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Comments on serious anaphylaxis caused by nine Chinese herbal injections used to treat common colds and upper respiratory tract infections

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ABSTRACT

Reports describing severe allergic shock and fatality following treatment of a common cold or upper respiratory tract infection (URTI) with a Chinese herbal injection were collected. Our analysis of the risks associated with this treatment suggested that the potential risk of serious, or even lethal, anaphylaxis should preclude its use in treating common colds and URTIs. In light of our findings herein, we propose the following five suggestions for improving the clinical safety of delivering Chinese herbal injections as medical treatments. First, Chinese herbal injections should not be delivered in the clinic to treat patients in accordance with Bian zheng lun zhi (broad-spectrum application based on holistic Traditional Chinese Medicine (TCM) theory and methodology), but rather they should be administered to target specific indicated disease processes. Second, Chinese herbal injection indications should be based on the results of double-blind randomized controlled clinical trials. Third, Chinese herbal injections should be used only in cases involving severe disease or to rescue patients in critical condition; they should not be used to treat mild, relatively innocuous diseases, such as common colds and upper respiratory tract infections, given the risk of doing harm. Fourth, Chinese herbal injection formulas should include materials from only a single or a small number of plant sources in known quantities. Fifth, more studies examining the toxicity and allergenic potential of Chinese herbal injections are needed.

1. Introduction

According to the Chinese State Food and Drug Administration (SFDA), modern Chinese hospitals used as many as 147 kinds of Chinese herbal injections from 400 pharmaceutical factories in China between 2004 and 2007, with total sales of the injections exceeding two billion U.S. dollars per year (Yang et al., 2007). The treatments were used to treat a wide variety of conditions, including cardio-cerebral vascular disease, respiratory disease, tumors, musculoskeletal disorders, and digestive system diseases (Liu et al., 2001; Tang, 2006; Tang et al., 2008). However, this form of treatment is known to produce some serious adverse drug reactions (ADRs) in some patients, including anaphylactic shock and fatal anaphylaxis (CNAMC Bulletin.31 December, 2007).

There has been a litany of poor outcomes in recent years following administration of Chinese herbal injections. Xuyingcao herbal injection (YHI), produced from a herbal extract of Houttuynia cordata, caused severe ADRs in four children, two of which were fatal, during the first half of 2006 (Ji et al., 2009). In response to these tragedies, the SFDA halted YHI use in hospitals in June 2006. After reviewing the manufacturing conditions and quality control parameters for YHI, the SFDA allowed a limited number of manufacturers to resume production (Ji et al., 2009). On October 6, 2008, six patients suffered serious adverse reactions to Ciwujia herbal injection, produced from a herbal extract from Acanthopanax senticosus (Rupr.et Maxim.) Harms; the reactions were ultimately fatal in three of these patients (SFDA Bulletin. 7 Nov, 2008). Less than 1 week later, on October 11, 2008, four neonatal infants suffered serious ADRs to Yinzhihuang herbal injections made by another Chinese pharmaceutical factory; one of the babies died at 9 days old as a result (HDHP Bulletin. 20 Oct, 2008). This Yinzhihuang herbal injection was made from the extracts of four plants: Artemisia capillaris Thunb., Gardenia jasminoides Ellis, root of Scutellaria baicalensis Georgi, and flower of Flos lonicerae. Following the October 11 incidents, the SFDA called for a halt in the administration of these injections and retracted all remaining products from the marketplace. In February 2009, Shuanghuanglian herbal injections resulted in severe side effects in three patients and one death (SFDA Bulletin. 12 Feb, 2009a). The Shuanghuanglian herbal injection is produced from the extracts of three plants: root of Scutellaria baicalensis Georgi, flower of Flos lonicerae, and fruit of Forsythia suspense (Thunb.) Vahl. The SFDA issued an emergency notice on February 12, 2009 to temporarily suspend the distribution and administration of this injection. Finally, on April 20, 2009, the Chinese National adverse drug reaction
monitoring center (CNARMC) posted a bulletin in which it warned of the potential for severe ADRs to Qingkailing injection (SFDA Bulletin. 20 Apr, 2009b). Qingkailing injection is a complex concoction made from extracts derived from four plant species (Fructus gardeniae, Radix isatidis, Radix scutellaria, and Flos lonicerae), a number of animal products, and several additives. More than a quarter of the people who died due to their ADRs to Qingkailing injection were children under 14 years of age (SFDA Bulletin. 20 Apr, 2009b).

The series of incidents summarized above highlights the grave risks associated with the casual use of Chinese herbal injection treatments in China. Here we collected papers published in public Chinese medical journals reporting cases of serious anaphylaxis caused by nine types of Chinese herbal injections. Our analysis focused on cases in which the injections were used to treat common colds and upper respiratory tract infections. We propose constructive suggestions for the future development of Chinese herbal injections and their rational and safe use in the clinic.

2. Cases

We retrieved a total of 150 case reports, published in 69 medical journals, of patients suffering ADRs to herbal injections in China (summarized in Table 1) (Chen, 2005; Guo, 2001; Huang, 1992; Huang et al., 2007; Li and Weng, 2008; Liu and Li, 2004; Ma, 2003; Niu and Zhou, 2000; Tan, 1985; Shi et al., 1999; Wei and Gong, 2006; Zeng and Zhang, 2003; Zhao et al., 2006; Zou, 1986). Only cases involving patients who were diagnosed with a common cold or an URTI and treated with a herbal injection that resulted in severe non-lethal allergic shock (N = 129) or fatality (N = 21) were included in our analysis. A total of nine different types of herbal injections were described in these reports. Of the 150 patients who suffered severe anaphylactic reactions, 27 were children under the age of 12, and one was a pregnant woman. All 150 of these patients received emergency rescue treatments. Unfortunately, there were also 21 lethal cases, six of which involved children under 12 years of age (Table 1). Given that it is improbable that all cases of severe anaphylaxis have been reported, the anaphylactic problems associated with herbal injection treatments for colds and URTIs are likely underrepresented in the literature. This review analyzes the published reports in order to examine whether the use of herbal injections should be continued or considered contra-indicated in cases of the common cold or URTI.

3. ADRs caused by Chinese herbal injections

There is ongoing debate about the safety of clinical use of Chinese herbal injections in light of the large number of ADR reports in China. For example, the CNARMC has reported that Traditional Chinese Medicine (TCM) therapies are responsible for approximately 13.5% of all drug-related ADRs. Moreover, from 2001 to
2003, 77.2% of TCM-related ADRs were due to Chinese herbal injections; and from 2004 to 2007, 80% of TCM-related ADRs were due to Chinese herbal injections (CNARMC Bulletin.31 December, 2007). The predominance of these injections among TCM-related ADRs is astounding given that they constitute a relatively small component of TCM as a whole. Hence, there is reason for concern that Chinese herbal injections may be more dangerous in the clinic than other drugs.

The CNARMC reported over 5000 ADRs to YHI from January 1988 to April 2006, including 222 serious cases (Ji et al., 2009). It also reported 6460 ADRs to Qingkailing injection alone in 2007, including 230 serious cases (CNARMC Bulletin.31 December, 2007). From 2001 to 2007, the CNARMC received notices of 580 serious ADR cases caused by Qingkailing injection, including 20 (3.45%) fatalities. ADRs reported for Qingkailing injection from 2001 through 2007 mainly included anaphylactic shock (33%), dyspnoea (23%), hypotension (10%), cataphora (5%), pulmonary edema (5%), laryngeal edema (2%), and convulsions (2%) (CNARMC Bulletin.31 December, 2007).

4. Recommendations

TCM has long been regarded as integral to the Chinese national essence. And the development of injectable traditional Chinese medicines is considered to be a great achievement of modernization of TCM. Indeed, the herbal injections have already proven to be a profitable industry. However, the herbal injections have come under greater scrutiny, including calls for the SFDA to promptly admonish the use of Chinese herbal injections. To date, most suggestions regarding the development of Chinese herbal injections have focused mainly on improving production technologies, including calls for adopting Good Agriculture Practice and quality control measures such as Chinese medicine fingerprint technology which may provide precise quantization or consistent batch-to-batch quality and component proportion control (Zhang et al., 2006; Zeng et al., 2006). Such technologies certainly can improve the quality of Chinese herbal injections and their clinical safety. In light of our analysis, it is our view that additional measures and changes should be made in order to improve clinical administration of Chinese herbal injections. Our suggestions, detailed below in Sections 4.1–4.5 are based squarely in consideration of patient safety.

4.1. Chinese herbal injections should target specific indicated disease processes rather than be delivered according to the traditional Chinese broad-spectrum philosophy

The variety of treatments included in TCM, including herbal medicine and acupuncture, are traditionally delivered in accordance with the Bian zheng lun zhi treatment philosophy (Lu et al., 2004). According to Bian zheng lun zhi, the patient’s health situation can be treated holistically. Holistic approaches may have their merits, especially in terms of promoting optimum health. However, in a clinical setting, it would be prudent to deliver biologically active compounds in accordance with specific empirically demonstrated indications rather than theoretical effects. Modern drugs produced by Western medical research are empirically tested in double-blind randomized controlled clinical trials and then delivered to treat specific conditions based on the results of the clinical trials. It is our view that this scientific approach to medicine would benefit clinical delivery of Chinese herbal injections.

The use of herbal medicine has a five thousand year history in China, predominantly in the form of decoctions (tea-like extract solutions produced by boiling of the herbs) rather than injections. The Chinese army developed the first intramuscular Radix Bupleuri herbal injection for anti-infection treatment during the World War II era because of the urgent need for medical care at that time (Hu and Zhou, 1983). Hence, the Chinese herbal injection has characteristics that distinguish it from more traditional forms of TCM: they are distilled down to a more potent form and they are injected directly into the patient’s system. Given these characteristics, it is reasonable to subject them to more rigorous clinical safety regimen, such as that applied to Western pharmaceutical products.

Labeling of Chinese herbal injections is still based on the theoretical Bian zheng lun zhi treatment philosophy, and therefore remains imprecise in terms of the injections’ indications and vague in terms of usage instructions. For example, in its usage explanation, Qingkailing injection is claimed to cure fever, dizziness, stroke paralysis, unconsciousness, acute hepatitis, URTI, pneumonia, cerebral thrombosis, and cerebral hemorrhage. Serious questions must be asked regarding both efficacy (does it really ameliorate all of these diverse conditions?) and safety (could the injection harm some patients?). In practice, such broad and general descriptions have led clinicians to misuse the injections, and the misuse of Chinese herbal injections has resulted in serious ADRs. For example, a 9-year-old boy with an URTI and 6-year-old girl with an URTI died of fatal anaphylaxis after being treated with Qingkailing injection (Table 1).

Given the gravity of the safety concerns associated with the misuse of drugs of any kind, be they from TCM or Western medicine, a debate over the merits of the Bian zheng lun zhi treatment philosophy relative to the Western approach of targeted therapies is not of great significance for the present discussion. All can acknowledge that the components of Chinese herbal injections are extremely complex and that their effective ingredients and their proportions are difficult to determine. Indeed, it may not be possible to efficiently complete a thorough component analysis of current Chinese herbal injection formulations strictly according to the practices of Western medicine. Nevertheless, for the sake of clinical safety, we strongly suggest that Chinese herbal injections be delivered for specified indications which have been demonstrated empirically. Though many TCM experts may be resistant to this suggestion, the benefits of empirical studies in terms of preventing herbal injection misuse are indisputable.

4.2. Chinese herbal injections should be approved by the SFDA according to the results of double-blind randomized controlled clinical trials

As mentioned above, a 9-day-old infant with icterus neonatorum, a condition that is self-healing in the majority of cases, died following Yinzhiihuang herbal injection. Another herbal injection, Yinxingdamo, is produced from extracts of Ginkgo biloba leaves plus the drug dipyriramol and recommended for prevention or treatment of coronary heart diseases and thromboembolic disease. However, Yinxingdamo herbal injection was given to a 32-year-old woman with an URTI and resulted in anaphylactic shock (Li and Weng, 2008). Likewise, a 26-year-old Iranian woman visiting China and a pregnant woman at 29 weeks gestation, both with URTIs, suffered from anaphylactic shock in response to YHI treatments (Chen et al., 2006; Zhang and Wang, 2004). Currently there are no precise statistics describing clinical adverse effects caused by misuse of herbal injections. But Chinese hospitals are increasingly becoming more cautious in the application of herbal injections (Yang et al., 2007). For example, some hospitals have forbidden the use of YHIs in patients with only a common cold or URTI. (Yang et al., 2007).

In TCM, Chinese herbal injections are often claimed to be effective in curing a wide variety of symptoms and diseases without any distinctions of age, gender, or inter-individual variations. Moreover, the veracity of the broad applications has not been demon-
strated scientifically. For example, we are unaware of any definitive clinical safety data for Qingkailing injection in the treatment of URTIs in children. Hence, we strongly suggest that Chinese herbal injections should be approved by the SFDA according to the results of double-blind randomized controlled clinical trials. More accurate instructions can be formulated according to the clinical results to avoid misusage and avert potential future tragedies.

4.3. Use of Chinese herbal injections should be restricted to treatment of severe diseases or critical cases

The pharmaceutical market for selling common cold and URTI treatments in China, a country with a population of approximately 1.3 billion people, is enormous. In the absence of Chinese herbal injections, there is a myriad of commercially available products that provide relief for cold and URTI symptoms. Moreover, people can normally recover from common colds and URTIs without any medical intervention whatsoever. Hence, given the low risk of conditions such as the common cold and the potential for herbal injection-induced allergic reactions, the continued use of Chinese herbal injections in patients with normally self-healing conditions is questionable from a medical ethical perspective.

Ginkgo biloba leaf extract tablets, oral drops and injections have become available in Germany (Yoshikawa et al., 1999). While the oral drops and tablets are available for discretionary use, the injections are instructed to be used only for severe diseases or in the urgent care of critical patients. We believe that this distinction is worthy of replication. We feel that traditional Chinese herbal injections should remain available for treating grave diseases and those without any other known efficient treatments, such as severe acute respiratory syndrome (SARS) (Wang et al., 2006a). For example, YHI was chosen as one of eight TCM remedies for SARS owing to its anti-inflammatory effects (Lu et al., 2006). Furthermore, Houttuynia cordata extract (the active ingredient in YHI) has been shown to have anti-viral effects including inhibition of SARS-CoV 3C-like protease and RNA-dependent RNA polymerase (Lau et al., 2008). Similar to SARS, infection with highly pathogenic avian influenza (H5N1) is associated with a high death rate. On February 5, 2004, the State Administration of Traditional Chinese Medicine of People’s Republic of China (SATCM) proposed three Chinese herbal injections for the therapy of the patients infected by H5N1: Qingkailing injection, YHI, and Shuanghuanglian herbal injection (SATCM Bulletin, 5 Feb, 2004). On April 29, 2009, Qingkailing injection was also recommended by SATCM for the treatment of potential infection with the new swine-origin influenza A (H1N1) virus strain in China (NGPCR Bulletin.30 Apr, 2009; Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 2009).

4.4. Chinese herbal injections should be restricted to only a single or a small number of plant sources in known quantities

Chinese herbal injections contain multiple chemical compounds from the source herbal extracts and it is not totally known which components are active in treating illnesses. Furthermore, the chemical structures and concentrations of bioactive components within the injections have not been accurately determined. These are nontrivial matters given that some herbal injections have numerous potentially bioactive components. For example, Qingkailing herbal injection is made from the extracts of four species of plants (Fructus gardeniae, Radix isatidis, Radix scutellariae, and Flos lonicerae) in combination with various animal products (cholic acid, hydodesoxycholic acid from pig bile, Concha margarifera Usta powder extract, and Bubalus bubalis Linnaeus horn powder extract), and additives (i.e., disodium edetate, sodium subsulfite and glycerol). Furthermore, each of the plant extracts themselves may contain a large number of chemical compounds. Elaborating upon our example of Qingkailing, Flos lonicerae extract alone contains chlorogenic acid, isochlorogenic acid, secolloganin, sweroside, loganin, loganic acid, hederagenin, disacidos B, fulvotomentoside A, α-hederin, sapindoside B, macranthoidin A and B, macranthoside A and B, linalool, shuang-hua-chun, geraniol, α-terpineol, and eugenol among others. Radix extract constituents include sinigrin, indirubin, indoxyl-lucoside, sitosterol, adenosine, hexadecanoic acid, and cane sugar. Meanwhile, Fructus gardeniae extract constituents include geniposide, gardenoside, shanzhiside, gardoside, geriposid acid, gardenin, crocin-1, 1-cro-cetin, scandoside and methyl ester (Zhang et al., 2006). Given the complexity of these mixtures, even the so-called advanced Chinese medicine fingerprint technology cannot provide precise quantization or consistent batch-to-batch quality and component proportion control (Zeng et al., 2006). Hence, while TCM decoctions and oral suspensions may include dozens of materials from animals and plants, we strongly suggest that the constituents of Chinese herbal injections should be restricted to only one or a few raw materials from plants. This limitation will facilitate quality control and should reduce the likelihood of ADRs, especially allergic reactions to plant and animal products.

4.5. More studies examining the toxicology and allergenic potential of Chinese herbal injections should be conducted

Among all ADRs attributed to Chinese herbal injections in the reviewed literature, allergic reactions had the highest incidence which accounted for 44.6–50.49% of all ADRs including anaphylactic shock and fatal anaphylaxis (Miao et al., 2006; Wang et al., 2006b). However, none of the evaluated reports described the exact mechanisms by which the herbal injections may have caused anaphylactic shock (Ji et al., 2009). Whether this deficiency is due to inadequate efforts or to the complexity of the potential mechanisms is not known. Anaphylactic reactions could be due to innate inter-individual differences among patients or to contamination of the injections with allergenic substances, such as chlorogenic acid (Yang et al., 2007).

5. Conclusion

The presently reported analysis of cases of severe allergic shock and fatality following treatment of a common cold or URTI with a Chinese herbal injection indicates that the injections involve risk of serious, or even lethal, anaphylaxis. This risk should preclude the use of Chinese herbal injections in treating normally self-healing conditions, such as common colds and URTIs. In addition, the safety of Chinese herbal injections would be improved if they were delivered as targeted treatments for indicated disease processes, if their constituent complexity and variability were reduced, and if controlled clinical trials as well as studies examining their toxicology and allergenic potential were conducted. We especially underscore careful application of herbal injections in clinics to avoid any misuse.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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