

Journal of Immunology Forecast

A Systematic Analysis of 314 Cases of Adverse Drug Reactions to *Acanthopanax* Injection

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Abstract

Background: *Acanthopanax* has been successfully administered for the treatment of many diseases, however, adverse drug reactions (ADRs) occur frequently.

Objectives: To probe the full profile and underlying basis for ADRs to *Acanthopanax* injection.

Methods: All related medical articles published from 1979-2012 were searched online using *Acanthopanax* injection keywords. The found articles were then systematically analyzed.

Results: Among the 691 relevant articles retrieved, 149 reports covering 209 ADRs cases and 41 clinical trials with 105 cases of ADRs were reviewed. Most patients presenting ADRs to *Acanthopanax* were 40-60 years old. Different serious and severe ADRs occurred either systemically or mainly in skin and respiratory systems. Serious ADRs and allergic reactions accounted for 38.2% and 75.8% of total ADRs, respectively. Broad primary clinical indications and/or unknown ingredients in the injection solution may have contributed to the side effects or ADRs observed in these patients.

Conclusions: Allergic reactions are the main cause of ADRs related to *Acanthopanax* injection. Attenuation of the allergenicity of *Acanthopanax* injection and strengthening of pharmacovigilance for ADRs to the injection is imperative.

Keywords: *Acanthopanax* injection; Adverse drug reactions; Drug allergy; Clinical indication; Clinical trial; Scattered report

Background

Traditional Chinese medicine (TCM) is produced from natural materials, generally does little or no harm to the human body and has special curative effects on some intractable diseases, thus attracting increasing attention for clinical application. Injection of Traditional Chinese medicine (TCMI) was developed in the 1950s [1] and is now considered as a milestone in the modernization of TCM. TCMI is efficiently absorbed by humans and can have faster acting effects than standard TCM when used for the treatment of certain diseases. Hence, TCMI has even been used as emergency drugs by TCM hospitals. However, adverse events and adverse drug reactions (ADRs) are frequently associated with the use of Chinese herbal medicines, more than 75% of which are induced by Chinese herbal injections [2]. Therefore, the safety of TCMI has been raised by public concerns, with some people refusing to use TCM, especially TCMI.

Acanthopanax injection is one of the most widely used TCMI in China. It has been reported that *Acanthopanax* injection has antifatigue, antioxidant, and anti-inflammatory effects, and might help reduce blood viscosity and blood lipid contents. This injection was also reported to have antitumor or anticancer activity and enhance immunity [3-8]. Because of these advantages, *Acanthopanax* injection has been used to treat a broad variety of diseases such as cerebrovascular disease, coronary heart disease, insomnia, diabetes, etc [9-12]. However, different adverse drug reactions have frequently occurred and can affect any organ system of patients injected with *Acanthopanax*. The purpose of this study is to probe the full profile and underlying basis for ADRs to *Acanthopanax* injection in order to make better use of this TCMI in clinical situations.

Methods

Data collection

This review was performed in adherence with PRISMA (Preferred Reporting Items for Systematic

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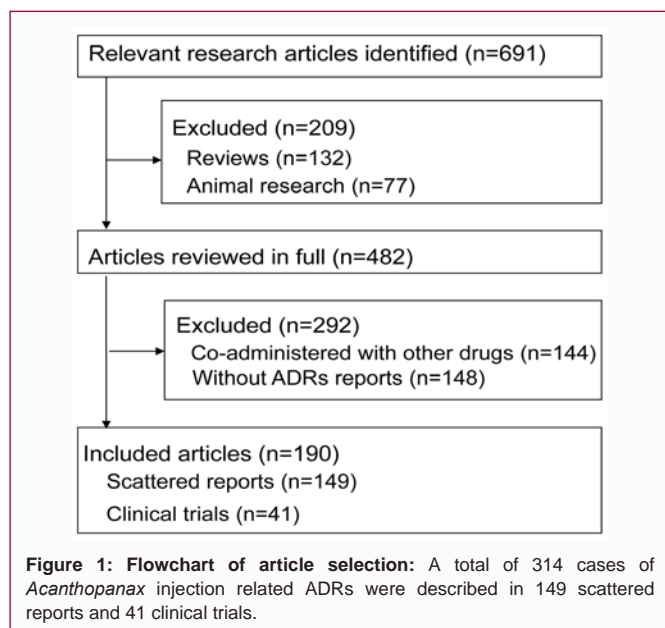
Received Date: 15 Dec 2017

Accepted Date: 12 Feb 2018

Published Date: 14 Feb 2018

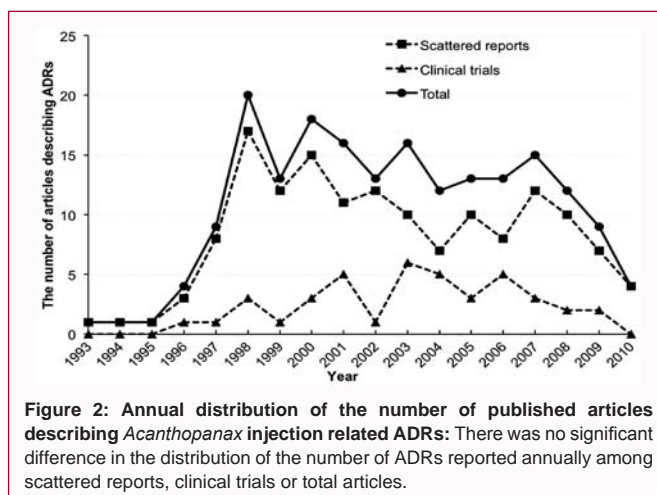
Citation: Yuhe G, Junbin Z, Xiaojun Z, Huiyan W, Xueting L, Ailin T. A Systematic Analysis of 314 Cases of Adverse Drug Reactions to *Acanthopanax* Injection. *J Immunol Forecast*. 2018; 1(1): 1003.

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Reviews and Meta-Analyses) guidelines [13]. The distribution and factors pertinent to ADRs were examined by analyzing the medical articles published between 1979 and 2012 retrieved in EMBASE, the Cochrane Library (1979 to December 2011), Highwire (with PubMed included), China National Knowledge Infrastructure and Google databases (most recent search in February, 2012) by using the terms in either English or Chinese as follows: “*Acanthopanax* injection/ adverse drug reactions”, “*Acanthopanax* injection/side effect”, “*Acanthopanax* injection /toxicity” and “*Acanthopanax* injection/ adverse event”. These terms were used as free-text and Emtree terms were used to search in EMBASE. Free-text terms and MeSH terms were used to search in the Cochrane Library and Highwire databases. Free-text terms (translated into Chinese) were used to search in the Chinese databases. Three reviewers, Guo YH, Wu HY and Tao AL, independently selected the trials and performed the data extraction. Discrepancies were resolved to avoid any bias by discussion among the reviewers.

The quality of all articles retained for review was assessed by two independent groups led by Ying He and Junyan Zhang. A grading scheme (A, B, and C) modified from our former description [14] was used to classify each of the five main criteria as follows: (1) Quality of Randomization: For clinical trials, A, randomized; B, no randomization. All case reports were graded as A because the adverse reaction case(s) was approved by the doctor group and their hospitals before submission for publication and the case(s) occurred occasionally among a large amount of patients administered with *Acanthopanax* injection. (2) Quality Control in Clinical Trials and Case Reports: A, contained both controls by other drugs and comparison before and after medication; B, contained only controls by other drugs or only comparison before and after medication; C, contained no controls or comparison. Case reports: Each case of an adverse event was evaluated for its connection with the injection by the author(s) and colleagues before submission for consideration for publication and peer-review. (3) Status of therapeutic regimen. A, no drugs used before *Acanthopanax* injection. B, other drugs used before *Acanthopanax* injection. C, other drugs used simultaneously with *Acanthopanax* injection. (4) ADR onset time: A, Early phase reaction; B, Undescribed; C, Late phase reaction. (5) *Acanthopanax* injection



dosage: A, Normal dosage; B, Undescribed; C, Abnormal dosage. Only studies that achieved an A grade were included in our analysis.

Eligibility criteria

Articles were selected for analysis if they included: (1) reports on *Acanthopanax* injections, (2) clinical trials using *Acanthopanax* injection, and (3) clinical trials using *Acanthopanax* injection that caused ADRs. The following topics were excluded: (1) reviews of *Acanthopanax* injection, (2) *Acanthopanax* injection used in animal experiments, (3) clinical trials using *Acanthopanax* injection coadministered with other drugs, and (4) clinical trials of *Acanthopanax* injection that did not cause ADRs.

Analysis and testing

Relevant information such as age, gender, original illness of the patients, onset time and *Acanthopanax* dosage causing ADRs was obtained and analyzed. The frequency distributions of patients in different categories were analyzed.

Results

Publications selected

When searched using the terms, “*Acanthopanax* injection/ adverse drug reactions”, “*Acanthopanax* injection /side effect”, “*Acanthopanax* injection/toxicity” and “*Acanthopanax* injection/ adverse event”, 2750, 3250, 2810, and 551 articles published from 1979 to 2012 were respectively retrieved. After excluding duplicates and unrelated articles, 691 relevant articles were retained of which 132 review articles and 77 articles involving animal experiments were further eliminated. Finally, 41 clinical trials and 149 scattered reports met the inclusion criteria (Figure 1), which described 105 and 209 cases of ADRs respectively (see Supplementary Table 1S and Supplementary References). The articles that we eventually selected to include in our analysis all included reports of a single or multiple ADRs following *Acanthopanax* injection. Results of the quality assessment demonstrated that the majority of the articles cited for review were graded as “A” level according to all five criteria and none of the articles was graded as “B” level on the five criteria (see Supplementary Table 3S). However, important information relating to the demographic characteristics of patients, such as age and gender, was missing in some clinical trials, resulting in a separate statistical analysis of the patient demographics for the clinical trials vs. the scattered reports.

Annual distribution

Analysis of the yearly reports of ADRs showed that there are similar distribution patterns of ADRs in age, gender, number and type of ADR whether it be in the scattered reports or clinical trials. Since 1993, more and more ADRs related to *Acanthopanax* injection have been reported with a peak being seen from 1998 to 2000 in the scattered reports and from 2003 to 2004 in the clinical trials. The annual number of reported ADRs continued to stay relatively high until 2008 when the administration of *Acanthopanax* injection from certain manufacturers began to be restricted, thus leading to a sharp decline in the number of reported ADRs (Figure 2). However, no changes have been observed in the type of ADRs seen with *Acanthopanax* injection even after clinical trials were conducted to evaluate an armada of new formulations designed for *Acanthopanax* injection (data not included, see Discussion).

Demographics of the ADR Patients

The average ages, 39.4-74.6, were reported in each of the 41 clinical trials for the 2126 subjects recruited, hence the overall average age were 54.8 and the occurrence rate of ADRs could be deduced to be 4.94% from 41 clinical trials. However, no detailed patient demographics were recorded among the 105 cases of ADRs in 41 clinical trials. Therefore, this analysis was conducted only on the 209 cases from 149 scattered reports. The age-gender distributions analysis showed that there was no difference in the ADRs between males and females, indicating that *Acanthopanax* injection-incurred ADRs had no gender bias. Significantly, the highest frequency of ADRs was in patients aged 40 to 60, which accounted for nearly 50% of the total ADR patients. Another notable point is that the frequency of ADRs in patients aged 21-30 was relatively low compared to the other age groups, possibly reflecting an age related resistance to these ADRs in younger patients.

Primary disease and the corresponding clinical manifestation of ADRs after *Acanthopanax* treatment

The patients that experienced ADRs after *Acanthopanax* treatment suffered from a variety of primary diseases that included involvement of the cardiovascular system, nervous system, respiratory system and endocrine system, etc. Specifically, ten major disease types accounted for most of the primary diseases treated with *Acanthopanax* injection: coronary heart disease, angina pectoris, brain infarction, neurasthenia, hypertension, headache and dizziness, diabetes mellitus, cervical spondylosis, neurosis, vertigo, etc., accounted for over 60% of the total 314 cases. Fifty other types of diseases accounted for nearly 40% of the total 314 cases, indicating that *Acanthopanax* injection has been used to treat a broad spectrum of diseases (supplementary Table 1).

In terms of the clinical manifestations, ADRs to *Acanthopanax* injection can be seen either systemically or individually in almost all body systems (Figure 3), especially respiratory, skin and systemic manifestations, which together were implicated in nearly three quarters of the total 314 cases of ADRs studied (Table 2).

All patients in both scattered reports and clinical trials were treated by intravenous drip as instructed. Data from the scattered reports of ADRs to *Acanthopanax* injection described either the dosage or onset time of ADRs but clinical trials did not provide this information. Although not very comprehensive, the data from the scattered reports showed that most ADRs occurred rapidly and within one minute after *Acanthopanax* injection. Nearly half of the ADRs

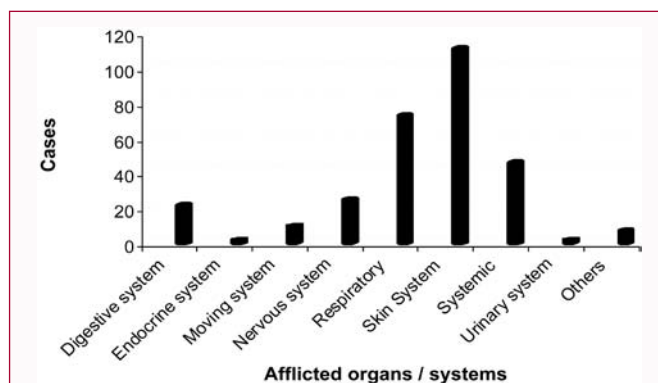


Figure 3: Afflicted organs/systems in 314 cases of ADRs to *Acanthopanax* injection: Others includes the following 7 cases: Conjunctival hyperemia, 2 cases; Blindness, 1 case; Local swelling, 1 case; Debilitation, 1 case; Lethargy, 2 cases.

happened within 10 minutes and over 80% within 30 minutes. It was noted that 15% of the ADR cases developed a late phase reaction one hour after *Acanthopanax* injection. Regarding dosage, greater than 75% of the patients presented ADRs after receiving less than 100mL of *Acanthopanax* injection solution, and nearly 50% after receiving less than 50mL. Notably, 8.6% of the cases developed late phase ADRs after receiving more than 200mL of *Acanthopanax* injection solution (see Supplementary Table 2S). In conclusion, ADRs to *Acanthopanax* injection are dose independent, unpredictable, and belong to Type B ADRs.

Further analysis showed that allergic reactions appeared to be the predominant type of ADRs (Table 3). The overall rate of allergic reactions, only deduced from the clinical trials, would be 2.68% of the *Acanthopanax* injected subjects and 54.3% of the ADRs in clinical trials were described as allergic reactions. Greater than 90% of ADRs occurred systemically in either the skin, respiratory or digestive systems and 75% of total ADRs were described as allergic reactions, implying that allergic reactions to *Acanthopanax* injection should be intensively monitored in these systems.

Fifty patients developed severe allergic reactions such as anaphylactic shock and death. Death by anaphylactic shock took place within 15 minutes after injection of 20mL of *Acanthopanax* solution.[15-18] Seventy other serious adverse events also occurred that resulted in damage or disruption of body functions in the patients such as laryngeal edema, drug eruption, atrioventricular block, cardiopalmus, angina pectoris, dyspnea, conjunctival hyperemia, blindness, allergic asthma, wheeze and polypnea, cardiac arrest, etc. (Table 3). In total, there were 120 serious adverse events, accounting for nearly 40% of the total 314 cases of ADRs to *Acanthopanax* injection.

Discussion

This study outlines the ADRs to *Acanthopanax* injection and demonstrates that ADRs to *Acanthopanax* injection belong to Type B ADR, show no gender bias and no dose-dependency, occur mainly within 30 minutes after injection, mostly in patients aged over 30, and especially in patients aged 40 to 60. Different serious and severe ADRs occur in different organ systems, especially skin and respiratory, and systemically. These data are worthy of attention by all clinicians who are still prescribing this treatment.

The question why *Acanthopanax* injection has caused so many

allergic reactions in particular remains to be elucidated. One study demonstrated that the percent of insoluble particles increased when traditional Chinese medicine injections were prepared with different diluents, thereby inducing side effects or serious ADRs [19]. These insoluble particles might also be responsible for the adverse events reported in the scattered reports and clinical trials. Another analysis suggested that the allergic reactions were associated with the ingredients in *Acanthopanax*. The main ingredients in *Acanthopanax* injection solutions include eleutheroside, hyperoside, water-soluble polysaccharide, alkali-soluble polysaccharide, amino and volatile oils and syringin, etc [20-24]. They are thought to be haptens or prohaptens that can bind covalently to larger proteins or peptides and form hapten-carrier complexes, which might subsequently induce allergic reactions [25-27].

Generally speaking, the injections used for clinical trials were critically prepared and had less possibility of production quality problems. However, ADRs were reported in both sporadic cases and clinical trials, inferring that the ingredients of the injection, independent of the good manufacturing practices used in the preparation of *Acanthopanax* injection solutions, could significantly contribute to the primary causes of ADRs. Moreover, serious ADRs and allergic reactions accounted for 38.22% and 75.80% of total ADRs, respectively, which further corroborates other published reports [28,29]. Therefore, it is of great importance to intensively monitor and attenuate the allergenicity of preparations used for *Acanthopanax* injection.

The clinical indications for *Acanthopanax* injection are so broad that this in itself may be another cause of ADRs. Thus, we strongly argue that until the cause(s) of the allergenicity of the injection is deciphered and attenuated, the primary indication for *Acanthopanax* injection should be critically determined and described. In addition, potential TCMI patients could be prescreened for potential ADRs by skin prick test with *Acanthopanax* solution before intensive regimens are offered. Should an ADR occur, all treatments with *Acanthopanax* should immediately cease. It should be further cautioned that any subsequent *Acanthopanax* injection in the allergic patient would dangerously increase their risk of anaphylactic shock or even death.

The need for strengthening of pharmacovigilance and research on ADRs to TCMI can not be overemphasized, especially the surveillance of sporadic cases directly related to the drugs administered. For example, Wandersun *Acanthopanax* injection resulted in six cases of ADRs in October 2008 in Yunnan Province, China, and included three fatalities, subsequently resulting in an immediate nation-wide cancellation of these injections. ADRs to *Acanthopanax* injection had been previously described in scattered reports and reached a peak in 1996-1998. However, these ADRs were not effectively eliminated even after clinical trials were conducted on an armada of new formulations of *Acanthopanax* injection and this resulted in ADRs continuing to be reported and peaking in 2003-2006. If more attention had been paid to the single ADR fatality that occurred in 2004 in Ledou County, Qinghai Province, and had the allergenicity of *Acanthopanax* injection been investigated and attenuated, it is tempting to think that such serious adverse events would not have continued to occur. Unfortunately, although considerable technical and medical practice advances have been made in the intervening years, the evaluation of TCMI allergenicity and its subsequent attenuation is still at an level unsuitable for continuing clinical trials of *Acanthopanax* injections or other TCMI.

However, should there be future clinical trials, this study shows that volunteers more than 30 years old should be expressly recruited for phase I clinical trials of *Acanthopanax* injection. In phase I clinical trials aiming to screen for the safety of drugs, volunteers aged 18-70 are routinely recruited, and this typically includes large numbers of college or university students who are generally less than 30 years old [30-32]. However, our study showed that *Acanthopanax* injection related ADRs happened infrequently in patients aged less than 30 years old, similar to the results presented by Kane-Gill SL, et al (2010) [33]. Hence, phase I clinical trials weighted with higher numbers of younger persons can not accurately reflect the safety of the injection over all age groups. It is therefore highly recommended that volunteers aged 30-70 years old are specifically selected for inclusion in Phase I clinical trials and that these volunteers are closely observed for any consequential adverse reactions to *Acanthopanax* injection or other TCMI.

Generally, because the use of the herbal medicinal products in China has been well established, TCMI, used as an alternative method for the administration of TCMI, usually have not been evaluated for safety and clinical efficacy as much as the injection of conventional Western medicines from the European Union or the United States has been studied [34]. ADRs and adverse events to TCMI, especially mild ones, have not been timely reported and the reporting, if any, is often incomplete and not presented in a standardized format. Much of the fundamental data on ADRs to TCMI is therefore missing [35]. Moreover, scattered reports have generally focused on serious cases and likely omitted relatively mild cases of ADRs. These circumstances could cause bias and affect the accuracy of this study. Especially, the general occurring rate (4.94%) of ADRs and the overall rate (2.68%) of allergic reactions to *Acanthopanax* injections induced by the clinical trial data would be underestimated. Using the allergy rate as example, the number of ADRs designated as allergic reactions averaged about 54.3% in the clinical trials which is significantly different from the 75.8% seen when clinical trials and scattered reports are analyzed together. Nevertheless, the seriousness of the ADRs and allergic reactions, especially anaphylaxis, can not be overlooked when considering the medical safety of this treatment. In this regard, the significance of this study is far more important than its absolute accuracy.

Conclusions

This review argues that broad primary clinical indications and the problem of unknown ingredients in *Acanthopanax* injections may contribute to the observed ADRs seen in the scattered reports and clinical trials. It is vitally important to strengthen pharmacovigilance and to attenuate the allergenicity of *Acanthopanax* treatments, especially in regard to the occasional but severe adverse events directly related to this injection. As to any future phase I clinical trials for safety screening of *Acanthopanax* injection, because ADRs have been infrequently reported in volunteers less than 30 years old, persons over age 30 should be specifically recruited for enrollment in order to accurately assess the safety of *Acanthopanax* treatments in all age groups.

Acknowledgements

We thank Lucinda Beck for her editing and critical reading of the manuscript. This work was supported by the Great Project (2016ZX08011-005) from the Major Program of National Science and Technology of China, The Scientific Research Project of

Guangzhou (201804020042). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors Contributions

GYH analyzed data, drafted the manuscript and was involved in the final approval of the manuscript;

ZJB was a co-investigator, helped with study design and data analysis and was involved in the final approval of the manuscript;

ZXJ was a co-investigator, helped with study design and data analysis, critically revised the manuscript, and was involved in the final approval of the manuscript;

WHY was involved in data collection and analysis;

LXT was a co-investigator and assisted in the study;

TAL designed the study, analyzed the data, wrote the manuscript and was involved in the final approval of the manuscript.

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