A real-world study on adverse drug reactions to Xuebijing injection: hospital intensive monitoring based on 93 hospitals (31,913 cases)

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Background: Although we have made tremendous medical advances in recent decades in modern antibiotics and supportive therapies, the treatment of sepsis has not experienced such rapid advancement. Xuebijing injection (XBJ) is a Chinese prescription consisting of *Carthamus tinctorius*, *Radix paeoniae* rubra, *Ligusticum wallichii*, *Radix salviae miltiorrhizae* and *Radix angelicae sinensis*. Clinical experience suggests that XBJ may provide a solution in the management of sepsis. However, the safety of this treatment is still controversial. This study aims to detect the occurrence of XBJ-related adverse drug reactions (ADRs) among individuals in clinical practice.

Methods: From the clinical application of XBJ in a real-world setting, patients in 93 hospitals using XBJ were monitored between August 2013 and August 2016. There was no limit on the treatment course and dosage. From data obtained in interviews or telephone follow-ups with hospitalized patients, the circumstances of patients' adverse events (AEs) during the course of drug treatment and during the 7 days after drug withdrawal were recorded and encoded by MedDRA18.0. The likelihood of ADRs was determined by the criteria of the Uppsala Monitoring Centre. Statistical analyses were performed by SAS9.2 software.

Results: In total, 31,913 participants enrolled, and none were lost to follow-up. AEs (suspected ADRs) occurred in 234 participants. ADRs occurred in 96 participants, and the incidence was 0.3%. The ADRs with the top three frequencies were skin pruritus (0.116%), erythra (0.066%) and chest tightness (0.044%). There was no significant relationship between ADRs and solvents (P=0.149), route of administration (P=0.640), unhealthy addiction (P=0.069), allergy (P=0.535), first use of XBJ (P=0.161) or dosage (P=0.743). There was a significant relationship between ADRs and irrigating syringe (P<0.0001) and fluid dripping too quickly (P=0.019).

Conclusions: This large-scale survey of hospitalized patients found that the incidence of ADRs was occasional (0.3%), while most of the ADRs were relatively mild or non-serious. XBJ should be administered rationally and according to its instructions to prevent the occurrence of ADRs.

Keywords: Adverse drug reaction (ADR); hospital intensive monitoring (HIM); real-world study; Xuebijing injection (XBJ)

Submitted Apr 04, 2018. Accepted for publication Sep 05, 2018.
doi: 10.21037/atm.2018.09.26
View this article at: http://dx.doi.org/10.21037/atm.2018.09.26

Introduction

Xuebijing injection (XBJ), an herbal prescription, is widely used in the treatment of sepsis systemic inflammatory response syndrome, multiple organ dysfunction syndrome and sepsis, according to Chinese guidelines (1). It consists of extracts from five Chinese herbs: Flos carthami, Radix paeoniae Rubra, Rhizoma chuanxiong, Radix salviae miltiorrhizae and Radix angelicae sinensis (2). The bioactive roles of XBJ include activating circulation, strengthening and consolidating body resistance, removing blood stasis and clearing away toxins (3).

The use of injections of Chinese materia medica is still controversial. The associated risk is a critical issue, and the challenge is how to ensure the safety and quality of injections for consumers (4). XBJ that has been approved for treating sepsis has been sold on the market all over China since 2004. A comprehensive safety assessment that focuses on adverse events (AEs) and adverse drug reactions (ADRs) should be a necessary prerequisite. According to the components of XBJ, the possible ADRs include allergic shock, skin lesions and cardiovascular system damage. Case reports/case series and resulting ADRs can be searched in medical journals (5,6). While two electronic English databases (PubMed, EMBASE) were searched up to March 2018, none of the studies systematically reported the AEs/ADRs of XBJ.

Hospital intensive monitoring (HIM) is the non-interventional observational study of large samples. It can be used to gather more information about ADRs (7). From the detailed information of monitoring sites, the pooled data are a useful supplement to drug safety and can be used in subsequent analysis. Therefore, a real-world study was conducted to provide reliable data and to fully recognize the ADRs of XBJ.

Methods

Study setup

This study was established in departments of 93 hospitals located in 25 Chinese cities. The study was conducted from August 2013 to August 2016.

Inclusion criteria for participants

Data were collected from all patients regardless of their age, disease, course, interaction and dosage of drug taken, on the condition that they were prescribed and took XBJ.

Data collection

Data were collected from case report forms and an Electronic Data Capture (EDC) data management system, including basic situation, background disease, therapeutic schedule and prescriptions. Patients were followed up by telephone within 7 days after drug withdrawal. During the treatment by XBJ, patients or clinical practitioners were encouraged to report any discomfort or symptoms; these data were recorded by researchers as AEs. The information about AEs contained the types of AEs, severity, risk factors, occurrence time, relief time, coping methods and outcomes. This information was recorded in the AE Daily Card if an AE was detected. AEs and ADRs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) (8).

Criteria for identification of AEs and ADRs

The AEs (suspected ADRs) after XBJ treatment were defined as any type of symptom, disease or syndrome that can have an influence on a patient's state of health, including any abnormalities from laboratory testing and other examinations during the observation period. ADRs refer to unintended injuries caused by XBJ rather than to the disease process (9).

ADR assessment was performed by global introspection. Seven representatives of the doctors in charge, including six traditional Chinese medicine (TCM) specialists and one ADR specialist with a senior professional post, discussed the causes of AEs (suspected ADRs) and assessed the probability of ADRs. We defined ADRs using three levels: certain, probable/likely, and possible. The causality categories, displayed in *Table 1*, were described by the Uppsala Monitoring Centre.

Statistical analysis

The data were imported into SAS 9.2 (SAS Inc., Tianjin University of Traditional Chinese Medicine version). Descriptive analysis, including numbers and percentages, was performed for every item. Fisher's exact test was applied in comparisons among several groups. Pearson's chi-square test or Cochran-Mantel-Haenszel test was used to compare the classified data on correlation analysis.

Results

A total of 31,913 patients from 93 hospitals were enrolled

Table 1 Causality categories and description by the Uppsala Monitoring Centre

Causality categories	Description
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary
Probable/likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations
Conditional/unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination
Unassessable/unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

in this study. During the follow-up, no patients had missing values in their records. Characteristics of all patients and their medication use of XBJ are displayed in *Tables 2*,*3*.

While patients had various types of diseases, the majority of their diseases resulted from injuries of the systemic inflammatory response (25.73%). The distribution of diseases among patients using XBJ is displayed in *Table 4*.

Occurrence of ADRs

Of the 31,913 patients monitored, AEs (suspected ADRs) occurred in 234 cases, with 245 occurrences. Additionally, 138 cases were assessed as unlikely to be related to the XBJ administered and could thus be attributed to other causes. The distribution of ADRs was as follows: certain ADRs (0 cases and 0% incidence), probable/likely ADRs (5 cases and 0.02% incidence), possible ADRs (91 cases and 0.29% incidence), unlikely ADRs (39 cases and 0.12% incidence), conditional/unclassified ADRs (92 cases and 0.29% incidence), and unassessable/unclassifiable AEs (7 cases and 0.02% incidence). Causality categories and descriptions of the relationship between AEs and XBJ are displayed in *Table 5*. By definition, there were 96 cases of ADRs, including skin pruritus (37 cases), erythra (21 cases), chest tightness (14 cases), fever (10 cases), laboured breathing (10 cases) and so on. The frequency and incidence of related ADRs for patients using XBJ are shown in *Table 6*.

Causal analysis

Eleven common potential factors contributing to ADRs were analysed. There were no correlations between ADRs and sex (P=0.278), age (P=0.781), ethnicity (P=0.245), unhealthy addiction (P=0.069), allergy (P=0.535), first use of XBJ (P=0.161), dosage (P=0.743), solvent (P=0.149) or amount of solvent (P=0.592). There were correlations between ADRs and dripping speed (P=0.019)/irrigating syringe (P<0.0001). The causal analysis of ADRs is displayed in *Table* 7.

Discussion

The real-world study covered 93 hospitals in China. There were 96 cases assessed as ADRs among 31,913 participants. No serious ADRs occurred, indicating that XBJ was well tolerated. The most frequently observed ADRs were skin pruritus (37 cases), erythra (21 cases) and chest tightness (14 cases). Analyses were conducted to determine the possible factors contributing to these ADRs. The main factors were dripping speed and irrigating syringe. Therefore, the standard use should be followed and strengthened. Allergic reactions (10) and skin rashes with

Table 2 Characteristics of patients from 93 hospitals in China using XBJ

Characteristics	Value
Sex, n (%)	
Male	17,051 (53.43)
Female	14,862 (46.57)
Age (years)	
Mean ± SD	57.53±18.25
Median (range)	58.61 (0.01–113.8)
≤14 (children), n (%)	137 (0.43)
15–60 (adult), n (%)	16,713 (52.37)
≥60 (elderly), n (%)	15,063 (47.20)
Ethnicity, n (%)	
Han	31,598 (99.01)
Minorities	315 (0.99)
Smoking, n (%)	
No	29,132 (91.29)
Yes	2,781 (8.71)
Drinking, n (%)	
Yes	829 (2.60)
No	31,084 (97.40)
Allergy, n (%)	
Yes	1,245 (3.90)
No	30,668 (96.10)
Family members' allergies, n (%)	
Yes	13 (0.04)
No	29,858 (93.56)
Unclear	2,042 (6.40)

Table 3 Characteristics of patients' XBJ medication use

Variables	Number (%)
Use for the first time	
Yes	28,627 (89.70)
No	914 (2.86)
Unclear	2372 (7.43)
Dosage (one time)	
<50 mL	5,603 (17.56)
50–100 mL	26,219 (82.16)
>100 mL	91 (0.29)
Medication time (days)	
Mean ± SD	6.5±4.55
Median	5.0
Range	1.0–40.0
Frequency	
1 time/day	20,947 (65.64)
2–3 times/day	10,948 (34.31)
4 times/day	18 (0.06)
Solvent	
0.9% normal saline	30,187 (94.59)
Others	1,726 (5.41)
Amount of solvents	
NA	485 (1.52)
<100 mL	387 (1.21)
100 mL	24,835 (77.82)
>100 mL	5,787 (18.13)
Administration	
Intravenous dripping	31,494 (98.69)
Others	419 (1.31)
Dripping speed	
<30 drops/min	1,724 (5.40)
30–60 drops/min	21,856 (68.49)
60–80 drops/min	7,604 (23.83)
80–100 drops/min	455 (1.43)
>100 drops/min	87 (0.27)
Unclear	187 (0.59)

itching (11) were also observed in previous studies. Thus, pyrogenic reactions may be a factor leading to skin lesions. Fingerprint technology should be widely used, strictly for quality control purposes.

The Surviving Sepsis Campaign in 2016 proposed professional recommendations for the management of sepsis: early resuscitation; control of the source of infection; intravenous supply of fluids; and administration of antibiotics, vasoactive agents, positive inotropic drugs

Table 4 Disease distribution of patients using XBJ

Type of disease	Number (%)
Systemic inflammatory response syndrome (SIRS)	19,842 (62.18)
Sepsis	1,645 (5.15)
Multiple organ dysfunction syndrome (MODS)	1,164 (3.65)
Others	9,262 (29.02)

Table 5 Causality categories and description of the relationship between AEs (suspected ADRs) and XBJ

Causality categories	Cases	Incidence[1]	Percentage (%)
Certain	0	0	0
Probable/likely	5	7	0.02
Possible	91	96	0.29
Unlikely	39	40	0.12
Conditional/unclassified	92	95	0.29
Unassessable/unclassifiable	7	7	0.02
Total	234	245	0.73

[1]The percentage was calculated by dividing the total number of cases by the number of AE cases for each level.

Table 6 Frequency and incidence of the related ADRs for patients using XBJ

Feature	Number of times	Incidence[2] (%)
Skin pruritus	37	0.116
Erythra	21	0.066
Chest tightness	14	0.044
Fever	10	0.031
Laboured breathing	10	0.031
Erubescence	7	0.022
Nausea	5	0.016
Shiver	4	0.012
Pain in the infusion site	3	0.009
Headache	3	0.009
Diarrhoea	3	0.009
Dizziness	3	0.009
Palpitation	2	0.006
Anhelation	2	0.006
Occult blood	1	0.003
Abnormal liver function	1	0.003
Joint pain	1	0.003
Convulsion	1	0.003
Emesis	1	0.003
Gastrectasia	1	0.003

[2]The percentage was calculated by dividing the total number of participants by the total number of cases of ADRs.

and glucocorticoids (12). Although we have made dramatic medical advances, the treatment of sepsis has not advanced as rapidly (13). Increasing levels of antimicrobial resistance is rightly viewed as a global crisis (14). Furthermore, antibiotics themselves also cause harm, for example, organ injury, mitochondrial dysfunction, microbiome impacts, and overgrowth by fungi and clostridium difficile (15,16). Safe and effective drugs are needed to improve the curative effect of current treatment.

A meta-analysis showed that XBJ combined with ulinastatin for sepsis treatment was superior to the sole administration of ulinastatin (17). XBJ has been proven to have the function of anti-endotoxins and resisting inflammation progress (18,19). The component senkyunolide I has been well-detected in the rat brain, suggesting that its effective penetration of the brain may explain the brain dysfunction seen in patients with sepsis (20).

There are many TCM injections made up of Flos Carthami, Radix Salviae Miltiorrhizae and Radix Angelicae Sinensis, such as Danhong injection and compound angelica injection. Eight published systematic reviews that included a total of 16,469 participants suggested that Danhong injection appears to be a safe treatment for ischaemic stroke (21). Therefore, TCM injections may be safe as a new form of drug. However, more rigorously designed studies are needed to verify their safety.

There are some limitations to this study. First, although the study covered 93 hospitals, the hospitalized population in the different provinces throughout the country might not be evenly distributed, given that the majority of the participants were Han Chinese in central and eastern China. A second limitation of this study is the lack of a control group, which lead to difficulty in inferring causality. A third limitation is that the follow-up time intervals were not sufficient to evaluate long-term effects.

Conclusions

Based on the data of this real-world study, we inferred that

Table 7 Causal analysis of ADRs for patients using XBJ

Elements	ADR		Correlation with ADRs
	No	Yes[3]	
Sex			c^2=1.18; P=0.278
Male	17,005	46 (0.27)	
Female	14,812	50 (0.34)	
Age (years)			c^2=0.49; P=0.781
≤14	137	0 (0)	
15–59 (adult)	16,656	57 (0.34)	
≥60 (elderly)	15,024	39 (0.26)	
Ethnicity			Fisher's exact test P=0.245
Han	31,598	94 (0.30)	
Minorities	315	2 (0.63)	
Unhealthy addiction			CMH test P=0.069
No	24,328	84 (0.35)	
Smoking	2,781	7 (0.25)	
Drinking	829	0 (0.0)	
Drinking + smoking	3,975	5 (0.13)	
Allergy			c^2 test P=0.535
No	28,575	87 (0.30)	
History of allergies	1,245	6 (0.48)	
History of hyper-sensitivity disease	38	0 (0.0)	
Family members' allergies	13	0 (0.0)	
Unclear	2,042	3 (0.15)	
First use of XBJ			c^2 test P=0.161
Yes	28,627	81 (0.28)	
No	914	3 (0.33)	
Unclear	2,372	12 (0.51)	
Dosage (one time)			c^2=0.59; P=0.743
<50 mL	5,603	19 (0.34)	
50–100 mL	26,219	77 (0.29)	
>100 mL	91	0 (0.0)	
Solvent			c^2 test; P=0.149
0.9% NS	30,187	94 (0.31)	
Others	1726	2 (0.12)	
Amount of solvents administration			c^2=1.91; P=0.592
NA	485	2 (0.41)	
<100 mL	387	0 (0.0)	
100 mL	24,835	79 (0.32)	
>100 mL	5,787	15 (0.26)	
Dripping speed			Chi-square test P=0.019
<30 drops/min	1,724	5 (0.29)	
30–60 drops/min	21,856	75 (0.34)	
60–80 drops/min	7,604	12 (0.16)	
80–100 drops/min	455	4 (0.88)	
>100 drops/min	87	0 (0.0)	
Irrigating syringe			c^2=13.44; P<0.0001
Yes	17,833	42 (0.24)	
No	8,416	43 (0.51)	
Unclear	3,561	11 (0.31)	
No account	2,103	0 (0.0)	

[3]The percentage was calculated by dividing the number of no-ADRs participants by the number of cases of ADRs. ADRs, adverse drug reactions; XBJ, Xuebijing injection; CMH, Cochran-Mantel-Haenszel.

XBJ could possibly induce ADRs, although most of these ADRs were relatively mild or non-serious. The incidence of ADRs attributed to XBJ was 0.30% (occasional). Among the ADRs, skin lesions were common. This large-scale survey of hospitalized patients found that XBJ showed relatively high drug safety and should be administered rationally and according to its instructions to prevent the occurrence of ADRs.

Acknowledgements

Funding: This work was supported by the second batch of "Ten thousand plan"-National high level talents special support plan (W02020052).

Footnote

Conflicts of Interest: S Liu and ZQ Feng are employees of Chase Sun Pharmaceuticals. All other authors declare that they have no potential conflicts of interest.

Ethical Statement: This study was granted ethical approval by the Ethics Committee, Tianjin University of Traditional Chinese Medicine (No. TJUTCM-EC20130001). All subjects signed the informed consent forms. For subjects under 18 years of age or for those with limited capacity for civil conduct, their caregivers signed the informed consent forms. The study outcomes will not affect the future management of the patients.

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Cite this article as: Zheng R, Wang H, Liu Z, Wang X, Li J, Lei X, Fan Y, Liu S, Feng Z, Shang H. A real-world study on adverse drug reactions to Xuebijing injection: hospital intensive monitoring based on 93 hospitals (31,913 cases). Ann Transl Med 2018. doi: 10.21037/atm.2018.09.26

