

REVIEW ARTICLE

Avoiding adverse drug reactions to Chinese medicine injections

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Keywords

Chinese medicine injections; Adverse drug reactions; Clinical rational use

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A total of 109 varieties of Chinese medicine injections (CMI) have been approved by the State Food and Drug Administration of China, all of which have the potential to induce adverse drug reactions (ADRs). Major ADRs include systemic anaphylaxis, anaphylactic shock, acute intravascular hemolysis, hepatorenal damage, skin lesion, cardiac damage, respiratory system injury, and gastrointestinal disorders. Contributing factors of ADRs include healthcare workers' inadequate attention to ADRs of CMI, complex ingredients, allergic uncertainties, and inappropriate drug use in children and the aged. To decrease ADRs resulting from CMI, it is essential to improve the selection of drug indications, delivery of proper dosage regimens, compliance with drug instructions, and selection of solvents for the drugs.

Received 01 January 2009; accepted for publication 30 November 2009.

doi: 10.1111/j.1756-5391.2010.01058.x

Introduction

Chinese medicine injection (CMI) is a novel dosage form developed on the basis of Chinese medicine preparations, which has a rapid onset of effect and favorable efficacy. Up to the end of 2005, a total of 109 varieties of CMIs had been approved by the State Food and Drug Administration of China, including 59 single Chinese herbs, and 50 multiherb combinations, of which 4 formulas was indexed by the Chinese Pharmacopoeia 2005 Edition (1). The introduction of CMI has provided more treatment options for various diseases. With its increasingly wide application in clinical practice, however, associated adverse drug reactions (ADRs) are becoming a worrisome problem. Almost all of the 109 varieties of CMIs approved by the state authorities have ever been shown to induce ADRs (2). In 2004–2005, the number of adverse events related to CMIs totaled 3414 in a single province, Henan, involved 66 varieties of injection preparations, and affected different human systems and organs. ADR related to CMI has a high incidence rate and varied clinical manifestations. The most frequently seen ADRs are allergic reactions. Considering the

complex ingredients and allergic uncertainties of CMIs, as well as patient individuality, ADRs associated with CMI are unpredictable.

In addition to drug preparation and quality factors, ADRs may also be attributed to irrational use of CMI and clinicians' inadequate attention to ADRs. It is reported that 70% of ADRs are caused by irrational use of CMI by clinical practitioners. Thus, rational use of CMI is an important challenge for clinicians.

Prevention of adverse drug reactions

Studies have found that clinical practitioners perform poorly in the prevention and close observation of ADRs, and response measures taken are not timely or appropriate. For instance, a total of 576 clinical reports involving Shenfu Injection were identified between 1993 and December 2008, among which 59.4% (342 articles) did not mention the occurrence of any ADRs (3). In our systematic review of clinical trials of Shengmai Injection, 647 articles involving 28,305 patients were included. Among these, 50.4% (326 articles) reported the occurrence of ADRs; 43 of these, however, were

case reports of ADRs, and thus only 283 (43.7%) articles actually mentioned ADRs. That is to say, more than half of the clinical literature merely reported the effectiveness of CMIs, and did not include their safety profiles. It is difficult for readers to understand the type and related factors of ADRs based on the brief description of ADRs in these clinical reports. Most of the articles only focused on clinical signs and symptoms, while safety observation of important organs was almost ignored. It has been demonstrated that most clinicians emphasize the effectiveness of drugs, while paying little attention to their safety. Therefore, it is essential to make healthcare professionals aware of the importance of adverse events.

Selection of indications

Within the theoretical framework of traditional Chinese medicine (TCM), the properties and flavors, as well as the functions and indications, of Chinese medicine are strictly defined. Also, for each variety of CMI, its functions and indications are well defined, and any overuse or abuse is forbidden. The application of CMI in clinical practice should also comply with the fundamental principle of TCM, i.e., treatment based upon syndrome differentiation. Only through accurate syndrome differentiation can rational and safe use of Chinese medicine be realized, so as to maximize efficacy and minimize toxicity. According to the statistics revealed by relevant organs, the application of CMI is usually based on disease differentiation rather than syndrome differentiation, especially by those doctors who are not familiar with TCM theory. CMI has tended to be used as a kind of Western medicine. Noncompliance with the traditional TCM theories is one of the major reasons for the rise in the incidence of ADRs.

The indications specified in the package insert are approved by the State Food and Drug Administration of China (SFDA), and are based on the findings of premarket clinical trials conducted in accordance with Good Clinical Practice (GCP) guidelines. These indications can never be extended without firm evidence. For example, Shenfu Injection, which consists of the extracts of hongshen (Gingseng Radix Rubra) and fuzi (Radix Aconiti Lateralis Preparata), has the function of restoring yang and rescuing the patient from collapse, nourishing qi, and relieving desertion. But its indications have been extended to heat exhaustion and excess syndrome, which is absolutely wrong. It is reported that Shenfu Injection has been mistakenly applied in clinical practice to treat such diseases as acute pancreatitis, leukemia, and bronchial pneumonia (3). Rational selection of target diseases and syndromes of CMI based on the TCM characteristics should be further emphasized.

Dosage and infusion velocity

As with all drugs, toxic reactions to Chinese medicine are related to dosage. Increasing dosage beyond CMI's margin of safety may lead to adverse outcomes. Overdose is not uncommon in clinical practice. According to the recent reports, 41 adverse events were linked with Huangqi Injection, 19 of which can be attributed to a single dose higher than the highest dose defined in the package insert (4). Our review indicated that (5), among the 576 articles on the clinical application of Shenfu Injection, most of the administered doses reported were higher than the dose specified in the package insert. More than half of the reported doses for intravenous injection were greater than or equal to 20 mL, with the highest reaching 120 mL; in 16 articles, the doses for intravenous infusion were at least 100 mL/day, with one of more than 480 mL/day. ADRs like dry mouth, facial flushing, fever/feverish dysphoria, and headache/distending pain of head are probably associated with overdose. Overdose certainly increases the incidence of ADRs. A survey conducted to evaluate the application of several commonly used CMIs in TCM hospitals found that up to 91.54% of injections had been overdosed at some time.

The occurrence of ADRs is associated with the infusion velocity, dosage, and concentration of CMIs. Rapid infusion velocity, a high dose, or a high concentration may cause an excessive dose of drugs to be infused into the veins in an instant. Particularly when used for the first time, the infusion velocity should be well controlled and close observation should be used. Specifically, CMIs should be diluted before use, because excessive particles may lead to a series of adverse reactions. Thus, the dosage regimen and infusion velocity defined in the package insert of CMIs must be strictly followed. Especially when used for the first time, the infusion velocity should never be higher than what is recommended, and close monitoring should be performed.

Based on the corresponding package inserts as well as the instructions and standards specified in the *Science of Chinese medicine Injection* (6), 39 cases of death resulting from improper use of CMIs were analyzed. Results showed that 11 (28%) of the 39 deaths were related to overdose or abnormally high concentration; the drugs involved were Shuanghuanglian (3 deaths), Caihu (2 deaths), Chuanxiongqin, Compound Danshen, Danshen, Mailuoning, Qingkailing, and Gegensu (7). In another instance, four patients diagnosed with coronary artery disease were treated with Shengmai Injection via intravenous infusion at a dose of 80–100 mL, after which all patients experienced severe abdominal flatulence. When the dose was reduced to 60 mL, abdominal flatulence still persisted; but when decreased to 40 mL, abdominal flatulence disappeared (8). When 2 other patients suffering from local pain were treated with 5% GS 100 mL plus Shengmai Injection 60 mL, both experienced

pain afterward. When diluted with 250 mL 5% GS, the pain was relieved (9). High-dose Shenfu Injection for direct intravenous injection or infusion without any solvent dilution resulted in 4 events of pain at the administration site.

Proper administration approaches

Since different administration approaches have different requirements for the quality of CMIs, these approaches should never be changed arbitrarily. Generally speaking, the acceptable administration approaches and dilution instructions are clearly defined in the package inserts of CMIs. Some injections are specifically designed for intramuscular injection, but some clinicians administered them intravenously, which is dangerous. For example, it is reported that Shenfu Injection did not induce any ADRs in the treatment of chronic bronchitis when administered through acupoint injection or intramuscular injection (10). However, it is also reported that Tanreqing Injection and Shenfu Injection designed for intravenous infusion could become very dangerous when used for aerosol inhalation (10, 11). For drugs designed for aerosol inhalation, specific requirements, such as the size of particles, must be satisfied. When injections are improperly used for aerosol inhalation, airway hypersensitivity may be induced, and drug particles may accumulate in the lungs and cause pulmonary fibrosis. Administering injections for via acupoint injection or external application also carries a heightened risk of ADRs. An experiment on Tanreqing Injection (Shanghai Kaibao Pharmaceuticals), conducted in rabbits, indicated that severe congestion and muscular degeneration occurred at the local injection site 48 hours after intramuscular injection of 1.0 mL. The authors concluded that, “this preparation is not indicated for intramuscular or subcutaneous injection.” However, the contraindications in the package insert of Tanreqing Injection still do not mention this.

Selection of solvent

Generally speaking, solvents serve as a drug carrier in clinical practice. When CMI is administered by intravenous infusion, its character will often be changed due to its complex ingredients and other influencing factors such as concentration, pH, and storage time.

Allergic reactions

There are a variety of allergenic ingredients in CMIs, including protein, starch, tannin, pigment, mucus, resin, and volatile oil. Once infused into the blood, they can stimulate the body to produce antibodies or sensitized lymphocytes, so that when the patient is re-exposed to the antigen, an allergic reaction occurs. Some impurities may bind plasma proteins

to form an antigen, evoking serious ADRs. Animal and plant proteins and tannins also easily cause allergic reactions. As ADR induced by Shuanghuanglian Injection reached 139 cases, accounting for 25.65%. The drug consists of extract from three Chinese medicines: honeysuckle, Scutellaria, and Forsythia. Forsythia contains chlorogenic acid, a highly allergenic antigen that can produce high sensitization in the body (12).

Particle additives

The hazards posed by insoluble particles have drawn much attention from the medical community. Many countries have limited the amount of insoluble particle in infusion agents. There also are recommended limits for infusion agents in *Chinese Pharmacopoeia*. The second version recommends that a volume of 100 mL or more of intravenous fluid should contain no more than 20 particles larger than 10 μm in diameter, and no more than two particles larger than 25 μm in diameter. An investigation of the use of several common CMIs in TCM hospitals found that overdose usage of drugs was as highly as 91.54%. Dillution of CMIs often leads to an increase in the number and diameter of drug particles (6). Changes in pH can also caused by excess particles. The insoluble particles in CMIs cannot be metabolized in the body; thus, they can cause partial or complete blood vessel blockage, tissue hypoxia, phlebitis, edema, and granuloma, as well as allergic reactions and fever.

Changes in pH

Chinese medicine intravenous fluids are stable under specific pH conditions. If the pH value changes, the drug's solubility also changes. Because of the complicated ingredients of Chinese intravenous fluids, its alkaloids, saponins, amino acids and other major components and some impurities are not divisible when combined with intravenous fluids, and may produce micro-precipitation reactions due to pH change or oxidation, condensation, hydrolysis, etc. (13). When the compounds Danshen, Houttuynia, astragalus, Shenmai, Passepartout, Acanthopanax, Mailuoning, safflower, and rock Shu—all ingredients in traditional CMI—were dissolved in 0.9% sodium chloride, the number of particles larger than 10 μm significantly increased. This phenomenon occurred because the pH value changed after combination and the active ingredient precipitated due to decreased solubility. For example, Qingkailing Injection consists of several traditional Chinese medicine extracts, and its optimum pH value is between 6.8 and 7.5. Adding 10% GS to the Chuanhuning Injection, would cause the injection to appear muddy in the course of intravenous infusion. The 10% GS lowered the pH, and Chuanhuning is volatile in an acidic environment (14).

High drug concentration

In general, the higher the concentration of CMIs, the deeper the color of the solution, and the greater the amount of active ingredients and impurities. For Danshen injection in a 5% glucose solution, the number of insoluble particles will increase as the concentration is increased. Adverse reactions can easily occur with excessive drug concentrations. Most CMI instructions state that the injection should be diluted before use, and inadequate dilution can cause serious consequences.

Heat accumulation

Adding CMIs into the infusion agent and using them in combination with a variety of pharmaceuticals may result in heat accumulation, fever and other adverse reactions.

Avoiding combination therapy

As with any complex composition, the nature of CMIs can often be affected by pH values, storage time, etc. Changes can arise through interactions between the components. For example, combining sulfuric acid with berberine Bupleurum injection, Ligustrazine injection, or Houttuynia cordata injection will produce precipitation. Mixing CMIs with medications such as antibiotics can likewise result in precipitation. Combining an injection such as ligustrazine injection (which contains alkaloids and sodium bicarbonate) with another alkaline solution will increase pH values and cause free alkaloids to precipitate. Vitamin C, a strong acid and reducing agent, can react with CMIs to increase the number of particles in solution (15). Two articles reported a case in which five patients were administered Shengmai Injection combined with a plasma substitute, and two went into anaphylactic shock. In another instance, puerarin injection combined with other drugs caused three deaths from haemolysis (16). Among 3414 cases of adverse reactions to CMIs, 51.61% (1762 cases) were caused by combining two or more kinds of drugs. Generally speaking, adding more varieties and a greater number of drugs increases the likelihood of ADRs. Thus, when infusing CMIs, attention should be paid to the variety and quantity of additional drugs, and, unless essential, drug combination should be avoided.

Treatment course and medication interval

Because of individual differences in age, gender, and body constitution, long-term application of CMIs should be avoided. Any potential allergic reactions should be closely monitored. Infusion should only be started after the former infusion has been completed; normal saline or 5% glucose

solution can be infused as pretreatment. Before beginning a new injection, the infusion tube should be flushed to remove any residual drugs that may react with the new infusion. In addition, with CMIs, we should infuse another liquid between CMIs and other drugs to avoid a reaction between the drugs. Generally, CMIs should not be used simultaneously with Western medicine. In one report, of 22 cases of adverse reactions following Houttuynia injection, 18 had infused other drugs in the same container. After CMIs are dissolved in prepared fluids, it is necessary to check for insoluble particles before use in order to avoid adverse reactions.

Most of the instructions provided with drug injections call for a certain amount of dilution before application. Healthcare providers should select the appropriate solvent with special attention to incompatibility, and should avoid increasing the concentration beyond what is recommended. It is best to do compatibility tests before use. When it is necessary to combine traditional Chinese medicine and Western medicine injections, special care should be taken with the preparation of the infusions and with the order of the doses. In some cases precipitation can be avoided by changing the mix order; in other cases, by diluting the solution after mixing.

Long-term use of CMIs should be avoided. The duration of use for each drug should be adequate, and the drug should be replaced with a different one if it is not effective. CMIs should be carefully checked before use, and if there is turbidity, precipitation, discoloration, leakage, and other issues, they should not be used.

Quality of infusion device

Insoluble particles can also be caused by infusion equipment.

Technology and equipment

The choice of preparation process and filtration equipment is important. Filtration is key to ensuring the clarity of the injection. Commonly used filters include sand filter rods, hanging melting glass filter balls, folding-type microporous membrane filters, and centrifuges. A sophisticated, high efficiency filters with a safe and reliable profile should be chosen for filtration (9).

Casting process and equipment

Compressed air purification and chemical composition affect the stability of CMIs. Incorrect handling or disinfection while cutting the ampoule may cause large numbers of glass particles to be absorbed into the liquid due to negative pressure in the ampoule, and repeated needle puncture of the ampoule may lead the rubber plug to fall off.

Preventing and treating allergic reactions

Medical personnel should identify patients with a history of allergic reactions and avoid the use of CMIs on these patients. A CMI skin test should also be carried out prior to use. Healthcare workers must be prepared to intervene if patients experience an allergic reaction. Once ADR occurs, the drug should be withdrawn immediately and the patient treated immediately. Between 1996 and 2006, a total of 786 cases of anaphylactic shock were recorded in the Chinese Biomedical Literature Database. In 82.70% (650) cases, drug-induced anaphylactic shock occurred within 30 min of administration of a drug. Therefore, during the first hour of administration, especially during the first 30 min, any potential drug reactions should be closely monitored.

Drug use in children

The body composition of children, especially premature infants, newborns, and infants, is quite different from that of adults. Their central nervous systems, gastrointestinal functions, hepatic and renal functions, and endocrine systems have not yet fully developed. Thus, the pharmacokinetic and pharmacodynamic characteristics of drugs in children can be significantly different from those in adults, including in vivo absorption, distribution, metabolism, and excretion of drugs, as well as the body's overall response to drugs. Moreover, premarketing clinical trials of new CMIs are rarely performed in children, so proper dosage regimens, indications, and instructions for CMI use in children are usually unknown. Therefore, caution must be taken for pediatric use to ensure children's safety, especially infants' safety. It is reported that the application rates of Shegan Antivirus Injection, Xiyanping Injection, Yanhunung Injection, Zedoray Turmeric Oil Injection, and Chuanhunung Injection have reached 100%, 90.62%, 85.29%, 62.96%, and 37.10%, respectively, and the incidences of ADRs and serious ADRs have been relatively high in pediatric patients, i.e., 19.74% and 33.82%, respectively. Among the cases of death caused by Qingkailing Injection, 27% were children younger than 14 years old, partly because of the mixture of multiple solvents and multiple drugs, as well as the large infusion volume. Two died of heart failure, which may be attributed to large infusion volume and rapid infusion velocity (2).

Drug use in the aged

It is estimated that the incidence of ADRs following CMI injection in the aged is as high as 27.13%, which is four to eight times that in younger adults (17). The nervous system, endocrine system, and various organ functions decline

gradually during the aging process; in addition, the in vivo environment, physiologic function, and anatomic structures change to some extent. Thus, absorption, metabolism, and excretion of drugs can be weakened in the aged. Changes in pharmacokinetics and the body's sensitivity to drugs, as well as poor tolerance, mean that the incidence of ADRs is expected to be higher in the aged.

Moreover, older patients usually have various concomitant diseases, which require combinations of several drugs. Thus, the incidence of ADRs related to drug interactions would also be increased. Among 32 cases of allergic shock or systemic anaphylactoid reactions induced by Shengmai Injection, 20 (62.50%) were in patients older than 60 years old. Rational and safe drug use is clearly of vital importance to the health of the aged.

Summary

Factors that contribute to ADRs following traditional CMI include complex drug composition, allergens, uncertainty factors such as patients with special physical circumstances, and inappropriate use of drugs. Managing these factors is critical to ensuring clinical treatment effect and safety.

Medical workers should learn more about the risks of traditional CMI, and gradually establish norms or standards for these injections. A decision in clinical medicine should be based on the basic principles of traditional Chinese medicine: syndrome differentiation and treatment, Chinese medicine theory, drug-induced taste, function, and objectives of attending syndrome.

The use of traditional CMI must be in strict accordance with the instruction booklets included with the drugs. Healthcare workers must not arbitrarily increase dose or concentration, employ a drip speed that is too fast, use an inappropriate solvent, skip the dilution step, or change the route of administration without cause. Before administering the injection, the healthcare worker must check for insoluble particles. Drugs should not be combined. Monitor the medication interval, treatment course, and drug withdrawal after the disease has been cured, and avoid medicating the patient long-term.

Medical personnel should identify patients with a history of allergic reactions and avoid the use of CMIs in these patients. A CMI skin test should also be carried out prior to use. Healthcare workers must be prepared to intervene if patients experience an allergic reaction. If an adverse reaction occurs, use of the medicine should be stopped immediately.

Due to the physiological characteristics of the elderly and children, special precautions should be taken to ensure medications administered are reasonable, effective, and safe.

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