Differential analysis of clinical efficacy on patients with serious infection in ICU by different meropenem regimens

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Abstract: To investigate the difference in clinical efficacy and safety of different meropenem regimens on patients with serious infection in ICU. Then, 228 patients with serious infection in ICU were divided by random into control group (intermittent administration in 1000mg/30min single dose) and research group (continuous administration in 200mg/10min +800mg/180min), respectively. The blood concentration of meropenem were recorded in two groups at different time points, and difference in treatment effectiveness, iconographic effectiveness, bacterial eradication rate, 28-day survival rate and many other clinical scoring indices (SOFA, APACHEII, CPIS, and SIRS) were compared between two groups. There were 212 patients completing the whole research, including 104 patients in research group and 108 patients in control group. The difference in treatment effectiveness (77.8% vs 53.7%), iconographic effectiveness (51.0% vs 18.5%), and 28-day survival rate (86.5% vs 64.8%) between two groups performed statistical significance ($P<0.05$). However, the difference in bacterial eradication rate (48.0% vs 46.3%) performed no statistical significance. Eight hours later, the difference in average blood concentration between two groups (9.61±3.63μg/ml vs 1.5±0.51μg/ml) showed statistical significance. Moreover, the difference in clinical scoring indices except APACHE II score between two groups performed statistical significance. It was helpful to maintain the blood concentration of meropenem by extending the transfusion time. Therefore, it could increase the clinical cure rate and 28-day survival of patients with serious infection in ICU, improve clinical indices, and reduce the usage amount of antibiotics.

Keywords: Meropenem, serious infection, ICU.

INTRODUCTION

At present, with combination of various underlying diseases and immunosuppression, patients sent to intensive care unit (ICU) have to endure various invasive operations (i.e. trachea cannula, artery or venous cannula, indwelling catheter, etc.). Besides, longer hospitalization, application of a large amount of broad-spectrum antibiotics, and sustaining mechanical ventilation are also important reasons for patients in ICU having 5-10 times of higher infection rate than those in public wards (Lilly, *et al.*, 2011). According to studies, hospital infection is mainly caused by gram-negative bacillus concentrating in lower respiratory tract (Castro, *et al.*, 2013). However, except antibiotics with strong sterilizing effects, there is no other effective measure to solve the increasingly severe problem of drug-resistance bacteria currently. As the preferred antibacterial agent in ICU, meropenem will also have drug-resistance problem with arbitrary injection. In addition, meropenem, a time-dependent drug, can effectively kill bacteria by maintaining blood concentration higher than the minimal inhibitory concentration (MIC) (Troger, *et al.*, 2012). This work discussed the metabolism of drug *in vivo* by changing meropenem regimens and compared the clinical effects on patients.

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MATERIALS AND METHODS

Study subjects

228 patients satisfying with inclusion criteria treated in intensive care unit (ICU) of our hospital from August 2013 to August 2015 were selected for prospective randomized controlled clinical trial. Then, these patients were divided into control group (intermittent administration in 1000mg/30min single dose) or research group (continuous administration in 200mg/10min + 800mg/180min), respectively, by random number table with 114 patients for each group. According to statistics, the difference in aspects of age, sex, clinical scores, temperature, white blood cell count, etc. had no statistical significance ($P>0.05$) as shown in table 1. This work was approved by Ethics Committee of our hospital and informed to patients and their families who signed consent form.

Inclusion criteria

Patients should have serious lung infection meeting standards issued by Infectious Diseases Society of America/American Thoracic Society in 2007 (Mandell, *et al.*, 2007). In other words, patients should meet one primary criterion or three secondary criteria. Primary criteria were 1) using invasive mechanical ventilation; 2) using angiotonics. Secondary criteria were 1)respiratory

rate ≥ 30 times/min; 2) oxygenation index ≤ 250; 3) several infiltrated lung lobe; 4) clouding of consciousness/disorientation; 5) white blood cell count ≤ 4×10^9/L; 6) BUN ≥ 20mg/dl or 7mmol/L; 7) blood platelet < 10.0×10^9/L; 8) temperature > 36°C; 9) liquid required to maintain blood pressure.

Exclusion criteria

1) patients who were allergic to drug; 2) having several parts with infection; 3) taking immunosuppressor or hormone drug in 6 months; 4) women in gestation and lactation period; 5) hepatorenal insufficiency.

Rejection or falling-off criteria

1) drug allergy test showed that meropenem was non-effective drug; 2) aetiological results showed that drug-resistance bacterial MIC ≥ 16μg/ml; 3) patients had bad reaction for drug intolerance in midway.

Therapeutic methods

The regimen for control group was intravenous drip of 50ml solution with 1000mg meropenem (SUMITOMO Pharma (Suzhou) Co., Ltd., code number approved by SFDA: J20100045) dissolving in 0.9% normal saline in 30min, q8h. The regimen for research group was intravenous drip of 10ml solution with meropenem in 50ml 0.9% normal saline in 10min and remaining 40ml in 3h. The drug was stopped if patients in two groups had no improvement or aggravation of clinical symptom after 72 hours. The treatment course was 1-2 weeks determined according to the severity of patients' condition. During the treatment, patients in two group received the same basic nursing and treatment.

Observation indices

1. Evaluation of clinical treatment effects: cured: symptoms, vital signs, microorganism inspection, radiographic examination, and laboratory report all recovered to normal; significantly efficient: One of above 5 items did not recover to normal; efficient: Disease was improved, but 2 or more items did not recover to normal; inefficient: Condition showed no improvement or aggravation. Therapeutic response rate = (cured patients + patients with significant efficiency)/total patients.

2. Evaluation of radiographic results were divided into complete absorption (inflammation in infectious part disappeared or filtration was completely absorbed); significant absorption (more than half of inflammation or filtration in infectious part disappeared or was absorbed); no change (no obvious change before and after treatment); aggravation (inflammatory scope and infiltration degree aggravated after treatment). Imaging efficiency rate = (patients with complete absorption + patients with significant absorption)/total patients.

3. Evaluation of bacteriological curative effects: the original infected samples (sputum, secretion, etc.) were cultured again in follow-up period after treatment. The results were divided into elimination (no original infected sample); partial elimination (one or several pathogenic bacteria were eliminated); no elimination (original pathogenic bacteria was cultured). Bacterial eradication rate = (patients with elimination + patients with partial elimination)/total patients.

4. Determination of serum meropenem concentration: 2ml blood specimen was selected from central vein of patients after administration for 0.25h, 0.5h, 0.75h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 7h and 8h. After natural coagulation, serum obtained by centrifugal as stored in refrigerator at -80°C. The determination was conducted by HPLC method in reference (Mendez, *et al.*, 2003).

5. Clinical scores: Sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation scoring system II (APACHEII), clinical pulmonary infection score (CPIS) and systemic inflammatory response syndrome (SIRS) were conducted for patients before and after treatment.

6. Other indices: Vital signs, laboratory reports, medication time, hospital stay in ICU, duration of mechanical ventilation, as well as adverse drug reactions and corresponding disposal were recorded.

STATISTICAL ANALYSIS

Statistical analysis was conducted by SPSS18.0 statistical analysis software for all data. According to the inspection, all the data were in normal distribution. Therefore, enumeration data was represented by patients or percentage for X^2 test, while measurement data by (x±s) for T test or variance analysis of repeated data. When $P<0.05$, the difference had statistical significance.

RESULTS

Therapeutic effects

There were 212 patients completing the whole research, including 104 patients in research group and 108 patients in control group. Patients exiting the research were those with negative drug allergy. According to comparison, the difference in therapeutic response rate, imaging efficiency rate, and 28-day survival rate (86.5% vs 64.8%, $\chi^2=13.51$, $P=0.009$) had statistical significance. (See table 2 and fig. 1).

Serum meropenem concentration

The blood concentration decreased rapidly 0.25 hours after intravenous dripping of meropenem but then significantly slowed down in research group. On contrary, the blood concentration rose rapidly 0.25 hours after intravenous dripping of meropenem and then decreased rapidly. After administration for 3 hours, the blood concentration decreased to 4μg/mL. Therefore, the

Table 1: Comparison in basic information of patients

Index	Research group (n=104)	Control group (n=108)	χ^2/t	*P*
Age	60.4±14.9	57.8±15.3	0.843	0.535
Sex (male/female)	63/41	70/38	0.407	0.981
APACHE II score	19.45±6.35	18.83±6.73	1.321	0.313
SOFA score	5.89±2.74	6.18±2.88	1.532	0.873
Organ failure (number)	2.51±0.84	2.71±0.92	0.941	0.282
SIRS indicators (number)	3.13±0.68	3.29±0.77	0.894	0.573
Site of infection			0.001	1.000
Lower respiratory tract	83 (79.8%)	86(79.6%)		
Intraperitoneal	21(21.2%)	22(21.4%)		
T(^{o}C)	38.13±0.23	38.21±0.43	0.863	0.914
WBC($\times10^9$/L)	13.66±0.41	13.31±0.37	0.764	0.854

Table 2: Therapeutic effects of patients in two groups

Index	Research group	Control group	χ^2/t	*P*
Treatment efficiency rate (n/%)	81(77.9%)	58(53.7%)	10.79	0.029
Imaging efficiency rate (n/%)	53(51.0%)	20(18.5%)	24.7	0.000
Bacterial clearance rate (n/%)	50(48.0%)	50(46.3%)	0.067	0.999
Acinetobacter bacteria	12(12/41)	11(11/43)	0.146	0.997
Pseudomonas aeruginosa	17(17/35)	14(14/37)	0.845	0.932
E. coli	9(9/14)	11(11/12)	2.729	0.604
Klebsiella pneumoniae	9(9/11)	9(9/11)	/	/
Others	3(3/3)	5(5/5)d	/	/

Table 3: Improvements in clinical scores of patients in two groups ($\bar{x} \pm S$)

Index	Research group	Control group	t	*P*
APACHE II score	5.42±1.45	4.98±1.32	0.346	0.642
SOFA score	1.21±0.67	3.21±0.94	4.352	0.034
CPIS score	0.94±0.18	1.53±0.33	3.234	0.043
SIRS score	2.67±0.94	3.53±1.13	3.443	0.039

Table 4: Analysis on other indicators of patients in two groups

Index	Research group	Control group	t	*P*
T(℃)	36.83±0.13	37.03±0.12	0.645	0.853
WBC($\times10^9$/L)	9.45±0.25	10.94±0.34	2.314	0.047
PaO_2(mmHg)	98.41±0.45	96.31±0.52	0.832	0.872
PaO_2/FiO_2	366.41±41.45	349.52±38.95	0.545	0.783
Duration of mechanical ventilation (day)	10.14±9.33	12.24±9.25	0.442	0.895
Time use of antibiotics (day)	11.7±1.9	8.7±1.6	3.425	0.049
ICU (day)	19.88±10.43	21.84±11.45	0.246	0.983

difference between two groups had statistical significance (F=14.352, *P*=0.015) (fig. 2).

Improvements in clinical scores

Restuls showed there was no statistical significance in APACHE II score, SOFA score, CPIS score and SIRS score of patients in two groups before treatment. However, at the end of treatment, the difference in three of them, except APACHE II score had statistical significance (table 3).

Inspection of other indicators

Results showed that the decrease level of WBC in research group was better than that in control group. Moreover, the days to antibiotic use in research group were less than those in control group with difference of statistical significance (table 4).

Adverse reaction

During treatment, there were 3 patients in control group and 5 patients in observation group having mild rise in

liver enzyme. Without special disposal, all of these patients recovered normal after treatment course. There was no statistical significance between two groups (χ^2=0.444, *P*=0.978).

DISCUSSION

ICU is a department having infection occurring frequently in hospital. For patients with serious condition, immunosuppression and combination of various underlying diseases, the rate to be infected may greatly increase for the long-term stay in closed environment with high concentration of pathogenic bacteria and the application of broad-spectrum antibiotic (Castro, *et al.*, 2013). In addition, inappropriate application of antibiotics may always induce and screen multiple resistant bacteria and extensive resistant bacterial causing serious consequences in later treatment. As Viehman *et al.* (2015) said that the bacterial drug resistance becomes increasingly serious at present. It is significant to reasonably administrate antibacterial agents and develop administration method for multi-drug resistance and bacterial infection with high MIC value when the development of new antibiotic is relatively hysteretic.

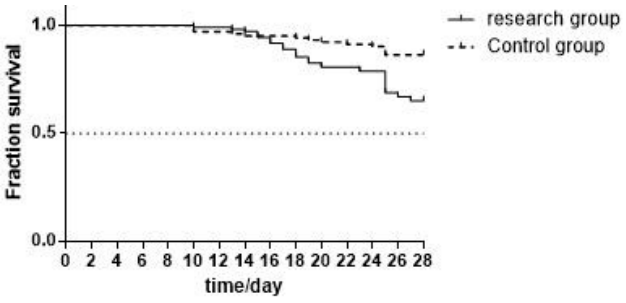

Fig. 1: Survival curves of 28 days

Studies show that the clinical therapeutic effects of antibiotic are mainly dependent on pathogenic bacteria, antibiotic, and organism. Therefore, pharmacokinetics/ pharmacodynamics (PK/PD) theory is introduced in clinical to better describe the relationship among three elements. PK can describe the rules of drugs in organism, including absorption, distribution, metabolic, and excretion, while PD mainly describes the mechanism of actions between drugs and organism (Perazella, 2012). However, there will be therapeutic effects when the blood concentration of drug is larger than 40% bacterial MIC value. Moreover, the antibiosis effect will never increase when blood concentration is up to 4-6 times of bacterial MIC value even if the antibiotics concentration increases. In other words, the combining capacity between antibiotic and receptor has been saturated at this time (Reis and Cassiani, 2011). According to this work, blood concentration was up to 4 times of common bacterial MIC value in 30 minutes after traditional injection. After then, the concentration decreased rapidly in next 2 hours and decreased to less than 4μg/mL after 4 hours. By sustaining transfusion, the drug stress will rapidly increase in a short time and then the remaining dose will be given in 3 hours. Such method can not only effectively ensure the drug sealing concentration, but also significantly delay the drug metabolism. Therefore, sustaining transfusion can rapidly combine with bacterial receptor for sterilization in short time, but also maintain the blood concentration without increasing the injection dose. Binder *et al.* (2013) studied 25 patients and found that some patients in ICU did not reach the minimum inhibitory concentration, while the drug clearance rate and distribution volume were larger than theoretical values. It can be seen that it is significant to monitor meropenem blood concentration in clinical application. This is helpful to not only administrate sufficient dose in time, but also avoid the injury to liver and kidney for drug accumulation.

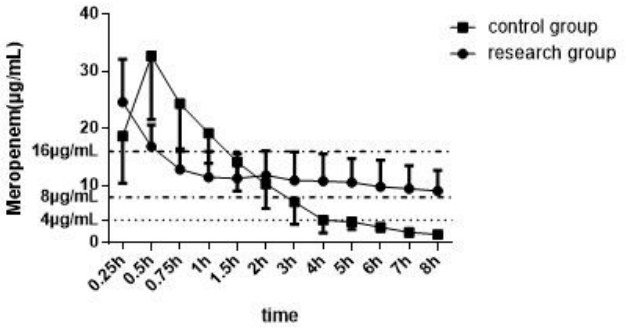

Fig. 2: Meropenem blood concentration of patients in two groups

As mentioned above, we have verified that different administration methods may cause the difference in blood concentration. However, will the difference affect clinical therapeutic effects on patients? This work determined final therapeutic effects according to the therapeutic efficiency rate, imaging efficiency rate, bacterial clearance rate and 28-day survival rate of patients in two groups. The results showed that 3-hour sustaining dripping had better therapeutic efficiency rate, imaging efficiency rate and 28-day survival rate than 30-minute injection. However, it is strange that 3-hour sustaining dripping cannot effectively improve the bacterial clearance rate. The blood concentration was always larger than 8μg/mL, more than MIC value of the most pathogenic bacteria in experiment group. Therefore, it can be known that baumanii and pseudomonas aeruginosa are major pathogenic bacteria in ICU by further analysis. However, meropenem which is drug resistant had a certain limit to the sterilizing effects on these two bacteria, so the difference in sterilizing effects between two groups was not significant. This also verified that the clinical therapeutic effects had no direct relevance to bacterial clearance rate. Some other studies concluded that different administration methods made no difference in in-hospital mortality rate, stay length, and final therapeutic effects according to the study on 242 patients

having intermittent administration and 261 having sustaining administration (Arnold, *et al.*, 2013). In this work, it was speculated that the blood concentration of drug did not maintain in theoretical value because of different drug metabolism of individuals according to PK/PD model and testing results. Therefore, further analysis is required to make conclusion.

In addition, common clinical scoring has some advantages to intuitively and conveniently show the difference in therapeutic effects between two groups. According to the comparison of 4 different clinical scoring standards for patients of two groups, research group was always better than control group in SOFA, CPIS, and SIRS scoring, while the difference in APACHE II scoring was not significant. It may be because items in SOFA, CPIS, and SIRS scoring were relatively concentrated to show more discriminable results, while APACHE II scoring could not distinguish the slight difference for its wide pertinence. Moreover, the difference in different physical signs of patients in two groups also further explained the scoring difference. For example, WBC amount and antibiotics dose in blood in research group were lower than those in control group. With the same dose, 3-hour sustaining dripping can effectively decrease the peak concentration to alleviate inflammatory reactions and promote the improvement of organs. Furthermore, the use cycle of antibiotics can be shortened for better therapeutic effects (Jamal, *et al.*, 2014).

CONCLUSION

It is conductive to monitor the blood concentration of meropenem for patients with serious illness in ICU when determining the drug metabolism and pesticide effects on patients. Therefore, empirical antibiotics in clinical can be avoided. Actually, when blood concentration maintains up to 8μg/mL, the clinical therapeutic effects on patients are the best. However, it requires further perspective, random, and large-amount double blind experiment to verify if such effects can be realized with further decrease of medication dose.

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