

SHORT COMMUNICATION

The Risks of Using Personally Imported Traditional Chinese Drugs (Decoction)

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In Chinese herbal drugs, different drugs have the same name, causing confusion of drug origin which might cause harmful effects when clinically applied. We examined a 19-year-old female who acquired Chinese herbs syndrome (aristolochia nephropathy) induced by a mixture of crude Chinese drugs. She had imported the Chinese drug (decoction) consisting of approximately 20 natural elements and taken it for atopic dermatitis over a course of approximately 3 years. We identified "Guan Mutong" of Aristolochiaceae as analyzed by means of thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC). We confirmed aristolochic acid, a known nephrotoxin, from stem slices of "Guan Mutong" in her drug. It is not known if "Guan Mutong" was intentionally included in her imported Chinese drugs or put in by mistake. However, the present study has suggested the possibility that the Chinese herb "Guan Mutong" which is potentially nephrotoxic, might be accidentally delivered in the plant fraction of the Chinese drug. The possible adverse effects of crude Chinese drugs should be emphasized for patients who self-administer them.

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Introduction

Recently, herbal remedies (or “phytomedicines”) are increasingly used by the general public on a self-selection basis to replace or complement conventional medicines¹⁾. Many patients take OTC (over the counter) drugs or traditional medicine without consulting doctors^{2,3)}, and some obtain them by personal import⁴⁾. Many problems through the use of Chinese medicine have been reported⁵⁻⁹⁾. Chinese herbs nephropathy (CHN) is a recently described entity characterized by rapidly progressive renal failure which occurred in young females who attended a weight reduction clinic⁶⁾. It has been tentatively attributed to the ingestion of Chinese herbs containing aristolochic acid¹⁰⁻¹²⁾. Histological examination of the kidney discloses intense interstitial fibrosis with severe tubular atrophy contrasting with the absence of primary glomerular abnormalities^{6,13,14)}. Aristolochic acids are well-known nephrotoxins^{10,11)}. Moreover, aristolochic acids are among the most potent carcinogens yet known in rodents¹²⁾.

In the present study, we report an inpatient who had imported traditional Chinese drugs (decoction) by herself and had taken them over a long period had terminal renal failure. Renal transplantation was necessary due to Chinese medicine that consisted of approximately 20 natural ingredients. Here, we discuss the possibility and risks that the renal disease was caused by the Chinese plants.

Case

1. Patient

A 19-year-old woman without a previous

medical history of nephrosis had taken Chinese medicine (decoction) which she had obtained by personal import for the treatment of atopic dermatitis for 3 years from age 16. Despite nausea and vomiting caused by the drug, she had continued to take it in expectation of improvement of the disease. When she consulted a physician because of increased fatigue, she was diagnosed as having renal failure. She no longer suffered from nausea and vomiting after discontinuation of the medicine. She had no past nor family history of renal failure. With knowledge of her past drug history, her illness was suggested to be Chinese herbs nephropathy. The result of renal biopsy was compatible with Chinese herbs nephropathy.

2. Clinical Data

Laboratory findings on the first admission ; WBC : 4,600 (3,300-9,400)/ μ L, RBC : 332 (380-510) $\times 10^4$ / μ L, Hb : 8.8 (12-15) g/dL, Ht : 27.9 (35-45) %, PLT : 14.5 (13-32) $\times 10^4$ / μ L, S-Cr : 7.0 (0.5-0.9) mg/dL, BUN : 43 (7-22) mg/dL, UA : 3.7 (2.5-5.5) mg/dL, AST : 14 (0-30) IU/L, ALT : 18 (0-32) IU/L, ALP : 199 (68-185) IU/L, TC : 152 (150-220) mg/dL, TG : 76 (30-150) mg/dL, Glu : 86 (70-110) mg/dL, HbA_{1c} : 5.5 (4.3-5.8) %, () : normal range.

Methods

1. Identification of the Components of Chinese Medicine

The Chinese medicine was prepared by cutting out 1~3 cm of stems, seeds, fruits, flowers, roots, leaves and so on. Based on the external and internal characteristics, the botanical origin of the commercial Chinese medicine was

determined.

2. Extraction and Isolation of Aristolochic Acids

Some small pieces of the dried stems judged to be "Guan Mutong" were used for identification. The total weight of small pieces was 0.13 g. They were powdered, extracted with 200 μ L of ethyl acetate, and centrifuged at 10,000 rpm for 30 min, then the extract was used as a TLC sample. A small amount of solution (20 μ L) of the extract was used for HPLC after filtration through a membrane filter. A small part was applied to a TLC plate: Silica gel plate (Merck kieselgel 60 F 254, pre-coated plate), and the plate was developed with benzene/acetic acid (10 : 1) and benzene/ethyl acetate (4 : 1). Identification of spots on the plate was performed on the basis of their Rf values.

HPLC was performed on a Shimadzu LC-10 A system (Kyoto, Japan) [detection : 250 nm, column : μ Bondasphere (3.9 \times 150 mm), eluent : 1% acetic acid/tetrahydrofuran=65/35, flow rate : 0.6 mL/min, temperature : 25°C].

Results

1. Analysis of Chinese Medicines

The identification of herbal ingredients constituting Chinese medicine was determined based on the external characteristics of Chinese plants and animals¹⁵⁻¹⁹. The patient had taken the Chinese drug made up 20 dried components as the decoction. The daily dose of the Chinese medicine was about 230 g. All components except "Chan tui (ZENTAI)" (cicada molting) and "Bai hua she (BYAKKADA)" (snake) had botanical origin. Table 1 summarizes the 20 components of her prescription, including the Chinese (Japanese) name, natural origin, the family and parts used. We identified "Guan Mutong" of Aristolochiaceae in her prescrip-

tion and its weight was about 6.6 g/day.

2. Detection of Aristolochic Acids

Aristolochic acid in the "Guan Mutong" was analyzed quantitatively using TLC and HPLC. The standard aristolochic acids (SIGMA, St. Louis, MO., USA) contains 52.0% aristolochic acid I, 40.3% of II. The spot of the TLC sample had the same Rf of 0.50 as that of the standard when they were developed on the silica gel plate with benzene/acetic acid (10 : 1) at the same time. The spot of the sample was the same yellow color and had the same ultraviolet absorption as that of the standard. Aristolochic acid I and II were not separated under this condition. When the TLC sample and the standard were developed with benzene/ethyl acetate (4 : 1), their spots appeared at the same Rf of 0.3, but their shapes were broad.

However, the HPLC of the standard showed two peaks. Their retention times, 7.1 min and 7.8 min are thought to correspond to aristolochic acid I and II. However, which peak corresponds to I and which to II is unknown. The sample also showed two peaks which have the same retention time as those of the standard (Fig. 1). The weight of the sample was 0.13 g. According to the HPLC analysis of the sample, it was concluded that more than 310 μ g of aristolochic acid was contained in it.

Discussion

Recently, many Japanese take a variety of health supplements, including Chinese herbs. Many patients take Chinese medicine and health supplements without consulting a doctor²⁰, this is especially true of elderly patients. Women prefer Chinese herbs as dieting aids. A serotonin-active slimming agent²¹ had been inadvertently mixed in slimming herbs imported from China. A unique type of rapidly pro-

Table 1 Herbal Ingredients of Traditional Chinese Formula

Name (Japanese)	Natural Origin	Family	Part Used (Element*)
Guan mu tong (KANMOKUTU)	<i>Aristolochia manshuriensis</i> KOM.	Aristolochiaceae	Stem (A)
Jin yin hua (KINGINKA)	<i>Lonicera japonica</i> THUNB. ex MURRAY	Caprifoliaceae	Flower (A)
Chuan xiong (SENKYU)	<i>Ligusticum chuanxiong</i> HORT.	Umbelliferae	Root (A)
Chan tui (ZENTAI)	A kind of Cicada	Cicadidae	Insect molting (B)
Lian qiao (RENGYO)	<i>Forsythia suspensa</i> VAHL	Oleaceae	Fruit (A)
Ju hua (KIKUKA)	<i>Chrysanthemum morifolium</i> HEMSL	Compositae	Flower (A)
Can ger zi (SOIJISI)	<i>Xanthium strumarium</i> L.	Compositae	Fruit (A)
Yi mu cao (YAKUMOSOU)	<i>Leonurus japonicus</i> HOUTTUYN	Labiatae	Whole plant (A)
Gan di huang (KANJIO)	<i>Rehmannia glutinosa</i> LIBOSCH. var. <i>hueichingensis</i> CHAO et SCHIH	Scrophulariaceae	Root (A)
Nan sha shen (NANSYAJIN)	<i>Adenophora</i> sp.	Campanulaceae	Root (A)
Di gu pi (JIKOPPI)	<i>Lycium chinense</i> MILL.	Solanaceae	Root bark (A)
Man jing zi (MANKEISHI)	<i>Vitex rotundifolia</i> L.	Verbenaceae	Fruit (A)
Huang jing (OSEI)	<i>Polygonatum</i> sp.	Liliaceae	Root (A)
Huang qin (OUGON)	<i>Scutellaria baicalensis</i> GEORGI	Labiatae	Root (A)
Gan cao (KANZOU)	<i>Glycyrrhiza</i> sp.	Leguminosae	Root (A)
Gou qi zi (KUKOSI)	<i>Lycium chinense</i> MILL.	Solanaceae	Fruit (A)
Mai men dong (BAKUMONDO)	<i>Ophiopogon</i> sp.	Liliaceae	Root-tuber (A)
Niu bang zi (GOBOUSI)	<i>Arctium lappa</i> L.	Compositae	Seed (A)
She chuang zi (JYASYOUSI)	<i>Cnidium monnieri</i> CUSS.	Umbelliferae	Fruit (A)
Bai hua she (BYAKKADA)	<i>Agkistrodon acutus</i> GUNTHER	Viperidae	The entire body with- out the head (B)

The natural origins of these commercial crude drugs were classified according to their external morphology.

* Element ; (A) : Plant, (B) : Animal

gressive renal fibrosis, designated Chinese herbs nephropathy, has been described in regimens containing the recently introduced Chinese herbs (*Stephania tetrandra*, *Magnolia officinalis* and *Aristolochia fangchi* named "Fangji" in China)^{10~12}. Vanhaelen et al.¹¹) reported that 70 cases of progressive interstitial fibrosis were identified in Belgium from 1991 to 1992 and were related to slimming regimens which contained Chinese herbs called Stephania powder, and almost all Stephania powder contained aristolochic acid which caused renal

failure. Therefore it might be more appropriate to change the nomenclature of Chinese herb nephropathy, which is ambiguous, to aristolochic acid nephropathy²².

The first two cases of Chinese herbs nephropathy were reported in UK²³. The herbal preparations were found to contain aristolochic acid. The investigators stated that "their cases were of great concern, since the herbal preparations were from different sources and were prescribed for eczema". And it is also of our great concern that the patient in UK had taken

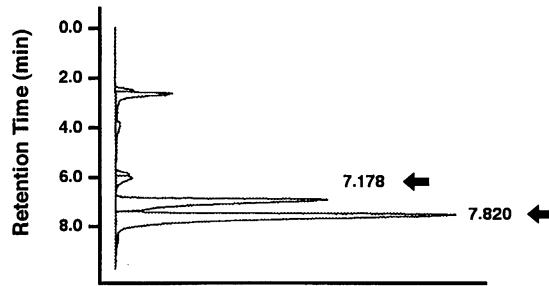
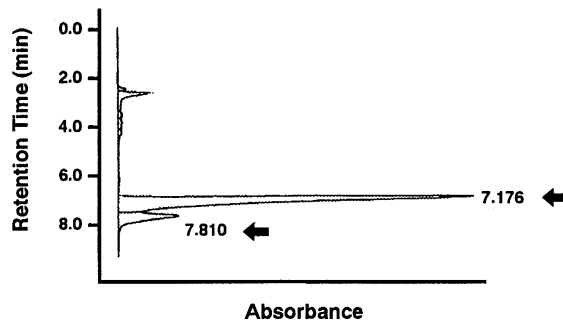
(A) Standard (Aristolochic acid I • II : →)**(B) Guan Mutong (KANMOKUTU) extract**

Fig. 1 Typical HPLC chromatogram of aristolochic acids obtained from Guan Mutong (KANMOKUTU) extract

Chinese herbal tea for chronic eczema for six years.

The present case had personally imported and taken the Chinese medicine. We analyzed almost all of the components of the herbal preparation and identified “Guan Mutong”. The total dose of “Guan Mutong” was approximately 6.6 g. The HPLC analysis revealed that more than 310 μg of aristolochic acid was contained in 0.13 g of “Guan Mutong”. The actual weight consumed by the patient was unclear, since she had taken the Chinese herbs as a decoction. We have proved the existence of aristolochic acid in the decoction.

The toxic component of the Chinese medicine in the present case was shown to be a plant of Aristolochiaceae known as “Guan Mutong” in

China. The name and origin of “Mutong” are quite different in Japan and China and also have local differences even within China^{17,18)}. There are also many confusing matters regarding “Mutong” and “Fangji”, including many plants in other families. These problems need to be carefully clarified.

In Chinese Pharmacopoeia²⁴⁾, the dried woody stem of *Akebia quinata* THUNB. DENCE. of Lardizabalaceae and *Aristolochia manshuriensis* KOM. of Aristolochiaceae are the origin of “Mutong”, “Tong Mutong” and “Guan Mutong”. “Hang Fangji” is the dried stem of *Stephania tetrandra* S. MOORE of Menispermaceae. In southern China, other plants of Aristolochiaceae are used as “Guang Fangji”. Whereas the Japanese Pharmacopoeia states

that “Mutong (MOKUTU)” is the dried stem of *Akebia quinata* THUNB. DENCE. in Lardizabalaceae. The origin of “Fangji” is listed in the Japanese Pharmacopoeia²⁵⁾ as also *Sinomenium acutum* REHDER et WILSON of Menispermaceae and is not the plant of Aristolochiaceae. It is necessary to compare the internal structure of the “Guan Mutong” of the present case with that of *Aristolochia manshuriensis* KOM. However it is impossible to obtain *Aristolochia manshuriensis* KOM. itself.

In Japan, herbal medicine is called Kampo. Although the word “Kampo” really means “medicine that comes from old Kan (Han) dynasty China”, the Kampo currently practiced in Japan and the traditional medicine in use at present in China are quite different^{15~18,26)}. It is important to acknowledge the differences between Japanese and Chinese medicines.

The present case shows the possible adverse effects of Chinese crude drugs on patients who self-administer them. First, the prescription of herbal medicines requires as much training as for the prescription of conventional drugs. Secondly, procedures for the identification and quality control of herbal medicines should not be less stringent than those applied to other medicines. Thirdly, medicines should never be combined without careful consideration of risk of interactions that may lead to toxicity. The present study highlights the risks of taking personally imported Chinese medicine without consultation of a medical professional.

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