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Multicenter, double-blind, randomized clinical trial of parenterally administered Cefoselis versus Cefepime for the treatment of acute bacterial infections

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Abstract. – AIM: This study aims to evaluate the clinical efficacy and safety of intravenous Cefoselis injection for the treatment of acute moderate and severe bacterial infections.

PATIENTS AND METHODS: A multicenter, double-blind, randomized clinical trial was carried out using Cefepime as control. Patients received 1.0 g of either Cefoselis or Cefepime for moderate infections or 2.0 g for severe infections at an interval of 12 hours for 7 to 14 days. A total of 276 patients (138 with Cefoselis, 138 with Cefepime) with respiratory or urinary tract infections were enrolled in the study. Up to 137 and 124 patients receiving Cefoselis and 132 and 125 patients receiving Cefepime were eligible for the ITT (intent to treat) and PP (per protocol) analyses, respectively.

RESULTS: At the end of the treatment, the cure rates and effective rates were 59.68% (74/124) and 93.55% (116/124) with Cefoselis, and 56.00% (74/124) and 90.40% (116/124) with Cefepime. The bacterial eradication rates of the two groups were 90.32% and 93.85%, respectively. No statistical differences were observed on the above-mentioned parameters between the two groups (all $p > 0.05$). Adverse events, mainly mild aminotransferase elevation and mild leukopenia, were observed in 11.59% (16/138) and 13.77% (19/138) of patients with Cefoselis and Cefepime, respectively ($p > 0.05$).

CONCLUSIONS: Cefoselis is an effective and safe choice against acute moderate and severe respiratory infections and UTI (urinary tract infection).

Key Words:
Cefoselis, Cefepime, Acute bacterial infections, RCT.

Introduction

Cefoselis sulfate is a fourth-generation cephalosporin administered through injection. The structure allows Cefoselis to retain excellent antibacterial activity maintained by aminothiazolyl cephalosporins. Additive 1-ethoxyl 5-aminopyrazoles enlarges the antibacterial spectrum of this compound. Previous publications[1-3] indicate that Cefoselis sulfate has a potent antibacterial activity against Gram-positive bacteria involving *Staphylococcus*, *Pneumococcus*, and *Streptococcus*, as well as Gram-negative bacteria involving *Pseudomonas*, *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus*, *Morganella*, and *Providencia*. This agent is mainly used for respiratory, urogenital, biliary, and abdominal infections caused by various susceptible bacteria[4-7].

Randomized, double-blind, controlled clinical trials were conducted in five centers in China from February 2009 to August 2010 to evaluate the safety and efficacy of Cefoselis sulfate injection in treating acute bacterial infection as approved by the State Food and Drug Administration (PJ No. 2005L01229). Cefepime hydrochloride was used as the control agent for the injection.

Patients and Methods

Study Design

This clinical study was multicenter, double-blind, randomized, and parallel-controlled. The

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study protocol was approved by the Institutional Ethics Committee/Institutional Review Board in West China Hospital, Sichuan University. Patients or their guardians provided written informed consent to participate in the study prior to enrollment.

Patient Enrollment

Inclusion Criteria: The inclusion criteria included hospitalized male or female patients aged between 18 years to 70 years with acute moderate to severe bacterial respiratory tract infections (acute bronchitis, acute episode of chronic bronchitis, bacterial pneumonia, bronchiectasis with infection, etc., giving priority to lower respiratory tract infections) and /or urinary tract infections (acute pyelonephritis, acute episode of chronic pyelonephritis, acute cystitis, and complicated urinary tract infection), showing patent signs, symptoms, and laboratory findings of acute infection; not subjected to other antibacterial medication within 72 hours before inclusion, showing positive bacterial culture findings and unremitted conditions after other antibacterial medications; with favorable compliance to the study; and voluntarily agreeing to participate and providing a written informed consent.

Exclusion Criteria: The exclusion criteria included patients with allergic history of penicillin or equivalent; patients with serious cardiac, hepatic, and/or renal insufficiency, hematopoietic dysfunction, bleeding tendency, or hemorrhagic disorders; women in pregnancy or lactation; patients with mental and nervous system disease and advanced malignancies; patients with unfavorable compliance or serious disease who cannot finish the course of the study treatment; and patients who have diseases other than bacterial infections.

Withdrawal Criteria: The withdrawal criteria included patients with unfavorable compliance, unwilling to take study medicines upon signing the informed consent, and did not receive at least one dose of study drug; patients who did not meet the inclusion or meet the exclusiion criteria during the study.

Drug Identification and Usage

The study drug, Cefoselis sulfate for injection, 0.5 g/vial, batch number E081210, was manufactured and supplied by Hunan Zhongnan Kelun Pharmaceutical Co., Ltd. (Changsha, Hunan, China). The control drug, Cefepime hydrochloride for injection, 0.5 g/vial, batch number 200809001, was manufactured by General Pharm. Factory, Harbin Pharmaceutical Group Co., Ltd. (Harbin, Heilongjiang, China).

Patients received 1.0 g of either Cefoselis or Cefepime for moderate infection or 2.0 g intravenous infusion for severe infection administered at an interval of 12 hours for 7 to 14 days.

Observational Parameters

Daily changes in the symptoms and signs of patients were monitored and recorded during treatment. Hematological parameters, routine urine analysis, hepatic and renal functions, and blood electrolytes were evaluated at baseline, at day 4, and at the end of the treatment period, respectively. At baseline and at the end of the treatment period, patients were subject to one bacterial culture and electrocardiogram (ECG), respectively. Those with respiratory tract infection received chest radiography once. Patients with abnormal laboratory findings after treatment underwent follow up until the value(s) returned to baseline level.

Bacterial Identification and in vitro Susceptibility

At baseline and on the first day upon completion of treatment, specimens were collected from infectious sites for bacterial culture and species identification. The susceptibility of isolated bacteria to five drugs, including Cefoselis, Cefepime, Ceftazidime, Levofloxacin, and Amikacin, were determined using the K-B method according to CLSI (Clinical and Laboratory Standards Institute) guidelines. All bacterial isolates were submitted to the site of principal investigator for species identification and MIC determination.

Efficacy Assessment Criteria

Clinical response was categorized as cure, significant improvement, improvement, and failure. The four-category classification was based on the following criteria: (1) complete resolution of signs; (2) complete recovery of symptoms; (3) eradication of the pathogens; and (4) normal laboratory findings and chest radiography. Cure indicates that the patient met all four criteria. Significant improvement indicates that the patient met three criteria. Improvement indicates that the patient met only one or two criteria. Failure indicates that the clinical signs and symptoms of infection persisted or worsened after 72 hours of treatment. Overall efficacy rate was defined as

the proportion of cured patients and significant improvement. Bacteriological effect was evaluated at the following five levels: clearance, part clearance, persistence, replacement, and relapse.

Adverse Drug Reactions

Adverse events (AEs) during the study were closely monitored and documented for their onset time, manifestations, severity, corresponding management, and outcome. The causality of the AEs was assigned to the following five levels: definitely related, probably related, possibly related, possibly unrelated, and definitely unrelated.

Statistical Analysis

Upon approval, all clinical data were inputted electronically by professional statistical analysts and statistically analyzed using the SAS statistics package (*t*-test for measurement data and chi-square test for numeration data) to determine the potential statistical significance between the two agents. The test level for all hypothesis tests was $p < 0.05$.

Results

General Conditions

In this study, a total of 276 patients who signed informed consent were enrolled (138 in the test group and 138 in the control group). A total of 20 patients (13 in the test group and 7 in the control group) dropped out due to withdrawal of the informed consent by the subject. A total of 7 subjects (1 in the test group and 6 in the control group) were withdrawn due to non-compliance to the study medication, conformance to the exclusion criteria, and/or prior use of other antibiotics. Therefore, 249 patients (124 in the test group and 125 in the control group) completed the study protocol. The dropouts and withdrawals accounted for 9.78% of all the subjects.

Baseline data regarding gender, age, height, weight, vital signs, type, and severity of disease, course of medication, and pathogenic bacteria composition between the test and control group were comparable ($p > 0.05$), indicating that the two groups matched.

Clinical Efficacy

The overall cure rate and effective rate at the end of the study treatment were 59.68% (74/124) and 93.55% (116/124) with Cefoselis, and 56.00% (74/124) and 90.40% (116/124) with Cefepime. There was no statistical difference between two groups on overall efficacy ($p > 0.05$), indicating similarity of the efficacy achieved by the two agents (Table I).

The cure rate and effective rate of the respiratory tract infection were 25% (21/60) and 86.67% (52/60) with Cefoselis, and 30.65% (19/62) and 82.26% (51/62) with Cefepime, without statistical significance ($p > 0.05$). No statistical significance was found on the cure rate and effective rate of the urinary tract infection between those with Cefoselis (82.81%, 53/64) and (100%, 64/64) and with Cefepime (80.95%, 51/63) and (98.41%, 62/63), both $p > 0.05$.

Bacteriological Efficacy

A total of 130 bacterial isolates were recovered from 249 per-protocol (PP) subjects, including 64 isolates in the test group and 65 isolates in the control group. The positive rate of bacteria in the test group and control group were 51.61% (64/124) and 52.00% (65/125), respectively.

Positive bacterial cultures were obtained from 64 patients in the test group, including 64 bacterial isolates obtained at the baseline, wherein 56 isolates were eliminated, 6 remained, and 2 replaced by other isolates after the study treatment, resulting in a bacterial elimination rate of 87.50% (56/64). Positive bacterial cultures were obtained in 60 patients in the control group, including 65 isolates obtained at the baseline (each 2 isolates obtained in 5 of the patients), wherein 59 isolates from 56 patients were eliminated, 1 was not eliminated, 2 partly eliminated, and 1 replaced by other isolates, resulting in a negative conversion rate of 93.33% (56/60) and bacterial elimination rate of 90.77% (59/65) (Table II). No statistical significance was found on bacterial elimination rates between the two groups ($p > 0.05$).

In vitro Antimicrobial Susceptibility Results

Antibacterial susceptibility disc test *in vitro* indicated that 83.94%, 86.86%, 68.61%, 86.13%, and 83.94% of 137 isolated strains were susceptible to Cefoselis, Cefepime, Levofloxacin, Ceftazidime, and Amikacin, respectively. A majority of bacteria isolated in the present study were susceptible to Cefoselis sulfate, Cefepime hydrochloride, Ceftazidime, and Amikacin, and less susceptible to Levofloxacin. Statistical significance was found on the susceptibility of isolated bacteria to the 5 antibiotics (= 20.5681, Friedman

Table I. Clinical efficacy of Cefoselis vs. Cefepime for the treatment of various bacterial infections (PPS).

Diseases	Cefoselis cases*	Cure	Significant improvement	Improvment	Failure	Cure rate (%)	Effective rate (%)	Cefepime cases*	Cure	Significant improvement	Improvment	Failure	Cure rate (%)	Effective rate (%)
Respiratory infection														
Acute suppurative tonsillitis	1	1	0	0	0	—	—	4	4	0	0	0	100.00	100.00
Bacterial pneumonia	22	5	13	4	0	22.73	81.82	19	4	13	2	0	21.05	89.47
Acute episode of chronic bronchitis	5	0	4	1	0	—	—	9	0	5	4	0	—	—
Acute bronchitis	21	15	5	1	0	71.43	95.24	22	11	9	2	0	50.00	90.91
Bronchiectasis with infection	10	0	9	1	0	0.00	90.00	8	0	5	3	0	—	—
Pulmonary abscess	1	0	0	1	0	—	—	0	0	0	0	0	—	—
Total	60	21	31	8	0	35.00	86.67	62	19	32	11	0	30.65	82.26
Urinary tract infection														
Acute urethritis	0	0	0	0	0	—	—	2	2	0	0	0	—	—
Acute cystitis	8	8	0	0	0	—	—	12	9	3	0	0	75.00	100.0
Acute pyelonephritis	31	25	6	0	0	80.65	100.0	28	24	3	0	1	85.71	96.43
Acute episode of chronic pyelonephritis	2	2	0	0	0	—	—	2	2	0	0	0	—	—
Complicated urinary tract infection	20	16	4	0	0	80.00	100.0	16	11	5	0	0	68.75	100.0
Others*	3	2	1	0	0	—	—	3	3	0	0	0	—	—
Total	64	53	11	0	0	82.81	100.0	63	51	11	0	1	80.95	98.41

*Including 4 cases of frequent cystitis and 2 cases of acute episode of chronic cystitis.

Table II. Bacteriological efficacy evaluation at the end of treatment based on the baseline bacterial genus data (PPS).

	Cefoselis cases*	Clearance	Persistence	Replacement	Reinfection	Eradication rate (%)	Cefepime No.	Clearance	Persistence	Replacement	Reinfection	Eradication rate (%)
Gram+ bacteria	9	9	0	0	0	100.00	11	11	0	0	0	100.0
Staphylococcus spp.	6	6	0	0	0	100.00	6	6	0	0	0	100.00
Streptococcus spp.	2	2	0	0	0	100.00	4	4	0	0	0	100.00
Enterococcus spp.	1	1	0	0	0	100.00	1	1	0	0	0	100.00
Gram- bacteria	55	47	6	2	0	85.45	54	50	3	1	0	92.59
Haemophilus spp.	8	7	1	0	0	87.5	9	8	1	0	0	88.89
Escherichia spp.	26	24	1	1	0	92.31	26	24	2	0	0	92.31
Klebsiella spp.	10	9	1	0	0	90.00	8	8	0	0	0	100.00
Enterobacter spp.	2	2	0	0	0	100.00	0	0	0	0	0	—
Proteus spp.	1	1	0	0	0	100.00	3	3	0	0	0	100.00
Citrobacter spp.	0	0	0	0	0	—		1	0	0	0	100.00
Acinetobacter spp.	1	1	0	0	0	100.00		2	0	1	0	66.67
Pseudomonas spp.	6	2	3	1	0	33.33	3	3	0	0	0	100.00
Rhizobium spp.	1	1	0	0	0	100.00	1	1	0	0	0	100.00
Total	64	56	6	2	0	87.50	65	61	3	1	0	93.85

test, $p = 0.0004$; *in vitro* antibacterial susceptibility disc results). Generally, the susceptibility of clinically isolated bacteria to Cefoselis sulfate was equivalent to Cefepime hydrochloride ($p > 0.05$, Table III).

The preserved bacterial strains were subjected to MIC determination. MIC_{50} and MIC_{90} were determined in species with at least 10 isolates. MIC ranges were provided as a unit of isolates for others. Result showed that most isolates had a comparable susceptibility to Cefoselis sulfate and Cefepime hydrochloride, which was consistent with aforementioned results.

Safety Evaluation

A total of 276 subjects (each $n = 138$ in the test group and control group) were eligible for the evaluation of adverse reactions. Up to 35 drug-related adverse reactions (16 in the test group and 19 in control group) were reported in 42 patients (19 in the test group and 23 in control group). Most of the adverse reactions were study drug-related laboratory abnormalities, including elevated aminotransferase, reduced WBC counts, or increased platelet counts. The clinical adverse reactions observed in both groups were mainly rash, dizziness, and fever, and were mild in severity, with a rapid resolution after discontinuation of the study drugs. Prevalences of adverse reactions were comparable between the two groups (11.9% with Cefoselis vs. 13.76% with Cefepime), without statistical significance ($p > 0.05$).

Discussions

Cefoselis is a fourth-generation cephalosporin, showing antibacterial activity to clinically isolated Gram-positive bacteria, including MRSA, and Gram-negative bacteria, including *Pseudomonas aeruginosa*. The principal mechanism of this drug suppresses the cross-linking of the mucopeptide chain during the synthetic process of the bacteria cell wall and disables the bacteria from forming a complete cell wall. Compared with former generations of cephalosporins, the fourth-generation cephalosporin Cefoselis shows stronger antibacterial activity against Gram-positive and Gram-negative bacteria, characterized by high efficiency, broad spectrum, and robust resistance to β-lactamase. Cefoselis has a plasma half life of 2 hours, is more distributed in the inflammatory tissue than in the blood, and is long-act-

Table III. *In vitro* susceptibility test of 5 antibacterial agents against clinical isolates (PPS).

Bacteria	Strains	Cefoselis			Cefepime			Ceftazidime			Levofloxacin			Amikacin		
		S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
G+ cocci	23	20	1	2	19	1	3	17	1	5	15	2	6	14	0	9
Staphylococcus spp.	13	12	1	0	12	1	0	10	1	2	9	2	2	13	0	0
Streptococcus spp.	7	7	0	0	7	0	0	7	0	0	6	0	1	1	0	6
Enterococcus spp.	3	1	0	2	0	0	3	0	0	3	0	0	3	0	0	3
G- bacilli	114	95	3	16	100	4	10	101	4	9	79	3	32	101	6	7
Haemophilus spp.	16	15	0	1	16	0	0	15	1	0	15	0	1	16	0	0
Escherichia spp.	53	41	1	11	42	4	7	47	2	4	26	3	24	43	5	5
Klebsiella spp.	19	18	1	0	19	0	0	17	1	1	18	0	1	19	0	0
Enterobacter spp.	3	1	1	1	2	0	1	2	0	1	1	0	2	1	1	1
Proteus spp.	5	5	0	0	5	0	0	5	0	0	4	0	1	5	0	0
Citrobacter spp.	1	1	0	0	1	0	0	1	0	0	0	0	1	1	0	0
Acinetobacter spp.	5	3	0	2	4	0	1	3	0	2	5	0	0	4	0	1
Pseudomonas spp.	10	9	0	1	9	0	1	9	0	1	8	0	2	10	0	0
Rhizobium spp.	2	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0
Total	137	115	4	18	119	5	13	118	5	14	94	5	38	115	6	16

ing, as shown by its 6 hours of elimination half life, which is longer than that of Cefepime[8]. Cefoselis can reach an antimicrobial concentration in urine, bile, peritoneal fluid, sputum, prostatic fluid, gallbladder, and skin soft tissue and can overcome inflammatory blood-brain barrier, which is extensively applicable for infections in various organs or systems.

In Gram-negative bacteria, Cefoselis is quite stable in the chromosomal β-lactamase, preventing the drug from being hydrolyzed in the bacterial cytoplasm. For *Escherichia coli*, a pathogen accounting for most of the infections in this study, the cure rate and the effective rate with Cefoselis were identical to that with Cefepime (both exhibited 81.48% and 96.30%). Likewise, the bacterial elimination rate of the two groups was the same (92.31%). The bacterial elimination rates between the two groups in Klebsiella were 90% versus 100%. Another study showed that the drug is also antibacterially active to a part of AmpC enzyme-producing Gram-negative bacteria[9]. The special zwitterion structure of Cefoselis can facilitate the drug molecule to quickly penetrate into the micropore channels in the outer membrane of Gram-negative bacteria, allowing for a rapid formation of locally high concentration in the bacterial cell, resulting in faster antibacterial actions[10]. Ardanuy et al[11] studied 10 clinically isolated *Klebsiella pneumoniae* strains resistant to multiple drugs due to the inactivation of one 35 kD pore protein. Five of the strains were susceptible to Cefoselis probably due to its potent capacity to penetrate through the bacterial cell wall. A report on the ESBLs (Extended spectrum beta-lactamases)-producing Enterobacteriaceae strains[12] indicated that fourth-generation cephalosporins, such as Cefoselis, were not superior to third-generation cephalosporins. However, a synergistic effect could be found against Enterobacteriaceae bacteria in combination with Amikacin, with an increased initial sterilizing rate in absence of the regeneration of bacteria. This result indicates that combination with Amikacin can both reduce the occurrence of drug resistance and strengthen antimicrobial activity. For the non-fermentative Gram-negative bacilli, such as *P. aeruginosa* and *Acinetobacter baumannii*, Cefoselis has a similar antimicrobial action compared with other third-generation and fourth-generation cephalosporins, without obvious advantages[13]. The cure rate and effective rate of acinetobacter and pseudomonas were comparably low in this study, which indicated the existence of clinically isolated strains resistant to fourth-generation cephalosporins despite general effectiveness. A previous publication[14] also reported that combined β-lactams and aminoglycosides antibiotics had a favorable efficacy for pseudomonas.

Due to its potent affinity to PBP3 (penicillin-binding protein3) and PBP2 of Staphylococcus, Cefoselis exhibits a stronger antibacterial activity in Gram-positive bacteria compared with third-generation and current fourth-generation cephalosporins (e.g., Cefepime and Cefpirome)[15]. A report from Ohki et al[16] showed that Cefoselis exhibits the strongest antibacterial activity to MRSA (methicillin-resistant Staphylococcus aureus) among all currently available cephalosporins. Several *in vitro* studies[12,13] indicated that the antibacterial activity of Cefoselis on *Staphylococcus aureus* strains (including MSSA and MRSA) is stronger than that of Cefepime, Cefpirome, and third-generation cephalosporins. The susceptibility rates of MSSA to Cefoselis reported in two literature were 93.5% and 100%, and 27.5% and 17.1% in MRSA, respectively. The present study showed that Cefoselis was sensitive to the clinically isolated Staphylococcus and Streptococcus strains, and to one of the three isolated Enterococcus strains, which were resistant to other antimicrobial drugs. This result indicates a favorable antibacterial activity of Cefoselis to Gram-positive bacteria.

No serious adverse effect was reported in the present study. The adverse reactions observed in a minority of patients were mainly mild in severity. The incidence of adverse reactions was 11.68% with Cefoselis and 13.97% with the control. Most of the adverse reactions were laboratory abnormalities, including increased aminotransferase, leukopenia, elevated platelet counts, and increased eosinophil counts. The clinical adverse reactions were mainly rash, dizziness, and fever, with a similar category and incidence between the two groups. Similar to previously reported results[6], the above findings indicated that Cefoselis sulfate is well-tolerated and safe in treating the above-mentioned infections[6].

Conclusions

For acute respiratory and urinary bacterial infections caused by clinically common pathogenic bacteria, Cefoselis sulfate for injection showed a non-inferior clinical efficacy, bacterial sensitivity,

and safety to Cefepime hydrochloride for injection. The results proved that Cefoselis sulfate for injection has a comparable clinical applicability versus Cefepime hydrochloride for injection.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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