Literature analysis of Acanthopanax anaphylactic shock in China

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Abstract

The aims of this study are to investigate the occurrence characteristics of Acanthopanax (刺五加 cì wǔ jiā) anaphylactic shock and to provide objective evidence for the rational use of the medicine. Fifty-seven cases of Acanthopanax anaphylactic shock were collected from several professional databases in China. The statistical data of the patients were analyzed with Visual FoxPro 6.0 and Office Excel 2003 by Microsoft (Redmond, WA, USA). The male:female incidence ratio was 0.5:1. Fifty-six (98.25%) patients were older than 30 years. Thirty-nine (68.42%) patients had an unknown allergy history. Nine (15.79%) patients used Acanthopanax for unlabeled indications. In most (98.25 %) patients, Acanthopanax was used in the form of dosage injection. Anaphylactic shock occurred within 30 minutes after treatment in 52 (94.54%) patients, and all episodes occurred during the infusion process. In two (3.51%) patients, the episode occurred when they used Acanthopanax for the second time. In one (1.75%) patient, the episode occurred during the third time of use. The clinical symptoms of anaphylactic shock are diversified, but all patients presented with cardiovascular and respiratory system symptoms. Acanthopanax injections that led to anaphylactic shock were produced exclusively by four manufacturers. Four (7.02%) patients died and 49 (85.96%) patients were cured, but the status of four patients is unknown. Because an Acanthopanax injection may cause anaphylactic shock and can be fatal in severe cases, physicians and patients must pay close attention to using it rationally. Clinicians should carefully consult the allergic constitution of their patients, strictly follow the guidelines of the drug, use Acanthopanax in the oral dosage form as much as possible, and strengthen therapeutic monitoring.

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1. Introduction

Acanthopanax (刺五加 cì wǔ jiā) injection is formulated with extracts from the stems and leaves of Acanthopanax senticosus. It contains a variety of active ingredients such as eleutheroside, iso-fraxidin, and hyperoside. An Acanthopanax injection can dilate blood vessels, increase coronary and cerebral blood flow, reduce myocardial oxygen consumption, improve microcirculation, reduce blood viscosity, scavenge free radicals, regulate immune function, regulate bidirectionally in the central nervous system, and reduce damage caused by virulence factors. In China, an Acanthopanax injection can be applied to treat transient ischemic attack, intracranial arteriosclerosis, intracranial thrombosis, intracranial embolism, coronary disease, angina pectoris, neurasthenia, and menopausal syndrome. An Acanthopanax injection is a necessary traditional Chinese medicine (中醫 zhōng yì; TCM) that is stocked in traditional Chinese hospital emergency departments in China. Despite widespread use, Acanthopanax could possibly lead to anaphylactic shock. Therefore, we collected several published Chinese literature reports on Acanthopanax anaphylactic shock to determine its occurrence characteristics and provide an objective basis for its clinical rational use (Fig. 1).

2. Materials and methods

2.1. Materials

In three Chinese professional databases, which were variable information processing (VIP) information, Chinese Journal Full-text Database, and Wanfang Data, we entered keywords such as...
“Acanthopanax”, “shock”, “allergy”, or “dead” to find published Chinese literature concerning Acanthopanax anaphylactic shock. Except for one duplicate report, 52 evaluable articles were collected that contained 57 cases of Acanthopanax anaphylactic shock.

Relevant information data of the 57 cases were collected as follows: (1) demographics (e.g., age, gender, allergy history); (2) drug use (e.g., dosage form, dosage, usage, solvent, concomitant medications, manufacturer, and production batch number); (3) occurrence of anaphylactic shock (e.g., time of shock occurrence, symptom distribution, complications, time to improvement or recovery, shock outcome); and (4) other data (e.g., reporting time of the case).

2.2. Statistical analysis

Visual FoxPro 6.0 (Microsoft) was used to establish an “Acanthopanax anaphylactic shock database management system” wherein relative data were input. A statistical analysis was then performed on the data involving the aforementioned information by Office Excel 2003 (Microsoft).

3. Results

3.1. General situation of the patients

3.1.1. Gender and age distribution of the patients

There were 38 (66.67%) female patients and 19 (33.33%) male patients. The male:female ratio was 0.5:1. This finding is consistent with the literature reports. The minimum age of the patients was 18 years and the maximum age was 97 years. Except for one patient of unknown age, 56 (98.25%) patients were older than 30 years.

Table 1 lists the age distribution. Among these patients, the ratio of the below-30-year-old patients to over-30-year-old patients was 1:55. However, because the sex ratio and age distribution of the patients treated by Acanthopanax (刺五加 cì wǔ jiā) is difficult to estimate accurately, further study is needed.

3.1.2. Allergy history

Among the 57 patients, 39 (68.42%) patients had an unknown allergy history, seven (12.28%) patients had a history of allergy to drugs or food, and 11 (19.30%) patients had no allergy history.

3.2. The primary disease distribution among the patients

Among the 57 patients, the primary diseases of five (8.77%) patients were unknown. The top three diseases were cardiovascular disease (e.g., coronary disease, angina pectoris) in 18 (31.58%) patients, cerebrovascular disease (e.g., cerebral infarction, intracranial arteriosclerosis) in ten (17.54%) patients, and neurasthenia in eight (14.03%) patients. There were nine (15.79%) patients who used Acanthopanax for unlabeled indications; their primary diseases were renal insufficiency, carbon monoxide poisoning, acute tonsillitis, fractures, hepatitis B, hyperthyroidism, cervical spondylosis, and chronic bronchitis (1 patient each).

3.3. Conditions of Acanthopanax use

3.3.1. Distribution of the dosage forms

Among the 57 patients, 56 (98.25%) patients used the injection formulation. The only exception was that one (1.75%) patient had
used > 50 tablets of Acanthopanax for suicide, which led to shock and arrhythmias.

3.3.4. The use times of the drug
Shock in the patients occurred during the infusion process. In two minutes after treatment, in 52 (94.54%) patients within 30 minutes, 3.4. Occurrence of anaphylactic shock
numbers repeatedly reported, and Zhenbao had one batch number. injections used by one (4.35%) patient. Wandashan had three batch pany Limited (Jia Musi city, Heilongjiang Province) produced the (8.70%) patients; and Heilongjiang Duoduo Pharmaceutical Com- city, Heilongjiang Province) produced the injections used by two (17.39%) patients; and Heilongjiang Wusuli Pharmaceutical Factory (Jixi city, Heilongjiang Province) produced the injections used by four (17.39%) patients. Among 46 patients with clear solvent records, 5% glucose injection was used in 29 (63.04%) patients; 10% glucose injection, in 14 (30.43%) patients; saline injection, in two (4.35%) patients; and glucose and sodium chloride injection, in one (2.17%) patient. Only eight patients used a big dosage transfusion of Acanthopanax.

3.3.5. Combined medication
Forty-two (73.68%) patients had no combined medication use; 14 (24.56%) patients used various combined medications, which primarily included antibiotics, energy mixtures, and cardiovascular system drugs. The combined medication use in one patient was unknown.

3.3.6. The Acanthopanax manufacturers and batch number
The manufacturer and batch numbers were reported for 23 patients. Among these manufacturers, Heilongjiang Wandashan Pharmaceutical Factory (Jixi city, Heilongjiang Province) produced the injections used by 16 (69.56%) patients; Heilongjiang Wusuli River Pharmaceutical Company Limited (Harbin city, Heilongjiang Province) produced the injections used by four (17.39%) patients; Heilongjiang Zhenbao Island Pharmaceutical Company Limited (Jixi city, Heilongjiang Province) produced the injections used by two (8.70%) patients; and Heilongjiang Duoduo Pharmaceutical Company Limited (Jia Musi city, Heilongjiang Province) produced the injections used by one (4.35%) patient. Wandashan had three batch numbers repeatedly reported, and Zhenbao had one batch number.

3.4. Occurrence of anaphylactic shock
3.4.1. Anaphylactic shock occurrence time distribution
Anaphylactic shock occurred in 28 (50.91%) patients within 10 minutes after treatment, in 52 (94.54%) patients within 30 minutes, and in three (5.45%) patients after 30 minutes but within 1 hour. All shock in the patients occurred during the infusion process. In two patients, the occurrence time of anaphylactic shock was unknown.

3.4.2. Distribution of the clinical symptoms of anaphylactic shock
The clinical symptoms of anaphylactic shock were diversified. The top 10 common shock symptoms were as follows: hypotension in 57 (100%) patients, dyspnea in 44 (77.19%) patients, chest distress in 33 (57.89%) patients, cyanosis in 33 (57.89%) patients, peripheral coldness in 30 (52.63%) patients, palpitations or tachycardia in 24 (42.10%) patients, pruritus and/or exanthema in 21 (36.84%) patients, fast pulse in 21 (36.84%) patients, paleness in 20 patients (35.09%), and sweating in 16 patients (28.07%). Twenty patients had severe shock symptoms such as blood pressure dropping to 0 mmHg in 18 (31.58%) patients, unconsciousness in 17 (29.82%) patients, respiratory arrest in 10 (17.54%) patients, lack of pulse in six (10.53%) patients, urinary incontinence in four (7.02%) patients, and cardiac arrest in three (5.26%) patients. Table 3 lists all clinical symptoms that involve multiple systems.

3.4.3. Complications
Complications only occurred in three patients. One patient suffering from brain edema was transferred to another hospital and the disease outcome is unknown. One patient suffering from multiple organ failure died. One patient suffering from blindness recovered 15 days after treatment.

3.4.4. Outcomes of Acanthopanax anaphylactic shock
Four patients were transferred to another hospital and their disease outcomes are unknown. Of the remaining patients, four (7.02%) patients died and 49 (85.96%) patients were cured. Forty-five patients had been marked the relief time; among these, 37 (82.22%) patients experienced relief in 30 minutes, six (13.33%) patients experienced relief in 31 minutes to 1 hour, and two (4.44%) patients experienced relief after 1 hour but within 2 hours. Thirty-three patients had been indicated the recovery time by medical staffs: 29 (87.88%) patients completely healed within 1 day, three (9.09%) patients healed within 1–5 days, and one (3.03%) patient healed in 15 days.

3.4.5. Relevance evaluation of Acanthopanax anaphylactic shock
The evaluation standard recommended by the Adverse Drug Reaction Monitoring Center of the People’s Republic of China is widely used in the Chinese adverse drug reaction (ADR) reporting system. The standard includes five points: (1) whether there is a reasonable time sequence between the medication and the ADR; (2) whether the ADR is consistent with the known adverse reaction

| System involved | Symptoms | No. of cases | Constituent ratio (%) |
|-----------------|----------|-------------|-----------------------|
| Cardiovascular system | Hypotension, chest distress, cyanosis, coldness, palpitations or tachycardia, fast pulse, paleness, flushing, lip or eyelid edema, weak heart sounds, blood pressure drop to 0 mmHg, no pulse, cardiac arrest, bradycardia | 57 | 100 |
| Respiratory system | Dyspnea, fast respiration rate, pulmonary rales or wheeze, laryngeal or bronchial edema, three depressions sign, respiratory arrest | 57 | 100 |
| Nervous system | Sweating, dysphoria, lip or limb numbness, shivering, fever, head distention or dizziness, tetany, sense of endangerment, unconsciousness, opisthotonos, body acupuncture-like pain, local skin numbness | 39 | 68.42 |
| Skin and appendages | Pruritus and/or exanthema | 18 | 31.58 |
| Gastrointestinal tract | Nausea and vomiting, abdominal pain, diarrhea | 12 | 21.05 |
| Eye | Visual disorder or amaurosis, conjunctival congestion, chemosis, papilledema | 11 | 19.30 |
| Urogenital system | Urinary incontinence | 4 | 7.02 |

### Table 2
The drug concentration distribution of Acanthopanax.

| Concentration (mg/mL) | No. of cases | Constituent ratio (%) |
|-----------------------|-------------|-----------------------|
| C < 1 mg/mL           | 36          | 70.59                 |
| 1 mg/mL ≤ C < 2 mg/mL | 7           | 13.72                 |
| 2 mg/mL ≤ C ≤ 3 mg/mL | 8           | 15.69                 |
| Total                 | 51          | 100.00                |

C – concentration.
type; (3) whether the withdrawal or reduction of the drug could lead to the disappearance or mitigation of ADR; (4) whether the same reaction appears again after re-exposure to the drug; and (5) whether the ADR could be explained by the combination of other medications or by disease progression. The relevance evaluation result can then be concluded in accordance with Table 4. Based on the aforementioned standard, the reactions in four (7.02%) patients were “positive”; in 50 (87.72%) patients, “probable”; in one (1.75%) patient, “possible”; and in two (3.51%) patients, “doubtful”.

3.4.6. Other data

Table 5 shows the time distributions of the case reports.

4. Discussion

4.1. The basic characteristics of the patients

Compared to the natural population structure, the female cases of Acanthopanax (刺五加 ch'i wu jia) anaphylactic shock were statistically and significantly greater. Its pathogenesis is unclear and demands further research. There also exists a significant difference in the distribution of age. Except for one patient, most patients were older than 30 years. The primary reason for this deference is that Acanthopanax is indicated for cardiovascular and cerebrovascular diseases such as coronary disease and cerebral arteriosclerosis. Because patients older than 30 years are in a very high risk group for these diseases, the use of Acanthopanax is greatly increased in these patients and therefore the risk of adverse reactions is increased.

If the patient tends to have an allergic constitution, the risk of drug-induced allergic reactions will be greatly increased. However, in this paper, the allergy history of more than one-half of the reported cases was unknown. This showed that the medical staff had ignored performing consulting work on the allergic constitution of patients. We suggest that a medical staff should carefully consult the allergic constitution of patients to effectively observe the patient reaction in the course of treatment, and give active treatment to the patient, as necessary.

According to our data, some patients used Acanthopanax for unlabeled indications. This implies that the medication usage guidelines should be strictly followed to reduce the risks of drug treatment.

4.2. Acanthopanax use

The exact mechanism of Acanthopanax anaphylactic shock is unclear. It may be related to the complex chemical composition of Acanthopanax, which contains a variety of ingredients that may cause an allergy. There are many kinds of Acanthopanax dosage forms such as capsules, tablets, mixture, granules, and injection. From the collected data, the Acanthopanax dosage form that results in shock is primarily injection. This is consistent with the findings of a published report that indicates that TCM injections are more likely to cause anaphylactic shock.

The reason TCM injections are more likely to cause anaphylactic shock probably lies in the following four points: (1) TCM injections contain impurities (e.g., proteins, starch, tannins, pigments, mucus, resins, and volatile oil) that result from poor purification techniques; these impurities may act as haptons and bind to plasma proteins and lead to anaphylactic shock; (2) certain unknown ingredients and adjuvants such as solubilizers and stabilizers may increase the likelihood of allergy; (3) allergens may be produced by oxidation, polymerization, and hydrolysis of ingredients during the process of high-temperature sterilization or storage; and (4) the intravenous administration of the medicine may induce a large number of antibodies in the human body. Because of the binding tendency of the antigen and antibody, Acanthopanax administered as an injection could cause a higher incidence of anaphylactic shock, compared to other administrative routes.

We suggest that Acanthopanax should be used in the oral dosage form as much as possible, especially in patients with an allergic constitution. After being damaged by digestive enzymes and the breaking down of large molecules into small molecules, antigens usually lost part or all of their antigenicity. In this paper, a 41-year-old female patient was included who used an Acanthopanax injection to cure Meniere’s disease and died because of Acanthopanax anaphylactic shock. If she had used Acanthopanax in the oral dosage form, the result would have been entirely different. We also propose avoiding using a solvent that contains electrolytes because salting reactions may occur and result in anaphylaxis.

Among the reported 57 patients, most (69.56%) patients used Acanthopanax injections that were produced by four manufacturers, in particular Heilongjiang Wandashan Pharmaceutical Factory. Because there were eight different manufacturers producing Acanthopanax injections, we speculated that the manufacturers of the Acanthopanax injections were different in their technical level. We recommend that manufacturers should closely track adverse reactions with the product use, improve their technical level, and strengthen quality control. Therefore, the risk of allergic reaction in clinical drug use could be reduced.

In 2008, Acanthopanax injections of Heilongjiang Wandashan Pharmaceutical Factory reportedly had important safety issues. There were >100 adverse events, which included one death, that occurred after the administration of their products. The Ministry of Health (Taipei, Taiwan) ordered a halt to the use of all injections produced by the Wandashan Pharmaceutical Factory. The findings of this paper confirm the event.

After the safety incidences by Wandashan Pharmaceutical Factory, the use of Acanthopanax injections decreased rapidly throughout the country. Compared to the number of Acanthopanax anaphylactic shock cases reported in the previous 10 years (1998–2007), the number of cases of anaphylactic shock recently decreased significantly in a 6-year period (2008–2013). This is associated with the decreased use of Acanthopanax injections.

4.3. Anaphylaxis shock occurrence

According to statistical evaluations, 52 (94.54%) patients experienced anaphylactic shock in <30 minutes after the drug's

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**Table 5**

| Year       | No. of cases | Proportion (%) |
|------------|--------------|----------------|
| 2008–2013  | 6            | 10.53          |
| 2003–2007  | 26           | 45.61          |
| 1998–2002  | 23           | 40.35          |
| Prior to 1997 | 2 | 3.51  |

The exact mechanism of Acanthopanax (刺五加 ch'i wu jia) anaphylactic shock is unclear. It may be related to the complex chemical composition of Acanthopanax, which contains a variety of ingredients that may cause an allergy. There are many kinds of Acanthopanax dosage forms such as capsules, tablets, mixture, granules, and injection. From the collected data, the Acanthopanax dosage form that results in shock is primarily injection. This is consistent with the findings of a published report that indicates that TCM injections are more likely to cause anaphylactic shock. The reason TCM injections are more likely to cause anaphylactic shock probably lies in the following four points: (1) TCM injections contain impurities (e.g., proteins, starch, tannins, pigments, mucus, resins, and volatile oil) that result from poor purification techniques; these impurities may act as haptons and bind to plasma proteins and lead to anaphylactic shock; (2) certain unknown ingredients and adjuvants such as solubilizers and stabilizers may increase the likelihood of allergy; (3) allergens may be produced by oxidation, polymerization, and hydrolysis of ingredients during the process of high-temperature sterilization or storage; and (4) the intravenous administration of the medicine may induce a large number of antibodies in the human body. Because of the binding tendency of the antigen and antibody, Acanthopanax administered as an injection could cause a higher incidence of anaphylactic shock, compared to other administrative routes.

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4.3. Anaphylaxis shock occurrence

According to statistical evaluations, 52 (94.54%) patients experienced anaphylactic shock in <30 minutes after the drug's
administration. In all patients, the anaphylactic shock occurred during the infusion process. For this reason, a medical staff should closely monitor drug reactions during the infusion process, especially in the first 30 minutes. However, because delayed-type hypersensitivity has been reported for other TCM injections, a medical staff should not ignore a patient’s reaction after a transfusion. Prior to treatment, the medical staff must inform the patient of the possibility of adverse reactions to Acanthopanax. Once an adverse reaction occurs, the patient should get timely medical treatment.

In this survey, anaphylactic shock occurred in two patients the second time they used the medication, and in one patient the third time the patient used the medication. To avoid the occurrence of severe anaphylactic shock, Acanthopanax should not be reused once a general allergic reaction has occurred.

4.4. Other suggestions

We suggest that the China Food and Drug Administration (SFDA) should organize relevant experts to re-evaluate the clinical safety of Acanthopanax injections, improve its quality standards, and be strict with the controlling the impurity content.

5. Conclusion

Acanthopanax (刺五加 / Cī wǔ jiā) injections can cause anaphylactic shock. For severe cases, it can result in death. This should arouse clinical medical staff and patients to attach great importance. Clinicians should adhere to the principle of rational drug use, strictly follow the indications of medication, strictly select the treatment group, and strengthen drug monitoring during use.

Conflicts of interest

I, Qian Zhan, author of the paper referenced above, have no financial and personal relationships with other people or organizations that could inappropriately influence this work.

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