stem of *Ephedra sinica* Stapf. This crude drug contains ephedrine that is a similar chemical structure to adrenaline and has a mixed sympathetic nervous system effect. The bronchodilating activity resulting therefrom can be said to be a scientific basis for the medicinal effects of ephedrae herba, but adverse effects sometimes occur including hypertension, tachycardia, palpitations, insomnia, and urinary retention.

<Case report>

68-year-old man. Two days ago, he arrived my clinic due to severe pain accompanied by swelling at the first toe of his right foot. Until now, it was pointed out that the uric acid level was high, but he said that he had left it alone. I diagnosed a gout attack, and prescribed eppikajutsuto extract. The patient came to my clinic the next day, and although the pain in the left first toe was alleviated, the patient said that after taking this prescription, urine was flowing only once. I thought this was a adverse effect of ephedrae herba and stopped it immediately, and i changed my prescription to ryutanshakoto. The dysuria disappeared, and the pain of the first toe of the left foot gradually resolved.

When administering Kampo prescriptions containing ephedrae herba to patients with circulatory disorders such as angina pectoris and myocardial infarction, with severe hypertension, renal disorder, hyperthyroidism, prostatic hypertrophy, prone to insomnia, careful observation and discretion should be taken not to exacerbate these diseases and conditions. The incidence of this side effect has individual differences and dose-dependency to some extent.

5. Aconite poisoning

Aconiti radix processa is the dried tuberous root of *Aconitum carmichaeli* Debeaux or *Aconitum japonicum* Thunberg (Ranunculaceae) prepared by the following processes. 1: Autoclaving. 2: Heating or autoclaving after rinsing in salt or rock salt solution. 3: Treating with calcium hydroxide after rinsing in salt solution. Before processing, contains aconitine, mesaconitine, etc., has strong analgesic activity, but also has strong toxicity [13; 14]. By heat-processing, aconitine and mesaconitine were hydrolyzed to become benzoylaconine and benzoylmesaconine, respectively, and their toxicity were reduced about 1,000-fold [14]. The Japanese Pharmacopoeia describes the upper limits on the contents of aconitine and mesaconitine in aconiti radix processa, that makes it relatively safe to use, but may still cause poisoning in sensitive patients. The initial symptoms of sticking poisoning are numbness and palpitations, and the patients with those symptoms need to stop using or reduce the dosage. Among the preparations of aconiti radix processa marketed in Japan, some manufacturers produce the contents of aconitine and mesaconitine near the upper limit to

have high analgesic effect, but these products may easily cause side effects. On the other hand, the active ingredient of aconiti radix processa for neuropathic pain is not the highly toxic alkaloid, but neoline, an alkaloid that does not hydrolyze. [15]. Therefore, even if the heat treatment is performed well to completely decompose highly toxic alkaloids, it is also useful for neuropathic pain.

<Case report>[16]

The patient is a 78-year-old woman. Since X–31 year ago, she has suffered from rheumatoid arthritis. She visited my clinic in the year X. Administration of daibofuto decoction containing 4.5 g of unprocessed aconiti radix markedly improved her joint pain and laboratory findings. However, the joint pain was exacerbated on October 7th, X+2 year. Then, the drug was changed to uzuto decoction containing 4.5 g of unprocessed aconiti radix. On October 11th, one hour after the oral administration, she developed blurred eyes and pharyngeal strangulation, and vomited three times. Since the heart rate dropped to 60/min and the blood pressure dropped to 90 mmHg, blood vessels were secured and the electrocardiogram was monitored. Although he did not receive any special treatment, it improved as it was.

6. Interstitial pneumonia and drug-induced liver injury

These side effects of Kampo medicines have been reported since 1989. Prior to that, it may have been, but never mentioned. Of particular note was the report that 88 patients who took Shosaikoto developed interstitial pneumonia in the three years since 1994, of which 10 died. However, its frequency is extremely low, and according to Homma's research, the frequency of occurrence is almost 100,000 per 4 people / year [17]. Among them, most of the patients had chronic hepatitis B and C, and interferon was used in almost all patients. Therefore, the concomitant use of shosaikoto and interferon preparations is currently contraindicated. In a survey of Tsumura ethical shosaikoto extract preparations from October 1995 to March 1997, 69 cases (2.8%) out of 2,495 patients were reported to have adverse effects including abnormal laboratory test.

<Case report>[18]

A 71-year-old woman was hospitalized with a diagnosis of pneumonia. She had fever, cough, dyspnea, and diffuse granular reticular shadows in both lung fields on chest X-ray. I suspected summer-type hypersensitivity pneumonitis, but I chose no medication since the condition is not but. However, her condition had been further exacerbated, I suspected drug-induced pneumonia, and all medications were discontinued and prednisolone was administered. Chest X-rays improved markedly. Transbronchial lung biopsy showed interstitial pneumonia, and lymphocyte stimulation test showed positive for shosaikoto. The challenge test revealed fever, hypoxemia, and the appearance of interstitial pneumonia on chest X-ray. This case report appears to be the first of drug-induced pneumonia caused by shosaikoto.

Following this report, the similar adverse effects were seen in more than 15 Kampo extract formulations including scutellariae radix that is the dried root of *Scutellaria baicalensis* Georgi (*Labiatae*), from which the periderm has been removed. Then, it was speculated that this adverse effect was probably due to scutellariae radix. It is predicted baicalin, which is contained in scutellariae radix in relatively large amounts binds to albumin to become hapten, and that the sensitization is established. However, this is only a prediction and future research is required.

Scutellariae radix has also been suspected to cause drug-induced liver injury. Some patients have increased ALT/AST in a short time after taking scutellariae radix [19]. Although the frequency is

extremely low, it is often asymptomatic. Therefore, it is desirable to conduct a liver function test within a few weeks after administration of the preparation. In addition, the cases of fever have been reported. Fever is also a subjective symptom, and is relatively easy to find. It is reported by Terashi et al. [20].

At present, about 40 kinds of Kampo formulas that caused liver disorders, and about 30 kinds of Kampo formulas that caused lung disorders have been reported. It is said that these cases are relatively common in the elderly, but this is not always the case, and the cause is thought to be due to a specific constitution such as allergy. Therefore, the only way to prevent these adverse effects is to carefully detect and respond to the history of drug or food allergies at the time of drug administration.

Formulas reported to cause interstitial pneumonia: Shosaikoto, daisaikoto, saikokeishito, saibokuto, saireito, saikokeishikankyoto, saikokaryukotsuboreito, hangeshashinshinto, shoseiryuto, bakumondoto, hochuchuekkito, goshajimkigan, seihaito, shin'iseihaito, junnchoto, seishinreshiin, boiogito, bofutsushosan, otsujito, orengedokuto, yokukansan, keigairengyoto, nijutsuto, unseii, gorinsan, sanoshashinto, shakuyakukanzoto, daikenchuto, ryuchoshakoto.

Formulas reported to cause drug-induced liver injury and jaundice: Otsujito, daisaikoto, shosaikoto, shosaikotokakikyosekko, saikokeishito, saikokaryukotsuboreitoto, saikokeishikenkyoto, saibokuto, saireito, orengedokuto, sanmotsuogonto, shakuyakukanzoto, hangeshashinto, unseiin, shoseiryuto, maobushisaishinto, kakkonto, seihaito, seijobofuto, shin'iseihaito, bakumondoto, nyoshinsan, keishibukuryogan, kamishoyosan, rikkunshito, hochuekkito, ninjinyoeito, daikenchuto, nijutsuto, juzentaihoto, boiogito, bofutsushosan, junchoto, inchinkoto, goshajinkigan, keigairengyoto, seishinrenshiin, yokukansan, ryutanshakanto, sanoshashinto, goshuyuto, goreisan.

Although interstitial pneumonia and drug-induced liver injury caused by Kampo prescriptions are not so frequent, these adverse effects should be noted. When fever, cough, dyspnea, or abnormal lung sounds (fine crackles) appears, the administration of Kampo prescriptions should be discontinued, chest X-rays should be immediately examined, and the appropriate treatment such as the administration of corticosteroids should be performed. It is also necessary to conduct liver function tests regularly to prevent drug-induced liver injury.

7. Mesenteric phlebosclerosis caused by gardeniae fructus

It has been reported that mesenteric phlebosclerosis caused by Kampo prescriptions. In 2013, the Research group funded from Ministry of Health, Labor and Welfare conducted national survey, and reported that over 80% of mesenteric phlebosclerosis patients took Kampo prescriptions containing gardeniae fructus. More than 90% of the patients had taken the drugs more than 5 years [21].

Gardeniae fructus is the dried fruit of *Gardenia jasminoides* Ellis (*Rubiaceae*). There are many Kampo formulas containing gardeniae fructus, but the special attention is needed for eight formulas such as kamishoyosan and orengedokuto. If the patients who have been taking these prescriptions for 5 years or more have repeated abdominal pain, diarrhea, constipation, abdominal bloating, nausea/vomiting, or have positive fecal occult blood (asymptomatic), it is necessary to conduct colonoscope and CT inspection. If there are characteristic symptoms such as dark purple or bronze color on the mucous membrane at the right colon, linear or dotted calcification along the colon wall or mesenteric vein on CT, the calcification of venous wall and the increased collagen fibers in the histopathology, the drugs should immediately be discontinued. The prognosis is generally good by the withdrawal of Kampo prescription, but it takes a long time to improve fibrosis and calcification. In the

case of long-term administration of Kampo prescription containing gardeniae fructus, it is desirable to conduct a fecal occult blood test, regular colonoscopy once every 1 to 2 years, simple abdominal CT test, etc. [22].

<Case report>[22]

The patient is a 65-year-old woman. In July in X year, she visited my hospital to take Kampo medication for hepatitis C. Initially, hochuekkito had been administered, and then changed to saikokeishikankyoto, keishibukuryogan, etc. Thereafter, the dosage of gardeniae fructus was temporarily reduced to 5 g/day, but had been soon returned to 15 g/day and continued. At X+13 year, her cumulative intake of gardeniae fructu was 5,379 g for 9.4 years. There were no findings such as abdominal pain, abdominal distension, abdominal tenderness, etc., but under the patient's consent, colonoscopy was performed in May in X+17 year. Blue pigmentation and mild edema were observed on the mucosa of the cecum, ascending colon, and transverse colon. Histopathological test also showed increased submucosal collagen fibers in the cecum, ascending, and transverse colon. This confirms the diagnosis of mesenteric venous sclerosis

8. Lactose allergy and intolerance

Drug adjuvants such as excipients are contained in Kampo extract prescriptions. Commonly used excipients are lactose, starch, cellulose and so on. Among these, lactose contained only a small amount of milk-derived protein as an impurity, which could be a problem for milk allergy patients. However, even patients with relatively severe milk allergy have no abnormalities in the results of oral lactose tolerance test [23]. Lactose intolerance has been reported to be less than 1% in ethical Kampo prescriptions using lactose as an excipient [24]. Therefore, it is considered to be of little concern clinically. However, since secondary lactose intolerance such as after gastroenteritis in infants and children is clinically experienced, it is better to use lactose-free Kampo preparations for the symptoms of prolonged diarrhea after gastroenteritis.

9. Aristolochic acid-induced kidney injury and cancer

It was reported in Belgium that people who took weight-loss herbal preparations developed kidney injury that required dialysis and transplantation between 1990 and 1992 [25]. In this preparation, *Aristolochia fangchi* (Aristolochiaceae) that contains aristolochic acid, which are nephrotoxic and carcinogenic, was found. In Japan, there have been some case reports of kidney injury caused by Tokishigyakukagosyuyushokyoto preparation using the stem of *Aristolochia manshuriensis* as an ingredient instead of akebiae caulis, the dried stem of *Akebia quinata* Decaisne or *Akebia trifoliata* Koidzumi (Lardizabalaceae), and herbal dietary supplements containing aristolochic acid [26; 27].

At present, the distribution of crude drugs containing aristolochic acid is banned not only in Japan but also in other countries. Therefore, it is thought that the toxicity of aristolochic acid will not occur with regular drugs. However, the possibility to use the products distributed in unregulated internet market or the old herbal product before ban is undeniable, care must be taken account.

Conclusion

As descried above, Kampo medicines also have many adverse effects. Diarrhea caused by rhei rhizoma, the dried rhizome of *Rheum palmatum* Linné (Legminozae), etc. or sal mirabilis, a mineral substance, mainly composed of sodium sulfate hydrate ($Na_2SO_4 \cdot 10H_2O$) is not adverse effect but the excessive mistaken dosage. However, in clinical practice, a wide variety of adverse effects from very slight allergies to severe liver damage has been experienced. These can be can be led quickly in a short period without any serious situation if the physician and pharmacist find it and perform

appropriate treatment immediately. Careful observation is the best way to deal with adverse effects.

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