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Analysis of Ornidazole Injection in Clinical Use at Post-marketing Stage by Centralized Hospital Monitoring System*

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Summary: This study aims to analyze the clinical use of ornidazole injection at the post-marketing stage by centralized hospital monitoring system method, and investigate its widespread use in patients, in order to regulate and guide the rational drug use, improve the drug specificity and provide a basis for drug therapy. The study adopts a prospective, multi-center, large sample size, centralized hospital monitoring system. We selected five leading hospitals in Hubei province, and observed the inpatients who received the ornidazole injection from July 1, 2015 to October 31, 2015. The basic information of patients was recorded, as well as the drug use and adverse events. The statistical analysis was performed based on these data. A total of 4396 individuals were enrolled in this study, most of them were middle-aged female patients and the ornidazole injection was mainly used as prophylactic prior to surgery to prevent the infections, and surgical treatment of anaerobic infections, abdominal infections and pelvic infections. The irrational drug use existed mainly in the prescribing and administration process, including unreasonable dosing frequency, rapid intravenous drip speed and extended duration of drug use. Eleven cases of adverse reactions were collected during the monitoring, incidence rate of adverse reactions was 2.5‰; adverse drug reactions occurred within 30 min. The study results fully reflected the usage of ornidazole injection in the real world. Based on the study, we calculated the adverse reaction incidence of ornidazole and identified the risk factors which may affect the safety of ornidazole injection. Study results strongly recommend that the manufacturers should publish standards for inpatient use and doctors should prescribe with caution accordingly.
Key words: ornidazole injection; centralized hospital monitoring system; post-marketing reassessment; clinical use; adverse reaction

Centralized hospital monitoring is one of active method measuring the safety of clinical medicine, based on the epidemiology in the real world and analyses of the data collected from signed hospitals[1, 2]. Through monitoring multiple hospitals in certain area at the same time, representative and unbiased data can be obtained during certain time period. These data showed the clinical use in the real world, including adverse reactions. Compared with passive self-reported system, centralized hospital monitoring could generalize the percentage of adverse reactions and risk factors of clinical use.

Ornidazole is the third generation of nitroimidazole derivatives after metronidazole and tinidazole; it exerts antiprotozoal and bactericidal effect[3, 4]. It is widely used for abdominal, pelvic, mouth cavity infections, prevention of infections at pre-surgery phase and treatment of infection at post-surgery phase[5–7]. Ornidazole injection is produced in China and has two dosage forms, including injections and powder-injections in either glucose or sodium chloride solvents. The study involves 6 pharmaceutical manufacturers; there is no published report or journal about clinical use of ornidazole injection in a great number of samples. Ornidazole was selected, using centralized monitoring in the real world, to analyze the population, drug use and adverse reaction, in order to improve patient instructions for pharmaceutical factories and the directions for inpatient usage.

1 SUBJECTS AND METHODS

1.1 Study Drug

The ornidazole injection was investigated.

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1.2 Patients

We surveyed a total of 4396 patients, who were injected with ornidazole from July 1st to October 31st 2015 in Wuhan Union Hospital (China), People's Hospital of Yichang Center (China), Enshi Central Hospital (China), Yingchen People's Hospital (China) and Wuxue People's Hospital (China). This study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (IORG No: IORG0003571).

1.3 Survey Methods

The research program was designed by the Hubei Adverse Drug Reaction (ADR) Monitoring Center, including the general coordinators and investigators (pharmacist or nurse) training, distributing and collecting observation sheet. The centralized hospital monitoring system method was adopted. Inpatients receiving ornidazole injection treatment as indicated were considered as test subjects. Investigators collected the basic information, medication and adverse reaction/adverse event occurrence of patients and then filled out the "Evaluation screening card of ornidazole injection". The observation ended in the absence of adverse reactions. Otherwise, a special reevaluation monitoring form was required to be filled.

1.4 Evaluation Index

To determine the safety, adverse reactions of ornidazole injection in the real-world clinical application, several evaluation indices were selected: 1) general physical background of the patients including gender, age, body weight, department, chief complaint, allergies, and other data; 2) medication: purpose, single-use dosage, frequency, type and dosage of solvent, formation of drug, compliment drugs; 3) ADR: duration, symptom and treatment of adverse reactions. Details of abnormal behavior and ADR were described and recorded.

1.5 Evaluation Criteria

Data was collected by multiple hospitals. ICH-10 was used as a guideline to catalog diagnosis; Chinese Internal Medicine was used as a guideline to catalog traditional Chinese diagnosis. All the data were put in by two investigators independently through EpiData 2.0 program. Data with missing information, error record, or lacking original source were not put into the system. All input data underwent the process of checking, monitoring and regular audit to assure the quantity and quality of the data.

1.6 Statistical Analysis

SPSS19.0 statistical software was used to analyze the data. The quantitative indicators (for instance, age, body weight, duration of treatment) were described by the mean value, standard deviation or median and minimum, maximum. Single variable hypothesis testing was using the χ^2 test, and P values less than 0.05 were considered statistically significant difference.

2 RESULTS

2.1 Analysis of Baseline Data

Five sentinel hospitals participated in monitoring patients who received ornidazole treatment during observational period. We received 4452 cases; 4396 of them were valid. The percentage of validity was 98.78%. Table 1 shows the distribution of adverse reaction in each hospital.

2.2 General Analyses of Clinical Demographics

There were 4369 valid samples (table 2). Gender ratio of male to female was 1:3.24. Most patients (91.24%) were from 18 to 50 years old. Totally, 247 patients had an allergy background, and allergy resource was mostly antibodies. Major antibody was penicillin G (70.44%), and minor antibody was cephalosporin (12.55%), ethanol (2.43%), traditional Chinese medicine (1.62%) and anesthetic (1.21%).

Total number of departments that used ornidazole injections was 34, the top 10 departments which most frequently used ornidazole injections were listed in table 3. The majority of patients were from general surgical department; other patients were from general internal department. Ornidazole injections were widely used in a variety of departments. Age was distributed differently in each department. In the department of obstetrics and gynecology, patients were mainly 30 to 50 years old; in the general surgery department and gastrointestinal surgery department patients were mainly 50 to 70 years old.

Major population that used orinidazole injections was distributed in the following conditions: obstetrics and gynecology (24.86%); pregnancy, delivery and puerperal stage (23.48%); oncology (19.59%) and gastrointestinal surgery (18.13%). Top 5 original suffering diseases were parturition (13.76%), hysteromyoma (8.80%), abortion (6.14%), cervical

Table 1 Distribution of monitoring sentinel hospitals and adverse reaction of ornidazole injection

Sentinel hospital	Number (n)	Proportion (%)	Incidence of ADRs (%)
Wuhan Union Hospital	1450	32.98	0.21 (3/1450)
People's Hospital of Yichang Center	263	5.98	0 (0/263)
Enshi Central Hospital	995	22.63	0.10 (1/995)
Yingchen People's Hospital	885	20.13	0.79 (7/885)
Wuxue People's Hospital	803	18.27	0 (0/803)
Total	4396	100.00	0.25 (11/4396)

Table 2 Baseline clinical demographics

Parameter	Category	Number of patients	Proportion (%)	Incidence of ADRs (%)	*P* value
All patients		4396	100.00	0.25 (11/4387)	
Gender	Male	1036	43.40	0.58 (6/1036)	0.026*
	Female	3360	56.60	0.19 (5/3360)	
Age	Mean±SD (years)	43.04±15.78			
	Minimum (years)	2			
	Median (years)	46			
	Maximum (years)	95			
Allergies	No	3436	78.16	0 (0/3436)	0.000*
	Yes	247	5.62	2.43 (6/247)	
	Unknown	713	16.22	5 (5/713)	

Table 3 Distribution of age and department for patients receiving ornidazole injection

Department	Age (year)								
	≤1	>1 and ≤3	>3 and ≤18	>18 and ≤30	>30 and ≤50	>50 and ≤70	>70	Unknown	Total
Department of Obstetrics and Gynecology	0	0	12	819	1268	360	35	8	2502
General Surgery Department	0	0	23	43	119	178	71	6	440
Department of Gastrointestinal Surgery	0	0	16	43	127	213	66	0	465
Department of Orthopaedics	0	0	2	23	65	90	10	1	191
Department of Stomatology	0	0	15	32	52	55	10	0	164
Department of Hepatobiliary Surgery	0	1	2	10	39	73	22	0	146
Cancer Center	0	0	0	6	38	52	9	0	105
Division of Gastroenterology	0	0	2	12	40	27	11	1	93
Department of Internal Medicine	0	0	0	3	8	17	20	0	48
Department of Otolaryngology	0	0	3	17	6	14	3	0	43

cancer (5.48%) and appendicitis (5.41%).

2.3 Analysis of Patient's Illness and Medications

2.3.1 Indications Mainly, ornidazole injection was used at prophylaxis phase and treated anaerobic bacteria at post-surgery phase. Otherwise, ornidazole injection was irrationally prescribed. Figure 1 shows that irrational prescription happened frequently in general internal department (31.25%), department of oncology (27.62%), department of gastroenterology (26.88%), department of stomatology (12.08%) and department of orthopaedics (12.04%). Ornidazole was prescribed in general surgery department more rational than in general internal department.

2.3.2 Analysis of Drug Specification According to the actual situation and the clinical characteristics of drug selection, each hospital adopted different formations of ornidazole injection, but mainly concentrated in ornidazole sodium chloride injection 100 mL: 0.5 g and ornidazole injection (0.25 g) two dosages. During the survey research, there were 6

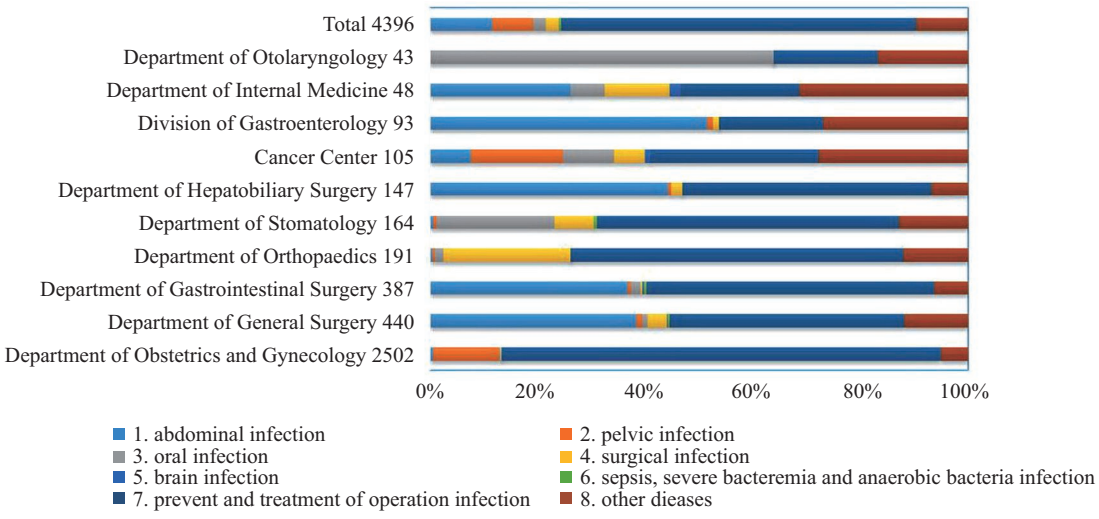

Fig. 1 Distributions of profile indications in different departments using ornidazole injection

Table 4 Statistical usage of Ornidazole injection

Parameter	Category	Poportion (%)	Incidence of ADRs (%)	*P* value
Dosage form	Injection	33.17	0.21 (3/1458)	0.678
	Powder-injection	66.83	0.27 (8/2938)	
Solvent dispensing	0.9 % sodium chloride injection	57.11	0.12 (2/1678)	0.185
	5 % glucose injection	41.32	0.49 (6/1214)	
	5 % glucose sodium chloride injection	0.61	0 (0/18)	
	Others	0.95	0 (0/28)	
Administration route	Intravenously guttae	99.8	0.25 (11/4387)	1.000
	Intravenous injection	0.02	0 (0/1)	
	Intramuscularly injection	0.09	0 (0/4)	
	Enema	0.045	0 (0/2)	
	Unknown	0.045	0 (0/2)	
Daily dose	<0.5 g	0.73	0 (0/32)	0.991
	0.5 g–1 g	99.1	0.25 (11/4396)	
	>1 g	0.10	0 (0/6)	
	Unknown	0.07	0 (0/3)	
Number of times dosed daily	1 time	15.74	0.14 (1/692)	0.938
	2 times	84.24	0.27 (10/3703)	
	3 times	0.024	0 (0/1)	
	Unknown	0.342	0 (0/15)	
Dripping speed	≤50 gtt/min	69.84	0.36 (11/3070)	0.095
	> 50 gtt/min	29.66	0 (0/1303)	
	Unknown	0.5	0 (0/23)	
Duration of treatment	≤10 days	94.22	0.27 (11/4142)	0.713
	>10 days	5.53	0 (0/243)	
	Unknown	0.25	0 (0/11)	
Concomitant drugs	Yes	100.00	0.25 (11/4396)	–
	No	0.00	0 (0/0)	

*P<0.05

dosages of ornidazole injection used in the investigated sites. The distribution and frequency of use were: 1=ornidazole sodium chloride injection 100 mL: 0.125 g in 1 case (0.023%); 2=ornidazole sodium chloride injection 100 mL: 0.5 g in 1450 cases (32.98%); 3=ornidazole sodium chloride injection 250 mL: 0.5g in 1 case (0.023%); 4=ornidazole injection (0.25 g) in 2938 cases (66.83%); 5=ornidazole injection 5 mL: 0.25 g in 2 cases (0.046%); 6=ornidazole injection 5 mL: 0.5 g in 6 cases (0.137%).

2.3.3 Analysis of Dosage and Formation Table 4 shows the dosage and formation analysis of ornidazole injection. Solvent of ornidazole was either 0.9% sodium chloride injection or glucose solution, other solvents were considered to be chosen incorrectly. Intravenous infusion was recommended, other formations, such as intramuscular injection, intravenous injection and clyster, were used incorrectly. Some journals reported ornidazole was administered by enema[8], which lacks theoretical support. Local application should be avoided to prevent the resistance development of the drug. Single-use dosages were 0.5 g (71.32%) and 1.0 g (27.78%). It was defined as overdosing when single use dosage was greater than 1 g. The frequency was mainly classified into qd (15.74%) and bid (84.24%). Only one patient received three times per day, which was counted as irrational daily frequency.

Irritation of ornidazole was prominent, the speed of intravenous infusion should not be greater than 50 gtt/min. In total, 3070 patients received the intravenous infusion with a speed of not greater than 50 gtt/min (69.84%); 1303 patients received the intravenous infusion with a speed greater than 50 gtt/min (29.66%). High speed of intravenous infusion caused discomfort to patients.

Based on the drug specificity, "Antimicrobial clinical medications guidelines" and the actual condition of clinical treatment, the duration of treatment should be less than 11 days, otherwise belongs to the unnecessary elongated duration. Recorded data from this study shows the duration of whole treatment varied from 1 day to 50 days. There were 4142 treatments with normal treatment duration (94.22%), 243 treatments with elongated duration (5.53%). Unnecessary elongated duration would cause greater chance of developing resistance and triggering adverse events.

2.4 Safety Evaluation of Ornidazole Injection Treatment

2.4.1 ADR Occurrence During center monitoring, 11 out of 4396 patients experienced adverse reactions (0.25%). Adverse reactions of these patients were painful feeling in injection area (table 5); intensity of painful feeling is "slightly". Averse reaction mostly

happened at first 5 to 30 min after injection.

2.4.2 Analysis of Laboratory Indexes Table 6 shows the laboratory indexes analysis of ornidazole injection. Six out of 11 patients with adverse reaction had completed complete blood count before ornidazole injection. Seven out of 11 patients had completed international normalized ratio test, 5 out of 11 patients had completed hepatorenal function test; 3 out of 11 patients had completed urine test. Blood routine tests showed the mean counts of white blood cells (WBC) and neutrophils (NEU) were beyond the normal range.

Table 5 Clinical manifestations and organs/systems distributions of ADRs

Organs/systems involved	ADR manifestations	Number of patients	Proportion (%)
Administration site	Injection spot ache	7	63.64
Skin and appendages	Itching/with diffuse erythema papula	2	18.18
Digestive system	Nausea	1	9.09
Nervous system	Dizziness	1	9.09

Table 6 Laboratory examination indexes

Blood routine (mean value)	RBC (10^{12})	WBC (10^9)	Hb (g/ L)	PLT (10^9)	Neutrophils (%)	Lymphocytic absolute value
	4.74	11.23	139.33	262.17	73.97	1.26
Coagulation function (mean value)	Prothrombin time (PT, s)	Partial thromboplastin time (APTT, s)	Thrombin time (TT, s)	FBG (g/L)		
	11.19	31.00	15.18	3.36		

Hepatorenal function (mean value)	ALT (U/L)	AST (U/L)	ALB (g/L)	GLB (g/L)	GGT (U/L)	ALP (U/L)	TB (μmol/L)	DB (μmol/L)	BUN (μmol/L)	CR (μmol/L)
	64.2	121.2	45.38	23.22	119	73.4	15.52	4.56	–	71.88

RBC: red blood cell; WBC: white blood cell; Hb: hemoglobin; PLT: platelet

2.4.3 ADR Processing and Outcome After adverse reaction happened, one patient no longer received the injection, and feeling of discomfort disappeared. 10 patients were able to stand the feeling of discomfort. Seven patients (63.64%) was completely healed afterwards, 4 patients (36.36%) was getting better.

After adverse reaction arose, one patient (9.09%) no longer received injection; patients received symptomatic and supportive treatment. Then, adverse reactions disappeared. Ten patients still received the injection after adverse reaction, and they were able to tolerate the feeling of discomfort. Patients recovered from the painful feeling in one or two day(s) after adverse reaction had happened. Ten patients recovered in 10 to 40 min (90.91%) and one patient recovered in two days (9.09%).

2.4.4 Analysis of ADR Influent Factors Tables 2 and 4 analyzed the difference in population characteristics (gender, allergy background etc.), formation and dosage (solvent, frequency, speed of intravenous injection, duration etc.). Adverse reactions had a significant difference in gender and allergic background (P<0.05). Different formation and dosage had lttle impact on adverse reaction (P>0.05).

3 DISCUSSION

According to China Food and Drug Administration (CFDA) Adverse Drug Reaction Monitoring Center, ornidazole infection was ranked into top 20 chemical injection medications with adverse reaction. To fully understand the safety of ornidazole, CFDA initiates the ADR monitoring and safety evaluation in Hubei providence. The active observation by centralized hospital monitoring system in designated time and area was more comprehensive, objective and accurate than traditional passive self-reported system. The recorded data from active monitoring was qualified for statistical analysis of ADR probability and identification of related risk factors.

3.1 Population Distribution

Major population out of 4396 patients was female over 40 years old. Ornidazole injection was used for prevention of infection at pre-surgery phase, treatment of anaerobic bacteria infection at post-surgery phase, abdominal infection and pelvic infection. Ornidazole is prescribed incorrectly, such as wrong frequency, high speed of intravenous fusion and unnecessary elongated duration. Total number of patients with adverse reaction was 11 (2.5‰). Drug use for children points out: “Children use with caution, children under 3 years old cannot be dosed”. One two-year-old patient received ornidazole injection. During central monitoring, none adverse reaction was observed in all children under 14 years old. Adverse reaction happens occasionally in investigated sites.

3.2 Evaluation Conclusion on Rational Use of Ornidazole Injection

There were 692 (15.74%) cases with ornidazole injection prescribed incorrectly, most patients had

overdose. All medical stuff should closely monitor the prescription of ornidazole. By following the pharmacokinetics and pharmacodynamics characters, ornidazole would reach the peak efficiency. Ornidazole injection is blood concentration-dependent, reaching the peak concentration in 2 h; elimination half-life is 12 h[9]. High concentration would cause adverse reaction. Adverse reaction increases with further increase of concentration. Low concentration would not maintain the efficacy of the drug. Speed of intravenous infusion should not exceed 0.5 g per 12 h.

Statistical analysis shows adverse reaction frequently happens in the area of injection. Seven out of 11 show the pain on the surface of skin near injection. PH value of ornidazole injection is lower than 7, injection would change pH value in blood and injure vascular endothelial cells. Platelet aggregation and chain reaction of phlebitis happen after the injection and cause the pain near injection area. Direction shows speed of intravenous injection should not be greater than 50 gtt/min. In clinical use, 3070 patients (69.84%) received intravenous injection which is not greater than 50 gtt/min; 1303 patients (29.66%) received intravenous injection which is greater than 50 gtt/min, this is defined as overspeed. Overspeed of intravenous injection might cause discomfort to the patients. Concentration of intravenous injection is 5 mg/mL. Different companies have slight differences on directions; it should be injected for more than 30 min per 100 mL. Intravenous injection formation (100 mL: 0.5 g) should be injected for 60 min. We suggest that the same standard for factory producing and prescription should be carried out to reduce the risk of adverse reaction.

3.3 Drug-drug Interaction

Based on the statistics, there were 4396 cases of combination therapy, mainly combined with electrolytes, acid-base balance and nutritional medicine, anti-microbial drugs, gastrointestinal drugs. Eleven patients were treated with multiple drugs. There were 8 cases of combined use with cephalosporins, respectively for cefotaxime sodium in 4 cases, cefoperazone sodium in 2 cases, cefazolin oxime in 1 case, cefathiamidine in 1 case. Three cases received continuous infusion of two drugs in this situation. Ornidazole package inserts and several references have pointed out the drug incompatibility of ornidazole and cephalosporins. Injection tube should be rinsed with 0.9% sodium chloride solution between different drugs during intravenous infusion.

3.4 Adverse Reaction

Ornidazole was released in the market in 1970's; there are two formations, powder-injection and injection, in Chinese market. There is only injection formation available in oversea market. The percentage of adverse reaction in injection formation is 2.06‰ (3/1458); the percentage of adverse reaction in powder-injection formation is 2.74‰ (8/2938). Adverse reaction has no significant difference between the two formations (P>0.05). Adverse reactions mostly happen 30 min after injections. Close observation is required at first 30 min of injection just in case patients feel discomfort. Allergy background has a significant difference on the probability of adverse reactions. Ornidazole should be prescribed after checking allergy background.

4 CONCLUSIONS

The majority of patients were female over 40 years old. Ornidazole was used for prophylaxis of infection at a pre-surgery phase, treatment of infection of anaerobic bacteria at post-surgery, and treatment of abdominal infection and pelvic infection. From the collected data, clinical use of ornidazole injection is relatively safe; percentage of adverse reaction is low. Gender and allergy history make great impacts on causing adverse reactions. Ornidazole is not allowed to inject with cephalosporin. Close observation is required at first 30 min of intravenous injection.

Post market re-evaluation of ornidazole injection monitors the medication use in the real-world. According to the study, CFDA published the clinical medication patient insert, suggesting pharmaceutics companies should initiate the study for drop speed, combination and drug-drug interactions related studies to improve the drug instruction. The supplement information would be used to guide the clinical pharmacists to adjust irrational use in the departments with a high abuse potential to improve the overall safety and efficacy.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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