

REVIEW ARTICLE

Adverse drug reactions linked to Ciwujia injection: a systematic review of 521 cases

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Keywords

Ciwujia injection; Adverse drug reactions; Clinical studies; ADR reports

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Received 1 December 2009; accepted for publication 5 January 2010.

doi: 10.1111/j.1756-5391.2010.01066.x

Abstract

Objective To analyze adverse drug reactions (ADRs) associated with Ciwujia injection and possible contributing factors.

Methods We searched all clinical studies and ADR reports of Ciwujia injection from the China National Knowledge Infrastructure (CNKI) database. Relevant information such as disease treated; menstruum and compatibility of the Ciwujia injection; age, gender, and allergic history of ADR cases; and the types, occurrence time and severity of the ADRs were collected and analyzed.

Results In the 800 clinical studies of Ciwujia injection's efficacy and safety, 97 (12.1%) reported 285 ADR cases. There were 144 ADR reports for the drug describing a total of 236 ADR cases. Most of the ADR reports described cases of anaphylactic shock, while the most common ADR reported in clinical studies was local pain; 27.7% of ADR cases were I to II class in all 521 cases, and four anaphylactic shock cases died.

Conclusion The relevant information of ADRs for Ciwujia injection was insufficiently reported in included studies. The ADR type distribution between clinical studies and ADR reports was inconsistency. Most of the reported ADRs were mild, and were treated successfully by slowing down the drip velocity or by withdrawing the drug and treating the symptoms. As Ciwujia injection was one of the highest numbers of ADR reports of traditional Chinese medicine injections, high quality ADR monitoring, standardized ADR reporting, and timely analysis risk factors of ADRs are extremely urgent.

Ciwujia injection is a kind of traditional Chinese medicine (TCM) injection. Its active ingredients, (chiefly Acanthopanax glycosides, isofraxidin glucoside, clove glycosides, and Acanthopanax polysaccharides) are extracted from Araliaceae Acanthopanax (1). Its major functions are expanding blood vessels, increasing coronary blood flow, reducing oxygen consumption, lowering blood viscosity and sedation, improving sleep, and increasing appetite (2). It is mainly used to treat cardiovascular and cerebrovascular diseases, neurasthenia, climacteric syndrome and diabetes, and lower extremity vascular disease (3–5). Ciwujia injection was approved for

marketing in 1983 by State Food and Drug Administration (SFDA). The first article of the injection was published in 1988 (6), and since then the number of studies on Ciwujia injection has increased year by year, as have reports of its adverse drug reactions (ADRs). As one often used drug, it has the fourth-highest number of ADR reports among 33 kinds of TCM injections, according to the 2004 edition of National Essential Medicine List (NEML). To guide clinical using of Ciwujia injection, we included published ADR studies for the injection to analyze ADRs associated with Ciwujia injection and possible contributing factors.

Subjects and methods

Study selection

We performed a systematic search of the China National Knowledge Infrastructure (CNKI) database for articles published between January 1983 and November 2009 indexed under the subject heading *Ciwujia*. Because CNKI is the largest index of Chinese scientific papers, so we chose it. Additional articles were found in the reference lists of the reviewed articles.

Inclusion and exclusion criteria

We included articles, which reported the ADRs of Ciwujia injection. These articles were classified into two groups: ADR reports and clinical studies, clinical studies including randomized controlled trials, non-randomized controlled trials, and case reports.

We excluded the summaries of ADRs from hospitals or monitoring centers, because we can't get the information of individual ADR case from these studies.

Data extraction

We drew up a standard data extraction form and extracted the following information: disease treated; menstruum and compatibility of the Ciwujia injection; age, gender, and allergic history of ADR cases; and the types, occurrence time and severity of the ADRs.

Results

Study selection

A total of 3629 potential studies were found. We excluded 1692 irrelevant studies, 386 animal experiments, 121 duplicate articles, and 486 secondary studies, and included the other 944 articles in our analysis. The 944 articles included 800 clinical studies and 144 ADR reports. The numbers of articles which published in 1988 to 2009 were described in Figure 1.

ADRs of Ciwujia injection in included studies

Number of ADR cases

The 144 ADR reports included 236 ADR cases. Of the 800 clinical studies, 511 (63.8%) did not mention ADRs, and most of the others stated that there were no ADRs. Ninety-seven studies described a total of 285 ADR cases (Table 1).

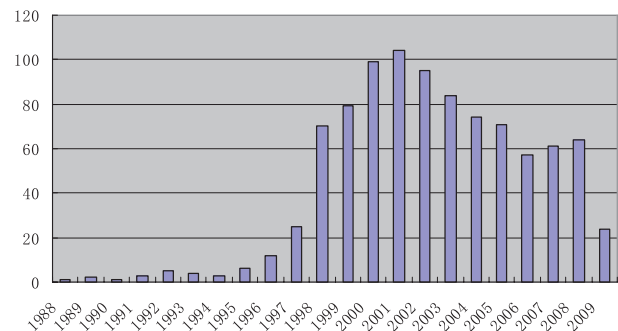


Figure 1 Publication years of included studies

Table 1 Ciwujia injection-associated ADR reporting in clinical studies

ADR	No. of studies	No. of patients	% of total studies
Not mentioned	511	26,267	63.8
Mentioned	289	11,185	36.2
ADRs absent	192	7602	—
ADRs present	97	3583	—
Total	800	37,452	100.0

Gender and age distribution of ADR cases

Because clinical studies lacked information on the gender and age distribution of affected patients, we only included ADR reports in our analysis of these factors. Of 236 ADR cases, 101 were male and 135 were female, for a male to female ratio of 1:1.34. The youngest case was 17 years old, and the oldest was 97 years old. The most commonly affected age group was 60–69 (53/236, 22.5%), followed by 50–59 (49/236, 20.8%) and 40 to 49 (48/236, 20.3%). Patient ages were not reported for 37 ADR cases (37/236, 15.7%) (Table 2).

ADR types

In ADR reports, ADR cases mainly were general reactions (allergic shock), skin lesions (urticaria), and

Table 2 The gender and age distribution of ADR cases in ADR reports

Age (years)	Male	Female	Total	%
<30	3	6	9	3.8
30 to 39	10	13	23	9.7
40 to 49	19	29	48	20.3
50 to 59	17	32	49	20.8
60 to 69	24	29	53	22.5
>70	10	7	17	7.2
Unclear	18	19	37	15.7
Total	101	135	236	100.0

Table 3 ADR types in included studies

Reaction	ADR reports		Clinical studies		Reaction	ADR reports		Clinical studies	
	No. of ADR cases	%	No. of ADR cases	%		No. of ADR cases	%	No. of ADR cases	%
Minor	0	0	32	11.2	Tachycardia	2	0.9	5	1.8
Fatigue /Lethargy	–	–	19	6.7	High blood pressure	3	1.3	0	0
Dry mouth	–	–	7	2.4	Hypotension	0	0	2	0.7
Dry throat	–	–	6	2.1	Skin lesion	57	24.2	54	18.9
General	105	44.3	2	0.7	Urticaria	31	13.1	3	1.0
Febrile	5	2.0	2	0.7	Itch of skin	15	6.4	2	4.2
Allergic shock	100	42.3	0	0	Rash	11	4.7	19	6.7
Nervous system	3	1.3	48	16.8	Flushing	0	0	20	7.0
Headache	2	0.9	25	8.8	Local reaction	5	2.1	59	20.7
Dizziness	1	0.4	23	8.0	Local pain	2	0.9	51	17.9
Alimentary system	6	2.5	47	16.6	Numbness of limb	1	0.4	2	0.7
Nausea and vomiting	3	1.2	20	7.0	Ecchymosis	0	0	4	1.4
Stomachache	1	0.4	11	3.9	Phlebitis	1	0.4	2	0.7
Diarrhea	2	0.9	5	1.8	Angioneurotic edema	1	0.4	0	0
Melena	0	0	6	2.1	Hematological system	0	0	11	3.8
Constipation	0	0	5	1.8	Gingiva bleeding	0	0	1	0.3
Respiratory system	50	21.2	6	2.1	Thrombopenia	0	0	10	3.5
Dyspnea	21	8.9	0	0	Other	3	1.3	6	2.1
Allergic asthma	15	6.4	0	0	Milk secretion	2	0.9	0	0
Laryngeal edema	5	2.1	0	0	Conjunctiva congestion	1	0.4	0	0
Cough	4	1.7	5	1.8	Hypoglycemia	0	0	4	1.4
Chest distress	5	2.1	1	0.3	Hunger sensation	0	0	2	0.7
Circulatory system	7	3.1	20	7.1					
Cardiopalms	2	0.9	13	4.6	Total	236	100.0	285	100.0

respiratory system reactions (dyspnea). In clinical studies, most ADR cases were local pain, skin irritation (flushing, rash, itchiness), nervous system symptoms (headache, dizziness), or alimentary system problems (nausea, vomiting) (Table 3).

ADR severity

ADR severity for each event as classified according to World Health Organization guidelines (7). Most of the 521 reported ADRs were mild (Table 4).

Fatal cases

Of the 521 ADR cases, four patients died, all from anaphylactic shock (Table 5).

Contributing factors for ADRs

Disease treated

The most frequently diseases for treatment were coronary heart disease and cerebral infarction in both ADR reports and clinical studies (Table 6).

Table 4 Classification of ADR severity for Ciwujia injection

Classification of ADR severity		No. of ADR cases	%
Class I	ADRs are deadly or life-threatening, patients need to withdraw drugs and treated immediately; or ADRs last for more than 1 month.	68	13.1
Class II	Patients have pathology and physiology change and be compelled to withdraw drugs and treated; or ADRs last for more than 7 days	76	14.6
Class III	Patients can't endure the ADRs and be compelled to do drug decrement or withdrawal, through symptomatic treatment, patients improved.	123	23.6
Class IV	Patients can endure the ADRs, don't need to do drug decrement or withdrawal, through symptomatic treatment or untreated, patients improved.	254	48.7
Total		521	100.0

Table 5 Fatal reactions to Ciwujia injection

Reporting study	Gender	Age (years)	Diseases treated	ADR occurrence time (from beginning of injection)	ADR
Qingwen Zhang 2007 (8)	Female	41	Vertiginous syndrome	Not given the time, only described as "Intravenous drip for 20 mL"	Allergic shock
Benhao Zhu 1998 (9)	Male	44	Coronary heart disease	10 min	Allergic shock
Xihong Chi 2003 (10)	Male	30	Tonsillar abscess	10 min	Allergic shock
Xianbin Lu 2006 (11)	Female	60	Chronic bronchitis; Emphysema; Pulmonary heart disease	15 min	Allergic shock

Patient allergic history

Because clinical studies lacked information on the allergic history ADR-affected patients, we only included ADR reports in this analysis. Of the 236 ADR cases reported in ADR reports, 153 (64.8%) had no indication of whether the patients had an allergic history. Of 27 cases in which the patient had a reported allergic history, penicillin was the most frequently allergy (9/236, 4%), followed by atopy (4/236, 2%) and aspirin (3/236, 1%) (Table 7).

Other drugs given

Most Ciwujia injections were diluted with 5% glucose, 0.9% NaCl, or 10% glucose in both ADR reports and clinical studies. Other drugs were administered along with Ciwujia injection in 14 ADR cases reported in ADR reports, including Danshen injection ($n = 3$), compound Danshen injection ($n = 2$), and Adenosine disodium triphosphate ($n = 2$). Other drugs were mentioned in 25 ADR cases reported in clinical studies, including Agkistrodon ($n = 10$), Lidocaine ($n = 4$), and Batroxobin ($n = 4$) (Table 8).

Table 6 ADR occurrence by disease treated with Ciwujia injection

Disease treated	ADR reports		Clinical studies		Disease treated	ADR reports		Clinical studies	
	No. of ADR cases	%	No. of ADR cases	%		No. of ADR cases	%	No. of ADR cases	%
Nervous system diseases	58	24.6	69	24.2	Somnopathy	10	4.2	12	4.2
Cerebral infarction	28	11.9	49	17.2	Neurasthenia	25	10.5	17	6.0
Cerebral circulation insufficiency	16	6.7	14	4.9	Headache	10	4.2	2	0.7
Vertigo	15	6.3	31	10.9	Climacteric syndrome	8	3.4	2	0.7
Transient ischemic attack	4	1.7	3	1.0	Digestive system diseases	5	2.2	24	8.4
Cerebral embolism	3	1.3	2	0.7	Hepatitis	2	0.9	19	6.7
Cerebral thrombosis	7	3.0	1	0.4	Peptic ulcer	1	0.4	3	1.0
Circulatory diseases	77	32.6	67	23.6	Gastritis	2	0.9	2	0.7
Coronary heart disease	62	26.3	51	17.9	Respiratory system diseases	8	3.4	6	2.1
Heart failure	5	2.1	12	4.2	Urinary system diseases	3	1.3	5	1.7
Arrhythmia	3	1.3	2	0.7	Others	4	1.8	23	8.0
Viral myocarditis	1	0.4	1	0.4	Carbon disulfide poisoning	0	0	12	4.2
Hypertension	6	2.5	1	0.4	Herpes zoster	0	0	6	2.1
Pneumocardial disease	3	1.3	1	0.4	Raynaud disease	0	0	3	1.0
Endocrine system diseases	10	4.3	26	9.1	Hyperlipemia	2	0.9	2	0.7
Diabetes and the complications	7	3.0	22	7.7	Sequela of carbon monoxide poisoning	1	0.4	0	0
Hyperthyreosis	3	1.3	0	0	Alopecia areata	1	0.4	0	0
Rheumatoid arthritis	0	0	4	1.4					
Mental system diseases	68	28.6	64	22.5	Total	236	100.0	285	100.0

Table 7 Allergic history of ADR-affected patients in included studies

	No. of ADR cases	%
Unspecified allergic history	153	65
No allergic history	56	24
Allergic history	27	12
Penicillins	9	4
Atopy	4	2
Aspirin	3	1
Streptomycin	2	0.9
Sulfamido	2	0.9
History of asthma	2	0.9
Unknown drug	2	0.9
Pollen	1	0.4
Metoclopramide	1	0.4
Dextran-40	1	0.4
Total	236	100

Occurrence time

Because information on ADR occurrence time was lacking in clinical studies, we only included ADR reports in our analysis. In 196 (196/236, 83.0%) of these cases, ADR occurred the first time the medication was given, usually in the first 30 min of use (Table 9). Seventeen ADR cases (17/236, 7.2%) occurred 2 min to 8 days after Ciwujia injection treatment stopped, and 13 ADR cases (13/236, 5.5%) occurred after 1–14 days of continuous medication use. In one case, ADR occurred after about 200 mL of Ciwujia injection was given on the 14th day of continuous medication use (12).

Table 8 Menstruums and co-administered drugs by ADR number

	ADR reports			Clinical studies		
	No. of ADR cases	%	Other drugs administered	No. of ADR cases	%	Other drugs administered
5% Glucose	129	54.7	Danao injection (n = 1); Danshen injection (n = 1); Shenmai injection (n = 1); Compound Danshen injection (n = 2)	122	42.8	Alginic sodium diester (n = 2); Lidocaine (n = 4); Shengmai injection (n = 1); Huangqi injection (n = 1);
0.9% NaCl	36	15.3	Xuesaitong injection (n = 1); Danshen injection (n = 1); Cefoperazone (n = 1)	88	30.9	Agkistrodon (n = 10); Batroxobin (n = 4); Huangqi injection (n = 1)
10% Glucose	37	15.7	Ribavirin injection (n = 1) Adenosine disodium triphosphate (n = 2)	42	14.7	None
Maitong	1	0.4	Ligustrazine injection (n = 1)	0	0	None
Betahistine	1	0.4	Citicoline injection (n = 1)	0	0	None
Unspecified	25	10.6	Danshen injection (n = 1)	30	10.5	None
No menstruum	7	3.0	None	3	1.1	Aciclovir (n = 3)
Total	236	100.0	n = 14	285	100.0	n = 25

Discussion

The main effect of Ciwujia injection is to nourish liver-kidney and strengthen bones. It is mainly used to treat transient ischemic attack, cerebral arteriosclerosis, cerebral thrombosis, and cerebral embolism caused by liver-kidney deficiency, as well as for coronary heart disease, angina pectoris combined neurasthenia, and climacteric syndrome. In our study, we analyzed ADRs associated with Ciwujia injection and possible contributing factors, and discussed as follows.

ADR reporting for Ciwujia injection

Of 800 clinical studies we found on Ciwujia injection, 506 did not mention whether ADRs occurred. A further 97 studies reported ADRs but left out at least one piece of this information: the age, gender, and allergic history of ADR patients, the occurrence time of ADRs. Inadequate reporting limits our ability to analyze the causes of ADRs. We suggest that researchers follow standardized ADR reporting guidelines when conducting clinical research (particularly randomized controlled trials) (13). Insufficient reporting of information such as allergic history, drug dosage, and drip speed also existed in ADR reports, again indicating the importance of standardized ADR reporting.

ADR severity

Of the 521 reported ADR cases linked to Ciwujia injection, 72.3% (377/521) were class I–IV ADRs, and were treated successfully by slowing down the drip velocity or by withdrawing the drug and treating the symptoms. The other 13.1% (68/521) of ADR cases were class I, and four patients died.

Table 9 ADR occurrence time after start of Ciwujia injection

	No. of ADR cases	%
First time injection	196	83.0
Less than 5 min	19	8.1
5 to 15 min	85	36.0
16 to 30 min	44	18.6
31 min to 1 hour	15	6.3
1 to 3 hours	16	6.8
2 min to 3 hours after treatment	11	4.7
1 to 8 days after treatment	6	2.5
Continuous treatment	13	5.5
1 to 4 days	7	3.0
5 to 8 days	3	1.3
More than 8 days	3	1.3
Unknown	27	11.4
Total	236	100

Although most ADRs linked to Ciwujia injection were mild, any occurrence of severe or fatal ADR must be treated with utmost seriousness. Practicing evidence-based medicine is the best way to ensure the safety of drugs and their usage.

ADR types in ADR reports and clinical studies

In ADR reports, ADR cases mainly were allergic shock, urticaria, and dyspnea, and four patients died. In clinical studies, most ADR cases were mild ADRs, such as local pain, skin irritation, headache, dizziness, and nausea/vomiting. The reporting inconsistency between ADR reports and clinical studies may be due to the very rare rate of serious ADR in a relatively small sample in clinical studies. So it is imperative to enhance the evaluation drugs and good clinical application after the drugs come into the market with evidence-based medicine (14).

Gender and age distribution, allergic history of ADR cases

In our study, the most commonly affected age group was 40 to 69 (63.6%). Ciwujia injection is also mainly used for cardiovascular and cerebrovascular diseases, which are common in middle-aged and old-aged patients. It indicated that we should pay more attention to the ADR monitoring to these population when using Ciwujia injection.

Fifty-eight ADR cases (11.5%) had allergic history in ADR reports, and the other 153 patients (64.8%) were not mentioned whether they had allergic history or not. We suggest that this information of allergic history of ADR cases be better reported.

Occurrence time of ADRs

196 (83.0%) ADR cases occurred the first time the medication was given, usually in the first 30 min of use. Seventeen ADR cases occurred 2 min to 8 days after Ciwujia injection treatment stopped, and 13 ADR cases occurred after 1–14 days of continuous medication use. So we suggest the paramedics carefully observe the early 30 min of first time medication used to avoid the ADRs of Ciwujia injection. In addition, we should also pay attention to the ADRs after medication and continuous medication used.

ADRs describing on the product manuals for Ciwujia injection

We found that the product manuals for Ciwujia injection state, “Due to occasional allergic reactions to Ciwujia injection, it must be cautiously used for allergic people” or “skin rash, dizziness, and even allergic shock occurred in very few patients,” but there is no information on occurrence rate and types of ADRs, populations most susceptible to ADRs, or what to do when ADR occurs. So we suggest that the pharmaceutical companies add more detailed descriptions on ADR to the product manual.

In addition, some studies have shown that a change in pH value, turbidity, or precipitation may occur when Ciwujia injection is mixed with other drugs. For example, Ouyang Rong (15) reported that when combined with Vitamin C, Ciwujia injection’s pH value increases and the total flavonoid content declines. Xu Yanhua’s study (16) showed that when Ciwujia injection is mixed with persantine and isoptin injection, precipitates appear. Tian Zigu (17) found that when Ciwujia injection was combined with compound Danshen injection, one patient experienced an allergic reaction, although in that case the liquid injection had been stored beyond the recommended time limit and may have degenerated. Zhang Limei (18) reported that mixing of Ciwujia injection and Ofloxacin injection resulted in turbidity and particulate matter. However, there is no information on pharmaceutical incompatibility in the product manuals for Ciwujia injection of any pharmaceutical company, making it difficult for clinicians to apply such findings in their practice. So we suggest that the pharmaceutical companies add detailed safety information on pharmaceutical incompatibility to the product manuals.

Limitations of our study

- We only searched the CNKI database, and didn’t ask pharmaceutical companies or SFDA for ADR records.
- In both ADR reports and clinical studies of Ciwujia injection, ADRs and adverse drug events (ADE) were not easily distinguishable, and key information about total prescriptions

and patients given the drug was missing, so we couldn't calculate the ADR rate.

- This study is a descriptive analysis of ADRs linked to Ciwujia injection; due to the quality of the extracted data, we did not do a comparative analysis of ADRs with control groups.
- Since we don't know how frequently Ciwujia is given and to what kind of patients, it's difficult to know what the risk factors for ADRs are.

Suggestions

- The researchers in clinical studies (including randomized controlled trials) should pay more attention to ADR monitoring and standardized ADR reporting.
- Pharmaceutical companies should add more detailed safety information to product manuals, such as ADR rate, pharmaceutical incompatibility, and how to deal with ADRs.
- Healthcare workers should watch closely for ADRs when using Ciwujia injection and take measures when ADRs occur.

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