

*Full Length Research Paper*

## A report on the analysis of 365 cases of adverse reactions of Chinese patent drugs for heart cerebrovascular diseases

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This research aimed to analyze the factors of heart cerebrovascular drugs that can lead to adverse reactions (ADRs) and to promote rational clinical drug use. Reports on cases of heart cerebrovascular diseases were collected in our hospital in 2001 to 2010, and medication and the clinical manifestations of the adverse reactions were analyzed. The incidence of adverse reactions was related with age, gender, routes of administration, dosage forms and other factors. The adverse reactions of heart cerebrovascular drugs were mainly related to dosage forms, the injections were especially more likely to cause adverse reactions, and the clinical manifestations were diversified. It was therefore suggested that doctors and patients pay more attention to the adverse drug reactions in the whole medication process.

**Key words:** Heart cerebrovascular, Chinese patent drugs, adverse reactions.

### INTRODUCTION

Heart cerebrovascular disease is the general term for cardiovascular and cerebrovascular diseases (Xiu-qing, 2012). Heart cerebrovascular diseases were featured as "four high and many" that is high incidence rate, high disability rate, high mortality rate, high recurrence rate, and many complications (Jian-hua, 2011). Therefore, heart cerebrovascular diseases have seriously threatened human physical and mental health, especially the incidence rate is higher in the middle-aged and aged population above 50 years old (Ming-yu and Jin-da, 2009). As people pay much attention to health and quality of life, the adverse reactions had been cause of extreme concern (Agnes et al., 2008; Jiang et al., 2012).

In this paper the analysis was made on the basis of recorded cases in the recent 10 years in our hospital, to provide references for rational drug use clinically in the

future.

### MATERIALS AND METHODS

#### Data sources

Analyses were done on cases of adverse reactions in patients with cardiovascular diseases after drug administration in our hospital in the past 10 years from 2001 to 2010.

#### Experimental methods

The adverse reactions were classified according to the regulation of the World Health Organization (WHO) Adverse Drug Reaction Monitoring Center and the gender, ages, allergic history, medication and clinical manifestations of adverse reactions were analyze (The Uppsala Monitoring Centre, 2005).

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**Table 1.** Distribution of gender of the cases with various adverse drug reactions.

Drug name	Male	Female	Unclear	Total
Huoxuetongmai tablet	1	2	0	3
Compound salvia miltiorrhiza tablet	2	1	0	3
Suxiaojiuxin pill	3	2	0	5
Xuezhikang capsule	3	2	0	5
Tongxinluo capsule	4	5	0	9
Naoan capsule	3	2	0	5
Panax notoginsenosides injection	10	17	0	27
Shenmai injection	15	20	0	35
Safflower injection	13	18	1	32
Ginkgo injection	9	13	0	22
Alginic sodium diester injection	12	18	0	30
Acanthopanax injection	20	22	1	43
Chuanqiongqin injection	14	15	0	29
Puerarin injection	12	19	0	31
Shengmai injection	17	19	0	36
Mailuoning injection	18	23	0	41

**Table 2.** Distribution of ages of the cases with adverse reactions.

Drug name	Age (<20)	Age (21-40)	Age (40-60)	Age (>61)
Huoxuetongmai tablet	0	0	1	2
Compound salvia miltiorrhiza tablet	0	0	0	3
Suxiaojiuxin pill	0	0	1	4
Xuezhikang capsule	0	0	1	4
Tongxinluo capsule	0	0	1	8
Naoan capsule	0	0	1	4
Panax notoginsenosides injection	0	0	3	24
Shenmai injection	0	0	5	30
Safflower injection	0	2	18	14
Ginkgo injection	0	0	10	20
Alginic sodium diester injection	0	0	5	25
Acanthopanax injection	0	0	8	33
Chuanqiongqin injection	0	1	9	20
Puerarin injection	0	0	6	25
Shengmai injection	0	0	7	29
Mailuoning injection	0	0	9	30

## RESULTS AND DISCUSSION

### Gender distribution

Of the 356 cases included in this study, which included 156 males and 198 females, 2 cases were of unclear gender. The distribution of gender of the cases with various adverse drug reactions is been shown in Table 1. It can be seen from the table that apparently the number of adverse reactions caused by the injection was significantly more than capsules or tablets, which suggested that we can reduce drug adverse reactions and help patients

take drugs scientifically by improving drug formulations or modifying the molecular structure of drugs.

The male-female ratio of ADR is 1:1.2, and this may be because the tolerance of males and the tolerance of females toward adverse reactions is slightly different.

### Age distribution

Of the 356 cases of adverse reactions and except for 5 cases had unclear ages, the others were distributed in each age range as shown in Table 2. It can be seen from

**Table 3.** Past allergic history.

Drug name	Allergic	Not allergic	Uncertain
Huoxuetongmai tablet	5		
Compound salvia miltiorrhiza tablet	1		
Suxiaojiuxin pill	0		
Xuezhikang capsule	2		
Tongxinluo capsule	4		
Naoan capsule	6		
Panax notoginsenosides injection	3		
Shenmai injection	5		
Safflower injection	2	158	145
Ginkgo injection	5		
Alginic sodium diester injection	4		
Acanthopanax injection	3		
Chuanqiongqin injection	3		
Puerarin injection	3		
Shengmai injection	4		
Mailuoning injection	0		

the age distribution that adverse reactions occurred in all the ages, mostly distributed in middle-aged and aged patients above 50 years old. The following were the main reasons: first, elderly patients had varying degrees of organ dysfunction, which lead to the demand of different drug doses, and the effective threshold of drug will have large individual differences, thus they were prone to adverse reactions (Yeung et al., 2010). Secondly, the elderly were susceptible to heart cerebrovascular diseases, so the probability of leading to adverse reactions was higher after taking the drugs which can improve the blood circulation (Wang, 2009). Thirdly, the elderly always had many diseases and need to take many drugs in combination; as a result, the function of kidneys in discharging and metabolizing the drugs would decline gradually and the detoxification function also decreases, all these combine to lead to the probability of higher adverse reactions (Cox et al., 2010).

### Past allergic history

Of the 356 cases of adverse reactions, 53 cases had past allergic history, 158 cases had no past allergic history, and 145 cases were unclear (but indicated no past allergic history), as shown in Table 3. From the statistics on the past allergic history of the 356 cases, we found that 56 cases had allergic history, 158 cases had no allergic history and 145 cases were unclear. For each specific drug, the cases without mentioning past allergic history also accounted for a large part; this indicated that patients had not been cared for effectively by the relevant staffs in hospital. When taking traditional Chinese medicine injection, patients with allergic history would have higher probability to get adverse reactions, and

patients without allergic history were also prone to ADRs and so much more attention should be paid on these kinds of patients.

### Medication

#### Route of administration

The routes of administration were mainly oral administration and intravenous injection. It can be seen from the statistical analysis related to routes of administration that intravenous administration was more likely to cause adverse reactions than oral administration, mainly because oral drugs are likely to be subjected to a series of metabolism in body, thus making them comparatively less liable to cause adverse reactions. On the other hand, since intravenous drugs are introduced, they have the higher tendency to cause ADRs.

#### Dosage forms

The dosage forms were mainly tablets, pills and injections. Regarding the drug dosage forms related ADRs, it was found that tablets, capsules and pills are much less likely to cause adverse reactions than injections. There may be three reasons: first, since these formulations forms have to pass through different paths of metabolism before reaching systemic circulation their potency and proclivity to produce ADR's may reduce. Even if they appear they are likely to be less severe and self limiting in nature, especially if the drug administration is discontinued (Morrison, 2003). Secondly, injections do not require passage across different barriers of absorption

**Table 4.** Number of ADRs Incidence on different Drugs in 10 positions.

Drug name	Incidence number									
	$\delta$	$\alpha$	$\beta$	$\chi$	$\delta$	$\epsilon$	$\Phi$	$\gamma$	$\eta$	$\zeta$
Huoxuetongmai tablet	3	2	0	0	1	1	1	1	2	0
Compound salvia miltiorrhiza tablet	2	1	0	0	2	2	3	1	2	0
Suxiaojixun pill	1	0	0	0	1	1	0	1	1	0
Xuezhikang capsule	1	0	0	0	2	3	0	1	1	0
Tongxinluo capsule	1	0	1	0	1	2	0	1	2	0
Naoan capsule	2	0	1	0	4	1	1	1	0	0
Panax notoginsenosides injection	8	9	6	0	3	2	1	2	3	0
Shenmai injection	6	7	7	3	3	3	1	2	4	0
Safflower injection	7	4	4	3	2	3	1	2	3	0
Ginkgo injection	10	5	5	2	2	2	3	3	4	1
Alginic sodium diester injection	12	7	4	1	3	0	2	3	5	1
Acanthopanax injection	11	8	4	2	2	0	5	1	3	1
Chuanqiongqin injection	7	6	5	2	1	0	2	1	1	1
Puerarin injection	9	2	3	1	0	3	3	1	1	1
Shengmai injection	10	3	1	0	3	3	2	0	0	0
Mailuoning injection	8	3	1	1	2	1	1	0	1	0
Total number	98	57	42	15	32	27	26	21	33	5
Proportion*100	27.5	16.0	11.8	4.2	9.0	7.6	7.3	5.9	9.3	1.4

The numbers:  $\delta$ ,  $\alpha$  and  $\beta$  have a big proportion in the whole ADRs, and the incidence of ADRs on injection drugs also take a great ratio.

and take effect fast. Doctors and patients are likely to be willing to use them even if adverse reactions occur (Xiao-mei and Guo-ji, 2008; Deepali et al., 2002). However, there are chances that after the drug enters into the blood circulation, some solubilizers, stabilizers and additives in the injections may react with the body's systems to produce harmful substances and to cause adverse reactions (Hai-tao and Jun-feng, 2009). Thirdly, the problems of drug quality should not be ignored: (1) Starting from Chinese herbal plants, control of the production processes from collection to baking. (2) Producers and drug administration and research institutions should strengthen the research and development of traditional Chinese medicine preparations, especially the improvement of quality standards of injections, effective control of the processes of extraction and preparation, and ensuring product quality to be safe and stable (Bone and Kerry, 2008).

### Adverse reactions and clinical manifestations

The 356 cases of adverse reactions were mostly skin reaction and allergic shock. The organs and systems affected by adverse reactions and the clinical manifestations are shown in Tables 4 and 5.

Table 5 reveals that when the involved organs and systems are Skin and mucosa, damage takes a high ratio of ADRs incidence. Alopecia, euphoria and mild infection were the least common symptoms to occur. It can also be

seen from Table 5 that clinical manifestations of adverse drug reactions involve many organs and systems, mainly in allergic reaction. Allergic reaction is a kind of immune reaction, that is the reactions occurring in contact sensitivity process after drug, as a hapten, binds with protein in body to form antigen. The reactions are mainly manifested as rash, fever, hematopoietic system suppression, liver and kidney dysfunction, shock, etc (Bao-Feng, 2008). The adverse reactions in other systems were relatively fewer, probably because they were difficult to be perceived by patients.

### Preventive measures and precautions

The phenomenon of adverse drug reactions are common, but as long as we follow the guidance of doctor, read the instructions carefully according to the patient's physical condition and take the drug rationally, it will reduce the incidence of adverse events (Ying and Gui-jun, 2007). Patients with phlegm or dizziness should not use Xinnaokang capsules, and patients with heart failure or shock should be cautious in using XinKeshu capsules (Yi-yong and Wei, 2008). When traditional Chinese medicine and Western medicines are used together, frequent observation was necessary and all the drugs should be stopped immediately when adverse reactions occur. Currently, some authors have indicated that injections of traditional Chinese medicine were used with other drugs clinically. When puerarin injection was taken by patients

**Table 5.** The proportion of the organs and systems affected by adverse reactions.

Position Number	Involved system	Clinical manifestations	n	Proportion (%)
○	Skin and mucosa damage	Rash, exudative erythema, papule	98	27.5
α	Digestive system	Nausea, vomiting, diarrhea, intestinal obstruction, gastric convulsion, liver dysfunction	57	16
β	Cardiovascular system	Palpitation, angina, arrhythmia, atrial fibrillation, atrioventricular block	42	11.8
χ	Skeletal system	Joint pain, tenosynovitis, lumbar numbness	15	4.2
δ	Respiratory system	Expiratory dyspnea, laryngeal edema, airway obstruction	32	8.9
Φ	Genitourinary system	Frequent micturition, hematuria, proteinuria	27	7.6
	Nervous system	Dizziness, epilepsy, convulsion	26	7.3
γ	Blood system	Allergic purpura, hemolytic anemia	21	5.9
η	Systemic damage	Fever, general allergic reaction, allergic shock, toxic reaction	33	9.2
ζ	Others	Alopecia, euphoria, mild infection	5	1.4

with another drug, the adverse reaction incidence rate was 18%, however, when taken with two drugs, the rate was 33% (Li-xin et al., 2002). A similar phenomenon would occur when using Shenmai Injection and alginic sodium diester Injection (Zeng, 2004; Jia-rui and Bing, 2009). Therefore, they should be used alone when the incompatibility is unknown.

In conclusion, both doctors and patients should try their best to avoid the ADRs. Before injection, the physicians should identify patients with a history of allergies and family history and so on. Additionally, in the medication process, physicians should track the physical condition of the patients carefully.

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