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Pareto-optimal analysis of adverse drug reactions induced by Chinese patent medicine and clinical medication management

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[Abstract] **Objective** To provide the optimal measure for the prevention and control of adverse drug reactions (ADRs) of Chinese patent medicine (CPM), high-risk factors of ADRs induced by CPM were explored. **Methods** ADR report data of CPM from patients hospitalized in a Level III Grade A Hospital for 7 consecutive years were collected, and Pareto-optimal analysis method was used to determine the high-risk characteristic values of patients' age, drug type, and involved systems/organs. **Results** The high-risk characteristics for ADRs included age ⩾ 51 years, blood-regulating drugs, and ADRs were observed most commonly in systemic damage, damage in the cardiovascular system, and skin and its accessories. **Conclusion** These high-risk characteristics should be considered when prescribing CPM. Drugs and medical instruments required for ADR treatment should be prepared before drug use, and early symptoms of ADRs should be monitored closely during CPM administration to timely discontinue suspected drugs, provide appropriate treatment, and improve prevention and control of ADRs.

[Key words] Chinese patent medicine; ADR; Pareto-optimal analysis; Clinical medication management

1 Introduction

Chinese patent medicine (CPM) is widely used in clinical management with stable characteristics, precise efficacy, and convenient usage and storage[1]. However, adverse drug reactions (ADRs) occur from time to time, which not only affect the recovery of patients, but also aggravate the medical burden[2]. Therefore, the high-risk factors of ADRs induced by CPM should be discussed to achieve prevention, in-process control, and post-action treatment. CPMs are mostly compound preparations with complex components, providing curative effect through multitargets and multipathways, which cause diverse and complex ADRs[3]. Pareto optimality, also known as the 80/20 rule, states that 80% of the result is due to 20% of the cause[4], suggesting that the overall situation may be controlled by a few important influencing factors[5]. Pareto-optimal analysis technique is

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a means of finding important factors from complex and diverse data[6], and it has been widely used in the analysis of the high-risk characteristics of ADRs[7-9]. At present, Pareto-optimal analysis is conducted more often in prescription comments[10-11] and outpatient withdrawal[12-13] of CPM, but it is little employed in the analysis of ADRs induced by CPM. In this study, Pareto-optimal analysis was used to retrospectively analyze the ADR report data of CPM in a Guangzhou Level III Grade A Hospital for 7 consecutive years to provide useful reference for clinical prevention and treatment of ADR caused by CPM.

2 Materials and Methods

2.1 Data sources

Data were obtained from ADR reports of 1 142 inpatients in a Level III Grade A Hospital for 7 consecutive years (January 2013-December 2019), of which four duplicate reports were excluded, leaving a total of 1 138 cases. The inclusion criteria were as follows: (1) the suspected drug causing ADR was a kind of CPM beginning with the national drug approval number "Z," and the causality assessment was sure, probable, or possible; (2) the suspected drugs causing ADRs were chemical drugs, the combined drugs contained CPM, and it was not confirmed whether the ADRs were caused solely by suspected chemical drugs. The exclusion criteria were as follows: (1) duplicate reports; (2) it was impossible to determine the ADRs directly related to CPM; (3) incomplete reports in which patients' age or gender, route of administration, causality assessment, ADR type, and outcome were recorded in the ADR reports. Of these, only 129 cases were of CPM-induced ADRs. According to the above inclusion and exclusion criteria, six cases with incomplete information and seven cases that were irrelevant for evaluation or unable to be evaluated were excluded. Finally, 123 cases of ADR caused by CPM were obtained.

2.2 Methods

In this retrospective analysis, according to the contents of the ADR reporting list, patients' gender and age, route of administration, name of the suspected drug, drug type, combination drug use, involved systems/organs, ADR types, outcomes, etc., were collected and counted. Pareto-optimal analysis was used to analyze the patients' age, drug type, and involved systems/organs, whereas the cumulative component ratio within the range of 0–80% was defined as high-risk characteristics (class A), within 80%–90% as secondary characteristics (class B), and within 90%–100% as general characteristics (class C), to quickly screen out the high-risk characteristics that influence the occurrence of ADRs[14].

3 Results

3.1 ADR causality assessment

The causality assessment according to the criteria of the World Health Organization showed that 59.35% of the ADRs were classified as sure, 19.51% as probable, and 21.14% as possible in relation to the administration of the CPM.

3.2 Proportion of ADR reports of CPM

From 2013 to 2019, the ADR Monitoring Office of the hospital received a total of 1,138 reports, 129 of which were caused by CPM (including six with incomplete information reports), accounting for 11.34%. The proportion of ADR reports of CPM in each year is shown in Table 1. In 2019, the total number of ADR reports and the number of ADR reports of CPM surged, which indicated that the hospital was giving increasing importance to the monitoring and reporting of ADR and that the safety of clinical drug use needed to be further strengthened.

3.3 Distribution of gender and age of patients with ADRs

With regard to patients' gender, 70 men (56.91%)

and 53 women (43.09%) experienced ADRs induced by CPM with a ratio of 1.3 ∶ 1. The youngest patient was 13 years old, the oldest was 92 years old, and the median age was 58.6 ± 16.3 years. The incidence rate of ADR was highest in patients aged ⩾ 51 years (71.54%), followed by those aged 31~50 years that accounted for 22.76% (Table 2).

3.4 Distribution of the involved drug types

The ADRs were induced by five types of CPM.

Table 1 Annual proportion of ADR reports of CPM

Year	ADR reports of CPM	Total ADR reports	Proportion of ADR reports of CPM /%
2013	19	140	13.97
2014	10	111	9.01
2015	12	125	9.60
2016	9	70	12.86
2017	23	185	12.43
2018	15	102	14.71
2019	41	406	10.10
Total	129	1 138	11.34

Note: Data contain six ADR reports of CPM with incomplete information. ADR, adverse drug reaction; CPM, Chinese patent medicine.

ADRs were mainly related to blood-regulating drugs (64.29%). Tonic drugs made up 23.81% of the reports received. The distribution and composition ratio of the involved drug types are listed in Table 3. Fig. 1 shows the top 6 CPMs that caused ADRs.

3.5 Involved systems/organs and clinical manifestations

As shown in Table 4, systemic damage was the most common ADR accounting for 38.17% of all ADRs reported, followed by the cardiovascular system and the skin and its accessories that represented 17.49% and 16.14%, respectively.

3.6 ADR types and outcomes

Among 123 cases of ADRs, 86.18% were classified as general, 5.69% as both new and general, 7.32% as new and serious, and 0.81% as serious ADRs. As outcomes, ADRs can be cured, relieved, lead to sequelae (i.e., permanent or long-term physiological dysfunction), or result in death.

Table 2 Distribution of gender and age of patients with ADR

Age (years)	Gender		Total	Proportion / %	Cumulative composition ratio / %	Class*
	Male	Female				
⩾ 51	45	43	88	71.54	71.54	A
31 ~ 50	20	8	28	22.76	94.31	C
11 ~ 30	5	2	7	5.70	100.00	C
Total	70	53	123	100.00		

*A, high-risk characteristics; B, secondary characteristics; C, general characteristics.

Table 3 Distribution and composition ratio of involved drug types

Drug type	Total	Proportion / %	Cumulative composition ratio / %	Class*
Blood-regulating drugs	81	64.29	64.29	A
Tonic drugs	30	23.81	88.10	B
Resuscitative drugs	10	7.94	96.04	C
Antipyretic drugs	4	3.17	99.21	C
Warming interior drugs	1	0.79	100.00	C
Total	126	100.00		

*A, high-risk characteristics; B, secondary characteristics; C, general characteristics. There were three cases of the combined use of CPM, so the total number of cases was 126.

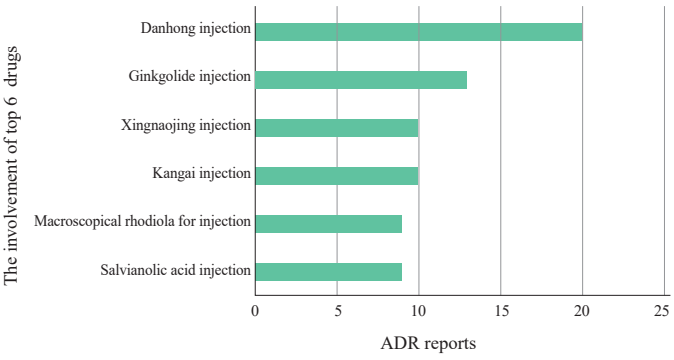

Fig.1 The involvement of top 6 CPMs in ADR reports
ADR, adverse drug reaction.

Table 4 Involved systems/organs and clinical manifestations

Involved systems / organs	Clinical manifestation	Total	Proportion / %	Cumulative composition ratio / %	Class*
Systemic damage	Shivering, rigor, chill, hypothermia, fever, trembling, hyperpyrexia weakness, sweating, discomforts	85	38.17	38.17	A
Cardiovascular system	Flushing, chest tightness, palpitations, cyanosis, abnormal heart rate, abnormal blood pressure, facial congestion	39	17.49	55.66	A
Skin and its accessories	Rash, pruritus, rubefaction, urticaria	36	16.14	71.80	A
Digestive system	Vomiting, nausea, abdominal pain, dry mouth, dysphagia	27	12.11	83.91	B
Nervous system	Dizziness, headache, confusion, numbness	20	8.97	92.88	C
Respiratory system	Expiratory dyspnea, polypnea, chest pain, shortness of breath, coughing	14	6.28	99.16	C
Urinary system	Constipation	1	0.42	99.58	C
Visual organ	Eyelid swollen	1	0.42	100.00	C
Total		223	100.00		

*A, high-risk characteristics; B, secondary characteristics; C, general characteristics. Owing to the presence of two or more clinical manifestations in some drugs at the same time, the total number of clinical manifestations was >123.

With regard to outcomes of CPM-induced ADRs, 70.73% were relieved and 29.27% were cured, and no patients developed sequelae or died. In this study, the clinical outcome data recorded by the medical staff were used as the basis for the statistical analysis of relieved and cured cases.

3.7 Occurrence of new and serious ADRs

Seven new and general ADRs were reported in four male and three female patients. Two patients were within 31 ~ 50 years old, and five patients were ⩾51 years old. The types of CPM involved were blood-regulating drugs, resuscitative drugs, and tonic drugs, including injection of macroscopic rhodiola, safflower yellow, and Kanglaite among others. With regard to the systems/organs involved, systemic damage and ADRs affecting the skin and its accessories, nervous system, and digestive system were recorded. Clinical manifestations were mainly shivering, chills, pruritus, headache, etc., and four cases were relieved and three were cured.

The nine new and serious ADRs were reported in six male and three female patients, of which three patients were within 31 ~ 50 years old and six were ⩾51 years old. The types of CPM involved were blood-regulating drugs, tonic drugs, resuscitative drugs, and antipyretic drugs including Xuebijing injection, Ginkgolide injection, Kangai injection, etc. In terms of the systems/organs involved, systemic damage, respiratory, cardiovascular, and nervous systems were affected. Clinical manifestations were mainly shivering, chest tightness, shortness of breath, cyanosis, palpitation, etc., and seven cases were improved and two were cured.

One case was serious ADR (not a new ADR), which was caused by Danhong injection. Clinical manifestations were chills and hyperpyrexia. The specific drugs, systems/organs involved, and clinical manifestations in new and serious ADRs are shown in Table 5.

4 Discussion

This study found that patients aged ⩾51 years were at a higher risk for ADRs caused by CPM, which was consistent with the results of the Pareto chart analysis of 96 cases of CPM-induced ADRs by Wang et al[15]. It was related to the decreasing function of the liver and kidney of the middle-aged and elderly patients[16]. In addition, patients with multiple diseases usually need more drugs,

Table 5 Specific drugs, systems/organs involved, and clinical manifestations in new and serious ADRs

ADR type	Involved drug (case)	Involved systems / organs	Clinical manifestations
New and general ADRs	Macroscopic rhodiola injection (2)	Systemic damage, nervous system	Weakness, chills, trembling, dizziness
	Safflower yellow injection (2)	Systemic damage	Shivering, fever
	Kanglaite injection (1)	Systemic, damage, digestive system	Chills, abdominal pain
	Aidi injection (1)	Systemic damage	Shivering, chills
	Ginkgo biloba diterpene lactone glucamine injection (1)	Skin and its accessories Nervous system	Pruritus, headache
New and serious ADRs	Xuebijing injection (2)	Respiratory, nervous, and cardiovascular systems	Expiratory dyspnea, dizziness, chest tightness, numbness
	Ginkgolide injection (2)	Nervous and cardiovascular systems	Dizziness, chest tightness, palpitations
	Kangai injection (1)	Cardiovascular and respiratory systems	Abnormal heart rate, expiratory dyspnea
	Kanglaite injection (1)	Respiratory system	Polypnea
	Compound Sophora flavescens injection (1)	Respiratory and cardiovascular systems	Polypnea, chest tightness
	Macroscopic rhodiola injection (1)	Respiratory system	Expiratory dyspnea
	Xingnaojing injection (1)	Systemic damage, cardiovascular system	Shivering, cyanosis, abnormal heart rate
Serious ADRs	Danhong injection (1)	Systemic damage	Shivering, hyperpyrexia

and the high probability of using both Chinese and western medicines leads to increased risk of ADRs[17]. Therefore, the influence of age on ADR should be considered in clinical practice, especially to strengthen the monitoring of drug use for patients aged ⩾51 years. The drug dose should be reasonably adjusted according to the patient's liver and kidney function and medication combination to facilitate personalized administration of medication and strengthen medication monitoring.

In this study, CPMs were divided into five categories, among which the number of ADR reports of blood-regulating drugs was the highest, which was consistent with the National ADR Monitoring Annual Report (2019)[18] on traditional Chinese medicine (TCM) that stated that the number of ADR reports of blood-regulating drugs was relatively high. Blood-regulating drugs can be divided into blood activating agents and hemostatic agents. In this study, the majority of ADRs were caused by CPM for the promotion of blood circulation, which may be related to its variety and widespread clinical use. However, evaluation of the clinical therapeutic effects of CPM in promoting blood circulation has still not been sufficient. Owing to the lack of detailed and complete criteria for discriminating efficacy and observation indicators, most clinical monitoring is not comprehensive and not implemented. There may be some bias and irrationality in the specific treatment which leads to the occurrence of ADR[19].

The top 6 drugs that cause ADRs were found to be Danhong, Ginkgolide, Xingnaojing, Kangai, macroscopic rhodiola, and salvianolic acid. The ADR of Danhong injection was mainly systemic damage caused by allergic reaction, which may be related to type I allergic reaction induced by the stimulation of immune system by tanshinone and pollen protein of safflower[20-21]. The ADR of Ginkgolide injection mainly occurred in the nervous system and cardiovascular system, and clinical manifestations include dizziness, flushing, among others, and two cases of serious dizziness and chest tightness were reported. The ADRs of Xingnaojing injection mainly involved the skin and its accessories, which was consistent with the drug

instructions and related reports[22-23]. The ADRs of Xingnaojing injection may be related to polysorbate 80, which, according to the literature[24], was mainly involved in anaphylaxis to injections, especially TCM injections, and manifested as skin lesions such as rash and pruritus. A study[25] reported that ADRs caused by Kangai injection were mainly skin rash, fever, and chills among others, and anaphylactic shock was rare, which was consistent with the findings of the present study. In addition, new and serious ADRs such as abnormal heart rate and dyspnea were reported. Sodium chloride solution was used as solvent in seven cases of ADRs of macroscopic rhodiola injection. Most TCM injections are TCM extracts or extracts with complex compositions, and most extracts contain macromolecular substances. Therefore, sodium chloride, potassium chloride, and other electrolytes should not be selected as the dispensing solvent. If sodium chloride is used in the dispensing solution, insoluble particles will likely be generated due to salting out, producing ADRs[26]. A study[27] showed that fructose solution was not recommended as solvent, however, fructose solution was used as solvent in two cases. The drug instructions clearly indicate the use of "5% glucose solution," so the dispensing solvent should be used in strict accordance with the instructions. The ADR of salvianolic acid injection was mainly systemic damage, manifested as chills, high fever, and chest tightness, among others, and no new or serious ADRs were found.

New and serious ADRs were the focus of drug safety risk monitoring, and their occurrence was one of the most important indicators to measure the overall reporting quality and data availability. The incidence of serious ADRs was an important indicator to measure the overall reporting quality of a medical institution[18]. An increase in the number of serious ADR reports does not mean a decline in the level of drug safety, it may also be due to more comprehensive use of information, better understanding of drug risks, more controllable risks, and more evidence-based evaluation of drugs[28]. In this study, serious ADRs were all clinical features that were intuitive and easy to observe, such as shivering, dizziness, chest tightness, whereas some late-onset and insidious ADRs, such as liver function impairment and renal function impairment that caused great harm to the human body, were rarely found. Therefore, in the clinical monitoring work, some biochemical items can be combined to eliminate the hidden but very dangerous ADRs in time to ensure the safety of patients. A new ADR refers to an ADR that is not stated in the drug product label. If the nature, degree, consequence, or frequency of ADRs is inconsistent with or more serious than that described in the manual, it shall be treated accordingly as a new ADR. The above 11 cases of new ADRs were not indicated in the instructions of the drugs involved which reminds clinicians or pharmacists to be vigilant. Manufacturers should also pay close attention to reports of ADRs of the same drugs and revise the drug instructions if necessary, so as to provide reference for clinical practice.

Furthermore, the frequency of ADRs for CPM was found in this order: systemic damage, cardiovascular system, and skin and its accessories, with clinical manifestations such as chills, rashes, flushing, itching, etc. For the above types of ADR, drug withdrawal and symptomatic treatment were usually implemented for clinical treatment. Some antihistamines (such as promethazine, chlorphenamine, and loratadine), hormone drugs (such as dexamethasone), and vasoactive drugs (such as epinephrine) were common drugs that are usually used for treating ADRs. For some of the serious ADRs such as anaphylactic shock, oxygen therapy is also required. Therefore, some drugs for ADR treatment and medical instruments should be kept in the ward, so that ADRs can be controlled, prevented, or dealt with in a timely and quick manner.

The above Pareto-optimal analysis of ADR reports indicated that the high-risk characteristics of ADRs included age ⩾51 years, blood-regulating drugs, and systems/organs involved were mainly systemic damage, cardiovascular system, skin and its accessories, and the frequency of occurrence was in this order: systemic damage, cardiovascular system, and skin and its accessories. In the future, doctors and pharmacists should pay attention to the above high-risk characteristics when prescribing CPM, review the CPM prescriptions, attach importance to the occurrence of new and serious ADRs caused by CPM, and carry out prevention and control measures specifically to reduce the occurrence of ADR or relieve the organ or systemic damage caused by ADRs.

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