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Traditional Chinese herbal injection: Current status and future perspectives

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ABSTRACT

Traditional Chinese herbal injection, frequently referred to as TCM injection, has evolved over 70 years as a treatment modality that parallels injections of pharmaceutical products. As the market reach has not been analyzed systematically in the past literature this article performed a descriptive analysis of various aspects of TCM injections based on the following data sources: (1) information retrieved from website of drug registration system of China, and (2) regulatory documents, annual reports and ADR Information Bulletins issued by drug regulatory authority. As of December 31, 2017, 134 generic names of TCM injections from 224 manufacturers were approved for sale. Only 5 of the 134 TCM injections are documented in the present version of Ch.P (2015). Most TCM injections are documented in drug standards other than Ch.P. The formulation, ingredients and routes of administration of TCM injections are more complex than conventional chemical injections. Ten TCM injections are covered by national lists of essential medicine and 58 are covered by China's basic insurance program (2017). ADR reports related to TCM injections accounts for > 50% of all ADR reports related to TCMs and the percentages have been rising annually. Making traditional medicine injectable might be a promising way to develop traditional medicines. However, many practical challenges need to be overcome by further development before a brighter future for injectable traditional medicines can reasonably be expected.

1. Introduction

Traditional Chinese medicine (TCM) is a Chinese medical practice with its own diagnostic system and treatment principles [1]. It has been used for the prevention, treatment, and cure of disorders or diseases for centuries [2]. With the increasing use of traditional medicine worldwide during the last few decades [3, 4] the use of TCMs in China has also been on the rise [5]. TCM has long been an important part in the healthcare system of China [6–8] and > 9000 TCM preparations have been approved for marketing [9, 10].

The use of injections to administer TCM, pioneered in the 1940s, introduced a new dosage form based on more modern technologies [11], and referred to as "TCM injection". The first TCM injection, Chaihu injection (*Bupleurum injection*), was developed in a field hospital in 1941 to meet the urgent demand for quick and effective antipyretics [12]. In 1950s and 1960s China developed > 20 TCM injections to meet the increasing demand for accessible, cheap and relatively effective medicine [13]. In 1970s > 700 TCM injections were used in practice, mostly as self-prepared hospital preparations [14]. In 1980s the number of TCM injections peaked at about 1400 preparations [15]. Many believed that more rapid introduction of the injected product would allow the TCM to work more effectively and would improve the treatment of critically ill patients and some particular diseases [16, 17]. However, after the 1980s increasing concern about the safety and quality of TCM injections led to the withdrawal of some products. The practice of compounding TCM injections in hospitals eventually stopped and the number of TCM injections declined sharply [8]. Nevertheless, TCM injections are still used widely in China and remain the most popular of all dosage forms of TCMs [18–20]. It has been estimated that sales of TCM injections have reached > 30 billion RMB and account for one third of all TCM sale in hospitals [21].

TCM products are usually developed and utilized according to the principles of traditional TCM so are TCM injections. However, modern TCM products also incorporate some elements of modern conventional medicine. In practice many TCM injections attempt to blend the terminology and science of traditional TCM with that of modern

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conventional medicine to describe the properties and usage. Such injections continue to be recognized principally as TCM preparations but the more modern elements are seen as assistive to assure their safety and efficacy.

TCM injections follow similar rules as those that govern other TCM products or conventional drugs. Because TCM injections have combined elements of traditional TCM and modern conventional medicine some TCM injections may be registered as chemical injections in China's drug registration system. The product will usually be registered as a chemical injection when it contains only one or a few well-characterized active ingredients extracted from herbal materials and mainly uses the language of modern medicine to describe the product's specifications and clinical usage. The product will usually be registered as a TCM injection when it contains many poorly characterized or unknown active or inactive ingredients. In this case, the language of traditional TCM will be used to describe the product's characteristics and clinical usage. In this study only herbal injections denoted by the letter “Z” in front of the registered identifier of approval, which is a symbol for TCMs in China's drug registration system, are taken into account.

In recent years, a number of serious adverse events have again raised concerns about the safety and potential toxicity of TCM injections currently in use [22–24]. The situation has affected the normal clinical use of TCM injections [25]. However, it is not clear how these trends have affected the use of TCM injections. Because their market reach has not been analyzed systematically in the past literature, this article aims to provide a descriptive analysis of several aspects of TCM injections, including general information, formulation and routes of administration, main categories, coverage by national essential medicine and health insurance programs, and safety issues based on information from China's national drug registry and other publically available information.

2. Methods

TCM injections in this article refer to injections containing extract of traditional Chinese herbs and denoted by the letter “Z” in front of the registered identifier of approval. This study used the following data sources: (1) registry information retrieved from the website of drug registration system of China [26], (2) China's regulatory documents and Adverse Drug Reaction Information Bulletin (2001–2017) [27] and Annual Reports of China's National Adverse Reaction Monitoring (2009–2017) [28]. Quantitative data were analyzed by descriptive statistics while other information was analyzed by qualitative approaches to describe the current status and future perspectives of TCM injections in China.

3. Results

3.1. General information

3.1.1. Registration information

As of December 31, 2017, 976 items of TCM injections were listed in the website of the drug registry of China Food and Drug Administration (CFDA) [26]. The 976 items correspond to 976 registered identifiers of approval that include 950 liquid solutions and 26 powders for Injection, with 134 generic names associated with 224 manufacturers.

Among the 134 generic names of TCM injections, 64 have singular registered identifier of approval and are produced exclusively without competition, 9 have multi-registered identifiers of approval associated with a single manufacturing company and are also produced exclusively without competition, 61 have multi-registered identifiers of approval and are produced by more than one manufacturer in competition. Detailed information on registered identifiers of approval and corresponding numbers of generic names of TCM injections is shown in Fig. 1.

Fifteen TCM injections have > 12 registered identifiers of approval.

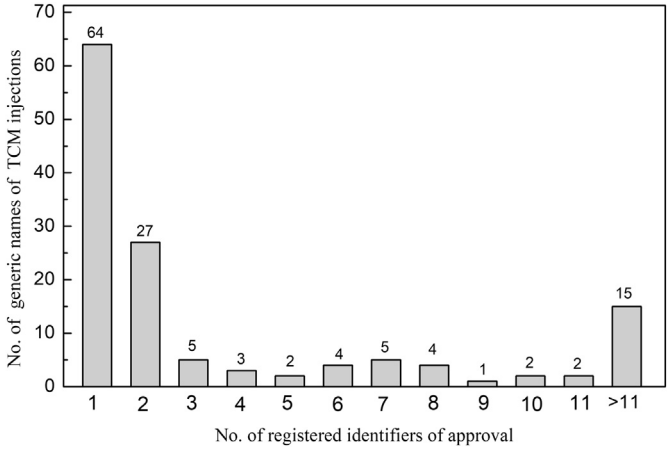

Fig. 1. Number of registered identifiers of approval and corresponding number of generic names of TCM injections.

Xiangdan injection and Yuxingcao injection (*Houttuynia cordata injection*) are two generic names of TCM injections with > 100 registered identifiers of approval. Detailed information on TCM injections with the highest numbers of registered identifiers of approval (Top15) is shown in Table 1.

3.1.2. The status of mandatory standards

The Chinese Pharmacopoeia (Ch.P) is an important technical code to guarantee the quality of drugs and safeguard the public interest [29]. Very few TCM injections are documented in the various editions of Ch.P. None were documented in the first edition of Ch.P (1953), 4 in the second edition (1963) and 24 in the third edition (1977). The number of TCM injections documented in Ch.P declined sharply in subsequent editions. Only 5 of the 134 TCM injections are documented in the present version of Ch.P (2015). Most TCM injections are documented in drug standards other than Ch.P, i.e. various non-periodical publications of drug standards issued by drug regulation agencies. Detailed information on TCM injections documented in different versions of Ch.P is presented in the Electronic Supplementary Material (ESM) Table S1.

3.2. Formulation and routes of administration

Among the 134 TCM injections 72 (53.7%) are made from one single traditional Chinese herb, whereas 62 (46.3%) are made from 2 or more traditional Chinese herbs. The distribution of formulation of TCM injections is illustrated in Fig. 2. The most complex formulations are Qingrejiedu injection containing ingredients from 12 traditional

Table 1
TCM injections with the highest numbers of registered identifiers of approval (Top15).

No.	Generic names	No. of registered identifiers	Percentage (%)
1	Xiangdan injection	115	11.78
2	Yuxingcao injection	113	11.58
3	Chaihu injection	77	7.89
4	Danshen injection	73	7.48
5	Banlangen injection	44	4.51
6	Xuesaitong injection	43	4.41
7	Honghua injection	34	3.48
8	Shenmai injection	33	3.38
9	Huangqi injection	27	2.77
10	Shengmai injection	25	2.56
11	Dengzhanhuasu injection	24	2.46
12	Chuanxinlian injection	21	2.15
13	Qingkailinginjection	19	1.95
14	Lurongjing injection	18	1.84
15	Shuxuening injection	13	1.33