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ORIGINAL RESEARCH

A Comparison of in-vitro Pharmacokinetics and Pharmacodynamics of Branded and Its Locally Produced Cefuroxime Sodium Against *Staphylococcus* and *Escherichia Escherichia coli*

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Purpose: To compare the in-vitro antibacterial effects of branded and its locally produced cefuroxime sodium against *Staphylococcus* ATCC29213, clinical strains of methicillin-sensitive *Staphylococcus aureus* (MSSA) 164342 and methicillin-sensitive coagulase-negative *staphylococci* (MSCNS) 117933, and *Escherichia coli* ATCC25922, and to provide a reference for their clinical use.

Methods: An in-vitro antibacterial susceptibility test, time-kill curve and pharmacokinetics and pharmacodynamics (PK/PD) modeling was used in the comparison.

Results: The minimum inhibitory concentrations (MIC) of the two types of cefuroxime sodium were identical against four bacterial strains; both types of cefuroxime sodium had MICs of 0.5 μg/mL, 8 μg/mL, 0.5 μg/mL, and 0.25 μg/mL against ATCC 29213, ATCC 25922, M164342 and MSCNS117933, respectively. There were no significant differences in the time-kill curves of the two forms against the four strains at three concentrations. At drug concentrations of 2×MIC and 4×MIC, the bacterial count of all the strains decreased from 6 log CFU/mL to around 4 log CFU/mL. The bactericidal efficacies of the two agents were generally similar in the pharmacokinetics model of simulated intravenous drug administration of 1 g q8h. Only the PD parameter of bactericidal rate (KR) for ATCC 29213 and the area difference between the drug bactericidal curve and the bacterial growth control curve (I_E) for ATCC25922 were statistically different. The KR and I_E of the locally produced form were 0.73±0.10 logCFU·h/mL and 83.73±12.69 logCFU·h/mL, respectively, while the KR and I_E of the branded form were 1.19±0.07 logCFU·h/mL and 104.02±16.28 logCFU·h/mL, respectively.

Conclusion: The in-vitro antibacterial effect of locally produced cefuroxime sodium against *Staphylococci* and *E. coli* is comparable to that of branded cefuroxime sodium.

Keywords: cefuroxime sodium, pharmacokinetics/pharmacodynamics, time-kill curves, in vitro

Introduction

Cefuroxime is a second-generation cephalosporin antibiotic developed by GlaxoSmithKline Public Limited Company. It exhibits effective antibacterial activity against a broad spectrum of pathogens, particularly Gram-positive *Staphylococcus* spp. and Gram-negative *Escherichia coli*. It is effective in treating a wide range of infections, including respiratory tract

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infections, urinary tract infections, and skin and soft-tissue infections.[1,2] It is included in China's National Essential Drugs Catalogue.[3]

At the end of the 1970s, ACS Dobfar Società per Azioni obtained a patent license from GlaxoSmithKline and was approved by the Food and Drug Administration (FDA) to market the product under the same brand in the United States on January 10, 1986. This product is recognized by both the FDA and China's National Medical Products Administration (NMPA) of China as a reference preparation for evaluating the consistency of the quality and efficacy of generic cefuroxime sodium.[4,5] On April 18, 2024, ACS Dobfar made a technological investment in Guangdong Jinsu Pharmaceutical Company Limited, which, after acquiring the production technology for cefuroxime sodium, utilized the active pharmaceutical ingredients (APIs) from the same supply chain and prescription craft as GlaxoSmithKline, achieving the localization of cefuroxime sodium in China. Generic drugs have lower research and production costs, making them significantly cheaper than branded medications. This cost advantage is particularly beneficial in situations where health insurance coverage is insufficient or patients have limited financial resources, as it can substantially reduce medical expenses, enhance treatment accessibility and equity, and effectively lower the overall costs for the healthcare system.

In-vitro pharmacodynamics and pharmacokinetics (PK/PD) models are widely used in many aspects of antimicrobial drug research. They can simulate and analyze a wide range of drug delivery modes, dosages, intervals and even indications, and can partially reflect the interaction and relationship between the drug, the organism and the pathogenic bacteria and the change in drug efficacy over time.[6,7] And in-vitro PK/PD models have certain limitations, such as the inability to replicate the body's immune system's ability to clear bacteria and the body's metabolism of the drug.[6,7] In this study, we used an in-vitro PK/PD model to compare the antimicrobial activity of branded and its locally produced cefuroxime sodium, to assess the pharmacodynamic consistency of the two forms, and to provide a reference for their clinical use.

Materials and Methods

Drugs and Culture Medium

The branded cefuroxime sodium (Zinacef®, production batch number 2013E2, expiration date May 2024) was purchased from ACS Dobfar Società per Azioni in Italy. Locally produced cefuroxime sodium (Lifurox®, production batch number 310240201, expiration date January 2026) was purchased from Guangdong Jinsu Pharmaceutical Company Limited. Mueller-Hinton broth culture medium (MHB, catalog number CM0405B) and Mueller-Hinton agar solid culture medium (MHA, catalog number CM0337) were both purchased from Oxoid Limited in the United Kingdom.

Experimental Strains

Staphylococcus aureus standard strain ATCC 29213, *Escherichia coli* standard strain ATCC 25922, clinically isolated Methicillin-sensitive *Staphylococcus aureus* 164342, and methicillin-sensitive coagulase-negative *Staphylococci* 117933 are preserved in our laboratory.

Determination of Minimum Inhibitory Concentration

The MIC values of locally produced and reference cefuroxime sodium against the four bacterial strains were determined by an agar dilution method with reference to the recommended method of the Clinical and Laboratory Standards Institute.[8]

Generation of Time-Kill Curves

After incubating the bacteria with MHB medium for 6 h at 37°C until they reached a logarithmic growth phase, a turbidimeter was used to adjust the bacterial suspension to 0.5 standard McCloud turbidity. After 10-fold dilution of the prepared bacterial suspension, 600 μL was taken and added to tubes containing drug concentrations of 0, 1×MIC, 2×MIC and 4×MIC (the volume of MHB broth in the tubes before adding the bacterial solution was 7.4 mL). At this point, the initial inoculum of bacteria was about 10^6 CFU/mL. The tubes were continuously shaken and incubated for

24 h after bacterial inoculation, and 100 μL of each sample was collected at 0, 1, 2, 4, 6, 8, 12, and 24 h. The samples were diluted with saline and inoculated into MHA plates, which were incubated at 37°C for 20 h and then the number of colonies on the MHA plates was counted. The experiments were repeated three times, and the time-kill curves were plotted according to the results of the three experiments.

In-vitro Simulation of Cefuroxime Sodium Pharmacokinetics

The 24-h pharmacokinetics of cefuroxime sodium were simulated according to the pharmacokinetic parameters of healthy humans. The peak concentration (C_{max}), half-life ($t_{1/2}$) and time to peak concentration (T_{max}) of branded cefuroxime sodium were 158 μg/mL, 70 min and 30 min, respectively.[9] The half-life of locally produced cefuroxime sodium was 80 min, and the other parameters were the same as those of the reference formulation.[10] The dosing regimen of each form of cefuroxime sodium was 1 g i.v. q8h. The simulated drug-time concentration profiles were based on a one-compartment model (Figure 1).

In-vitro PK/PD Simulation

A PASS-400 blood concentration automated simulator (Dainippon Seiki, Japan) was used for the in-vitro PK/PD study, which was manipulated by the companion software PASS-402W (version 2.00, Dainippon Seiki, Japan). The instrument is divided into four parts; a central chamber, a culture medium reservoir, an antimicrobial drug reservoir and a waste liquid chamber. These parts are interconnected by sterile syringes, sterilized tees and piping to form a closed system. A magnetic stirrer in the central chamber maintains a consistent drug concentration. After the pharmacokinetic parameters have been entered into the PASS-402W software, the software manipulates the PASS-400 instrument to model the PK of cefuroxime sodium that occurs in vivo.

In our experiments, a syringe pump moved the antimicrobial drugs from the drug reservoir into the central chamber at a constant rate. Fresh broth was pumped from the medium reservoir into the central chamber, and the drug-containing medium was pumped out of the central chamber at different elimination rates to simulate the metabolic process of the drugs. During the simulation, the volume of liquid in the central chamber was constant, and the central chamber, the medium reservoir and the antimicrobial drug reservoir were maintained at 37°C in a water bath (Figure 2).

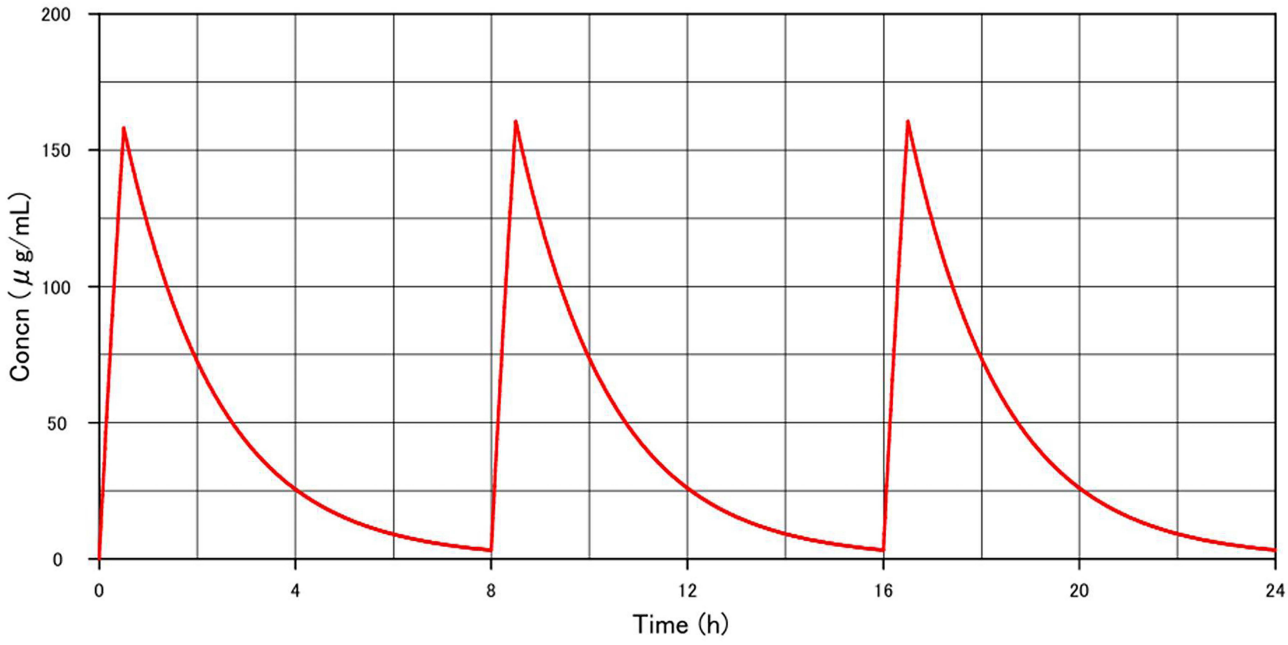

Figure 1 Simulation of the pharmacokinetics of cefuroxime sodium in humans after administration at 1 g intravenously every 8 hours.
Abbreviation: Concn, concentration.

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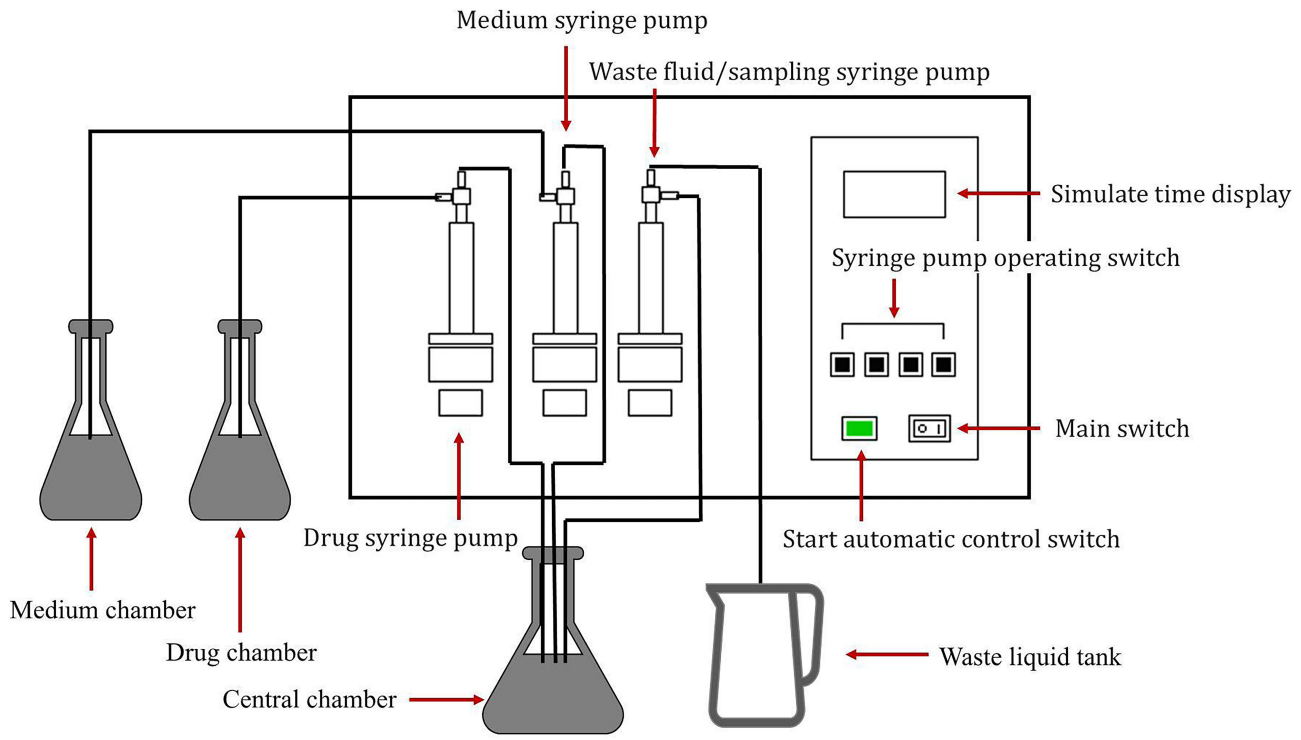

Figure 2 An illustration of the PASS-400 pharmacokinetics auto-simulation system.

The parts of the PASS-400 instrument were autoclaved before and after the experiment, and aseptic operation was used when assembling the parts. An appropriate amount of cefuroxime sodium solution was added to the antimicrobial drug reservoir containing 800 mL of 0.9% physiological saline, and the concentration of branded and its locally produced cefuroxime sodium in the reservoir was 250 μg/mL (the drug concentration was simulated by the PASS-402W software). The bacterial suspensions cultured to logarithmic growth phase were adjusted to 0.5 standard McCloud turbidity, then 1 mL was inoculated into the central chamber containing 100 mL of MHB broth to give an initial inoculum of about 10^6 CFU/mL. Samples were collected at 0, 1, 2, 4, 6, 8, 10, 12 and 24 h of the simulation, diluted using saline and inoculated into MHA plates and colonies counted after 20 h of incubation at 37°C. All the experiments were repeated three times, and the results of the three experiments were statistically analyzed.

Determination of PD Parameters

The maximum kill down (MKD) and 24 h change in bacterial concentration (ΔlgN_{24}) were analyzed using the PASS-400 system, and the area under kill curve (AUKC) and the difference in area between the drug-kill curve and the blank control curve (I_E) were obtained using GraphPad Prism v8.0.2 software, and the kill rate (KR) was calculated as shown in the following equation[11] (Figure 3).

$$KR = \frac{(N_{Administered(0h)} - N_{Control(0h)}) - (N_{Administered(2h)} - N_{Control(2h)})}{-2}$$

$N_{Administered\ (0h)}$: Bacterial concentration at 0 h in the administered group
$N_{Administered\ (2h)}$: Bacterial concentration at 2 h in the administered group
$N_{Control\ (0h)}$: Bacterial concentration at 0 h in the control group
$N_{Control\ (2h)}$: Bacterial concentration at 2 h in the control group

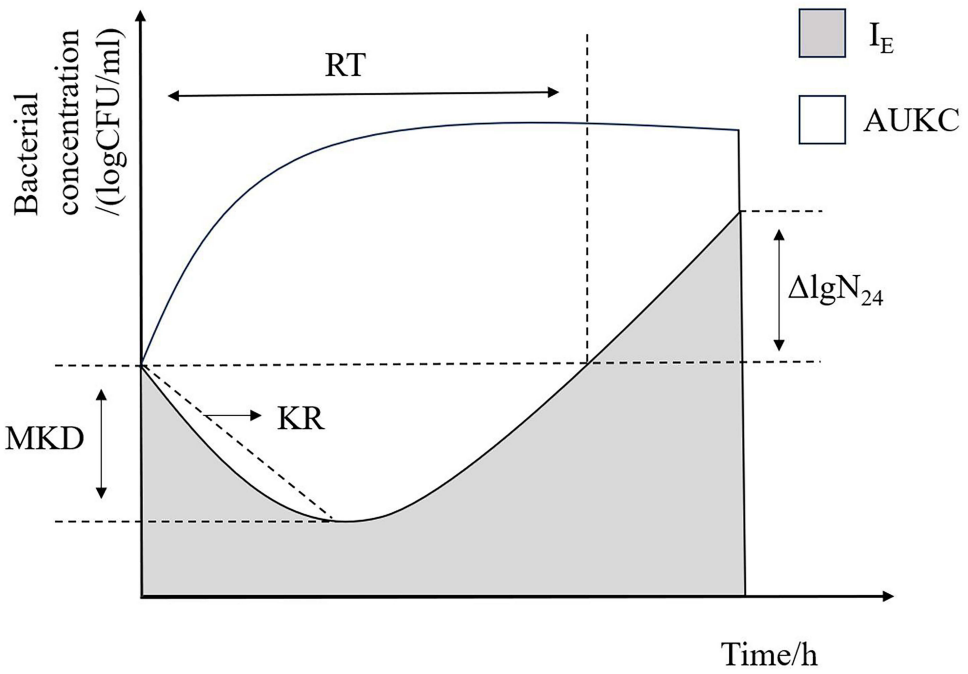

Figure 3 A schematic representation of PD parameters.
Abbreviations: CFU, Colony-Forming Unit; MKD, the maximum kill down; ΔlgN_{24}, 24 h change in bacterial concentration; AUKC, the area under kill curve; I_E, the difference in area between the drug-kill curve and the blank control curve; KR, and the kill rate.

Statistical Analysis

The data were analyzed using GraphPad Prism v8.0.2 software (GraphPad Software, Inc., USA) and the values of the PD parameters of the two forms of cefuroxime sodium against the four strains were presented as $\bar{x} \pm$ SD The independent samples *t*-test was used to compare differences between the PD parameters and $P<0.05$ was considered statistically significant.

Results

Antibacterial Susceptibility Test

All four bacterial strains were sensitive to both the locally produced and reference forms of cefuroxime sodium, and the MIC values of both forms were identical (Table 1). The susceptibility breakpoint for cefuroxime against Enterobacteriaceae is ≤8 μg/mL, the intermediate breakpoint is 16 μg/mL, and the resistance breakpoint is ≥32 μg/mL.[8] Methicillin (oxacillin)-susceptible *Staphylococcus aureus* is considered to be susceptible to cefuroxime.[8]

Time-Kill Curves

There was no significant difference between the time-kill curves of the locally produced and reference forms of cefuroxime sodium against the four bacterial strains at 1×MIC, 2×MIC, and 4×MIC. The strains ATCC29213,

Table 1 MICs of Branded and Its Locally Produced Cefuroxime Sodium Against Four Strains

Drug	MIC/(μg/mL)			
	ATCC25922	ATCC29213	MSSA 164342	MSCNS 117933
Locally produced	8	0.5	0.5	0.25
Branded	8	0.5	0.5	0.25

Abbreviations: MIC, the minimum inhibitory concentrations; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSCNS, methicillin-sensitive coagulase-negative *staphylococci*.

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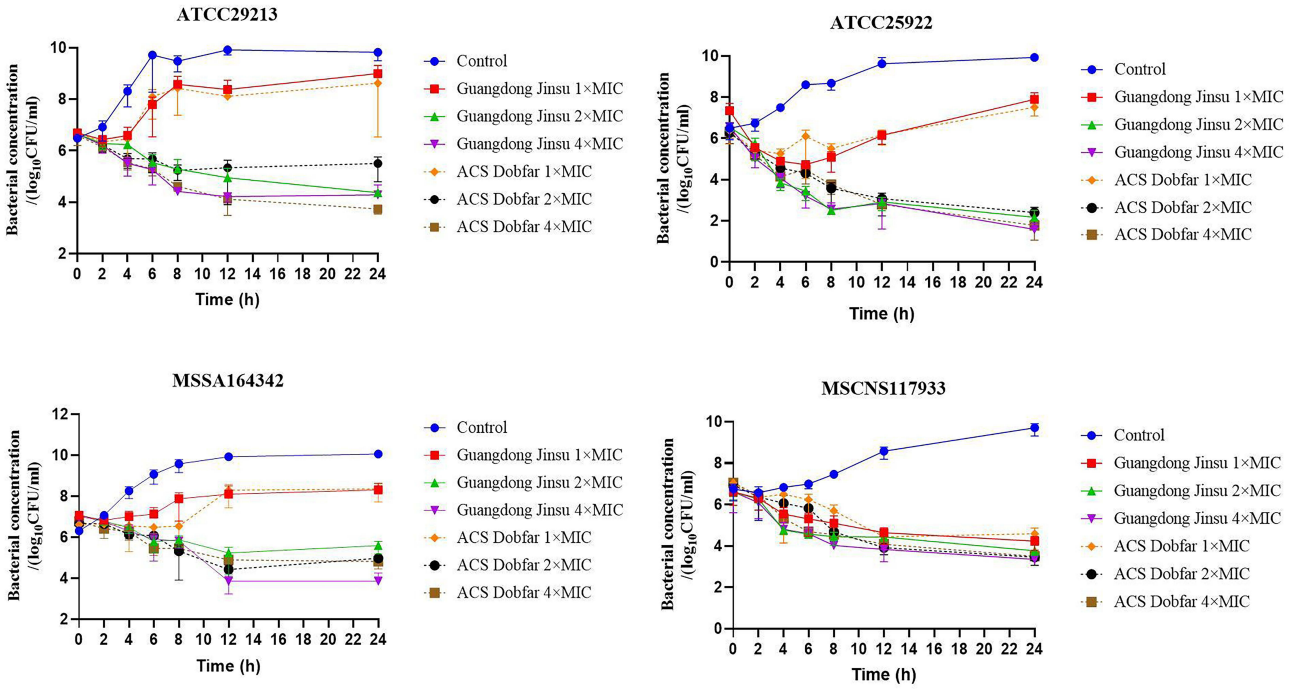

Figure 4 In-vitro time-kill curves of strains exposed to branded (ACS Dobfar) and its locally produced (Guandong Jinsu) cefuroxime sodium at concentrations of 1×MIC, 2×MIC and 4×MIC. MIC, the minimum inhibitory concentrations.
Abbreviations: CFU, Colony-Forming Unit; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSCNS, methicillin-sensitive coagulase-negative *staphylococci.*

ATCC25922, and MSSA164342 treated with 1×MIC of either drug form showed a slower increase in bacterial concentration than the control (untreated) group, with the difference at each time point ranging between 1 logCFU/mL and 3 logCFU/mL. For strain MSCNS117933, the bacterial concentration gradually decreased to 4 logCFU/mL after 24 h. At drug concentrations of 2×MIC and 4×MIC, the bacterial concentrations of the four strains gradually decreased from 6 logCFU/mL at 0 h to 4 logCFU/mL at 24 h (for strain ATCC25922, the bacterial concentration decreased to 2 logCFU/mL) (Figure 4).

PK/PD Time-Kill Curve

The overall bactericidal effect of the locally produced and reference forms of cefuroxime sodium was similar. The bacterial concentration of strain ATCC25922 treated with either form decreased from 6 lgCFU/mL first to l gCFU/mL and then increased to about 9 lgCFU/mL. The bacterial concentration of strain ATCC29213 decreased from 6 lgCFU/mL at 0 h to 2 lgCFU/mL at 10 h, after which the bacterial concentration remained constant. During this continuously decreasing bacterial concentration phase, the bactericidal curve of locally produced cefuroxime sodium was always above that of reference cefuroxime sodium, with a difference of about 1 lgCFU/mL. For strain MSCNS117933, the bacterial concentration decreased to 1 lgCFU/mL at 1 h and then remained relatively constant until 8 h when it continued to decrease to 0 lgCFU/mL. The bacterial concentration of strain MSSA164342 decreased to approximately 1 lgCFU/mL at 1 h and then remained constant until 24 h (Figure 5).

PD Parameters Analysis

There were no statistically significant differences in the PD parameters MKD, ΔlgN_{24}, AUKC, I_E and KR between branded and its locally produced cefuroxime sodium for the strains MSSA164342 and MSCNS117933. Only the KR of strain ATCC29213 and the I_E of strain ATCC25922 were statistically different. The KR and I_E for locally produced cefuroxime sodium were 0.73±0.10 lgCFU/(mL·h) and 83.73±12.69 lgCFU·h/mL, respectively, and the KR and I_E for branded cefuroxime sodium were 1.19±0.07 lgCFU/(mL·h) and 104.02±16.28 lgCFU·h/mL, respectively (Table 2).

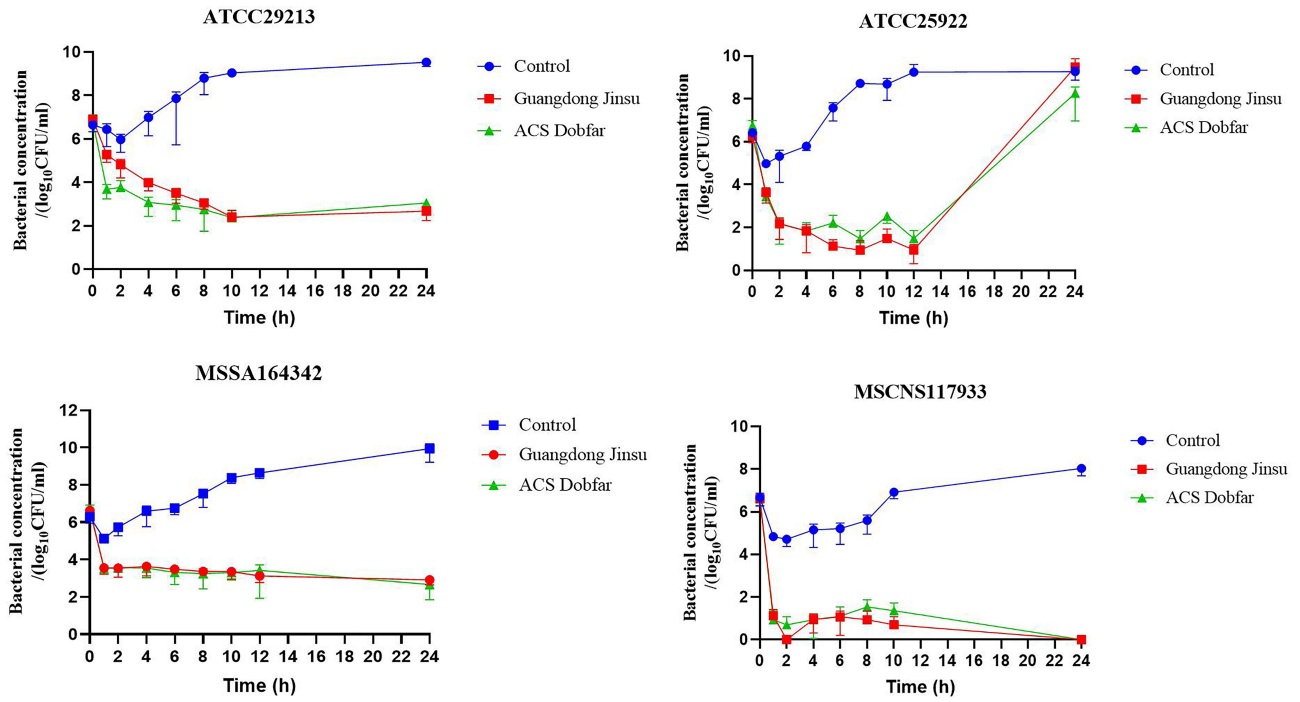

Figure 5 Time-kill curves of branded (ACS Dobfar) and its locally produced (Guandong Jinsu) cefuroxime sodium after administration at 1 g intravenously every 8 hours.
Abbreviations: CFU, Colony-Forming Unit; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSCNS, methicillin-sensitive coagulase-negative *staphylococci*.

Discussion

Since there is no requirement in China to evaluate whether the pharmacodynamics of generic and reference injectable preparations are consistent, it is hard to fully understand whether generic and reference forms have similar efficacy in clinical use.[12] The Expert Consensus on the Management of Centralized Banded Purchasing of Antibacterial Drugs in

Table 2 Comparison of PD Parameters Between Branded and Its Locally Produced Cefuroxime Sodium Against Four Strains

PD Parameters		Strains			
		ATCC29213	ATCC25922	MSSA164342	MSCNS117933
MKD/(lgCFU/mL)	Locally produced	−4.82±0.06	−6.07±0.52	−4.20±0.47	−6.91±0.31
	Branded	−4.87±0.11	−7.07±1.25	−4.25±0.62	−7.24±0.46
	P value	0.67	0.27	0.10	0.35
ΔlgN_{24}/(lgCFU/mL)	Locally produced	−4.27±0.54	−2.83±0.90	−3.73±0.11	−6.42±0.10
	Branded	−3.61±0.57	−1.72±0.32	−4.09±0.71	−6.57±0.21
	P value	1.46	0.11	0.70	0.32
AUKC/(lgCFU·h/mL)	Locally produced	153.38±12.14	151.51±12.78	157.46±8.13	100.35±13.78
	Branded	149.27±1.20	131.23±14.52	159.12±9.93	90.98±8.38
	P value	0.58	0.14	0.83	0.37
I_E/(lgCFU·h/mL)	Locally produced	84.78±12.23	83.73±12.69	80.38±8.56	125.59±14.85
	Branded	88.89±4.13	104.02±16.28	78.72±10.01	134.96±5.27
	P value	0.55	0.016	0.84	0.36
KR/[lgCFU/(mL·h)]	Locally produced	0.73±0.10	1.38±0.55	1.27±0.37	2.31±0.17
	Branded	1.19±0.07	1.59±0.23	1.21±0.30	2.12±0.32
	P value	0.003	0.16	0.84	0.42

Abbreviations: PD, pharmacodynamics; MKD, the maximum kill down; ΔlgN_{24}, 24 h change in bacterial concentration; AUKC, the area under kill curve; I_E, the difference in area between the drug-kill curve and the blank control curve; KR, and the kill rate; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSCNS, methicillin-sensitive coagulase-negative *staphylococci*.

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Medical Institutions encourages Chinese medical institutions to improve methodological systems that are used to evaluate the clinical efficacy of collectively purchased antimicrobial drugs.[13] The Expert Consensus encourages the full use of real-world data, and states that medical and healthcare institutions should clinically evaluate antimicrobial drugs in accordance with the Guidelines on the Management of Comprehensive Clinical Evaluation of Pharmaceuticals (Trial Implementation in the 2021 Edition).[14]

Whether generic and reference drugs have comparable efficacy has been determined by several studies using a variety of in-vitro and in-vivo experiments. These experiments include comparing in-vitro antimicrobial activities through antibacterial susceptibility tests and time-kill curves,[15,16] comparing the probability of PK/PD target attainment under specific dosing regimens and different MICs through Monte Carlo simulations,[17] and using in-vitro PK/PD modeling to dynamically study the relationship between antimicrobial drugs and bacteria, as well as generating bactericidal curves and comparing PD parameters.[11,18] In addition, in-vivo antimicrobial efficacy comparisons using animal infection models[16] and clinical trials have been used.[19–21] The results show that some generic drugs that have undergone bioequivalence evaluations are not as effective as the reference drug. This may be due to the lower potency of generics compared with reference preparations,[17] or the effect of different excipients or additives that alter the quality of the generic drug.[16,22,23]

The current study showed that the antimicrobial effects of branded and its locally produced cefuroxime sodium were generally the same against four strains of *Staphylococcus* and *Escherichia coli*. Firstly, the MICs of both forms were identical when tested against the four strains. The MICs of both forms against ATCC 29213, ATCC 25922, MSSA 164342, and MSCNS 117933 were 0.5 μg/mL, 8 μg/mL, 0.5 μg/mL, and 0.25 μg/mL, respectively. The MIC_{90} of cefuroxime against 64 strains of MSSA and 105 strains of MSCNS has been reported in the literature to be 4 μg/mL, whereas the MIC_{90} of cefuroxime against 146 strains of *Escherichia coli* (that were not purposely selected as resistant strains) is 512 μg/mL; this value is significantly higher than the MIC_{90} of cefuroxime against staphylococci.[23] In addition, according to the monitoring results of the National Bacterial Resistance Investigation Collaborative System for Bloodstream Infections, the resistance rates of *Escherichia coli* to cefuroxime in 2014 and 2015 were 64.8% and 58.7%, respectively; these rates are much higher than those of 39.0% and 35.1% for *S. aureus*.[24] Although second-generation cephalosporins were designed to have better antibacterial activity against Gram-negative bacteria while maintaining antibacterial activity against Gram-positive bacteria, the antibacterial activity of cefuroxime against *Escherichia coli* is weaker than that against Gram-positive staphylococci.

There was no difference in the time-kill curves of branded and its locally produced cefuroxime sodium at 1×, 2× and 4×MIC against the four strains. The bacterial concentration of four strains gradually decreased from 6 lgCFU/mL to 4 lgCFU/mL at 2× and 4×MIC drug concentrations (for strain ATCC25922, the bacterial concentration decreased to 2 logCFU/mL); this finding is consistent with the time-dependent characteristics of antibacterial drugs. At different multiples of the MIC drug concentration, the bacterial concentration changes of the four strains showed slight variations, which may be related to the inherent characteristics of the strains. The growth rates of different strains in the culture medium may vary, and their metabolic activity can also influence their sensitivity to the drug. Additionally, although the target of cefuroxime is penicillin-binding proteins (PBPs) in all cases, the types and quantities of PBPs may differ among bacterial species, which can affect the binding efficiency of the drug to its target, thereby leading to variations in bactericidal effects.[25]

The results of the PK/PD simulation showed there was no difference in the dynamic kill curves of the two forms of cefuroxime sodium against the four strains. Of interest, strain ATCC25922 showed strain regrowth, with the bacterial concentration decreasing from 6 lgCFU/mL to 1 lgCFU/mL and then increasing to about 9 lgCFU/mL at 24 h. The monoclonal clone at 24 h was chosen for antibacterial susceptibility testing, and we found that the MIC increased from 8 μg/mL to 256 μg/mL. A possible explanation for this phenomenon is heterogeneous resistance, where different subpopulations of bacteria have different resistance characteristics. In general, most subpopulations are susceptible to antibiotic, a small number of subpopulations is resistant, and a very small number of subpopulations have a high level of resistance.[26] When cefuroxime sodium kills the sensitive subpopulation, the resistant subpopulation is dominant and multiplies to bring strain regrowth. Further analysis of the PD parameters of branded and its locally produced cefuroxime

sodium against the four strains showed that only the KR of the two forms on strain ATCC29213 and the I_E of the two forms on strain ATCC2592 were statistically different. The differences in KR and I_E values may not be excluded as being caused by experimental variability.

This study has some limitations, as the in-vitro PK/PD model we used is unable to simulate the interactions between the organism, the bacteria and the drug. Such interactions include the ability of the immune system to clear the bacteria, the effect of the drug on the immune system, the body's metabolism of the drug, and the effect of metabolites as well as the physicochemical properties of the internal environment on the drug, and the physical and chemical properties of the internal environment on the drug, etc.[27] Therefore, further validation of our findings, which show that the overall antimicrobial effects of branded and its locally produced cefuroxime sodium are similar, is needed in animal and clinical studies.

Conclusion

The results of this study showed that the overall antibacterial effects of branded and its locally produced cefuroxime sodium were similar against four strains of *Escherichia coli* and *Staphylococcus*. The results help counter the lack of clinical efficacy studies of locally produced cefuroxime sodium and may be used as an important reference for the clinical use of locally produced cefuroxime sodium, increasing the confidence of physicians, pharmacists and patients and alleviating economic pressure. The in-vitro PK/PD model reflects changes in drug efficacy with drug concentration and time and so is more effective than in-vitro PK models when used for bioequivalence studies.

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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