TCM Ideology and Methodology

The Safety-influencing Factors in Use of the Tonics of Chinese Medicine: A Meta-analysis Based on the Case Reports in Periodicals

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Objective: To identify the possible safety-influencing factors in use of the tonics of Chinese medicine.
Methods: The related case reports published in periodicals published from 1949 to 2006 were analyzed with the bibliometrics method. Possibility on safety assessment of Chinese materia medica was discussed as well with the method of link analysis.
Results: The total number of the tonics selected for the present study was 101, including 44 single drugs and 46 set prescriptions with adverse drug reactions (ADR) found in these tonics. It was found that ADR of 10 single drugs and 29 preparations were not specified in authoritative Chinese materia medica monographs. Among all the set prescriptions, the problem of injection has been standing on the top. Statistical analysis on single factor demonstrates that the most frequently referred ADR come from drug abuse (accounting for 29.20%), and overdose (24.54%).
Conclusion: The safety problem of injection remains in a trend of robust growth at least for a period of time, thus reappraisal of the safety issue for the tonics of injection is imperative. It is essential for the public to take doctor's advice to guarantee safe administration of the tonics, especially for the patients with allergic constitution or those suffering from the liver and heart diseases.

Keywords: *safety-influencing factors; tonics of Chinese medicine; case reports*

"The generalized untoward effect" refers to any adverse drug reactions (ADR) to drug.[1] It is defined as every harmful effect toward human body under various circumstances, such as proper drug application, medication errors, application of clinical prescription and household remedies. Therefore, the ADR mentioned in the present study refer to the domain of "generalized untoward effects".

Sources and Collection Methods of the Case Reports

1. Variety criteria for the tonics of Chinese medicine

The selected drugs should be classified as tonics in *Zhongyaoxue* (中药学 Chinese materia medica) published respectively by China Press of Traditional Chinese Medicine in 2002, People's Medical Publishing House in 2002, Press of Ancient Books of Traditional Chinese Medicine in 2002, Academy Press in 1998, China Press of Traditional Chinese Medicine in 1993, Hunan Science & Technology Press in 1985 and Sichuan Science & Technology Press in 1978. The drugs should be described as tonics in both *Yaodian* (药典 Pharmacopeia, 2005 edition) and *Zhongyao Dacidian* (中药大辞典 Dictionary of Chinese Materia Medica). And the nomenclature of the drugs should be standardized according to *Thesaurus for Traditional Chinese Medicine*.

2. Achieving process of the bibliographical references

Nomen proprium was adopted to do primary retrieval of the key words in Bibliographic Database of TCM Periodicals, Chinese Biomedical Literature Database and Chinese Medical Current Contents Data Base with the time rage set from 1949 to 2006. Then, "adverse reaction, side effect, toxicity, intoxication and safety" were adopted to do secondary retrieval of the key words. Afterwards, unconcerned bibliographical references of adverse reaction of the tonics, side effect, toxicity, intoxication and safety were deleted, such as "Tu Ren Shen (Talinum Paniculatum) / toxicity", "formaldehyde / toxicity, Bai Shao (Radix Paeonia Alba) / pharmacology". And finally, summarizing and duplicate checking were conducted.

3. File downloading and searching

Full texts were downloaded according to bibliographical references from Full-text Periodical Database and Full-text Past Issue Database of National Knowledge Infrastructure (CNKI), Wanfang Full-text Database of Digitizing Periodicals and VIP Chinese Periodical Database. The full texts failed to be searched in the above sources should be sought from paper periodicals.

4. Inclusion criteria

Documents included in the present study should be ADR reports, which mean that detailed conditions of the cases should be described in the reports. Preparations involved in the cases should conform to one of the following requirements: 1) The tonic ingredients in the preparations

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should not be those included in *A Dictionary of Poisonous Chinese Materia Medica of the People's Republic of China* and their ratio in the preparations should be 75% or above (without consideration of the dosage of the medicine); 2) If the components of the formula are unknown, 2/3 or more of its function should be described as tonic.

5. Exclusion criteria
The documents which should be excluded: Reviews, notes and experiences, document analysis, duplicates of same cases or same subjects, cases before 1949, documents on toxicology and clinical safety evaluation, group case-reporting of ADR (case reports without detailed description of specific cases), case reports of food poisoning and case reports which are not correspondent with the inclusion criteria.

Data Collection and Analysis
1. Variety statistics: Variety statistics of the tonics of Chinese medicine with safety problems were collected respectively according to the categories of the single drug and the set prescription.

2. Time analysis: Times of documents concerning drugs with more safety problems were collected and the variation trends were analyzed.

3. Univariate analysis: the safety-influencing factors involved were extracted and summarized. And the single factors with high appearance frequency were analyzed.

4. Link analysis of the interrelationship among various impacts: The WEKA software developed by Prof. ZHOU Xue-zhong of Beijing Jiaotong University was adopted for the analysis. Significant linked results were found after the establishment of extracting rules through data generalization (for example, if ten years are taken as one unit, the age of patients can be generalized as early youth group 1, youth group 1, middle aged group 1 and aged group 1; duration of drug application can be generalized as one day, one week, half a month and one month etc.).

Result and Analysis
1. Statistics of drug inclusion
The total number of the tonics selected for the present study was 101. Their standardized names are as follows: Ren Shen (Radix Ginseng), Ren Shen Ye (Folium Ginseng), Hong Shen (Panax Ginseng), Xi Yang Shen (Radix Panacis Quinquefolii), Tai Zi Shen (Radix Pseudostellariae Heterophylly), Dang Shen (Radix Codonopsis), Zhu Jie Shen (Rhizoma Panacis Japonici), Huang Qi (Raidix Astragali), Zhi Huang Qi (Radix Astragali Preparata), Hong Qi (Radix Hedysari Manyinflorescenced), Zhi Hong Qi (Radix Hedysari Preparata), Bai Zhu (Rhizoma Atractylodis Macrocephalae), Shan Yao (Rhizoma Dioscorease), Bai Bian Dou (Semen Lablab Album), Gan Cao (Redix Glycyrrhizae), Zhi Gan Cao (Radix Glycyrrhizae Praeparatae), Da Zao (Fructus Jujubae), Yi Tang (Saccharum Granorum), Feng Mi (Mel), Lu Rong (Cornu Cervi Pantotrichum), Lu Jiao Jiao (Colla Cornus Cervi), Lu Jiao Shuang (Cornu Cervi Degelatinatum), Lu Jiao (Cornu Cervi Elaphi), Ba J Tian (Radix Morindae Officinalis), Yin Yang Huo (Herba Epimedii), Xian Mao (Rhizoma Curculiginis), Bu Gu Zhi (Fructus Psoraleae), Yi Zhi (Fructus Alpiniae Oxyphyllae), Hai Gou Shen (Callorhinus), Hai Ma (Hippocampus), Rou Cong Rong (Herba Cistanches Deserticolae), Suo Yang (Herba Cynomorii), Tu Si Zi (Semen Cuscutae), Sha Yuan Zi (Semen Astragali Complanati), Du Zhong (Cortex Eucommiae), Xu Duan (Radix Dipsaci), Jiu Cai Zi (Semen Allii Tuberosi), Yang Qi Shi (Actinolitum Actimolite), Hu Lu Ba (Semen Trigonellae), He Tao Ren (Semen Juglandis), Ge Jie (Gecko), Dong Chong Xia Cao (Cordyceps), Zi He Che (Placenta Hominis), Dang Gui (Radix Angelicae Sinensis), Shud Di Huang (Radix Rehmanniae Praeparata), Bai Shao (Radix Paeoniae Alba), Zhi He Shou Wu (Radix Polygoni Multiflori Preparata), E Jiao (Colla Corii Asini), Long Yan Rou (Arillus Longan), Bei Sha Shen (Radix Glehniae), Nan Sha Shen (Radix Adenophorae), Bai He (Bulbus Lilii), Mai Dong (Radix Ophiopogonis), Tian Dong (Radix Asparagi), Shi Hu (Herba Dendrobii), Yu Zhu (Rhizoma Polygonati Odorati), Huang Jing (Rhizoma Polygonati), Gou Qi Zi (Fructus Lycii), Mo Han Lian (Herba Ecliptae), Nü Zhen Zi (Fructus Ligustri Lucidi), Sang Shen (Fructus Mori), Hei Zhi Ma (Semen Sesami Nigrum), Gui Jia (Carapax et Plastrum Testudinis), Gui Jia Jiao (Colla Carapacis et Plastri Testudinis), Bie Jia (Carapax Trionycis), Shan Mai Dong (Radix Liriopes), Ci Wu Jia (Radix Acanthopanacis Senticosi), Gou Ji (Rhizoma Cibotii), Gu Sui Bu (Rhizoma Drynariae), Sang Ji Sheng (Herba Taxilli), Sang Piao Xiao (Oötheca Mantidis), Hong Jing Tian (Radix et Rhizoma Rhodiolae Kirilowii), Hu Ji Sheng (Herba Visci), Yi Yi Ren (Semen Coicis), Ling Zhi (Ganoderma Lucidum seu Japonicum), Shan Zhu Yu (Fructus Corni), Lian Zi (Semen Nelumbinis), Hai Long (Syngnathus), Fu Pen Zi (Fructus Rubi Chingii), Du Zhong Ye (Folium Eucommiae), Shou Wu Teng (Caulis Polygoni Multiflori), Ji Xue Teng (Caulis Spatholobi), Qian Shi (Semen Euryales), Ha Ma You (Oviductus Ranae), Zhu Zi Shen (Rhizoma Panacis Majoris), Chu Sh Zi (Fructus Broussonetiae), Xue Lian Hua (Herba Saussureae Laniceptis), Wu Wei Zi (Fructus Schisandrae), Jiao Gu Lan (Herba Gynostemmatis Pentaphylli), Sha Ji (Fructus Hippophae), Zi Shi Ying (Fluoritum), Qi Dai (Funiculus umbilicalis), Huang Gou Shen (Testis et Penis Callorhimi), Yang Hong Shan (Radix seu Herba Pimpinellae), Ming Dan Shen (Radix Changii), Xiong Can E (Bombyx Batryticatus), Xin'E Jiao (Susscrofa domestica Brisson Pigskin), Yin Er (Tremella Fuciformis), Feng Jiao (Colla Apis), Lu Xian Cao (Herba Pyrolae), Rui Ren (Nux Prinsepiae). Ten single drugs and twenty-nine preparations were specified in neither of the above 2 monographs. The 10 single drugs included Mai Dong (Radix Ophiopogonis), Dang Gui (Radix Angelicae Sinensis), Xu Duan (Radix Dipsaci), Lu Jiao Jiao (Colla Cornus Cervi), Bei Sha Shen (Radix Glehniae), Zi He Che (Placenta Hominis),

Gui Jia (Carapax et Plastrum Testudinis), Ming Dang Shen (Radix Changii), Hu Lu Ba (Semen Trigonellae) and Hong Jing Tian (Radix et Rhizoma Rhodiolae Kirilowii). The 29 preparations are Gan Cao Xin (Licorzine Capsules), Fufang Gancao Tianshu Zhusheye (复方甘草甜素注射液 Compound Glycyrrhizin Injection), Ganlixin Zhusheye (甘利欣注射液 Diammonium Glycyrrhizinate Injection), Shouwu Pian (首乌片 *Shouwu* Tablet), Shenqi Fuzheng Zhusheye (参芪扶正注射液*Shenqi Fuzheng* Injection), Dongchong Xiacao Jiaonang (冬虫夏草胶囊 *Dongchongxiacao* Capsule), Zhibansu (制斑素 Psoralen Injection), Zhenqi Fuzheng Chongji (贞芪扶正冲剂 *Zhenqi Fuzheng* Granules), Zaoren Anshen Jiaonang (枣仁安神胶囊 *Zaoren Anshen* Capsule), Yixuesheng Jiaonang (益血生胶囊 *Yixuesheng* Capsule), Yangxue Anshen Pian (养血安神片 *Yangxue Anshen* Tablet), Yangshen Chongji (洋参冲剂*Yangshen* Granules), Xueshan Hongjingtian Koufuye (雪山红景天口服液 *Xueshan Hongjingtian* Oral Liquid), Xintong Koufuye (心通口服液 *Xintong* Oral Liquid), Xinganbao Jiaonang (心肝宝胶囊 *Xinganbao* Capsule), Shengfa Wan (生发丸 *Shengfa* Pill), Renshen Fengwang Jiang (人参蜂王浆 Ginseng with Royal Jelly), Nüjin Jiaonang (女金胶囊 *Nvjin* Capsule), Kang'erxin (康尔心 *Kang'erxin* Capsule), Guiyuan Bu Gao (桂圆补膏 *Guiyuan* extract), Gancaosuan Dan'an Zhusheye (甘草酸单胺注射液 Ammonium Glycyrrhetate Injection), Fufang Gancao Tiansu (复方甘草甜素片 Compound Glycyrrhizin Injection), Fufang Gancaogan Pian (复方甘草酸苷片 Compound Glycyrrhizin Tablets), Fufang Ejiao Koufuye (复方阿胶口服液 Compund *Ejiao* Oral Liquid), Erkangning (儿康宁 *Erkangning* Syrup), Danggui Jisheng Zhenji (当归寄生针剂 *Danggui Jisheng* Injection), Shenqi Wuweizi Pian (参芪五味子片 *Shenqi Wuweizi* Tablet), Buguzhi Zhusheye (补骨脂注射液 *Buguzhi* Injection), Ejiao Gai (阿胶钙 *Ejiaogai* Oral Liquid).

2. Results and analysis with bibliometrics method

1) Reporting frequency of single drug

Since Ren Shen (Radix Ginseng) and Hong Shen (Radix Ginseng Rubra), He Shou Wu (Radix Polygoni Multiflori) and Zhi He Shou Wu (Radix Polygoni Multiflori Preparata), Gan Cao (Radix Glycyrrhizae) and Zhi Gan Cao (Radix Glycyrrhizae Praeparatae) were not clearly specified in some of the literatures, Renshen/Hongshen (hereinafter referred to as the single drug of Renshen), Heshouwu / Zhiheshouwu (hereinafter referred to as the single drug of Heshouwu), Gancao and Zhigancao were counted under unified names.

There are 30 drugs which only involved in 1 to 2 reports, and 14 single drugs with 3 or more reports. The single drug of Renshen had the most reports with a total number of 50. The single drug of Heshouwu took the second place with total reports of 25, followed by 17 of the single drug of Gancao, 16 of Huang Qi (Raidix Astragali Membranous), 11 of Feng Mi (Mel), 10 of Dong Chong Xia Cao (Cordyceps) and Xi Yang Shen (Radix Panacis Quinquefolii American ginseng) respectively.

Statistics of 7 drugs which involved in more reports (≥10) were collected and listed with 10-year as a unit. See table 1 for details.

Table 1. Literatures on ADR of the single tonics with reports≥10

Single drugs	1949-1969	1970-1979	1980-1989	1990-1999	2000-2006	Total
Single drug of Renshen	1	1	22	20	6	50
Single drug of Heshouwu	0	0	3	13	9	25
Single drug of Gancao	1	0	3	11	2	17
Huang Qi	0	0	2	7	7	16
Feng Mi	0	1	6	1	3	11
Dongchong Xiacao	0	0	0	8	2	10
Xi Yang Shen	0	0	0	7	3	10
Total	2	2	36	67	32	139

Table 1 showed that the summit reporting of the single drug of Ren Shen (Ginseng), appeared in 1980s'. Since the concept of "ginseng abuse syndrome" was raised in 1979 abroad, it was supposed as the reason for the increased cases of ginseng abuse. Resulting from those reports, prevention of ginseng abuse was enhanced, which led to dropping of the curve finally.

Feng Mi (Mel) is often taken as a common food. Though the curve fluctuation is not obvious, it is quite incomprehensible for its ADR. However, through summarization and analysis, it is supposed to be caused by taking the unprocessed honey with honeycomb or toxic pollen.

In 21 Century, the number of case reports on the above mentioned 7 single drugs declined. And no definite conclusion has been drawn yet since lack of enough literatures and unbalanced distribution among various age units.

2) Bibliometric analysis for the set prescriptions

There are totally 15 set prescriptions involved in 3 or more ADR reports, including 11 injections. Ciwujia Zhusheye (刺五加注射液 *Ciwujia* Injection) had the most reports of 75, followed by 49 for Huangqi Zhusheye (黄

芪注射液 *Huangqi* Injection), 48 for Shenmai Zhusheye (参麦注射液 *Shenmai* Injection) and 11 for Compound Ammonium Glycyrrhetate Injection (Table 2).

Four set prescriptions involved in relatively more reports (≥10) were collected and listed in Table 3 with 10-year as a unit.

Table 2. The set prescriptions with ≥3 cases reported on ADR

Name of the set prescription	Number of cases reported on ADR
Ciwujia Injection	75
Huangqi Injection	49
Shenmai Injection	48
Compound Ammonium Glycyrrhetate Injection	11
Diammonium Glycyrrhizinate Injection	8
Shouwu Tablet	7
Shenqi Fuzheng Injection	7
Danggui Injection	5
Lurongjing Injection	5
Zhuanggu Guanjie Pill	4
Licorzine Capsules	4
Shengmai Injection	3
Compound Glycyrrhizin and sodium chloride Injection	3
Compound Danggui Injection	3
*Congrong Tongbian o*ral liquid	3

Table 3. The tonics with ≥10 cases reported on ADR (from 1949 to 2006)

Name of the set prescriptions	Number of cases reported on ADR					
	1949-1969	1970-1979	1980-1989	1990-1999	2000-2006	Total
Ciwujia Injection	0	0	0	24	50	74
Huangqi Injection	0	0	0	11	36	47
Shengmai Injection	0	0	2	8	37	47
Compound Ammonium Glycyrrhetate Injection	0	0	0	4	6	10
Total	0	0	2	47	129	178

Notes: Five case reports for the above four injections did not mention the written year, including one for Ciwujia Injection, two for *Huangqi* Injection, and one respectively for *Shenmai* Injection and Compound Ammonium Glycyrrhetate Injection.

Among all the set prescriptions, the safety issue problem in injection has been standing on the top, indicating that the safety issue of injection remains in a trend of robust growth at lease for a period of time, so, reappraisal of the safety in use of the tonics of injection is imperative.

3) Year distribution of the case reports

As shown in Table 4, there was only one case report on ADR for the tonics in the period from 1949 to 1969. In 1970s, the number of the case reports were no more than 6. Nevertheless, the number of the case reports have skyrocketed to 13.7 per year since 1990s, and the increasing tendency continues in this century. It is indicated that the public has been paying more attention on the safety issue of the tonics, and it reminds us that the development of traditional Chinese medicine would be affected if no proper measurements are taken in time.

Table 4. Year distribution of the case reports on ADR for the tonics

Year distribution	Cases reported on ADR for the tonics
1949-1969	1
1970-1979	6
1980-1989	88
1990-1999	225
2000-2006	269

3. Analysis on the single factor

'The positive impact' refers to the potential possibility leading to ADR; and it has played a key role in the safety issue of the tonics.

Statistics of the single factor underlines the ADR of each corresponding case report respectively from negative, positive and no refer so as to analyze the 'positive impact' (Table 5 and Figure 1).

Table 5. Statistical results of the negative and positive impacts and no refer for the number of cases of ADR

Impacts	Negative (%)	Positive (%)	No refer (%)
Constitution	51 (7.19)	94 (13.26)	564 (79.55)
Pathological condition	83 (11.71)	175 (24.68)	432 (60.93)
Compatibility	706 (99.57)	3 (0.43)	0
Processing	6 (0.85)	1 (0.14)	702 (99.01)
Decoction	0	0	709 (100)
Quality	32 (4.51)	24 (3.39)	653 (92.10)
Differentiation	58 (8.18)	29 (4.09)	622 (87.73)
Abuse	444 (62.62)	207 (29.20)	58 (8.18)
Drug combination	35 (4.94)	128 (18.06)	546 (77.00)
Dose	466 (65.73)	174 (24.54)	69 (9.73)

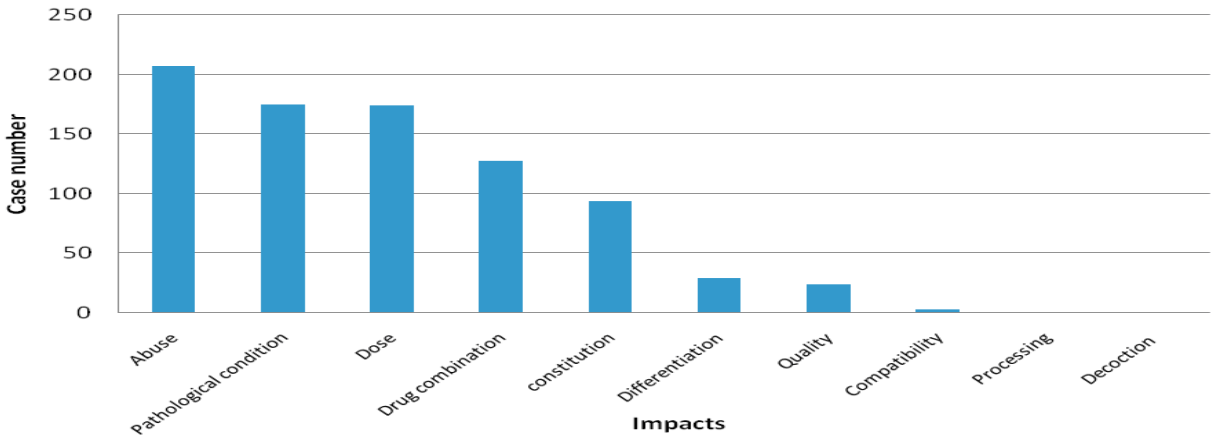

Figure 1. Statistics for ADR due to the positive impacts

As shown in Figure 1, the impacts from left to right are Abuse, Pathological condition, Dose, Drug combination, Constitution, Differentiation, Quality, Compatibility, Processing, and Decocting. The most frequently referred ADR come from drug abuse (accounting for 29.20%), and the proportion of overdose was 24.54%. So, it is clear that the major causes concerning safety issue of the tonics are abuse and overdose.

The percentages of impacts like 'Pathological condition', 'Drug combination' and 'Constitution' are relatively higher than the other factors; however, from the view of single factor diseases of the heart, liver and kidney, drug combination and allergy may have potential influence on the safety issue of the tonics.

4. Analysis on the linked results

The intense distracters were excluded from the linked results, the interesting connections emerged in13 groups with the confidence coefficient ≥90% (Table 6).

Table 6. The linked results (confidence coefficient ≥90%)

The interesting connections	Confidence coefficient (%)	Support coefficient (%)
Middle aged group 2==>injection	100	7.47
Male, drug combination ==>injection	100	6.91
Youth group 2 ==> injection	100	5.36
Old aged group 1 ==>injection	100	5.22
Allergic consititution ==>injection	100	5.22
Liver disease ==> injection	100	4.94
Female ==> injection	99.00	18.89
Male ==> injection	99.00	16.92
Heart disease ==> injection	99.00	10.58
Drug combination ==> injection	98.00	11.42
Middle aged group 1==>injection	98.00	7.76
Heart disease, female==> vein injection	98.00	5.92
Overdose, oral administration ==> abuse	90.00	8.46

There is no significant difference between 'Female ==> injection' and 'Male ==> injection' in the support coefficient, and their confidence coefficients are the same. So it is clear that one's gender shows no significance in terms of 'injection'.

The confidence coefficients in the middle aged group 2, youth group 2, old aged group 1 and middle aged group 1, are respectively 100%, 100%, 100% and 98%, with almost no difference among the four groups. As for the support coefficients in the four groups, the difference is also limited, they are respectively 7.47%, 5.36%, 5.22% and 7.76%, and the four groups happen to be connected from age 30 to 69. The present study shows that ADR strongly correlates with the people aged 30–69, but sufficient theoretical and data supports are needed to confirm the inevitability between the age range of '30–69' and ADR after injection.

The above linked results remind us that it is necessary to reduce the us of injection for patients with allergic constitution or those suffering from the liver and heart diseases. For the cases with injection prescribed, the doctor should carefully observe the reactions, and for the safety reason, try to reduce the combined use of drugs so as to lower down the possible accidence.

DISCUSSION

ADR can not be simply attributed to the Drug Itself

Many people consider the safety problem of the tonics as ADR and attribute all to the drug itself, sometimes resulting in rejection and seizure of those drugs. According to the definition of adverse drug reactions by WHO, any harmful or unexpected reactions to medicines which occur at normal dosage used for prevention, diagnosis or treatment of diseases, or for improving physiological functions, are called ADR. So, the prerequisite should be proper use of the drug.

It was found in the present study that *abuse* and *overdose* accounted for a considerable proportion; and the impact results indicated that there was a close connection between these two factors,. So, the ADR described in some case reports is the consequence of improper administration of the drugs.

ADR can not be simply attributed to the drug itself, and the assessment should be made with abuse and overdose excluded.

Enhance the Public Awareness for Safe Administration of the Tonics

Drug abuse commonly exists, and the public awareness for safe administration of the tonics should be enhanced. For instance, honey can be taken as food and drug; it can hardly be considered as the cause for ADR or the reason for death. In fact, the safety problems are related with the un-processed raw honey, which contains toxic honeycomb or pollen. The second example is the so-called 'Ginseng Abuse Syndrome' caused by overdose of Ginseng, which in severe case may lead to death. Therefore, it is necessary to take doctor's advice to guarantee safe administration of the tonics.

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