



REVIEW ARTICLE

Adverse events to Houttuynia injection: A systematic review

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Keywords

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Abstract

Objective To systematically assess the main clinical features of Houttuynia injection-associated adverse drug reactions (ADRs), as described in published reports, and to contribute to the post-marketing re-evaluation and clinical practices of Houttuynia injection.

Method We searched the electronic databases- PubMed, EMBASE, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Journal Full-text Database (VIP) and the Chinese Biomedical Disc (CBMdisc), for articles published through June 2010. We then extracted and analyzed the data.

Results A total of 645 articles were included, with a total of 1232 ADR cases reported. Respiratory diseases accounted for 52.44% of all cases of Houttuynia injection ADRs, followed by reproductive system diseases (4.30%) and urinary system diseases (3.73%). Multiple systems or organs were involved in the ADRs, the top five were: respiratory system (37.42%), skin (34.66%), digestive system (25.49%), circulatory system (25.41%), and nervous system (23.96%). Serious systemic adverse reactions accounted for 22.56% of total ADRs. Of the reported 1,232 ADR cases, 286 ADR cases reported previous allergies in detail; allergy to penicillin accounted for 15.03% of the total cases with the allergic history, followed by unknown drugs (8.05%), and sulfonamides (3.15%). Among the ADR cases, Houttuynia injection was commonly used together with cephalosporins, penicillins, and macrolides. Macrolides combined with Houttuynia injection showed higher ADR risk than Houttuynia injection used alone (RR = 8.80, 95% CI 6.12 to 12.65, $P < 0.0001$). The ADR risk for intravenous injection of Houttuynia injection was higher than that of intramuscular injection (OR = 6.86, 95% CI 1.88 to 56.95, $P = 0.0016$). We used the WHO ADR Classification Criteria to divide the ADR cases into four grades. There were 22.56%, 36.28%, 16.48%, and 24.68% cases of Grade I, II, III, and IV, respectively. Anaphylactic shock accounted for 58.99% of the most serious ADRs (Grade I). All cases of death were caused by allergic shock, except one, who died of multiple organ failure caused by anaphylactic purpura. The fastest-onset three ADR cases occurred in one minute after injection.

Conclusion The respiratory system was the most common system treated in Houttuynia injection ADR cases. It was also the most common site of ADR symptoms. The ADRs of Houttuynia injection were serious. The precautions should be taken to prevent the anaphylactic shock. Intravenous injection and the combination with cephalosporins, penicillins, and macrolides increased the ADR risk of Houttuynia injection.

Houttuynia is the whole grass plant of *Houttuynia cordata* (Saururaceae) with the medicinal and edible characteristics. Houttuynia injection is a traditional Chinese medicine used in China. In 1978, its intramuscular injection was approved in China, then its intravenous formulation was approved in 1994. It has played unique roles in the therapy of infectious diseases owing to its anti-inflammatory effect (1).

As the serious of adverse reactions to Houttuynia injective were reported, China's State Food and Drug Administration (SFDA) temporarily suspended the use and approval of seven kinds of Houttuynia injective preparations since June 1, 2006 (2). In September of 2006, SFDA allowed the pharmaceutical companies could apply for the re-use only with the intramuscular formulation after the re-evaluation of the safety of Houttuynia injective preparations (3), and have to add drug warning information—"This product can cause serious allergic reactions" in the drug instruction (4).

However, there is no sufficient evidence on the safety of Houttuynia injection, and the severity of its adverse drug reactions. We tried to systematically assess the main clinical features of Houttuynia injection-associated adverse events and adverse reactions, as described in published literature, so as to contribute to the post-marketing re-evaluation and rational use of Houttuynia injection.

Materials and methods

Search strategies

We searched electronic databases such as PUBMED (1978 to June, 2010), EMBASE (1978 to June, 2010), the Chinese National Knowledge Infrastructure (CNKI, 1979 to June, 2010), the Chinese Science and Technology Journal Full-text Database (VIP, 1989 to June, 2010), and the Chinese Biomedical Disc (CBMdisc, 1978 to June, 2010). Computer searches were performed using the terms "Houttuynia cordata," "Houttuynia injection," and "response," "role" "adverse reaction," "adverse event (AE)," "allergy," "side effects."

Selection criteria

We only included the randomized controlled trials (RCTs), non-randomized controlled trials (non-RCTs), case-control studies, cross-sectional studies, case series, and case reports, which reported the adverse drug reactions (ADRs) or adverse events of Houttuynia injection administered by intravenous drip or intramuscular injection. No limitation was used in the patient gender, age, or primary diseases. We excluded the studies where ADR information or data was not available.

Study selection and data extraction

Endnote X2 was used to manage included literature. We developed a standardized, piloted forms for study selection and

data extraction. Two researchers independently screened the studies for eligible, and extracted data. Any discrepancies was resolved by third party. We extracted the following information: 1) patient information of ADR/AE cases (eg. age, gender, primary diseases, allergic history); 2) the dosage, duration, route of administration of Houttuynia injection, and the co-intervention; 3) ADR/AE information and its severity (according to World Health Organization (WHO) ADR/ADE classification standards).

Data analysis

We conducted a descriptive analysis for Houttuynia injection-associated ADR/AE, including allergic history, primary diseases, administration of Houttuynia injection, co-interventions, the involved systems and severity of ADR/AE. The primary diseases were classified according to the textbook of Internal Medicine (20). The drugs combined with Houttuynia injection were categorized according to the textbook of Pharmacology (21). We used Chi-square test to analyze ADRs associated with different routes of injection, and calculated relative ratios (RR) with 95% confidence intervals (95% CI) using the statistics software Stata 9.1 (19).

Results

Literature screening

Figure 1 showed the process of study screening.

Distribution according to publication year of included studies

Of the 645 included studies, 244 (38%) were case reports, 239 (37%) were RCTs, 67 (10%) were cross-sectional studies, 66 (10%) were non-randomized controlled trials, and 29 (5%) were case series (Table 1). All 645 papers had been published between 1979–2009. From 1979–1998, a total of 45 included articles were published, including 14 case reports, 21 cross-sectional studies, five non-randomized controlled trials, and five RCTs. Since 2000, the number of RCTs and case reports has increased significantly (Fig. 2). When the National Adverse Drug Reaction Monitoring Center of China warned in September 2003 that Houttuynia injection may cause serious ADR, the number of ADR reports began to drop down, especially after SFDA suspended the use and approval of seven Houttuynia injection in 2006 (Fig. 2).

The 645 included articles reported a total of 1232 ADR cases. Of these, 927 (75%) were reported in case reports and case series, while the rest appeared in cross-sectional studies, RCTs, and non-RCTs. The cross-sectional studies, RCTs, and non-RCTs reported a total of 36,541 users of Houttuynia injection and 305 ADR cases, for an ADR rate of 0.83%.

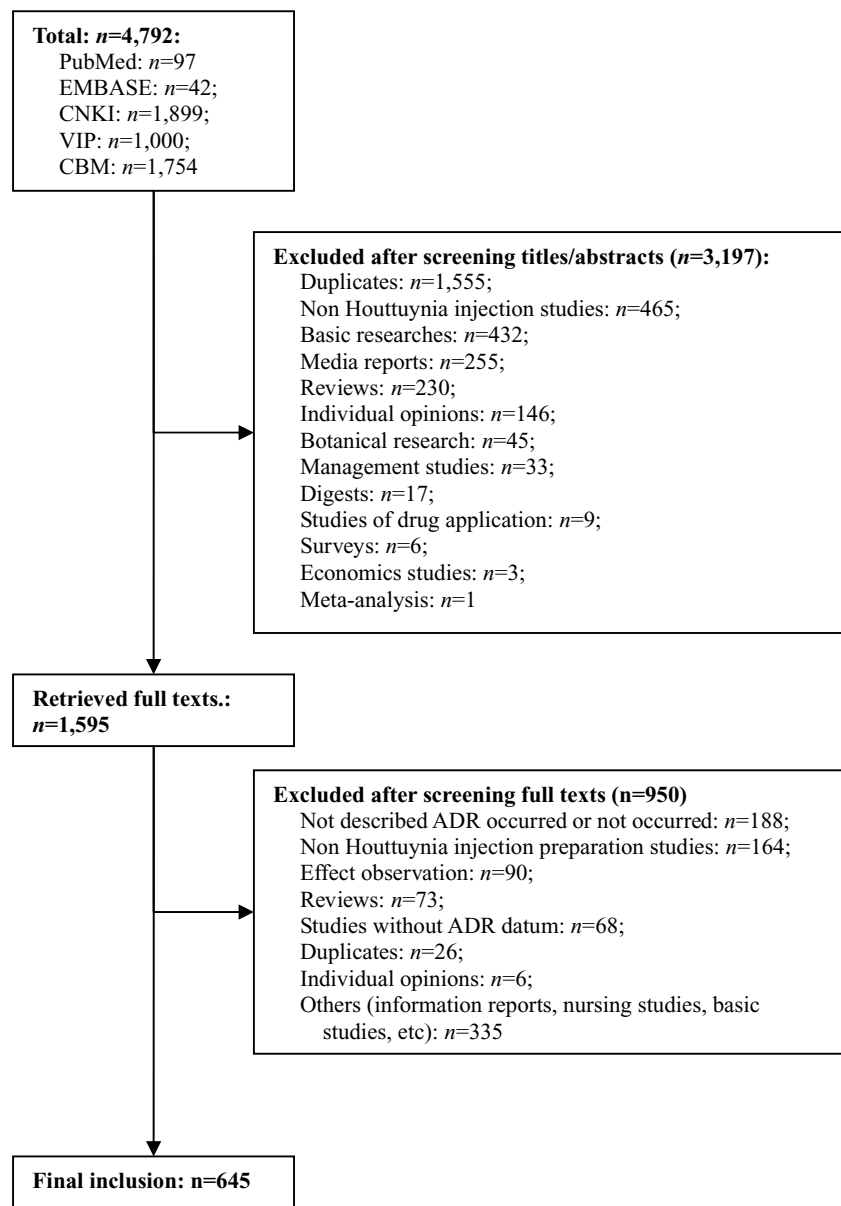


Figure 1 Flow diagram of study screening.

ADR cases and primary diseases

Of the 645 included ADR articles with 1232 ADR cases, 342 articles with 784 ADR cases described the specific primary diseases treated with Houltuynia injection. 303 studies with 448 ADR cases are not described the primary diseases. Respiratory diseases were the most common diseases with the treatment of Houltuynia injection (accounting for 52.44% of the total ADRs reported); reproductive system diseases and urinary diseases accounted for 4.30%, and 3.73%, respectively. Few cases used Houltuynia injection to treat the digestive system, skin and other infectious diseases (Table 2).

Systems affected by ADRs

The 1232 ADR cases involved multiple systems and organs (Table 3). Of particular concern were 278 serious ADR cases (22.56% of total ADR cases), including anaphylactic shock, laryngeal edema, pulmonary edema, respiratory arrest, allergic purpura, coma, cardiac arrest, hypotension, bullous eruption, and hemolysis.

Allergic histories

172 studies with 286 ADR cases reported the allergic history of patients. 64.69% of ADR cases reported no allergic history,

Table 1 Designs of included studies and number of reported ADRs/AEs

Type of study	Studies		ADR/AE cases	
	Number	Proportion (%)	Number	Proportion (%)
Case reports	244	37.83	334	27.11
Case series	29	4.50	593	48.13
Cross-sectional studies	67	10.39	159	12.91
non-RCTs	66	10.23	36	2.92
RCTs	239	37.05	110	8.93
Total	645	100	1,232	100

while 4.9% of ADR cases did not clearly describe allergic history. Penicillin was the most common drug for allergy, followed by sulfonamides, cephalosporins, aminoglycosides, and a history of asthma (Table 4).

Drug combination

The most common drugs combined with Houttuynia injection in ADR cases were cephalosporins, penicillins, and macrolides (Table 5). Houttuynia injection was used alone in 1039 ADR cases. Macrolides increased the risk of ADR when combined with Houttuynia injection (RR = 8.80, 95% CI 6.12 to 12.65).

Routes of injection

A total of 372 documents (including cross-sectional studies, RCTs, and non-RCTs) described 34,969 cases of intravenous Houttuynia injection, of which 303 experienced ADRs, for 0.87% ADR incidence. Two out of 1572 intra-

Table 2 Primary diseases treated in ADR cases

Protopathies	Number of ADR cases	Constituent Ratio (%)
Respiratory diseases	646	52.44
Upper respiratory tract infection	461	37.42
Respiratory tract infection	180	14.61
Chronic obstructive pulmonary disease	4	0.32
Pulmonary heart disease	1	0.08
Reproductive diseases	53	4.30
Tubal infertility	20	1.62
Reproductive system infection	19	1.54
Pelvic inflammatory disease	12	0.97
Dysfunctional uterine bleeding	1	0.08
Acute mastitis	1	0.08
Urinary diseases	46	3.73
Urinary tract infection	44	3.57
Chronic glomerulonephritis	1	0.08
Nephrotic syndrome	1	0.08
Other	39	3.17
Gastrointestinal diseases	12	0.97
Skin diseases	8	0.65
ophthalmopathy	6	0.49
Infectious diseases	7	0.57
Tuberculosis	3	0.24
Intracranial infection	2	0.16
Acute leukemia	1	0.08
unclear primary diseases	448	36.36
Total	1,232	100.00

muscular injection cases experienced ADRs, for 0.13% ADR incidence. We found the intravenous injection significantly increased the risk of ADR than intramuscular administration ($\chi^2 = 9.93$, $P = 0.0016$; OR = 6.86, 95% CI 1.88 to 56.95) (Table 6).

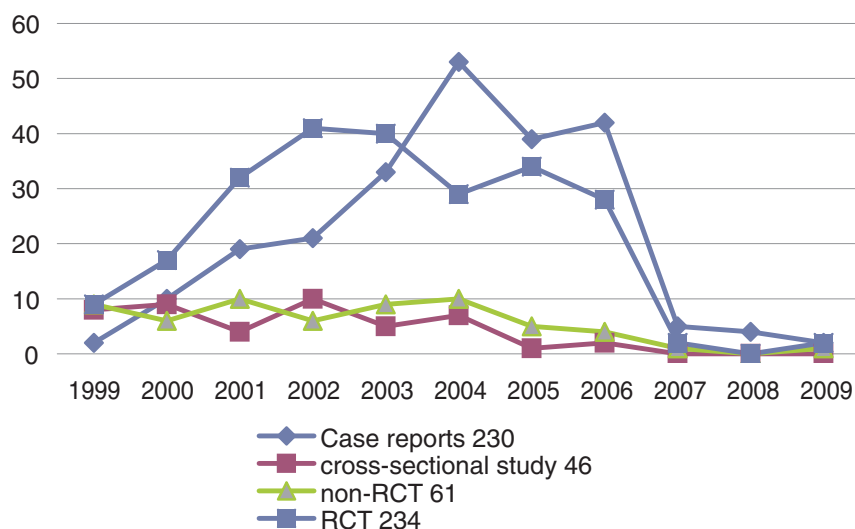
**Figure 2** Study distribution by publication year and design type.

Table 3 Systems and organs involved in ADR cases

ADR type	Number of ADR cases	Proportion (%)
Respiratory symptoms	461	37.42
Chest distress, dyspnea	289	23.46
Cough, laryngeal foreign body sensation/parathria	95	7.72
Pulmonary edema	44	3.57
Laryngeal edema	25	2.03
Anaphylactic asthma	7	0.57
Respiratory arrest	1	0.08
Skin	427	34.66
Rash, pruritus	421	34.17
Allergic purpura	5	0.41
Bullous drug eruption	1	0.08
Gastrointestinal diseases (Nausea, vomiting, abdominalgia, diarrhea)	314	25.49
Circulatory system	313	25.41
Anaphylactic shock	164	13.31
Palpitation	112	9.09
Blood pressure decline, arrhythmia	36	2.92
Cardiac arrest	1	0.08
Nervous system diseases	172	13.96
Dizziness, headache	75	6.70
Numbness in face or extremities, convulsions	43	3.49
Disturbance of consciousness (content change)	46	3.72
Coma (change in degree of consciousness)	8	0.65
Systemic reactions (Chill, fever)	134	10.87
Local reactions (Pain at injection site, local phlebitis)	27	2.19
Others	29	2.36
Visual blurring or tinnitus	15	1.22
Spine or joint pain	4	0.32
Vaginal bleeding	2	0.16
Gross hematuria	2	0.16
Hemolysis	1	0.08
Thrombocytopenic purpura	2	0.16
Neutropenia	2	0.16
Glutamic-pyruvic transaminase (GPT) increased	1	0.08
Subtotal*	1,232	100.00

Severity classification for Houttuynia injection ADRs

Clinical manifestations, outcomes, and prognosis of 1232 cases were described in detail in the 645 included articles, which allowed to classify the severity of Houttuynia injection ADRs into four levels according to the WHO Drug ADR Classification Criteria (5). More than half (59%) of the ADRs fell into grades I and II, meaning that they were severe adverse events (Table 7).

Table 4 Reported allergic histories of ADR cases

Allergic history	Number of ADR cases	Constituent ratio (%)
Penicillins	43	15.03
Unclear pharmaceuticals	23	8.05
Sulfonamides	9	3.15
Cephalosporin	6	2.01
Aminoglycoside	5	1.75
Herbal injections (Acanthopanax, Shenmai, Shuanghuanglian, Mailuoning)	4	1.40
Asthma	3	1.05
Houttuynia injection	3	1.05
Food, pollen, etc.	2	0.70
Lincomycin	1	0.35
Liquid compound aminopyrine	1	0.35
Hair dye	1	0.35
No allergic history	185	64.69
Total	286	100

Clinical characteristics of fatal cases

The included studies reported 11 cases resulting in death, of which 10 were caused by anaphylactic shock, while one patient died of multiple organ failure caused by thrombocytopenic purpura (Table 8). The primary diseases in nine cases were respiratory diseases, and the rest two cases

Table 5 Drugs combined* with Houttuynia injection in ADR cases

Drug	Number of ADR cases	Proportion (%)
Cephalosporin	53	4.30
Penicillins	47	3.81
Macrolides	43	3.49
Azithromycin	38	3.08
Erythromycin	3	0.24
Leucomycin	1	0.08
Lincomycins	9	0.73
Quinolones	8	0.65
Aminoglycoside	5	0.41
Fosfomycin	4	0.33
anti-anaerobic and antiamoebic medicine	6	0.49
Antiviral medicines	7	0.57
Herbal Injections (Daqingroot, Shuanghuanglian)	4	0.33
Others	7	0.57
Dexamethasone	3	0.24
Liquid compound aminopyrine	2	0.16
Blood acting polypeptide injection	1	0.08
Amino acetate	1	0.08
Houttuynia injection used along	1039	84.25
Total	1232	100.00

*Drug combination refers to administering drugs in the same solvent sequentially or simultaneously.

Table 6 Routes of Houltuynia injections and ADR cases

Routes	Number of patients treated	Number of ADR cases	OR*	95%CI
intravenous injection	34,969	303	6.86	(1.88, 56.95)
Intramuscular injection	1,572	2	–	–

*According to the included cross-sectional studies, RCTs, and non-RCTs, the number of ADRs following intramuscular injection was very small, so we used OR and 95% CI to assess ADR risk.

suffered from chronic eczema. Among them, 10 cases administered by intravenous Houltuynia injection, while one by intramuscular formulation.

In three of the cases, anaphylactic shock occurred within one minute of the start of intravenous injection. Four cases of anaphylactic shock occurred between two and five minutes, while the other cases occurred within 15, 80, 82, and 120 minutes, respectively. In four of the fatal cases, Houltuynia injection was combined with antibiotics.

One patient (6) had previously been given a combination of cefotaxime and ribavirin without any ADR happened. However, when given Houltuynia injection combined with cefotaxime and ribavirin in the same dilution (0.9% NaCl), he died, suggesting that anaphylactic shock may have been due to incompatibility and the allergy. In another fatal case (14),

the intravenous drip speed was 80–90 drops/min, which was much faster than that of drug instruction required.

Discussion

In this study, multiple systems or organs were involved in the ADRs, including the respiratory system (37.42%), skin (34.66%), digestive system (25.49%), circulatory system (25.41%), and nervous system (23.96%). More than half of total ADRs were severe adverse events (Grade I and II of ADR accounting for about 59%), including 11 deaths. It may suggest that Houltuynia injection contains allergens. Since it is injected directly into the blood, any impurities in Houltuynia injection are potentially quite dangerous. Anaphylactic shock accounted for 58.99% of the most serious ADRs (Grade I). Because of its serious ADR, SFDA has issued the protocols and related criteria for the re-evaluation of Traditional Chinese Medicine Injections (TCMIs), and taken the Houltuynia injection as one necessary kind of TCMIs for re-evaluation, which forces the pharmaceutical manufacturers to re-evaluate its safety with higher quality criteria and quality control.

Houltuynia injection is extracted from the grass plant of Houltuynia cordata (Saururaceae), which contains complicated components. Twenty two components from Houltuynia injection were identified by the analysis of gas chromatography or mass spectrometer (1). However, its pharmacological

Table 7 Severity classification for ADRs of Houltuynia injection

WHO ADR Severity Classification (Definition)		Clinical manifestation	Number of ADR cases	Constituent Ratio (%)
Grade I	Fatal or life-threatening, requiring immediate drug withdrawal and urgent treatment; or ADR lasting for at least one month	Respiratory arrest; Laryngeal edema; Pulmonary edema; Anaphylactic shock; Cardiac arrest; Bullous drug eruption; Allergic purpura; Coma; Hemolysis, etc.	278	22.56
Grade II	Significant symptoms, together with organ pathological/physiological changes or examination abnormalities, requiring drug withdrawal and special treatment, which may exert impact on patients' recovery directly; or ADR lasting for more than seven days	Chest distress, dyspnea; Asthma; Disturbance of consciousness; Blood pressure decline, Arrhythmia, etc.	447	36.28
Grade III	Unbearable reaction, requiring withdrawal of or reduction in drug use; improved by symptomatic therapy, without direct harm on patient	Nausea, Vomiting, Abdominalgia, Diarrhea, Rash, Pruritus, Local phlebitis, etc.	203	16.48
Grade IV	Tolerable without withdrawal or reduction in drug use. Recovery rapid after general symptomatic therapy or without any therapy; no direct harm to patient.	Cough, Dizziness, Headache, Pain at injection site, etc.	304	24.68
Total	1,232			100.00

Table 8 Clinical characteristics of fatal ADR cases

Studies	Gender of patient*	Age (years)	Primary Diseases	Dosage (ml)	Routes	Pharmaceutical production factory, number	onset Time of ADR (min)	Combined drugs	Clinical manifestation
Zhu 2005 (6)	M	47	Upper respiratory tract infection	20	Intravenous injection	No description	1	cefotaxime sodium+ Ribavirin+ NaCl	Anaphylactic shock
Wei 2006 (7)	No description	58	Chronic eczema	20	Intravenous injection	No description	1	None	Anaphylactic shock
Liu 2004 (8)	M	54	Upper respiratory tract infection	4	Intramuscular injection	No description	1	None	Anaphylactic shock
Zhao 2006 (9)	F	5	Respiratory tract infection	10	Intravenous injection	Zhengdaqingchunbao Pharmaceutical: 0507181	2	Azithromycin	Anaphylactic shock
Xue 2006 (10)	M	57	Chronic eczema	20	Intravenous injection	Shuanghe Pharmaceutical, Shanxi Province: 200505065	2	None	Anaphylactic shock
Jiang 2005 (11)	M	3	Upper respiratory tract infection	40	Intravenous injection	No description	5	None	Anaphylactic shock
Yao 2008 (12)	M	42	Upper respiratory tract infection	60	Intravenous injection	Bawang Pharmaceutical, Shanxi Province: 22-5247	5	None	Anaphylactic shock
Zhang 2006 (13)	F	1.5	Respiratory tract infection	5	Intravenous injection	No description	15	None	Anaphylactic shock
Wei 2006 (14)	M	26	Upper respiratory tract infection	80	Intravenous injection	Generic Pharmaceutical, the 3rd company, Shanghai: 050124	80	None	Anaphylactic shock
Wen 2004 (15)	M	10	Upper respiratory tract infection	20	Intravenous injection	No description	82**	Leucomycin	Anaphylactic shock
Liao 2005 (16)	M	46	Upper respiratory tract infection, skin purpura	100	Intravenous injection	No description	120	Netilmicin sulfate injection	Thrombocytopenic purpura

*M-male; F-female.

**Primary sources reported ADR onset after administration of about 220ml by intravenous drip; time estimated based on rate of 40 drops/min according to the normal drop speed of drug instruction.

and toxicological functions still remain unknown. In 2006, SFDA issued the sample of drug description of Houttuynia injection only for intramuscular administration. It required the pharmaceutical companies to supplement adequate information on drug interactions, and the results from pharmacological and toxicological studies, as well as the clinical trials to clarify the safety and efficacy of Houttuynia injection (17).

We found that case reports and case series provide most of ADR information of Houttuynia injection, which have unique advantages in rare adverse event reporting. However, they cannot be used to estimate ADR incidence since they lack the denominator of the number of drug users. More than one-third of included studies in our review were RCTs, but less than one-tenth of the ADRs we found were reported in these studies. We also found 188 articles that did not specify whether ADRs had occurred or not. Thus, it is important to strengthen ADR reporting in clinical research in order to improve the overall assessment of ADRs.

Houttuynia injection had a higher ADR risk when combined with other antibacterial medicines. Of the 11 fatal ADR cases, four had been given Houttuynia injection in combination with other drugs (three combined with macrolide antibiotics). In addition to increasing ADR risk, drug combination can make it more difficult to identify the causes of ADR. Intravenous injection of Houttuynia injection showed higher risk of ADR than intramuscular injection. The intravenous administration of Houttuynia injection has been banned by SFDA in 2006. More studies should be conducted to identify its safety and efficacy.

We found that irrational use of Houttuynia injection was apparent among the included studies, including irrational use among the children and the patients with allergic history to Houttuynia injection (which are the contraindications of the injection), improper use among patients beyond the indications (eg. reproductive system diseases, gastrointestinal diseases, ophthalmopathy, acute leukemia, which accounting for nearly 40% of total ADRs), inappropriate solvent (using sodium chloride injection as the solvent may change PH value to increase the produce of anaphylactogen (18)), high risk drug combination, too fast drop speed, and the other failures to comply with the drug instruction of Houttuynia injection. Evidence-based guidelines for the use of Houttuynia injection are required to promote the rational use of it.

All of this shows the urgency and importance of monitoring and risk management of Houttuynia injection. Therefore, Houttuynia injection from production to clinical use should be closely monitored and managed. More evidence-based guidelines and clear drug introduction should provide to guide the practice of clinicians. Doctors should also be aware of how to prevent and treat life-threatening serious adverse events. States should continually improve technical

monitoring, production processes, quality control monitoring, and ADR reporting systems to obtain the best balance between risk and benefit.

Our analysis was limited by the incomplete information which provided by the included literature. It may overestimate or underestimate the risk of ADRs of Houttuynia injection. Further studies on the safety and rational use of Houttuynia injection are required.

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