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ORIGINAL RESEARCH

Determining optimal dosing regimen of oral administration of dicloxacillin using Monte Carlo simulation

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Background: Dicloxacillin, a semisynthetic isoxazolyl penicillin, exhibits antimicrobial activity against a wide variety of Gram-positive bacteria, as well as stability against penicillinases and low level of toxicity. The objective of this study was to obtain optimal dosing regimen of oral administration of dicloxacillin by analyzing the pharmacokinetic (PK) index in healthy volunteers and in vitro antibacterial activity by using Monte Carlo simulation.

Materials and methods: A total of 867 clinical isolates from community-onset infections were collected from 31 secondary hospitals in People's Republic of China. The minimum inhibitory concentration (MIC) values of dicloxacillin were determined by the agar dilution method. Based on the MICs and the PK parameters of different dosage regimens, Monte Carlo simulation was performed to simulate the PK/pharmacodynamic indices of 250 mg once-daily (qd), 500 mg qd, 1,000 mg qd, 2,000 mg qd, 250 mg every 6 hours (q6h), and 500 mg q6h, respectively. The probability of target attainment was estimated at each MIC value, and the cumulative fraction of response (CFR) was calculated to evaluate the efficacy of these regimens.

Results: Dicloxacillin showed poor antibacterial activity against *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. Resistance to dicloxacillin was observed in 7.5% of coagulase-negative *Staphylococcus* (CNS) isolates and 9.2% of other *Streptococcus* isolates, whereas 1.5% of methicillin-sensitive *Staphylococcus aureus* (MSSA) was resistant to dicloxacillin. Multiple-dose regimens could obtain higher CFR than single-dose regimens against *H. influenza* and *S. pneumoniae*. However, all dosing regimens against MSSA achieved CFR ≥90%. Meanwhile, dosing regimen of 2,000 mg qd, 250 mg q6h, and 500 mg q6h could achieve >90% of CFR for CNS. For other *Streptococcus* isolates, multiple-dose regimens achieved CFR ≥90%.

Conclusion: Dicloxacillin has a significant antibacterial activity against MSSA, CNS, and other *Streptococcus* isolates. The simulation results suggest that dicloxacillin 250 mg q6h and 500 mg q6h dosing regimens may be recommended for clinical applications, especially for community-onset infections.

Keywords: pharmacokinetics, pharmacodynamics, PK/PD index, dosage regimens, MSSA, CNS

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Introduction

Dicloxacillin, as a semisynthetic penicillin antibiotic, acts by inhibiting the biosynthesis of bacterial cell walls. It is used in the treatment of infections caused by susceptible Gram-positive bacteria, especially for mild-to-moderate *Staphylococcal* infections.[1–3] It is worthy of note that dicloxacillin is insensitive to β-lactamase secreted by many penicillin-resistant bacteria.[4] The main cause lies in the presence of the isoxazolyl group on the side chain of the penicillin nucleus with relatively intolerant side-chain

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steric hindrance, resulting in unbound or inactivated β-lactamase.[5] In addition, several retrospective studies showed that definitive therapy for penicillin-susceptible *Staphylococcus aureus* bacteraemia with dicloxacillin was associated with a significantly lower mortality than was associated with cefuroxime therapy.[6,7]

In an era of increasing resistant pathogens prevalence, pharmacokinetics/pharmacodynamics (PK/PD) theory is helpful in optimizing the antimicrobial therapy to patients.[8] Studies on β-lactams against organisms have demonstrated that successful treatment outcome is associated with time-dependent bactericidal activity, and the efficacy of penicillins is dependent on the amount of time during which the serum drug concentration exceeds the minimum inhibitory concentration (MIC) of the antibiotic (%*T*> MIC). The optimal PK/PD target of %*T*> MIC has been estimated to be 40% for penicillins.[9]

Monte Carlo simulations are mainly used in three distinct problem classes: optimization, numerical integration, and generating draws from a probability distribution. The clinical probability of success for different dosing regimens of antibiotics can be predicted by Monte Carlo simulation.[10,11] Dicloxacillin is not marketed in Mainland China; however, the safety and PK data for a generic formulation of dicloxacillin sodium in healthy Chinese volunteers have been published in 2015.[12] Therefore, the primary objective of this study was to combine the results of PK with antibacterial activity to explore reasonable dosage regimens of dicloxacillin by using Monte Carlo simulation. The results will be provided as a basis for rational use of dicloxacillin in Chinese population in further clinical applications.

Materials and methods

Bacterial isolates

A total of 867 clinical isolates from community-onset infections were collected between August 2010 and December 2011 from 31 secondary hospitals in People's Republic of China. *Haemophilus influenzae* (n=54), *Moraxella catarrhalis* (n=56), methicillin-sensitive *S. aureus* (MSSA; n=388), coagulase-negative *Staphylococcus* (CNS; n=53), *Streptococcus pneumoniae* (n=262), and other *Streptococcus* isolates (ie, *β-hemolytic streptococcus*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Streptococcus dysgalactiae*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, and *Streptococcus viridans*; n=54) were included. Pathogens were isolated by using standard microbiological methods and identified by using API20 (bioMérieux, Durham, NC, USA). Isolates that had MIC of oxacillin ≤2 were identified as MSSA. All the pure cultures were frozen at −80°C and shipped to our central laboratory for definite identification and further analysis. Identification of species was ratified by Matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (VITEK® MS; bioMérieux, Nürtingen, Germany) as described previously.[13] Table 1 shows the basic characteristics of the isolates.

Antimicrobial susceptibility testing

The MICs for dicloxacillin (Bright Future Pharmaceuticals Factory, Hong Kong, People's Republic of China) were determined by the agar dilution method according to Clinical and Laboratory Standards Institute (CLSI).[14] The results were interpreted according to oxacillin interpretive standards of CLSI criteria (≤2 mg/L susceptible; ≥4 mg/L). *Escherichia coli* American Type Culture Collection (ATCC) 25922 and *S. aureus* ATCC 29213 were used as quality controls.

Monte Carlo simulation

Dicloxacillin, like other penicillins, displays time-dependent PD, and the bactericidal effect of it best correlates with %*T*> MIC.[9] In the present study, we simulated different dosing interval PK/PDs on the basis of a previous PK trial.[12] %*T*> MIC of 40% has been identified as the target for near-maximal bacterial killing.[9] In order to obtain the probability of target attainment (PTA) of MIC, the Crystal Ball software

Table 1 Basic characteristics of 867 clinical isolates

Isolates	Sex (n)		Age (years)	Infection site (n, %)						
	F	M		as	bl	dr	se	sp	ur	csf
Haemophilus influenzae (n=54)	20	34	6 (1–32)	–	–	–	–	54 (100%)	–	–
Moraxella catarrhalis (n=56)	27	29	2 (6 m–4)	–	–	–	–	56 (100%)	–	–
MSSA (n=388)	171	217	27 (6–48)	142 (36.6%)	28 (7.2%)	3 (0.8%)	132 (34.0%)	76 (19.6%)	7 (1.8%)	–
CNS (n=53)	30	23	30 (18–43)	2 (3.8%)	20 (37.7%)	2 (3.8%)	11 (20.8%)	2 (3.8%)	12 (22.6%)	4 (7.5%)
Streptococcus pneumoniae (n=262)	87	173	3 (1–55)	–	3 (1.1%)	2 (0.8%)	3 (1.1%)	248 (94.7%)	2 (0.8%)	4 (1.5%)
Other *Streptococcus* isolates (n=54)	29	25	36 (18–52)	13 (24.1)	3 (5.6%)	2 (3.7%)	13 (24.1%)	16 (29.6%)	7 (13%)	–

Note: '–' indicates no specimen.

Abbreviations: as, abscess; bl, blood; CNS, coagulase-negative *Staphylococcus*; csf, cerebrospinal fluid; dr, drainage; F, female; M, male; m, month; MSSA, methicillin-sensitive *Staphylococcus aureus*; se, secretion; sp, sputum; ur, urine.

was used to perform a 10,000 subject Monte Carlo simulation (MICs obey the discrete distribution, the PK index, volume of distribution, and half-life obey log-normal distribution). According to the PK index of different dosage regimens and MIC results, Monte Carlo simulation was used to simulate different dosage regimens' PK/PD characteristics (ie, 250 mg once-daily [qd], 500 mg qd, 1,000 mg qd, 2,000 mg qd, 250 mg every 6 hours (q6h), 500 mg q6h, respectively), in order to obtain the best dosing regimen. The cumulative fraction of response (CFR) was calculated to evaluate the efficacy of these regimens, and the results of %$T>$ MIC were calculated by using the following PK/PD equation:[15]

$$\%T > \mathrm{MIC} = \ln\left(\frac{\mathrm{Dose}}{\mathrm{Vd}\times\mathrm{MIC}}\right)\times\frac{T_{1/2}}{\ln(2)}\times\frac{100}{\mathrm{DI}}$$

where %$T>$ MIC is the proportion of time that the free serum concentration exceeds the MIC, ln is the natural logarithm, Dose is the intermittent dose in milligrams, Vd is the volume of distribution in L, MIC is the minimum inhibitory concentration in mg/L, $T_{1/2}$ is the half-life in hours, and DI is the dosing interval in hours.

Results

Determination of MICs

Table 2 shows the susceptibility test results for the 867 strains, and the MIC interpretive standards of dicloxacillin were usually interpreted according to oxacillin. Dicloxacillin showed poor antibacterial activity against *H. influenzae* and *M. catarrhalis*, with sensitive rates of 9% and 2%, respectively. Resistance to dicloxacillin was observed in 7.5% of CNS isolates and 9.2% of other *Streptococcus* isolates, whereas 1.5% of MSSA was resistant to dicloxacillin. Meanwhile, the MIC50 and MIC90 were lower (0.03 and 0.125, respectively). Less than 25% of *S. pneumoniae* isolates were susceptible to dicloxacillin.

Monte Carlo stimulation

In this study, based on the PK data of dicloxacillin oral administration with 250 mg qd, 500 mg qd, 1,000 mg qd, 2,000 mg qd, 250 mg q6h, and 500 mg q6h.[12] Crystal Ball software was used to perform a 10,000 subject Monte Carlo simulation for PK indices.[16] Tables 3 and 4 show the %$T>$ MIC of different dosage regimens and the target attainment rates, respectively. Among the single-dose regimens, %$T>$ MIC values of 250 mg qd, 500 mg qd, 1,000 mg qd, and 2,000 mg qd were achieved 40% only for dicloxacillin MIC ≤0.125 mg/L, ≤0.25 mg/L, ≤0.5 mg/L, and ≤0.1 mg/L, respectively. However, multiple-dose regimens (250 mg q6h and 500 mg q6h) against the strains with the MIC ≤4 mg/L and ≤8 mg/L could achieve 40% of %$T>$ MIC (Table 3). The target attainment rates of regimens 250 mg qd, 500 mg qd, 1,000 mg qd, 2,000 mg qd, 250 mg q6h, and 500 mg q6h against isolates with MIC ≤0.06 mg/L, ≤0.125 mg/L, ≤0.25 mg/L, ≤0.5 mg/L, and ≤4 mg/L, respectively, exceeded 90% (Table 4; Figure 1).

Table 2 Frequency distributions of dicloxacillin MIC against 867 clinical isolates

Isolates	Index	MIC range (mg/L)																MIC50 (mg/L)	MIC90 (mg/L)
		<0.015	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>128		
Haemophilus	n	0	0	0	0	0	0	1	1	3	9	9	17	6	3	1	4	16	64
influenzae	CN	0	0	0	0	0	0	1	2	5	14	23	40	46	49	50	54		
(n=54)	CP (%)	0	0	0	0	0	0	2	4	9	26	43	74	85	91	93	100		
Moraxella	n	0	1	0	0	0	0	0	0	0	0	0	1	1	6	27	20	128	>128
catarrhalis	CN	0	1	1	1	1	1	1	1	1	1	1	2	3	9	36	56		
(n=56)	CP (%)	0	2	2	2	2	2	2	2	2	2	2	4	5	16	64	100		
MSSA	n	52	0	273	0	47	6	3	1	0	1	1	1	3	0	0	0	0.03	0.125
(n=388)	CN	52	52	325	325	372	378	381	382	382	383	384	385	388	0	0	0		
	CP (%)	13	13	84	84	96	97	98	98	98	99	99	99	100	0	0	0		
CNS	n	36	0	2	0	0	1	5	4	1	1	0	2	0	1	0	0	<0.015	1
(n=53)	CN	36	36	38	38	38	39	44	48	49	50	50	52	52	53	0	0		
	CP (%)	68	68	72	72	72	74	83	91	92	94	94	98	98	100	0	0		
Streptococcus	n	0	1	4	0	7	12	15	15	8	19	80	82	19	0	0	0	8	16
pneumoniae	CN	0	1	5	5	12	24	39	54	62	81	161	243	262	0	0	0		
(n=262)	CP (%)	0	0	2	2	5	9	15	21	24	31	61	93	100	0	0	0		
Other	n	0	1	5	11	1	3	14	12	2	0	4	0	1	0	0	0	0.5	2
Streptococcus	CN	0	1	6	17	18	21	35	47	49	49	53	53	54	0	0	0		
isolates (n=54)	CP (%)	0	2	11	31	33	39	65	87	91	91	98	98	100	0	0	0		

Abbreviations: CN, cumulative number; CNS, coagulase-negative *Staphylococcus*; CP, cumulative percentage; MIC, minimum inhibitory concentration; MIC50, 50% of tested isolates were inhibited; MIC90, 90% of tested isolates were inhibited; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Table 3 %*T*> MIC of dicloxacillin at different dosage regimens

Dosage regimens	MIC (mg/L)									
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8
250 mg qd	57±6	52±5	46±5	40±4	35±3	29±3	23±3	17±2	12±2	6±2
500 mg qd	65±7	59±6	53±5	47±5	41±4	35±3	29±3	23±3	17±2	11±2
1,000 mg qd	73±7	67±7	60±6	54±5	48±5	41±4	35±4	29±3	22±3	16±2
2,000 mg qd	87±9	80±8	73±7	66±7	59±6	52±5	45±4	37±4	30±3	23±3
250 mg q6h	245±25	220±3	1,945±3	170±4	145±3	120±3	95±3	71±3	46±3	21±2
500 mg q6h	258±26	234±23	210±22	186±19	162±16	138±14	114±12	90±10	67±7	43±5

Note: Data are presented as mean ± SD.
Abbreviations: MIC, minimum inhibitory concentration; qd, once-daily; q6h, every 6 hours.

As shown in Table 5, none of the dosing regimen reached 40% of CFR against *M. catarrhalis*. Multiple-dose regimens could obtain higher CFR than single-dose regimens against *H. influenza* and *S. pneumoniae*. However, all dosing regimens against MSSA obtained CFR ≥90%. Meanwhile, dosing regimens of 2,000 mg qd, 250 mg q6h, and 500 mg q6h could obtain >90% of CFR for CNS. For other *Streptococcus* isolates, multiple-dose regimens achieved CFR ≥90%.

Discussion

Dicloxacillin is a semisynthetic isoxazolyl penicillin antibiotic, which has high β-lactamase stability and excellent activity against Gram-positive microorganisms.[1,5] Previous studies have proved that it showed time-dependent bactericidal activity and could be well tolerated in patients and volunteers.[12,17] Several studies on PK properties of dicloxacillin revealed that it can be rapidly absorbed after oral administration, with the higher serum concentration, absolute bioavailability, and cumulative urinary excretion compared with other isoxazole penicillins, such as oxacillin and cloxacillin.[18,19] In the present study, we provided the first comprehensive assessment of dicloxacillin dosing regimen against *H. influenzae*, *M. catarrhalis*, MSSA, CNS, *S. pneumoniae*, and other *Streptococcus* isolates for Chinese population, in order to optimize the use of dicloxacillin and reduce drug resistance.

Previous publication trial of dicloxacillin in healthy Chinese volunteers provides reference PK parameters for our Monte Carlo simulation.[12] They found that C_{max} and $AUC_{0-\infty}$ were approximately four times and five times higher in healthy Chinese subjects compared with Western population.[12,20] Part of that is due to lower body weight of Asian population, resulting in greater dicloxacillin exposure. Thus, it is necessary to apply the individual treatment for Easterners and Westerners, respectively; also worth noting that much of Chinese people live in rural areas and small towns, where county hospitals provide the first medical service most. Our study collected the community-onset strains from various secondary hospitals to estimate the effectiveness of dicloxacillin, in order to provide guidance on the clinical application in county hospitals. In this study, we observed that dicloxacillin has good bactericidal effect against MSSA, CNS, and other *Streptococcus* isolates. Previous studies proved that dicloxacillin had a significant antibacterial activity against *S. aureus*, *S. pneumonia*, *S. viridans*, and *S. agalactiae*.[21–23] However, the resistance rate of *S. pneumonia* is as high as 76.3% in the present study. Therefore, our results suggest that dicloxacillin had better antibacterial effect against MSSA, CNS, and other *Streptococcus* infection from the community, but not against infections caused by *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*. Beyond that, the propensity-score-adjusted retrospective cohort studies have demonstrated that 90-day mortality was higher for patients receiving cefuroxime compared with dicloxacillin.[6,7]

In our study, we used Monte Carlo simulation to compare PTA of different dosing regimens of dicloxacillin.

Table 4 PTA of 40% time above MIC for dicloxacillin at different dosage regimens

Dosage regimens	MIC (mg/L)										
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16
250 mg qd	99.97	99.27	91.03	51.71	7.78	0.05	0	0	0	0	0
500 mg qd	100	100	99.76	94.3	58.95	9.35	0.08	0	0	0	0
1,000 mg qd	100	100	100	99.88	95.74	63.01	9.84	0.1	0	0	0
2,000 mg qd	100	100	100	100	99.98	99.52	85.69	25.5	0.45	0	0
250 mg q6h	100	100	100	100	100	100	100	100	95.26	0	0
500 mg q6h	100	100	100	100	100	100	100	100	100	68.29	0

Abbreviations: MIC, minimum inhibitory concentration; qd, once-daily; q6h, every 6 hours; PTA, probability of target attainment.

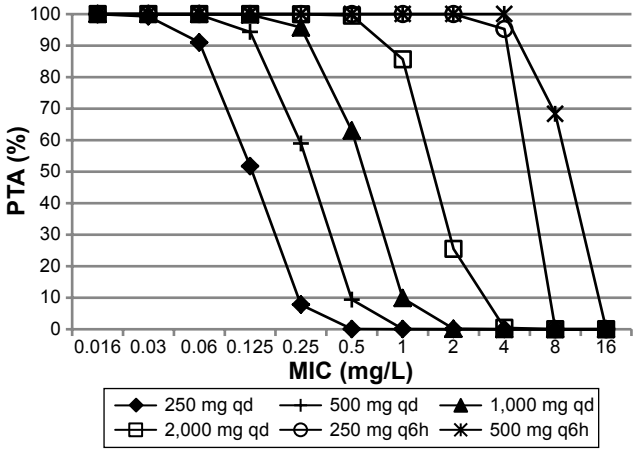

Figure 1 PTA-MIC curves of dicloxacillin at different dosage regimens.
Abbreviations: MIC, minimum inhibitory concentration; PTA, probability of target attainment; qd, once-daily; q6h, every 6 hours.

Monte Carlo simulation incorporates the variability of PK parameters in human and the range of possible MIC values in the given bacterials. The results could predict drug effect more accurately and comprehensively, thereby providing sound scientific evidence for empiric treatment of infection. For the penicillins, *T*%> MIC is the optimal PK/PD index associated with the drug-related responses. For these agents, optimizing the duration of exposure to effective concentrations could increase the rate or extent of killing. Sandberg et al[24] examined the intracellular and extracellular activities of dicloxacillin against two MSSA strains in vitro using macrophages and in vivo by using a mouse peritonitis model. They demonstrated that the %*T*> MIC index is best correlated with both intracellular and extracellular infection outcome. Although a value of ~10% is sufficient for a static effect, a value of 100% is required to obtain a maximal effect. With estimated mean MICs for penicillin-susceptible *S. aureus* of 0.125 mg/L for dicloxacillin, the free non-protein-bound plasma drug concentration %*T*> MIC would achieve 67% for dicloxacillin at doses of 1 g q6h.[7] We found that %*T*> MIC of dicloxacillin 250 mg q6h and 500 mg q6h achieved 40% against the strains with the MIC ≤4 mg/L and ≤8 mg/L. Furthermore, all dosing regimens against MSSA obtained CFR ≥90%. A prospective study indicated that dicloxacillin sodium of 1 g four times daily or 2 g three times daily with %*T*> MIC of 100% was superior to 1 g three times daily with %*T*> MIC of 75% in the treatment of *S. aureus* bacteremia infection.[25] Therefore, when the dosage and other conditions remain unchanged, shortening the intervals between each drug administration could obtain a satisfactory therapeutic effect.

To our knowledge, our study is the first to address the PK/PD target values of different dosage regimens in Chinese patients with community-acquired infection. The findings of this study are positive and encouraging in terms of dicloxacillin against MSSA, CNS, and other *Streptococcus* isolates by using Monte Carlo simulations, considering as a recurrence of a large number of cases in reality.

Limitations

However, it also has several limitations. First, the PK parameters of dicloxacillin were obtained from healthy subjects, which is not wholly equal to older population or patients with diseases. In addition, Monte Carlo simulations are a broad class of computational algorithms. Clinical application from our study should be made with caution until a randomized clinical trial could be performed.

Conclusion

Dicloxacillin has a significant antibacterial activity against MSSA, CNS, and other *Streptococcus* isolates. Based on PK/PD index values from volunteers, Monte Carlo simulations of 250 mg q6h and 500 mg q6h dosing regimens are recommended for clinical applications, especially for community-onset infections. The dosage regimen can be adjusted according to patients' infection status and expected target. Future prospective randomized controlled clinical trials are required to investigate the tolerability and clinical cure rates of dicloxacillin.

Table 5 CFR for dicloxacillin at different dosage regimens

Dosage regimens	*Haemophilus influenzae* (n=54)	*Moraxella catarrhalis* (n=56)	MSSA (n=388)	CNS (n=53)	*Streptococcus pneumoniae* (n=262)	Other *Streptococcus* isolates (n=54)	Gram-positive bacteria (n=757)	Total (n=867)
250 mg qd	0.0%	1.8%	89.6%	71.8%	3.6%	31.0%	54.4%	47.6%
500 mg qd	0.2%	1.8%	96.2%	73.7%	7.7%	38.9%	59.9%	52.4%
1,000 mg qd	1.4%	1.8%	97.9%	80.2%	13.1%	57.2%	64.4%	56.4%
2,000 mg qd	4.9%	1.8%	98.4%	89.9%	20.6%	84.7%	69.9%	61.5%
250 mg q6h	25.1%	1.8%	98.7%	94.3%	30.6%	90.7%	74.2%	66.5%
500 mg q6h	37.3%	1.8%	98.9%	94.3%	51.8%	95.8%	82.0%	74.1%

Abbreviations: CFR, cumulative fraction of response; CNS, coagulase-negative *Staphylococcus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; qd, once-daily; q6h, every 6 hours.

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Author contributions

YHX and WY developed the concept and designed the experiments. JRJ, TTX, and CQY performed the experiments. WY and JRJ performed Monte Carlo simulation. JHF and PS gave conceptual advice. WY wrote the paper. All the authors discussed the results and implications and commented on the manuscript at all stages. All authors contributed toward data analysis, drafting and revising the paper 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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