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A Critical Look at the Injection Form of Traditional Chinese Medicine-The History, Problems and Future

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Review Article

Abstract

This article describes the frequent occurrence of adverse reactions in the use of traditional Chinese medicine (TCM) *via* injection forms. TCM injections could be innovative aspirations because of the characteristics of high efficiency and rapid action. TCM injections have been considered important achievements in the modernization of TCM and are highly anticipated. However, chemical components in the TCM injections are unclear, and standard pharmacological and toxicological evaluations are insufficient. This not only prevents the injection forms from going outside China, but more importantly, the frequent adverse reactions and even mortality events related to the TCM injections have obstructed their development.

Keywords: Traditional Chinese Medicine (TCM); Injection; Adverse reaction; TCM theory

Introduction

Treatment using Traditional Chinese medicine, is known to be slow acting and with weak effects. The emergence of the injection form might be able to change the obvious disadvantages. The unique innovative dosage form of TCM injection preparations could be break-throughs in the traditional methods of TCM administration offering better utilization of the drug and more rapid action [1], it has been regarded as a significant achievement in the modernization of TCM and is highly expected. However, many chemical components in the TCM injection are yet unclear and the pharmacological and toxicological evaluations are insufficient. Not only is this form of drug delivery not welcome outside China, but more seriously, frequent adverse reactions and even mortality related have made its development difficult.

Although some experts believe that the basic principles of TCM injection are still based on TCM theories, historically the injection form has never been applied. Theories of TCM are unable to explain the metabolic processes and mechanisms of action of the drugs directly injected into the human body. Because traditional Chinese medicine does not have an injection dosage form, the use of traditional Chinese medicine injections remains controversial. Many unfavorable reports related to TCM injections: from the "Yuxingcao injection incident" in 2006 to the "Ciwujia injection incident" and "Yinzhihuang injection incident" in 2008 and the "Shuanghuanglian injection incident" and "Xiangdan Injection Incident" in 2009, have raised concerns over the safety issues of the injection form [2-6].

Review of Literature

The first reported adverse reaction to a TCM injection occurred in March 1980. A patient with primary hypertension died due to an allergic reaction to an intramuscular injection of deer antler extract. Resuscitation measures were unsuccessful [7]. Subsequently, there were more reports of adverse reactions to TCM injection [8-15].

The incidences of adverse reactions to TCM injection are much higher than those of TCM oral preparations. Almost all of the TCM injections on the market have reported on their adverse reactions, some of which are quite serious. Among the currently known adverse effects of TCM injections, allergic reactions, allergic shock, palpitations, rashes, are most common [16].

In March 2022, the WHO expert group concluded that the evidence of the benefits of TCM injections in the "three drugs and three prescriptions" for critically ill patients suffering from COVID-19 was limited and further evaluation was needed [17].

In 1941, the Pharmaceutical Department of the 129th Division of the Eighth Route Army ventured to produce Bupleurum injections for the prevalent endemic influenza. It saved a lot of lives and was awarded high honor by the government of the Shanxi-Hebei-Shandong-Henan Border Region [18-20]. In December 1954, Wuhan pharmaceutical factory re-evaluated the Bupleurum injection, verified its efficacy

and put it into mass production. Since then, it has become the first industrialized Chinese medicine injection in China. After the founding of the people's republic of China, the development of TCM injections was accelerated and the appearance of Bupleurum injection in the 1940s marked the birth of TCM injections. From the mid-1950s to the early 1960s, more than 20 varieties such as "Anti 601 injection" and "Banlangen Injection" were developed for clinical use. In the 1970s, hundreds of TCM injections were developed. However, due to insufficient information, poor technology, poor efficacy and safety, many varieties have now been phased out. The 1963 edition of "Chinese Pharmacopoeia" included TCM injections for the first time. The 1977 edition of "Chinese Pharmacopoeia" (Part 1) contains 23 kinds of TCM injections, such as *Salvia miltiorrhiza* injection, Maodongqing injection, ligustrazine hydrochloride injection and Yinhuang injection etc. The 1985 edition of the Chinese Pharmacopoeia only included one traditional Chinese medicine injection, ligustrazine hydrochloride injection; while the 1990 edition did not include any. The 1995 and 2000 editions of the Chinese pharmacopoeia included only two kinds of injections Shuanghuanglian and Zhichuanling. The 2005 edition of the Chinese Pharmacopoeia recorded 4 varieties including Shuanghuanglian injection and Qingkailing injection. At present, there are 70 varieties of TCM injections issued by the Ministry of Health and 109 varieties of TCM injections approved by the State Drug Administration (SDA).

Current available TCM injection preparations in market are listed in editions of the "Chinese Pharmacopoeia" (Table 1).

Table 1. TCM injection products listed in editions of the Chinese Pharmacopoeia [21].

Pharmacopoeia committee	Edition	Annual collection quantity/type	Collected varieties	Remarks
First Edition	1953	0	-	Not included
Second Edition	1963	4	Magnoflorine injection, Digitalis linarolii injection, Digitalis verticillatae injection, and Aconitine hydrochloride injection.	Included in chemical drug section
Third Edition	1977	24	Ding Gongteng Injection, Ba Li Ma Toxin Injection, Mao Dongqing Injection, Danpi Phenol Injection, Danshen Injection, Sodium Bisulfite Andrographolide Injection, Han Ji Song Injection, Han Tao Ye Injection, Tian Ji Huang Injection, Bingliang Flower Glucoside Injection, Erigeron breviscapus Injection, Nonglilline Hydrochloride Injection, Qingyedan Injection, Hollow Lotus Seed Injection, Octagone Hydrochloride Injection, Ligustrazine Hydrochloride Injection Ephedrine hydrochloride injection, Zedoary turmeric oil injection, Zedoary turmeric oil emulsion injection, Motherwort injection, Huangtensu injection, Wild papaya injection, Daijisong injection, Yinhuang injection	First recorded use of compound Chinese herbal injection
Fourth Edition	1985	1	Ephedrine hydrochloride injection	
Fifth Edition	1990	0	-	Not included
Sixth Edition	1995	1	Zhichuanling Injection	
Seventh Edition	2000	2	Zhichuanling injection, Shuanghuanglian injection (freeze-dried)	First recorded use of freeze-dried powder
Eighth Edition	2005	4	Zhichuanling injection, Shuanghuanglian injection (freeze-dried), Qingkailing injection, Dengzhanxixin injection	
Ninth Edition	2010	5	Zhichuanling Injection, Shuanghuanglian Injection (freeze-dried), Qingkailing Injection, Dengzhanxixin Injection, and Breviscapine Injection	
Tenth Edition	2015	5	Zhichuanling Injection, Shuanghuanglian Injection (freeze-dried), Qingkailing Injection, Dengzhanxixin Injection, and Breviscapine Injection	

Current situation

Currently, among the officially approved TCM injections that are still under production and being used in China, the TCM injections of single herbs account for 54.13%; those with two herbs accounts for 14.68%, and those with three herbs accounts for 10.09%. Overall, about 80% of TCM injections are made from 1 to 3 herbs [22]. Due to the complex chemical compositions of TCM and weak supporting researches, the effective ingredients are often unclear. To elucidate the comprehensive efficacy of multi-component and multi-target treatments, current research often uses total extracts as raw materials to prepare injections, which further increases the difficulty of research and quality control for traditional Chinese medicine injections [23].

According to the composition and variety distributions of TCM injections that have been marketed in China, there are 77 varieties of TCM injections from single herbs. The highest number of herbs that TCM injections contained reaches 12 [24].

In the 1960s and 1970s, TCM injections developed rapidly, and by the 1980s, more than 1400 TCM injections had been developed [25]. Currently, over 90% of the 1400 TCM injections have been eliminated due to unfavorable historical and clinical reasons, leaving the number to 134. TCM injections are different from other TCM dosage forms, as they originate from traditional Chinese medicine with the characteristics of complex components, it is very difficult to separate and analyze the ingredients. Unfortunately, because it belongs to the injection form, the special administration route demands that its quality standards must be rigorously maintained.

The national standards in China for injection products generally only require the testing of one or two main substances in the TCM injections. The standards for testing accessory substances are quite deficient. In the formulations containing multiple types or rare forms of Chinese medicinal herbs, it is not possible to ensure safety due to the presence of unknown substances. Taking the Qingre Jiedu Injection as an example, the prescription consists of 12 herbs including Honeysuckle, Huangcen, *Forsythia suspensa, Gentian,* Gypsum, *Anemarrhena asphodeloides, Gardenia jasminoides,* Banlangen, *Rehmannia glutinosa, Ophiopogon japonicus, Sweet glutinous rehmannia* and *Scrophulariae*. The chemical components could be over hundreds, but the national drug standard request only requires the standard data of one chemical component. According to industry reports, traditional Chinese medicine injections currently account for less than 3% of the entire traditional Chinese medicine market. However, the adverse reactions reported for them account for approximately 70% of the entire traditional Chinese medicine industry.

Problems

Standard medicinal injections require proper testing and must be labeled with their pharmacological effects. Only 32.14% of TCM injections are labeled with their pharmacological effects. Due to the complex composition of TCM injections, which contain many unknown components, it is difficult to completely remove macromolecular impurities such as plant proteins and resins. Plant proteins can form haptens or tannins in the human body and combine with plasma proteins to form larger molecule complexes, which may cause allergic reactions and affect the efficacy and safety of injections. In addition, the proportion of TCM injections that do not indicate possible adverse reactions in the instructions is as high as 42.86% [26].

“Oral administration instead of intramuscular injection, intramuscular injection instead of intravenous injection and drip” is the key principle mentioned by industry experts for TCM injection. The actual situation is that there are many other Proprietary Chinese Medicine (PCM) with the same prescription in market that can replace TCM injections. Currently, there are many types of proprietary Chinese medicines (pCm) which are in the same compositions but in different dosage forms (oral forms and injection forms). Many pCms are used to treat common diseases and chronic diseases. It is debatable whether “strong” traditional Chinese medicine injections are needed in the treatment of these common diseases [27].

The adverse reactions of TCM injections have the following characteristics:

- **Multiplicity and universality:** Almost all TCM injections have experienced adverse reactions.
- **Diversity of clinical manifestations:** Adverse reactions of traditional Chinese medicine injections can cause damage to multiple organs and systems in the body.
- **Unpredictability:** Due to the complex composition of TCM injections and many unknown ingredients, adverse reactions are unpredictable.
- **Uncertainty:** It is impossible to determine how much adverse reactions a TCM injection may cause. For example, there are as many as a dozen clinical manifestations of adverse reactions of Xiangdan injection.
- **Batch to batch variability:** Due to the poor quality standards of TCM injections, there are large differences in the types of adverse reactions between different manufacturers and different batches and no definite conclusion can be drawn.

There should not be assumption that the historical safe use of TCM can be taken for granted in the injection form.

Discussion

The incidence of adverse reactions to TCM injections is much higher than those of oral preparations. The two most common routes of administration in clinical practice are oral and injection. These two routes of administration have significant differences in the metabolic processes, related

to the recipient, and subsequent safety considerations. After oral administration, selective absorption occurs through the intestinal mucosa, and substances such as tannins and bio-macromolecules that cannot be absorbed are eliminated through the intestinal tract. After the absorbed components enter the bloodstream, they are metabolized and detoxified by the liver before entering the systemic circulation. Oral administration is therefore a relatively safe route that is slower to take effect. After injection, the drug enters the tissue directly or enters the systemic circulation, bypassing the gastrointestinal barrier. Once adverse reactions occur, they develop rapidly and are difficult to rescue. Injection is a fast but demanding route of administration in consideration of safety. Oral administration is widely used, while injection is commonly used in emergency situations or when oral administration is not appropriate.

Although the foundation of TCM injection is claimed to be based on the theory of traditional Chinese medicine, there has never been any classical description on the injection in TCM theory, nor has there been any theory and experience of directly injecting herbal medicine into the human body. The theory of TCM is unable to explain the metabolism process and mechanism of action of herbal drugs after injection into the human body. The injection administration is not related to the theory of TCM itself. TCM had never been injected in the long history of Chinese Medicine.

The use and indications of TCM injections have developed widely, yet their scientific, safety, and rationality have not been worked out. The quality and even the validity of TCM injections need to be questioned after series of adverse reaction incidents.

In the National Medical Insurance directory, the use of TCM injections has been restricted: confining to e.g. Shuanghuanglian injection, Qingkailing injection, Lianbizhi injection, Reduning injection, Xiyanping injection, Houttuynia cordata injection, Tanreqing injection etc. which are limited to hospital or medical institution use of level II or above. (In the past, these products were widely used in medical institutions below level II.) Due to fear of adverse reactions, many top-level hospitals have even “banned” the use of TCM injections. Many top-level hospitals in Beijing, Shanghai, Shenzhen and Guangzhou have been increasingly cautious in the use of TCM injection preparations [28].

Conclusion

Due to the frequent occurrence of adverse reaction events, there has been much debate over the abolition of TCM injections. TCM injections are neither traditional nor modern practice. Their raw materials come from TCM, but the injection method used is copied from Western medicine. Is TCM injection part of TCM? The theoretical basis of TCM injection is claimed to be related to TCM theories, but TCM neither had the concept, nor the practical experience of directly injecting drugs into the human body. TCM theory cannot explain the mechanisms of action after drug injection. Plant proteins may form semi-antigens or complex materials with blood plasma proteins to form larger molecules, which can cause allergic reactions which challenge the efficacy and safety of injection. Up to 42.86% of TCM injections do not provide lists adverse reactions in their commercial labels. The technical requirements and quality standards for all injection preparations should be strict; the injection materials must be known chemicals with high purity, known efficacy, and safe. This is a consensus in the international medical community. TCM injections violate the basic technical requirements.

This unique form of drug delivery of TCM formulation not only contradicts the traditional theories and experiences, but also violates the basic principles of modern medicine. The future development of the injection form of delivery of TCM deserves much more careful scrutiny.

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Conflict of Interest

The authors state no conflict of interest.

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