

Progress in the Study of Skin-related Adverse Reactions Caused by Traditional Chinese Medicines

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Abstract: As early as in the “Shennong Ben Cao Jing” there are: “medicine has sour, salty, sweet, bitter and pungent five flavors, but also cold, hot, warm and cool four qi and toxicity,” the record, the later also said: “is a medicine three times poisonous,” and modern medicine that the Chinese medicine of the “toxicity” that is, the adverse effects of the drug. Toxicity” is the adverse reaction of drugs. The combination of Chinese and Western medicine has achieved twice the result with half the effort in clinical practice, so the adverse reactions of traditional Chinese medicine are usually easy to be ignored. However, in recent years, the number of reports on the adverse reactions of traditional Chinese medicine has gradually increased, and the number of reports on the adverse reactions of orally consumed traditional Chinese medicine preparations, traditional Chinese medicine patches, or traditional Chinese medicine injections has been on a rising trend, which indicates that the adverse reactions of traditional Chinese medicine have been taken seriously by the people, and it also reveals that there are problems with the clinical use of traditional Chinese medicine as well as with the management of traditional Chinese medicine. This indicates that the adverse reactions of traditional Chinese medicines are being emphasized, and also reveals the problems in clinical use and management of traditional Chinese medicines. In this paper, we will discuss the current situation of the clinical application of Chinese medicine, skin-related adverse reactions and their causes produced by Chinese medicine patch and Chinese medicine injection, aiming to provide reference for the clinical application of Chinese medicine.

Keywords: Herbal medicine, Skin, Adverse reactions, Research progress.

1. Introduction

Most of the Chinese medicines come from natural ores, plants, and animals, and are popularly regarded as non-toxic and harmless. With the development of Chinese medicine, Chinese medicines have been widely used in clinical practice and achieved good therapeutic effects, but due to therapeutic needs, the dosage forms and routes of administration have become diversified, such as oral proprietary medicines (pCms) and Chinese medicine injections (CMPs), in addition to Chinese herbal tonics (CHTs). However, the number of adverse reactions during use has also increased. Relevant studies have shown that intramuscular and intravenous injections cause the most allergic reactions. Therefore, it is very important to improve patients' awareness of drug safety and management of traditional Chinese medicine. In this paper, we will summarize and analyze the causes of skin-related adverse reactions during clinical use of some traditional Chinese medicines (TCM) patches, TCM fumigation, and TCM injections, so as to provide certain reference for the subsequent use of TCM in the clinic.

2. Topical Application of Chinese Medicines Causes Skin-related Adverse Reactions

2.1 Skin-related Adverse Reactions Caused by Single Chinese Medicine Patches

Wu Lingling [1] found that the clinical manifestations of skin-related adverse reactions caused by traditional Chinese medicines are dominated by contact dermatitis, which is not only eczema-like lesions, but also urticaria-like, purpura-like, erythrodermic, and erythema multiforme-like changes. Lei Li [2] and others showed that there have been a variety of Chinese medicines as well as proprietary Chinese medicines that can cause skin-related adverse reactions, for example,

Andrographis paniculata, Fritillaria, Scutellaria baicalensis, etc. can induce urticaria, whereas Taraxacum officinale and Xintong Oral Liquid can cause polymorphic erythema-like rash, and Pogostemon cinerea can cause purpura-like rash. Chinese medicine injection can cause scarlet fever, urticaria, erythema multiforme and other diseases. And often lead to skin allergies is the Chinese medicine patch, because the treatment method makes the Chinese medicine and the skin direct contact, often lead to adverse reactions. There have been many reports [3], for example, a single Chinese medicine Cang Er Zi in the process of external application of the treatment of knee pain in the patient's skin redness, swelling, burning, erythema, blisters and other allergic reactions, and Cang Er Zi dorsal patch experimental procedure positive. This also indicates that Cang Er Zi is prone to cause adverse reactions in the process of external application. Cang Er Zi was first recorded in [4] “Shen Nong Ben Cao Jing”, and Shen Jin Ao's “Essential Medicines” pointed out that Cang Er Zi “enters the lung meridian and is a sweating product that disperses wind and prevents dampness”, which can be seen as its flavor is pungent, warm, poisonous, and is attributed to the lung meridian. The main effect is to disperse wind-cold, nasal orifices, dispel wind-dampness, is the treatment of nasal abyss of the key medicine. It is commonly used clinically for the treatment of rheumatic headache, knee and leg pain. Chen Ke [5] and others showed that the adverse drug reactions caused by Cang Er Zi, in addition to respiratory, digestive and urinary adverse reactions, localized redness, swelling, itching and other uncomfortable reactions. However, the mechanism of skin adverse reactions caused by Cangzhi is not clear. Zhang Likun [6] and others showed that the process of external application of He Shouwu powder mixed with water found that the local skin was hot and flushed with itching, followed by redness and swelling, and the skin temperature increased on touch. Subsequently, the allergic reaction aggravated, and the whole body appeared rice grain size papules. After anti-allergic

treatment, patch test was positive. Crowberry is commonly used in dermatology, used to treat corns, warts, etc. In the process of use, some patients experienced swelling of the lips and mouth, large swollen erythema on the trunk and limbs, and even anaphylactic shock.

To summarize, although Chinese herbs play an important role in the treatment of diseases by virtue of their unique composition, many factors in the process of using them may cause adverse reactions, such as concoction methods, dosage, time of use, and the patient himself.

2.2 Acupressure Points Cause Adverse Skin Reactions

Acupressure [7] is based on the meridian theory of traditional Chinese medicine, grinding traditional Chinese medicine into powder and making various dosage forms to be applied on the corresponding acupoints in order to play a therapeutic effect. Although this treatment is simple, and its transdermal absorption of drugs reduces the gastrointestinal reaction caused by oral administration, so it is easy to be accepted by the majority of patients, and also plays a better therapeutic effect in the treatment of diseases, but in recent years the frequency of application of acupoints dressing is increasing, and the skin-related adverse reactions have also appeared. Wang Hui [8] et al. found that, through the clinical observation of acupoint application for the treatment of constipation in the process of research, a part of the patients in the use of 4-6h after the skin appeared erythema, a small number of patients with localized skin blisters.

Xu Shanshan [9] et al. showed that in the clinical use of acupoint patch patients in some patients' skin will appear pimples, itching, tingling, ulceration and even delayed-type metamorphic reactions. Liu Ting et al. [10] found that, due to the use of acupoint patch in the use of many factors in the process of uncontrollable, clinical acupoint patch after the emergence of different degrees of adverse reactions, mainly in the local skin swelling, erythema, papules, blisters and even blisters, accompanied by broken areas of itching, pain, and contact dermatitis clinicopathological features consistent with the modern research has also confirmed that the adverse reactions produced by acupoint patching attributed to the contact dermatitis. Liu Lanying [11] and others through clinical research showed that the skin at the site of the contact patch drugs often appear and the shape of the drug patch is basically the same blisters, the contact local skin sensation to itching, visible erythema, papules and other lesions are also similar to the contact dermatitis clinical manifestations. Wang and Sheng [12] and others showed that the blisters caused by acupoint plastering are mainly related to the proportion of drug components, the time of plastering, and the residual situation of drug powder on the skin. And the blisters appeared earlier in patients with a history of allergy than in patients without a history of allergy. These studies have shown that the adverse reactions caused by acupoint compresses can be attributed to contact dermatitis according to the performance of local lesions, and patients with a history of allergy are more likely to develop lesions, which can be summarized as most of the causes of this type of dermatitis are uncontrollable.

To summarize, although acupressure can play a very good therapeutic effect, but in the process of using it will still cause skin-related adverse reactions. Therefore, it is necessary to strictly control the time of application, timely clean up the residual components of the drug on the skin, the patients with a history of allergy should pay attention to the application site skin changes in a timely manner, to avoid the occurrence of serious allergies.

2.3 Skin-related Adverse Effects of Herbal Fumigation

Chinese medicine fumigation makes the medicine directly contact with the lesion and directly enters the body through heat, effectively exerting the effect of clearing heat and removing toxins, dispersing knots and relieving pain, drying dampness and relieving itching. Although playing a better therapeutic effect, there are still skin-related adverse reactions. You Zhengqin [13] and others showed that Chinese medicine fumigation is to decoct a variety of medicinal herbs, using their steam, fumigation of the affected area, in the process of which will make the patient's skin breakouts, rashes, allergies and other adverse reactions. Most of them are simple rashes and a few are simple rashes combined with itching. Pang Mimi [14] et al. found that in some patients during the process of fumigation with traditional Chinese medicine, the fumigation site appeared to have red papules with rice grains, petechiae, or even with itching. During this period, the patients did not use new drugs, did not eat special food, and the lesions were reduced and gradually improved after stopping the traditional Chinese medicine fumigation treatment.

3. Skin-related Adverse Reactions Caused by Chinese Medicinal Preparations

In traditional cognition, Chinese medicinal preparations are less toxic, relatively safe, and do not produce adverse reactions, and in recent years, relevant studies [15] have shown that the cases of Chinese medicinal preparations producing adverse reactions have been increasing year by year, growing from 20.64% in 2021 to 41.28% in 2023. Among them, the proportion of Chinese medicine injection causing adverse reactions was 62.39%, followed by oral dosage forms accounting for 24.77% and topical dosage forms accounting for 12.84%. And the most cumulative system was skin and mucous membrane. Song Cheng [16] investigated and found that the proportion of adverse reactions of Chinese medicinal preparations involving the skin was 28.58%, which would appear as rash, itching, flushing, dermatitis, erythema, and so on. Song Lei et al. showed that too long a period of taking herbal medicines or too large a dose of medicines can cause liver injury or even liver failure, while 33% of patients will have symptoms such as rash, itching of the skin and jaundice. Among them, jaundice accounts for 64.63%. For example, in the process of long-term use of commonly used Chinese medicines such as Huo Xiang Zheng Qi Shui and Liu Wei Di Huang Wan, some patients may suffer from liver injury. This shows that although the clinical use of Chinese medicinal preparations has good therapeutic effects, there are still safety risks.

3.1 Skin-related Adverse Reactions Due to Chinese Medicine Injections

Chinese medicine injection [17] is a new dosage form unique to China, which is made by extracting effective substances from Chinese medicine using modern science and technology under the guidance of Chinese medicine theory. Compared with traditional Chinese medicine, it has the advantages of rapid onset of action, high bioavailability and significant effect, etc. It is widely used in clinical applications and has become an important part of modern drug therapy. However, due to the complexity of the components of TCM injections and the irrational use of drugs in clinical practice, TCM injections are frequently affected by adverse reactions. Zhou Huifen et al. showed by analyzing 65 cases of adverse reactions to Chinese medicine injections that the incidence of skin involvement was the highest, with a total of 45 cases, accounting for 47.35%, and the main symptomatic manifestations were rashes, itching, maculopapular rash, and so on. Peng Tai [18] found through investigation and research that Chinese medicine injection contains macromolecular substances, which enter the blood circulation of the organism through the vein, and such substances may cause an immune response, followed by systemic damage, with symptoms such as allergy, fever, and so on. Yuan Liuli [19] and others found that the Chinese medicine injection produced the majority of adverse reactions in elderly patients, in which the adverse reactions produced by the patients were concentrated in the skin and adnexa, and symptoms such as skin redness, swelling, wind, itching, etc., and redness and swelling reactions were seen in the local skin of the injected area. Hou Yanjie [20] found that some patients injected Shuanghuanglian injection 10-20min after the appearance of skin lesions, from the head and face spread to the whole body, showing a pink airball-like, the pressure of the receding color. Some patients had adverse reactions such as peripheral itching, red papules and skin flushing on the neck and forehead after 20min of Shuxianin injection. A few patients developed generalized itching, gradual palpitations, and then unconsciousness after Thromboxane Injection. Phlegm-heat Qing Injection may cause some patients to develop densely distributed red, different-sized maculopapular rash on the face and neck, forehead and back.

3.2 Adverse Skin Reactions Due to Oral Administration of Herbal Preparations

Most oral Chinese medicinal preparations have concise instructions and are not labeled with possible adverse reactions, therefore, there may be drug abuse during use, which increases the incidence of adverse drug reactions. Su Kaiyan [21] et al. showed that adverse reactions of oral Chinese medicinal preparations can involve the skin and its adnexa. For example, oral administration of Dan Knee Granules, Nourishing Blood and Hair Capsule, and Bone Kang Capsule can lead to itching of the skin on the shoulders, neck, and scalp. Li Yuehong [22] investigated 42 patients with adverse drug reactions and found that oral Chinese medicinal preparation adverse reactions accounted for 28.5% of patients with redness and swelling of the skin, as well as dermatitis, rash and fever. Ren Lixi [23] showed that Chinese medicinal preparations may cause itching, mucosal edema, and rash, and with the long-term use of compound licorice

tablets, patients develop dependence, and the sudden discontinuation of the medication can lead to the above symptoms.

3.3 Adverse Skin Reactions from Chinese Medicine Granules

As a new dosage form of traditional Chinese medicine, Chinese medicine formula granules are widely used in clinical practice due to their convenience in carrying and ease of administration. However, due to the complexity of its components and the variety of its compositions, adverse reactions occur from time to time. Chen Huijun [24] showed that especially children's physiological structure is not yet fully developed, the metabolism of drugs is still insufficient, more sensitive to drugs are more likely to produce adverse reactions. Clinical findings of some children in the process of taking Chinese medicine formula particles appear rash. Sun Xinxin [25] et al. investigated 1, 580 cases of adverse drug reactions in which 376 patients had symptoms such as itching and rash, accounting for about 24.5 %. This shows that although Chinese medicinal granules have their unique advantages, they can still cause adverse skin reactions.

4. Main Skin Lesion Manifestations of Adverse Drug Reactions

The skin manifestations of adverse reactions caused by Chinese medicines are similar to those of chemical medicines, but due to the complexity of the components of Chinese medicines (e.g. alkaloids, glycosides, heavy metals, etc.), and the possible involvement of inappropriate concoctions, contraindications in compounding, or individual differences, the skin manifestations of the lesions may be more complicated, or even appear as unique reactions. These include maculopapular rash, i.e. measles-like drug rash, in which the patient's skin can be seen as diffuse red maculopapular rash or papules all over the body, which can be fused into patches, accompanied by itching. Examples include Panax ginseng, Salvia miltiorrhiza, He Shou Wu, and Lei Gong Teng, which are commonly used in clinical practice. Urticaria, i.e. rubella-like rash, sudden reddish windy bumps with itching, and even angioedema or anaphylactic shock. Examples include herbs such as centipede and scorpion, as well as danshen injection. There are also patients with fixed drug rashes with well-defined round or oval erythematous spots, and blisters or vesicles may form in the center. Common heavy metal drugs such as andrographis and vermilion can trigger fixed-shaped drug rashes. Some patients may develop severe drug rash with widespread erythema, blisters, and epidermal peeling all over the body, accompanied by mucosal erosion and high fever. Examples include He Shou Wu, Lei Gong Teng, Guan Mu Tong and many other herbs. A small number of patients may develop photosensitive dermatitis, with erythema and blisters on sun-exposed areas, similar to sunburn or eczema-like lesions. Commonly, there are tonic acid, Angelica dahurica, Fangfeng and other Chinese herbs containing photosensitive ingredients. It can be seen that the skin manifestations of common clinical adverse drug reactions to traditional Chinese medicine are more diverse, and should be carefully diagnosed in conjunction with the actual situation of the patient.

5. Analysis of the Causes of Adverse Reactions

5.1 Drug Composition

The composition of Chinese medicines and their preparations is complex, and the method of preparation and the process of preparation itself can lead to changes in the composition of the medicines, and some of the ingredients are allergens that are prone to cross-reactivity. One report showed that after a concoction staff member's face and right arm came into contact with the hot vapor of vinegar-braised Gansui, erythematous papules appeared, partially fused into patches, moderately erythematous and swollen, and elevated above the skin, which were diagnosed as contact dermatitis. Xiang Liling [26] and others showed that toxic Chinese medicines can reduce their toxic side effects by external application, and confirmed through a large number of cases that the main reasons for the adverse reactions of external application of Chinese medicines: toxic components of drugs, irrational use of combined medicines, inaccurate identification of evidence, and inaccurate use of medicines. Zhang Jin [27] et al. found that through data mining, single-flavored Chinese medicines used externally to cause adverse reactions of the drugs, the flavor of pungent medicines, accounting for 31.7%, "Suwen - five Tibet generates the chapter," "the lung wants to Xin the five flavors of the combination of also". The lung is the main skin and hair, it can be seen that pungent drugs on the human skin stimulation is the strongest, so it is easy to produce adverse reactions. Compound topical Chinese medicine, in addition to the extraction of a variety of herbal ingredients, but also added ethanol, etc., which will also increase the risk of sensitization. Ni Xiuyi [28] et al. showed that according to the statistics of the route of administration, injections caused 55.1% of adverse reactions. And it is believed that this is closely related to the composition, multi-target and multi-pathway of Chinese medicine injection. The composition of TCM injections is complex, and most of the injections contain macromolecular substances, such as tannins, starch, proteins, etc., and these macromolecular substances can induce adverse reactions through some special conditions after entering the human body.

5.2 Patient's Own Factors

Drugs produce allergic reactions and the patient's own constitution has a certain relationship, some patients have a better constitution, the use of drugs will not produce adverse reactions, if the physical condition is poor, the existence of underlying diseases, or even have a history of allergy patients, easy to cause adverse drug reactions. Qiu Lingling [29] and others also showed that the age, gender, physiological state of patients will have different degrees of differences, so in the process of drug metabolism, the body's receptivity to the drug is different, and different reactions occur. Patients of different ages have different probabilities of adverse drug reactions due to the large differences in the organism's organic state of the drug, and usually, the probability of adverse drug reactions is higher in the elderly and children, who are prone to allergic reactions because of their lower resistance and muscular tolerance and weaker drug metabolism.

5.3 Clinical Factors

There is the problem of unstandardized use of drugs in clinical practice. Chinese medicine focuses on the identification and treatment, and most of the Chinese medicine injection in the process of clinical use is to identify the disease treatment, for example, Qingkailing injection applied to fever fever and not for cold fever, clinical if not divided into cold and heat, see fever that is, Qingkailing injection, it is easy to occur adverse reactions. Clinically, there is a problem of improper compounding, the composition of Chinese medicine injection is complex, and used in conjunction with other drugs may be its precipitation, the increase in particles of the drug solution. Ni Xiuyi believes that Chinese medicine injection is prone to adverse reactions mainly due to differences in solvents, irrational choice of solvents and too long a period of time, for example, the instructions for saffron injection indicate that 5% to 10% glucose injection should be used to dissolve, with a dosage of 250-500 mL, while there are cases of using 0.9% sodium chloride injection to dissolve, with a dosage of 100 mL as a solvent in the clinic. This also increases the risk of adverse reactions to herbal injections.

6. Discussion

The efficacy of traditional Chinese medicine is varied and its dosage form is also variable, while in the process of clinical use due to many factors make the patients have adverse reactions. From the patient's point of view, each patient's body state is different, the metabolism ability of the drug is different, and many patients themselves have a history of drug allergy, which requires the clinical use of traditional Chinese medicine, according to the patient's different situations, specific treatment. For patients with a history of allergy should pay attention to, if necessary, timely do allergen testing. Clinical evidence-based treatment is very important, the use of Chinese medicine injections in the clinic, can not simply identify the disease with drugs, if the identification is not accurate, it is easy to cause adverse drug reactions. The concoction and usage of many topical medicines, the dosage, and the duration of dressing may be the cause of adverse reactions. Therefore, it is necessary to strictly regulate the concoction process and improve the quality of medicines. As a doctor, we should pay attention to observing the changes of skin lesions at the site of application of topical medicines, and strictly control the dosage, concentration and duration of application of topical medicines, so as to bring into play the therapeutic efficacy of traditional Chinese medicines and to reduce the incidence of skin-related adverse reactions caused by traditional Chinese medicines.

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