Postmarketing studies on safety of Dengfeng® shenmai injection

Lianxin Wang, Wen Zhang, Yanming Xie, Yang Bai, Mulan Wang, Qinghua Ai

Lianxin Wang, Wen Zhang, Yanming Xie, Qinghua Ai, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China
Yang Bai, Mulan Wang, Marketing Department, Research Department of Chiatai Qingchunbao Pharmaceutical Company, Ltd., Hangzhou 310023, China
Supported by National Science and Technology Major Projects for "Major New Drugs Innovation and Development": Study on Key Technologies of Postmarketing Evaluation for Chinese Medicine (No. 2009ZX09502-030)
Correspondence to: Prof. Yanming Xie, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China. datamining5288@163.com
Telephone: +86-10-64014411-3302
Accepted: November 16, 2013

Abstract

OBJECTIVE: To systematically research the postmarketing safety of Dengfeng® shenmai injection, identify potential risk factors, and ensure its clinical safety.

METHODS: We investigated a comprehensive series of studies on the production process, quality standards, pharmacology, postmarketing clinical studies, and safety evaluation of Shenmai injection, including literature analysis of adverse drug reaction (ADR) case analysis and systematic review. Data from the hospital information system (HIS) and spontaneous reporting system (SRS) were also analyzed.

RESULTS: The approximate dosage leading to death in dogs is 45.0-67.5 g raw drug/kg and the toxic reactions are restlessness, skin irritation, salivation, and vomiting. The results of chronic toxicity tests in mice and dogs, and the other tests such as 6-month toxicity, drug safety, genetic toxicity, and reproductive toxicity of rats and dogs, were positive or qualified. Patient ADR history and ADR family history were closely associated with itching based on the data analysis from SRS. There was no damage to renal function from Shenmai injection use at a dosage and a treatment course outside the recommended dosage and treatment course as specified based on data analysis from HIS. The most common ADR from Shenmai injection are difficulty breathing, facial flushing, nausea, vomiting, chest tightness, skin itching, rash, and back pain.

CONCLUSION: This study includes complete information on Shenmai injection ADR incidence rate. We found that Shenmai injection is safe and this study can provide clinical, research, and production institutions with an objective, reliable, and scientific basis for use of Shenmai injection.

Key words: Product surveillance, postmarketing; Medicine, Chinese traditional; Safety; Shenmai injection

INTRODUCTION

Shenmai injection is a Chinese medicine injection originating from the ancient formula Shengmaisan. The formula was reformed by modern technology based on the ancient formula shendongyin recorded in Zheng Yin Mai Zhi Volume II by Jingming Qin in the Ming Dynasty. Today the Shenmai injection on the market is provided with seven specifications and 33 license numbers contributed by seven manufacturers. This study investigates only Dengfeng® shenmai injection made by Chiatai Qingchunbao Pharmaceutical
Co. Ltd. (CTQ, Hangzhou, China). Dengfeng® shenmai injection is made from Hongshen (Radix Ginseng Rubra) and Maidong (Radix Ophiopogonis Japonici) from Zhejiang, China. The injection can benefit Qi to prevent exhaustion, nourish Yin to generate body fluid, and promote pulse. It is usually used to treat shock, coronary heart disease, viral myocarditis, chronic pulmonary heart disease, and neutropenia. In addition, it can improve the immunity of cancer patients and can be used as an adjunct to chemotherapy, while reducing toxic adverse reactions. Its adverse reactions include occasional allergic reactions.

Since its introduction to the market in 1986, this injection has been widely used clinically. CTQ carried out a comprehensive series of studies on the production process, quality standards, pharmacology, postmarketing clinical studies, and safety evaluation, to continuously improve effectiveness, safety, and control of drug quality. These studies ensure clinical safety and effectiveness, and identify potential risk factors of the drugs as early as possible to further improve drug safety.

**MEDICINE QUALITY CONTROL**

**Quality control of raw herbal medicinal material**

Dengfeng® shenmai injection is made from Hongshen (Radix Ginseng Rubra) and Maidong (Radix Ophiopogonis Japonici). The Hongshen (Radix Ginseng Rubra) is supplied by a certified manufacturer of Chinese crude drugs by the National good manufacturing practice (GMP), which is involved in the planting and processing of ginseng. Maidong (Radix Ophiopogonis Japonici) is supplied by the planting base of CTQ, which is certified by good agriculture practice (GAP) in Cixi, Zhejiang, China.

**Quality control of the production process**

CTQ collected data from different batches, developed scientific and reasonable process specifications, and performed a systematic workmanship study on the processes of extraction, purification, decolorization, alcohol removal, and ultrafiltration, to ensure the uniformity and stability of product quality. In 2011, CTQ introduced fingerprint check items and formulated current quality standards for Shenmai injection (WS3-B-3428-98-2010Z). Furthermore, in addition to the existing standards, CTQ developed rigorous internal control standards, which added the measurement of borneol glycoside content, which is the characteristic ingredient of Maidong (Radix Ophiopogonis Japonici). CTQ also added a series assay items like protein, resin, oxalate, potassium, total solids, ignition residues, arsenic salt, and heavy metals. The sampling amount of the stability test was increased, the injection dose of heat source examination was added, and the requirements for the content measurement of total baicalin were raised. Additionally, ginsenoside rgl and re were added to existing content measurement items and internal control standards adopted more stringent fingerprinting technology for materials, intermediate products, and finished products. For stability studies, CTQ used high-temperature tests, glare tests, frozen process experiments, low-temperature tests, retrospective analysis of finished product, retained samples, and intermediate product, long-term stability studies (24 months), and acceleration tests. The projects of inspection include related substance inspection, total ginseng saponin content, fingerprinting, abnormal toxicity, hemolysis and agglutination, and heavy metals. Intermediate internal control standards were established with satisfactory results. Study on the compatibility of Shenmai injection and drugs commonly used in clinic found that: 5% dextrose injection, 10% dextrose injection, dextrose and sodium chloride injection, 0.9% sodium chloride injection, and 22 other kinds of medicines are suitable for application in combination with Shenmai injection at various specifications.

**Studies on non-clinical safety and pharmacology**

In 2009, CTQ authorized a safety evaluation research center at Zhejiang Academy of Medical Sciences (Zhejiang, China) to perform non-clinical safety studies on Dengfeng® shenmai injection. General pharmacology studies, chronic toxicity tests in mice and dogs after intravenous injection, 6-month toxicity, drug safety, genetic toxicity, and reproductive toxicity of rats and dogs after intravenous injection were comprehensively investigated.

For the acute toxicity tests, the dosage of Dengfeng® shenmai injection tolerable to mice is 40 g raw drug/kg. The approximate dosage leading to death of beagle dogs is: 45.0-67.5 g raw drug/kg.

For chronic toxicity tests, beagles were given 20, 6, and 3 g of Dengfeng® shenmai injection intravenously for 6 months. Toxic reactions such as restlessness, skin irritation, salivation, and vomiting occurred.

For tests on genetic toxicity, undue toxicity, irritation, allergies, and hemolysis, the results were positive or qualified. Genetic toxicity tests include reproductive and early embryonic developmental toxicity tests on rats with the rat embryo-fetal developmental toxicity test. The results showed that some maternal toxicity and mild embryo-fetal developmental toxicity appeared in the SD rat groups receiving 20, 6, and 3 g raw drug/kg·d. However, there was no maternal toxicity or embryo developmental toxicity found in the groups receiving 2 g raw drug/kg·d.

In general pharmacological tests, there were no effects on the nervous system or cognitive ability in mice receiving an intravenous dosage of 5, 15 g raw drug/kg. However, the administration of 12, 3, and 1 g raw drugs of Dengfeng® shenmai injection slowed the heart rate of dogs until the 120 min after administration. Then, the heart rate returned to normal. There were no significant effects on each electrocardiogram indicator, body temperature, or breathing rate of the dogs.
In 2011, the concept "Network pharmacology for Chinese medicine" was introduced in the National Key Technological Project Technical Reform of Shenmai Injection (No. 2008ZX09202), and the network pharmacology of Dengfeng® shenmai injection was researched for the first time. A gene regulating network model of Dengfeng® shenmai injection for resisting myocardial infarction in rats was built with gene and chip technology, and its regulating effect was found in several signal pathways such as the cell cycle, neurotransmitters, and Wnt. This demonstrated the "multi-target and multi-channel" effect of Dengfeng® shenmai injection. This project provided a scientific basis for the establishment of drug quality evaluation methods and guidance for clinical use.

**Postmarketing clinical safety studies**

CTQ monitored ADR from Dengfeng® shenmai injection in cooperation with the Shanghai ADR Monitoring Center, Zhejiang ADR Monitoring Center, and Shanghai Production-Study-Research Cooperation Project Team. From 2004-2009, Shanghai ADR Monitoring Center found 121 ADR from Shenmai injection (including combined medications), including four severe ADR. Overall, 79 patients were relieved, 42 patients were cured, and no patients died or permanently worsened. According to estimates from the digital data display system, the total incidence of ADR from Shenmai injection is 0.014%, while the incidence of serious ADR is 0.0058%. That means that Shenmai injection is relatively safe. Since 2007, Zhejiang ADR Monitoring Center found 331 ADR and 23 severe ADR (6.95%) from Dengfeng® shenmai injection. Overall, the vast majority ADR patients were cured or relieved and no patient was died or experienced a worsened condition. Most ADR are relatively mild allergic reactions such as rash, fever, and chills. All ADR were cured and improved after treatment or drug withdrawal.

From February 2009 to December 2011, CTQ launched the Postmarketing Intensive Monitoring Study on Shenmai Injection in cooperation with the Shanghai Production-Study-Research Cooperation Project Team to research the clinical safety of Dengfeng® shenmai injection. This was a prospective, multi-center, open-label study and active observation based on pharmacoepidemiology. The research was conducted via questionnaires distributed by Shanghai ADR Monitoring Center. Data were collected from 72 medical institutions in Shanghai, Anhui, and Zhejiang. Overall, 20,924 cases were recorded. According to the monitoring results of contract research organization, 18 ADR patients were reported with an incidence rate of 0.086%. Based on ADR incidence classification standards, the ADR incidence rate as a result of the monitoring is classified as rare.

Since Dengfeng injection entered the market, CTQ has carried out effectiveness evaluation study with Zhejiang Chinese Medical University, Thoracic Obstruction Emergency Collaborative Group of Division of Medical Affairs, State Administration of Traditional Chinese Medicine, and the Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine. In the 1990s, Luming Liu of Zhejiang Chinese Medical University studied the effect of Shenmai injection for increasing effectiveness and reducing toxicity toward malignant cancers in chemotherapy. The results showed that, combined with chemotherapy, Shenmai injection significantly increased effectiveness while reducing toxicity. In addition, patient immunity was improved.

In 1996, an expanded clinical verification of Shenmai injection was jointly carried out by 11 agencies including Beijing Branch of Thoracic Obstruction Emergency Collaborative Group of Division of Medical Affairs, State Administration of Traditional Chinese Medicine, Ruijin Hospital Affiliated to Shanghai Second Medical University, and Zhongshan Hospital Affiliated to Shanghai Medical University. The research incorporated 1163 emergency cases of various types including 736 cases of cardiovascular disease. Results showed that Shenmai injection has the following clinical effects: Shenmai injection can significantly reduce the outbreak of coronary heart disease and angina, and relieve the symptoms of chest choke, palpitations, shortness of breath, fatigue and burning sensation of five centers due to coronary heart disease. Shenmai injection can improve a variety of arrhythmias and the symptoms of chest choke, palpitations, dizziness, shortness of breath due to arrhythmias. When used in combination with conventional anti-heart failure drugs, Shenmai injection can significantly improve heart function in patients with congestive heart failure, shorten the time to improving heart function, and improve symptoms in patients with heart failure. Moreover, it is able to effectively reduce the heart rate and blood pressure of heart failure patients. When used in combination with conventional anti-myocardial infarction drugs, Shenmai injection can effectively control arrhythmias, and significantly improve hypotension and heart failure induced by acute myocardial infarction. The efficacy of Shenmai injection is much better than that of conventional anti-myocardial infarction drugs used alone. For patients with acute exacerbation of pulmonary heart disease, Shenmai injection significantly improves remission rates of disease and improves blood analysis parameters, and oxygen and carbon dioxide levels return to normal. Shenmai injection significantly relieves shock due to allergic, infectious, or hemorrhagic events (in particular shock due to cardiovascular events), and can increase and stabilize blood pressure, and improve symptoms of syncope. Shenmai injection can significantly improve the therapeutic efficacy of acute pneumonia symptoms and shorten the number of days to the disappearance of all signs compared with the use of conventional anti-infection drugs alone.
Postmarketing clinical trials on the treatment of coronary heart disease and chronic heart failure (deficiency of both Qi and Yin)

From 2010-2012, CTQ carried out postmarketing clinical trials on the treatment of coronary heart disease and chronic heart failure (Deficiency of both Qi and Yin) with Dengfeng® shenmai injection. Parallel, double-blind, randomized, and placebo controlled trials were performed, which were the first double-blind postmarketing clinical trials of a TCM injection. The trials were conducted by professors Shaoxiang Xian and Zhongqi Yang as principal researchers at the First Affiliated Hospital of Guangzhou University of Chinese Medicine in collaboration with seven sub-centers. The trials showed that primary efficacy indicators such as the efficacy on cardiac function and TCM syndromes in the experimental group were better than those in the control group. In addition, in the 6 min walking test, the rate of patients with relief of severe heart failure symptoms was far higher in the Shenmai injection group than that in the control group. Safety results showed that patients appeared in good medication compliance, and no ADR were found in the patients from the experimental group. Laboratory tests showed no abnormalities in laboratory test indicators. Therefore, Shenmai injection has good tolerability and high safety for patients suffering chronic heart failure and coronary heart disease.

Registry-based postmarketing clinical safety monitoring study

Since November 2011, at the request of CTQ, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences carried out postmarketing safety evaluation study. The postmarketing safety evaluation study Registry-based intensive hospital monitoring of postmarketing clinical safety of Dengfeng® shenmai Injection comes from the Study on Key Technologies of Postmarketing Evaluation for Chinese Medicine (No. 2009ZX09502-030), a national key technological project "Major New Drug Development" overseen by Yanming Xie, a researcher at the Institute of Basic Research in Clinical Medicine. Currently, the project has passed the review of Ethics Committee of Institute of Basic Research in Clinical Medicine (Approval document No. 9-2), and completed international registration at clinicaltrials.gov (ID: NCT01612611). Meanwhile, the study has completed the safety literature related to the injection, and finished the safety, effectiveness, and economics study based on HIS data. The safety study based on the Spontaneous reporting system data provided by the National Adverse Drug Reaction Monitoring Center has also been completed. Registry-based intensive hospital monitoring of clinical safety of the drug has achieved staged progress. Leading institutions and 22 sub-centers have participated in the postmarketing clinical safety intensive hospital monitoring. The clinical monitoring of 30 000 patients will be completed by 2014. To further strengthen quality control, from May-June 2013, the research team organized experts to perform site inspections on two leading institutions (the First Affiliated Hospital of Guangzhou University of Chinese Medicine and the First Affiliated Hospital of Tianjin Medical University) and one sub-center (Anhui Tumor Hospital). The three institutions completed monitoring over 3696 patients, and reported six ADR/ADE cases. The audit experts carefully examined the qualification of hospitals, researchers, monitoring sheets, and original data, found problems in the work, and drew a spot conclusion on the auditing results of the hospitals.

SRS data analysis

Analysis' of the 4220 cases reports involving ADR after using Dengfeng® shenmai injection from 2005 to 2012 from State Adverse Drug Reaction Monitoring Center shows that serious ADR account for 10.19% and newly reported ADR account for 36.82%. Those who suffer from ADR/ADE are mostly middle-aged and old patients, and women are slightly more prone to ADEs than men. ADR/ADE mainly include damage to the central and peripheral nervous system, damage to the skin, or systemic damage. The top 10 ADR symptoms are shortness of breath, skin rashes, allergic reactions, itching, chills, palpitations, flushing, dizziness, nausea, and breathing difficulties. Bayesian confidence propagation neural network and proportional reporting ratio methods were used to capture suspicious early warning signals of ADR. Then, a test was made based on the results of the analysis using the propensity scoring method. The analysis found that shortness of breath, allergic reaction, and flushing are early warning signals of ADR to Shenmai injection. In addition, association analysis and data mining were made on the factors related to ADR of Shenmai injection based on association rules. The results show that patient ADR history and ADR family history are most closely associated with itching. Additionally, ADR family history is closely related to excessive dosage, itching, nausea, and difficulty in breathing.

Hospital information system (HIS) data analysis

An analysis' was conducted on data including basic information, Western/TCM diagnostic information, doctor information, and physical and chemical indicators collected from HIS database and laboratory information system database of inpatients from 18 domestic hospitals Grade Ⅲ Level A. Information on indications population, death population, regimen, suspected allergic reactions, and drug safety were analyzed with descriptive statistics and statistical modeling oriented to the whole population. There are two categories of medicines used in combination with Shenmai injection. One category is conventional Western Medicine
targeting the indications of Shenmai injection such as nitroglycerin, insulin, penicillin, pantoprazole, or diazepam. The other category is anti-allergy drugs such as promethazine or vitamin C. For patients receiving a dosage and treatment course in excess of the recommended dosage and treatment courses, further analysis was made on whether the medicine damages renal function. Analysis based on existing data found no damage to renal function arising from use of Shenmai injection at a dosage and a treatment course outside the recommended dosage and treatment courses.

**Literature analysis**

There are 11 clinical ADR reports on Shenmai injection in the literature. The reports concern 21 cases, of which no patients died, but six suffered serious adverse reactions. Three patients experienced anaphylactic shock, while three experienced a severe anaphylactoid reaction. Among the 21 patients with adverse reactions, the earliest occurred 3 min after commencement of infusion, while the latest one occurred 3 days after continuous infusion. The most common ADR symptoms of Shenmai injection reported are difficulty breathing, facial flushing, nausea, vomiting, chest tightness, skin itching, rash, and back pain.

Studies in the systematic review on the treatment of acute myocardial infarction with Shenmai injection show that use of the injection combined with conventional treatment can reduce mortality of acute myocardial infarction, morbidity of heart failure, and shock and reinfection in patients during hospitalization. However, the drug does not have an obvious effect on improving coronary recanalization rate. However, these results need to be further verified by high-quality randomized controlled trial because of the poor quality of the included studies. Systematic review did not find any ADR/ADE occurring during the treatment of acute myocardial infarction with Shenmai injection. This review introduced the combination of active monitoring with passive monitoring, combination of prospective with retrospective studies, and combination of literature studies with effect studies. We have reviewed the information on ADR incidence rate to provide evidence for the safety of Shenmai injection and to provide clinical, research, and production institutions with an objective, reliable, and scientific basis for safe medication.

**CONFLICT OF INTEREST**

The authors have no conflict of interest.

**REFERENCES**