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# A case of Aconiti Tuber (烏頭) poisoning following with change of Kampo formulae ; determining the cause

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**Abstract**

We experienced a case of Aconiti Tuber (烏頭) poisoning after only changing of Kampo formulae, both of which contained the same amount of it. An 80 year-old woman had been admitted because of severe low back pain by osteoporosis and compression fracture of the lumbar spine for about four months. Two days after changing the Kampo prescription from a decoction of Bukuryo-shigyaku-to (茯苓四逆湯) and pills of Hachimi-jio-gan (八味地黄丸, HJ) to a decoction of HJ mixed with Ninjin-to (人参湯) including 6.0 gm/day of Aconiti Tuber, she felt numbness of the lips and tongue, and chest discomfort. The electrocardiogram showed junctional premature contractions and intraventricular aberrant conduction. This period of arrhythmia lasted for about five hours and spontaneously disappeared. Analysis of the decoctions of these formulae showed that the highly toxic alkaloids derived from Aconiti Tuber in the latter prescription were five times greater in the former prescription. This increase in aconitine-type alkaloids was considered to be the cause of this Aconiti Tuber poisoning. There has been no report concerning an increase in aconitine-type alkaloids concentrations by changing from one to another Kampo formulae containing Aconiti Tuber.

**Key words** Aconitine-type alkaloids, Aconiti Tuber, Bukuryo-shigyaku-to, Hachimi-jio-gan, Ninjin-to.

**Abbreviations** BSG, Bukuryo-shigyaku-to, 茯苓四逆湯 ; HJ, Hachimi-jio-gan, 八味地黄丸 ; HJ-deco, decoction of Hachimi-jio-gan ; HJ-pills, pills of Hachimi-jio-gan.

## Introduction

Aconiti Tuber is one of the essential medical plants which has been empirically used in traditional Japanese Oriental (Kampo) medicine, and it possesses anti-inflammatory, analgesic and cardiotonic effects. In Kampo medicine, Aconiti Tuber is usually used as an ingredient of formulations for the treatment of painful disorders which are sometimes difficult to treat with modern Western medicine. However, Aconiti Tuber contains the highly toxic aconitine-type alkaloids of aconitine, mesaconitine and hypaconitine,[1,2] which are known to result in severe, and sometimes fatal poisoning.[3–7] Accordingly, we have always used it very carefully under the concept of traditional medicine.

We experienced a case of Aconiti Tuber poisoning following only the changing of Kampo formulations containing the same dose of it. In this report, we described this case and determined that the reason for this poisoning was an increase of aconitine-type alkaloids in the decoction.

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## I A case report

An 80-year-old woman was admitted on November 8, 1995, with a two-week history of low back pain. She could not stand and walk by herself because of severe pain. Her height, body weight and body temperature were 140 cm, 33 kg, 37.2°C, respectively. Her blood pressure was 130/70 mmHg and pulse rate was 68 beats/min. and regular. The heart sound had no murmur. Edema was not observed. There was no abnormality in the laboratory findings including blood and biochemistry examinations. A chest radiograph and an electrocardiogram (ECG) showed normal silhouette and sinus regular rhythm, respectively. Roentgenologic findings of her lumbar spine revealed severe osteoporosis and deformity (Fig. 1).

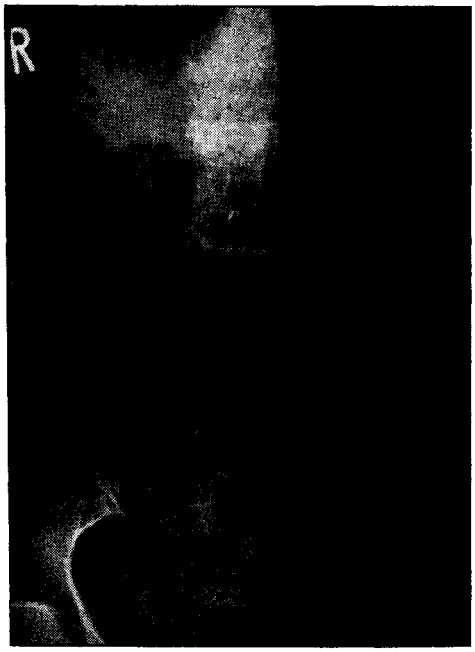


Fig. 1 Roentgenologic findings of the lumbar spine. This roentgenogram shows severe osteoporosis and deformity of her lumbar bone.

Her severe low back pain had been gradually improving by treatment with some Kampo prescriptions including Aconiti Tuber and rehabilitation (Fig. 2). The quantity of Aconiti Tuber given to her was adjusted according to the severity of her pain. Since Jan. 10, 1996, Bukuryo-shigyaku-to (BSG) was administered to improve not only her low back pain but also the coldness of her extremities. The pills of Hachimi-jio-gan (HJ-pills) which also include a slight amount of Aconiti Tuber, and had been used for her for some aging symptoms such as cataract, pollakysuria and numbness of legs previously, were started seven days after beginning BSG.

In March, her pain improved to a quarter level as compared to that on admission, but she also complained of epigastral discomfort which she already had before admission. Then, the decoction of BSG and HJ-pills were changed to the decoction of Hachimi-jio-gan (HJ-deco) mixed with Ninjin-to to treat gastro-intestinal symptoms rather than pain. The new prescription, which included the same amount of 6.0 gm/day of Aconiti Tuber, was given to the patient from noon on March 21. The medicinal plants in these prescriptions are listed in Table I. On the following

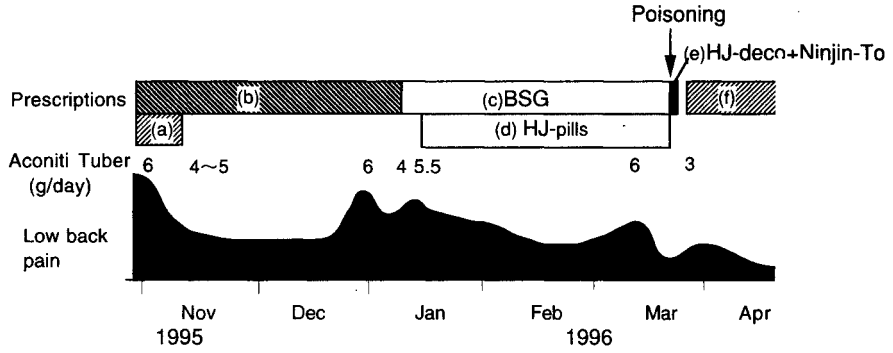


Fig. 2 The course of Kampo prescriptions, amount of Aconiti Tuber, and low back pain of the patient during admission. Prescriptions were as follows: (a) Dai-uzu-sen, (b) Shakuyaku-kanzo-to mixed with Shigyaku-to, (c) BSG, Bukuryo-shigyaku-to, (d) HJ-pills, pills of Hachimi-jio-gan, (e) HJ-deco+Ninjin-to, decoction mixed Hachimi-jio-gan and Ninjin-to, (f) Bushi-to.

Table I Medicinal plants composing Kampo prescriptions used in this study. Each value represents gm/day. Prescriptions indicated with* were given to the patient. Abbreviations : BSG, Bukuryo-shigyaku-to ; HJ-deco, decoction of Hachimi-jio-gan.

| Medicinal plants | HJ-deco +Ninjin-to* | HJ-deco | BSG* |
|---|---|---|---|
| Aconiti Tuber | 6 | 6 | 6 |
| Poria | 3 | 3 | 8 |
| Ginseng Radix | 4.5 | | 2 |
| Zingiberis Siccatum Rhizoma | 3.5 | | 3 |
| Glycyrrhizae Radix | 3 | | 4 |
| Rhemanniae Radix | 5 | 5 | |
| Corni Fructus | 3 | 3 | |
| Dioscoreae Rhizoma | 3 | 3 | |
| Alismatis Rhizoma | 3 | 3 | |
| Moutan Cortex | 3 | 3 | |
| Cinnamomi Cortex | 1.5 | 1.5 | |
| Atractylodis Rhizoma | 4.5 | | |

day, she felt mild numbness of the lips and tongue for about one hour after meals. Unfortunately, she conveyed this to us after more severe symptoms from the poisoning had already set in.

At 12 : 50 on March 23 (two days after changing prescriptions), she developed symptoms of hard numbness of the lips and tongue, and chest discomfort. Blood pressure rose to 154/92 mmHg, and pulse rate was 60/min. and irregular. ECG showed junctional premature contractions and intraventricular aberrant conduction (Fig. 3). We considered that these were signs of aconitine poisoning, and promptly gave 100 ml of cold-water intake and started intravenous infusion of 5 % glucose at a rate of 100 ml/hr.

At 14 : 10 she also complained of epigastral discomfort. The blood pressure decreased to 92/58 mmHg, and her pulse rate was 72/min. and irregular. ECG still showed similar arrhythmia, but the frequency of extrasystoles became less.

By 16 : 30 these symptoms except for numbness of the tongue had disappeared. ECG still sometimes showed junctional premature contractions.

At 18 : 00 her pulse recovered to a regular rhythm of 60/min. Slight numbness of the tongue remained until the next morning. The ECG in the next morning recovered to sinus regular rhythm.

## II Analysis of some decoctions including Aconiti Tuber

### Materials and Methods

*Medicinal plants*

Aconiti Tuber (*Aconitum carmichaeli* DEBEAUX, Gunma Prefecture) without any process, Corni Fructus (*Cornus officinalis* SIEB. et ZUCC., China), Rehmanniae Radix (*Rehmannia glutinosa* LIBOSCH. var. *hueichingensis* CHAO et SCHIH, China), Glycyrrhizae Radix (*Glycyrrhiza uralensis* FISCHER, China), Atractylodis Rhizoma (*Atractylodes ovata* DC, China), Dioscoreae Rhizoma (*Dioscorea batatas* DECAISNE, China), Mountan Cortex (*Paeonia moutan* SIMS, China), Alismatis Rhizoma (*Alisma plantago-aquatica* L. subsp. *orientale* SAMUELSSON, China), Zingiberis Siccatum Rhizoma (*Zingiber officinale* ROSCOE, China), Ginseng Radix (*Panax ginseng* C.A. MEYER, Korea), Poria (*Poria cocos* WOLFF, North Korea) and Cinnamomi Cortex (*Cinnamomum cassia* BLUME, Vietnam) were used in this analysis.

*Preparation of extracts*

Decoction of BSG, HJ-deco, HJ-deco mixed with

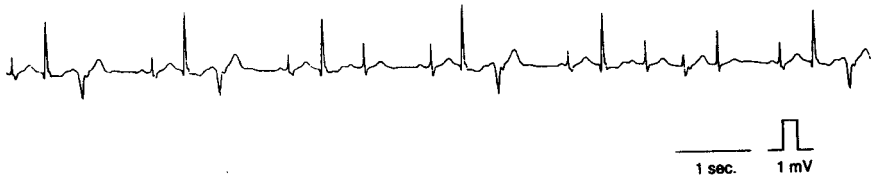


Fig. 3 Electrocardiogram at the time of Aconiti Tuber poisoning. This electrocardiogram (Lead II) was recorded 30 minutes after the beginning of poisoning symptoms (at 13 : 10 on March 23). Junctional premature contractions and intraventricular aberrant conduction are seen.

Ninjin-to and only Aconiti Tuber were analyzed in this study. The medicinal plants composing these prescriptions are listed in Table I.

Each Kampo prescription was decocted with 800 ml water in an earthen teapot on an electric heater (Toshiba ; HP-634 600W) for 60 minutes until the volume of extractant was reduced to about 400 ml. The extract was filtered through a tea strainer while it was hot, and lyophilized after cooling.

*Standard compounds*

Mesaconitine, hypaconitine and aconitine were isolated from the raw tubers of Aconitum carmichaeli Debx. according to the method of Mori *et al.*[8]

*HPLC conditions*

HPLC was performed with a Shimadzu high-performance liquid chromatograph system ( pump, LC-10AD ; system controller, SCL-10A ; autoinjector, SIL-10A ; UV-VIS detector, SPD-10AV ; column oven, OTO-10A ; peak area measurement, Chromatopac C-R7A) by the following conditions : column, TSK-GEL ODS-80TM (4.6×150) ; mobile phase, 0.05M phosphate buffer (pH 2.7)-tetrahydrofuran (183 : 17) ; flow rate, 1.0 ml/min ; detection, UV231nm ; column temperature, 40°C. The quantity of each constituent was estimated by the absolute calibration method.

*Preparation of sample solutions for HPLC*

Each freeze dried sample (0.5 g) was extracted three times with ether (20 ml) and aqueous ammonia (10 % : 1.0 ml) for 30 min. The combined organic phases were evaporated under reduced pressure at a temperature not exceeding 40°C to give a residue. The residue was dissolved in 0.05M phosphate buffer (pH 2.7) -acetonitrile to give exactly 5 ml of solution.

**Result**

The amounts of aconitine-type alkaloids of the respective extract are shown in Fig. 4. The BSG decoction contained 120 μg/day of hypaconitine, whereas HJ-deco mixed with Ninjin-to contained 280 μg/day of hypaconitine, as well as mesaconitine and aconitine. HJ-deco also contained a similar amount of 230 μg/day of hypaconitine. The amounts of aconitine-type alkaloids in HJ-deco mixed with Ninjin-to increased to five times as much as the ones in BSG.

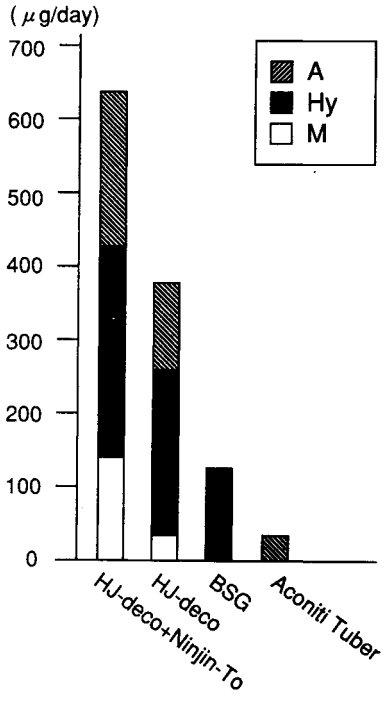


Fig. 4 Aconitine-type alkaloids in each decoction. All columns represent average values (n=3). Abbreviation of each decoction : BSG, Bukuryo-shigyaku-to ; HJ, Hachimi-jio-gan. Abbreviation of each product : A, Aconitine ; Hy, Hypaconitine ; M, Mesaconitine.

## Discussion

There are some reports about accidental aconitine poisoning such as by natural edible grasses[3] and also about suicide. Some reports about this toxicity have also been mentioned in regard to Japanese traditional (Kampo) medicine, but severe, or even fatal cases seemed to be rare from using prescriptions containing Aconiti Tuber, as traditional physicians were usually alert to its use by increasing daily dosage by only slight amounts such as 0.5 gm, adjusting the boiling time, or selecting its indication strictly. A case of aconitine poisoning following only the changing of Kampo formulae which were boiled with Aconiti Tuber of the same amounts has until now not been reported.

Our analysis determined that aconitine-type alkaloids of Aconiti Tuber in HJ-deco mixed with Ninjin-to increased by about five times compared to those in BSG. This result strongly suggested that this Aconiti Tuber poisoning was due to an abrupt increase in aconitine-type alkaloids of the decoction after changing prescriptions.

Nausea, numbness of the lips and extremities, hot flushing of the face and hypersecretion of the salivary gland are known symptoms of aconitine poisoning. Yoshioka *et al.*[3] reported that these toxic symptoms were quickly cured by gastric lavage and intravenous administration of physiological solution. Otherwise, it is written in Fukusho-Kiran-Yoku (a texbook of Kampo medicine published in 1809)[9] that Miso soup, decoction with black beans and Glycyrrhizae Radix, and cold water are effective against this poisoning. These remedies have been taught in traditional medicine in spite of the lack of current evidence.

Ventricular arrhythmia which is the most important symptom in this poisoning, may result in death. Aconitine-type alkaloids activate the sodium channel, which affects the membranes of cardiac myocytes, causing tachyarrhythmias.[4,5] Fukuda[6] reported that a young man with ventricular tachycardia due to aconitine intoxication with the intention of suicide, could be rescued within 24 hours after the ingestion of dry powder of Aconiti Tuber by the general treatment for shock including intravenous administration of fluid and steroids. That case might have been fortunate because the dry powder of Aconiti Tuber is less toxic than the raw materials. Effective treatment for arrhythmia was unknown, and it could only be supportive.[7] The reason why our patient did not come to be in a severe state was thought to be because the high dose of 6.0 gm/day of Aconiti Tuber may have improved her tolerance to an abrupt increase in aconitine-type alkaloids, and prompt intravenous administration of fluid improved her toxic symptoms and helped to maintain her cardiac state.

The reason for the acute elevation of aconitine-type alkaloids in the decoction is still unknown. We suppose that some medicinal plants composing HJ-deco mixed with Ninjin-to might inhibit the hydrolysis of Aconiti Tuber when boiled together. We are now attempting to identify the medicinal plants responsible for this phenomenon.

Our findings serve as a strong reminder that we should be alert not only to the quantity of Aconiti Tuber but also to other medicinal plants that are to be boiled with it. Further, a patient must be advised of the signs of aconitine poisoning before the first administration of prescriptions containing Aconiti Tuber. Moreover, at the time of changing prescriptions that both include Aconiti Tuber, even if the amounts are the same, particular caution must be exercised.

## 和文抄録

烏頭の量を維持していたにもかかわらず，漢方方剤の変更に伴って烏頭中毒をきたした一例を経験した。患者は80歳の女性で骨粗鬆症と腰椎圧迫骨折による腰痛にて入院中であった。茯苓四逆湯（烏頭6 g/日）を八味丸合人参湯に変更して2日後，口唇と舌のしびれと胸部不快感を自覚。心電図にて房室性期外収縮と心室内変行伝導を認め，約5時間持続後自然軽快した。煎液中の成分の検索を行ったところ，烏頭由来の有毒性アルカロイドが八味丸合人参湯では茯苓四逆湯の約5倍の高値を呈しており，このことが中毒の原因として考えられた。これまで漢方方剤の変更によりアコニチン系アルカロイドの増加を指摘した報告はみられない。

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