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Is there a pharmacodynamic need for the use of continuous versus intermittent infusion with ceftazidime against *Pseudomonas aeruginosa*? An *in vitro* pharmacodynamic model

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***Objectives*: In order to explore the pharmacodynamic need for continuous versus intermittent (three times a day) administration of ceftazidime in critically ill patients, a pharmacokinetic computerized device was used to simulate concentrations of ceftazidime in human serum after 6 g/day.**

***Methods*: Efficacy was measured as the capability of simulated concentrations over time to reduce initial inoculum against four strains of *Pseudomonas aeruginosa*. MICs of the strains matched NCCLS breakpoints: one susceptible strain (MIC = 8 mg/L), two intermediate strains (MIC = 16 mg/L) and one resistant strain (MIC = 32 mg/L). C_{max} was 119.97 ± 2.53 mg/L for intermittent bolus and C_{ss} (steady-state concentration) was 40.38 ± 0.16 mg/L for continuous infusion. AUC_{0-24} was similar for both regimens (~950 mg·h/L). Inhibitory quotients were three times higher for the intermittent administration whereas $t > MIC$ was higher for continuous infusion (100%) versus intermittent administration (99.8%, 69% and 47.6% for the susceptible, intermediate and resistant strains, respectively).**

***Results*: Against the susceptible and intermediate strains, no differences were found between both regimens with $\geq 3 \log_{10}$ reduction from 8 to 24 h. Against the resistant strain, only the continuous infusion achieved this bactericidal activity in the same time period, minimizing the differences between resistant and susceptible strains. Significantly higher initial inoculum reduction at 32 h was obtained for the continuous versus the intermittent administration (83.35% versus 38.40%, respectively).**

***Conclusions*: These results stress the importance of optimizing $t > MIC$, even at peri-MIC concentrations, of ceftazidime against resistant strains. Local prevalence of resistance justifies, on a pharmacodynamic basis, electing for continuous infusion versus intermittent administration.**

Keywords: *P. aeruginosa*, ceftazidime, continuous infusion, pharmacodynamics

Introduction

Pseudomonas aeruginosa is a nosocomial pathogen responsible for infections in immunocompromised hosts, in whom antibiotics are the only agents from which we should expect efficacy. Ceftazidime is one of the most active antimicrobials against this bacterium, with 15% non-susceptibility prevalence (MIC ≥ 16 mg/L) in Spain.[1]

Time–kill curves for β-lactams against *P. aeruginosa* show time-dependent killing which is maximal at relatively low concentrations,[2,3] with concentrations of 2× MIC still demonstrating *in vitro* bactericidal activity 6–8 h after exposure, supporting the hypothesis that peri-MIC concentrations may be sufficient to achieve killing over a 24 h period.[4] β-Lactams are concentration-independent drugs and the rate of bactericidal activity is not significantly increased when the concentration is increased by multiples of the MIC.[5] The time above the MIC ($t > MIC$) is considered the best parameter to predict the extent of bactericidal activity and the *in vivo* activity of β-lactam antibacterial agents,[6,7] and one particularly attractive option to increase $t > MIC$ for parenteral agents is the use of continuous infusion.[8]

This study aimed to determine the ability to decrease initial inocula over time of ceftazidime serum simulated concentrations after 6 g daily dose administered as continuous infusion (CI) versus intermittent administration (2 g/8 h). The 6 g/day dose was used for both administrations to explore which administration

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regimen is more efficacious, with regard to the susceptibility of the *P. aeruginosa* strains tested, by using the same daily dose that resulted in similar AUC_{0-24} (i.e. same antibiotic amount/24 h). This AUC_{0-24} is similar to that obtained in humans with the 2 g/8 h regimen.[7] To this end, one strain fully resistant to ceftazidime (MIC = 32 mg/L), two intermediate-resistant strains with MIC = 16 mg/L and one susceptible strain with MIC = 8 mg/L were tested.

Materials and methods

Bacterial strains

One strain of *Pseudomonas aeruginosa* with ceftazidime MIC of 8 mg/L, two strains with MIC of 16 mg/L, and one strain with MIC 32 mg/L were studied in this *in vitro* pharmacodynamic model. All strains were clinical isolates from ventilator-associated pneumonia obtained in the intensive care unit.

Antibiotic

The laboratory reference standard of ceftazidime was supplied by GlaxoSmithKline (Worthing, UK).

MIC determination

MICs were determined by microdilution following NCCLS methodology[9] in Mueller–Hinton (Difco Laboratories, Detroit, MI, USA) broth supplemented with calcium and magnesium. All determinations were carried out at least five times and modal values were considered.

In vitro kinetic model

The model, with full computer-controlled devices, is derived from the original two-compartment kinetic model proposed by Blaser and colleagues.[10,11] The central compartment, representing the systemic circulation, consists of a spinner flask with 400 mL of culture broth, tubing and lumina of capillaries within a dialyser unit (FX50, Fresenius Medical Care S.A., Barcelona, Spain). The inclusion of a second compartment—peripheral or infection compartment—consisting of the extra-capillary space of the dialyser unit plus external circulation tubing, allows the simulation of first order kinetics but avoids the dilution of the bacterial inoculum together with the antibiotic. The 1 m^2 of surface area between the two compartments (between the hollow fibre and the extra-capillary space of the dialyser) and the high permeability of the helixone membrane of FX class dialysers, allow a rapid rate of drug equilibrium to be reached across dialyser membranes, allow bi-directional diffusion of antibiotics and nutrients and prevent bacterial penetration into the central compartment. Dialysers are placed in a 37°C incubator. Computerized peristaltic pumps (Masterflex, Cole-Parmer Instrument Co., Chicago, IL, USA) draw the medium, at a programmed rate, from the reservoir of fresh medium [placed in a 37°C waterbath (HB 4 basic, IKA, Staufen, Germany)] to the central compartment for antibiotic dilution. The antibiotic was supplied by direct infusion into the central compartment at the target C_{max}. The antibiotic-containing medium is pumped at a 32 mL/min rate to the peripheral compartment, where it diffuses through the capillary membrane and it is distributed in the extra-capillary space, where the antibiotic interacts with bacteria. Additional pumps circulate the antibiotic-medium mixture at a 25 mL/min rate within the extra-capillary space through external tubing. Afterwards, the mixture is re-circulated back to the central compartment. The elimination of the medium at the same rate as the replacement of fresh medium in the central compartment, allows the simulation of the antibiotic half-life ($t_{1/2}$).

Kinetic simulations

Ceftazidime serum concentrations obtained after intermittent intravenous administration of 2000 mg/8 h (total daily dose 6 g) and after intravenous administration of a loading dose of 1000 mg followed by 6 g/day in continuous infusion were simulated over 32 h. The target pharmacokinetic parameters, based on values reported in humans, were C_{max} = 120 mg/L and $t_{1/2}$ = 1.9 h for the intermittent administration[7,12] C_{max} = 60 mg/L (after the loading dose) and steady-state concentration (C_{ss}) = 40 mg/L for the continuous infusion administration.[13,14] To simulate the continuous infusion profile using the same clearance (2.43 mL/min) as the intravenous administration, 1 h after the loading dose, ceftazidime was administered into the fresh medium reservoir at a final concentration of 40 mg/L. The reservoir was replaced periodically to avoid temperature degradation of ceftazidime.

Experiments

Before each experiment, 1–2 colonies from a fresh passage on Mueller–Hinton agar supplemented with cations and 5% lysed sheep blood, were incorporated in 60 mL of Mueller–Hinton broth supplemented with cations. The resulting suspension was allowed to grow to obtain a final concentration of 10^8 cfu/mL as measured by a UV-spectrophotometer (Hitachi U-1100). An aliquot of 50 mL of this initial inoculum was introduced into the peripheral compartment of the *in vitro* simulation model. All initial inocula were in the range of 2.0×10^7 to 1.0×10^8 cfu/mL. Samples (0.5 mL) from the peripheral compartment were collected at 0, 2, 4, 6, 8, 10, 24, 26, 28, 30 and 32 h. Each sample was 10-fold serially diluted in 0.9% sodium chloride for bacterial counting in supplemented Mueller–Hinton agar with 5% sheep blood incubated at 37°C for 24 h. At least five dilutions of each sample (including the non-diluted sample) were plated. Each experiment was carried out in triplicate. The limit of detection was 2×10^1 cfu/mL.

Pharmacokinetic analysis

Pharmacokinetic analysis was carried out, in bacteria-free dialysers under the same conditions as those carried out with bacteria. Experimental antibiotic concentrations were confirmed by bioassay[15] using *Bacillus subtilis* ATCC 6633. To this end, samples (0.5 mL) from the peripheral compartment were obtained at 15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 8 h, 8 h 15 min, 8 h 30 min, 16 h, 16 h 15 min, 16 h 30 min, 24 h, 24 h 15 min, 24 h 30 min and 32 h. The samples or standard concentrations were deposited into 4 mm wells of agar inoculated with an even spread of the indicator organism. Plates were incubated for 18 to 24 h at 37°C. All pharmacokinetic determinations were carried out in triplicate.

Drug concentrations were analysed by a non-compartmental approach (iv-bolus input model or constant infusion input model) using WinNonlin Professional program (Pharsight, Mountainview, CA, USA). The apparent elimination rate constant (k_{el}) was calculated as the best-fit slope obtained from linear regression using the last measurements in the terminal phase of the curve (at least three time–concentration pairs). The area under the concentration–time curve (AUC) over the dosing interval was calculated by the trapezoidal rule, and C_{max} was estimated by log-linear regression of the first two time points. The time that concentrations exceeded the MIC (t > MIC) was calculated graphically by plotting mean

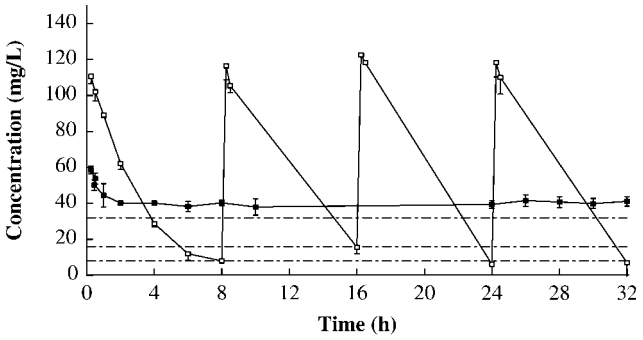

Figure 1. Mean ± S.D. experimental antibiotic concentration profiles over 32 h determined for the 6 g continuous infusion (filled squares) and the 2 g/8 h intermittent (open squares) administration. MICs are represented by dotted lines.

concentrations at each time point versus time. Inhibitory quotients (IQs) were calculated: IQ = C_{max}/MIC for intermittent administration and IQ = C_{ss}/MIC for continuous infusion.

Statistical analysis

Mean cfu/mL were calculated from the three values of colony counts at each time point of the 32 h simulation. Initial inoculum reduction (IIR) at a particular time point was calculated using the expression:

$$\%\text{IIR} = 100 - (100 \times I_t)/I_o$$

where I_t is the bacterial count at the desired time point and I_o is the initial inoculum (time 0). The initial inoculum was set at 100% (IIR at time 0 = 0%). Differences in %IIR between treatments at each time point were compared with the two-tailed Student's *t*-test. Analysis of variance with Tukey's *post-hoc* test for multiple comparisons was used to compare %IIR among strains at each time point. Owing to multiple comparisons, a P value ≤ 0.01 was considered statically significant.

Results

Figure 1 shows the experimental antibiotic concentration profiles over 32 h and Table 1 shows the experimental pharmacokinetic/pharmacodynamic parameters determined for the 6 g continuous infusion and the 2 g/8 h intermittent administration. C_{max} and C_{trough} (concentration before the next dose) with intermittent administration were (mg/L): 119.97 ± 2.53 and 9.17 ± 4.33, respectively, whereas C_{ss} was 40.38 ± 0.16 mg/L for continuous infusion.

Tables 2 and 3 show initial inoculum reduction (IIR; as percentage) over 32 h for the four strains with intermittent and continuous infusion, respectively. Figure 2 shows reductions in $\log_{10}$ cfu/mL at 8, 24 and 32 h. From 10 h on, both regimens produced a ≥ 3 $\log_{10}$ reduction against the susceptible and intermediate strains. Differences were found between these strains and the fully resistant strain, with the intermittent administration, that produced reductions of 2–3 $\log_{10}$ from 16 to 28 h and < 1 $\log_{10}$ afterwards against the resistant strain (differences were significant at 30 and 32 h). These differences between the resistant strain (MIC = 32 mg/L) and the other strains tested (MIC = 8–16 mg/L) were minimized with the continuous infusion since, against the resistant strain, reductions > 2 $\log_{10}$ were obtained from 4 to 26 h, with ∼1 $\log_{10}$ reduction afterwards (significant difference at 32 h).

As shown in Tables 2 and 3, a uniform IIR (≥ 99.99%) from 24 h on was obtained against strains 1, 2 and 3, with both intermittent and continuous infusion. Against strain 4, and in comparison with strains 1, 2 and 3, at times 30 and 32 h for intermittent infusion and at 32 h for continuous infusion (but not

Table 1. Experimental pharmacokinetic parameters for ceftazidime as intermittent administration and as continuous infusion

Parameter (unit)	Value (mean ± S.D.)	
	Intermittent bolus	Continuous infusion
C_{max} (mg/L)	119.97 ± 2.53	58.59 ± 2.21[a]
C_{ss} (mg/L)[b]	–	40.38 ± 0.16
$t_{1/2}$ (h)	1.82 ± 0.25	–
AUC (mg·h/L)[c]	322.22 ± 19.25	944.76 ± 25.52
IQ[d] strain 1 (MIC = 8 mg/L)	15.00	5.05
IQ[d] strains 2 & 3 (MIC = 16 mg/L)	7.50	2.52
IQ[d] strain 4 (MIC = 32 mg/L)	3.75	1.26
t > MIC (%)[e] strain 1 (MIC = 8 mg/L)	99.8	100
t > MIC (%)[e] strains 2 & 3 (MIC = 16 mg/L)	69.0	100
t > MIC (%)[e] strain 4 (MIC = 32 mg/L)	47.6	100
AUC_{0-24}/MIC strain 1 (MIC = 8 mg/L)	120.83	118.10
AUC_{0-24}/MIC strains 2 & 3 (MIC = 16 mg/L)	60.42	59.05
AUC_{0-24}/MIC strain 4 (MIC = 32 mg/L)	30.21	29.52

[a] C_{max} of the loading dose.
[b] Steady-state concentration.
[c] 0 to 8 h for intermittent bolus and 0 to 24 h for continuous infusion.
[d] IQ, inhibitory quotient; C_{max}/MIC for intermittent administration, C_{ss}/MIC for continuous administration.
[e] t > MIC (%) = percentage of the dosing interval that serum concentrations exceed the MIC.

Table 2. Mean reduction (%) in initial inocula over 32 h obtained with intermittent infusion (2 g/8 h) against the four strains tested

Time (h)	Strain 1 (MIC = 8 mg/L)	Strain 2 (MIC = 16 mg/L)	Strain 3 (MIC = 16 mg/L)	Strain 4 (MIC = 32 mg/L)
2	95.29 ± 0.52	96.46 ± 1.49	90.71 ± 2.99	80.75 ± 14.45
4	95.71 ± 0.37	94.03 ± 8.57	97.86 ± 2.35	99.64 ± 0.20
6	97.78 ± 0.52	97.87 ± 2.93	98.65 ± 0.33	97.62 ± 3.20
8	99.97 ± 0.02	99.85 ± 0.19	99.88 ± 0.07	95.84 ± 5.44
10	99.96 ± 0.02	99.98 ± 0.02	99.98 ± 0.01	99.51 ± 0.68
16	99.97 ± 0.03	> 99.99 ± 0.00	> 99.99 ± 0.00	95.73 ± 6.03
24	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00	97.75 ± 2.65
26	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00	98.94 ± 1.12
28	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00	96.58 ± 4.04
30	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00	88.85[a] ± 5.84
32	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00	38.40[a] ± 29.93

[a]Statistical differences ($P < 0.01$) versus all other strains.

Table 3. Mean reduction (%) in initial inocula over 32 h obtained with continuous infusion (6 g/24 h) against the four strains tested

Time (h)	Strain 1 (MIC = 8 mg/L)	Strain 2 (MIC = 16 mg/L)	Strain 3 (MIC = 16 mg/L)	Strain 4 (MIC = 32 mg/L)
2	97.98 ± 0.58	92.10 ± 3.18	67.92 ± 5.47	83.56 ± 13.18
4	98.65 ± 1.26	97.72 ± 2.20	90.69 ± 10.73	99.26 ± 0.63
6	99.90 ± 0.07	99.89 ± 0.04	99.11 ± 1.02	99.97 ± 0.01
8	99.98 ± 0.01	99.98 ± 0.01	99.93 ± 0.06	99.99 ± 0.01
10	99.99 ± 0.01	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00
24	> 99.99 ± 0.01	> 99.99 ± 0.00	> 99.99 ± 0.00	99.86 ± 0.10
26	> 99.99 ± 0.01	> 99.99 ± 0.00	> 99.99 ± 0.00	99.53 ± 0.37
28	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00	97.22 ± 2.73
30	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00	92.35 ± 7.57
32	> 99.99 ± 0.00	> 99.99 ± 0.00	> 99.99 ± 0.00	83.35[a,b] ± 5.75

[a]Statistical differences ($P < 0.01$) versus all other strains.
[b]Statistical difference ($P < 0.01$) at this time point between intermittent and continuous infusion with this strain (Table 2).

at previous time points), significantly ($P \leq 0.01$) lower IIR values were obtained, meaning a regrowth of strain 4. As can be seen, at these time points, IIR values were lower (≤90%) than IIR values at previous time points (≥95%). This regrowth was much lower for continuous than for intermittent infusion, as shown by the significant ($P \leq 0.01$) differences between IIR values at 32 h (83.35 ± 5.7 versus 38.40 ± 29.93).

As can be seen in Figure 2, a ≥3 $\log_{10}$ reduction against all strains was only obtained in the first 24 h with continuous infusion, and never with the intermittent infusion against the resistant strain.

Discussion

Ceftazidime is one of the most active antibiotics against *P. aeruginosa* as shown in a multicentre study in 136 Spanish hospitals.[16] Since there are no antimicrobials uniformly active against *P. aeruginosa*,[1] it is convenient to have available pharmacodynamic alternatives to achieve the highest antibacterial activity with the same amount of drug.

β-Lactam antibiotics do not exert concentration-dependent killing and do not have a post-antibiotic effect against Gram-negative bacilli,[17] and the possibility that resistance emerges, implies the need to keep concentrations over time well above the MIC.[17] There is pre-clinical and clinical evidence that serum drug concentrations should reach 4–5 times the MIC to exert

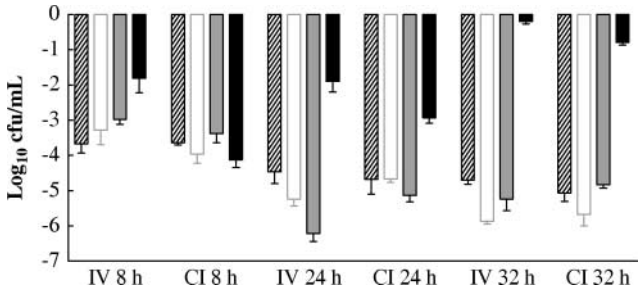

Figure 2. Reductions in $\log_{10}$ cfu/mL at 8, 24 and 32 h obtained with intermittent administration (IV) and continuous infusion (CI) against strains with MIC = 8 mg/L (striped bars), MIC = 16 mg/L (white and grey bars), and MIC = 32 mg/L (filled bars).

maximum bactericidal effect.[2,18] These values are difficult to obtain with *P. aeruginosa*.

In this study, from the pharmacodynamic point of view, a daily dose of 6 g/day was tested as continuous infusion or intermittent infusion, in both cases obtaining similar AUC_{0-24} ($\sim$950 mg·h/L), to match the value obtained in critically ill patients with Gram-negative infections after 2 g/8 h administration.[7] Pharmacodynamic differences between the regimens were $t>MIC$ that was higher for the continuous infusion (100%), and IQs that were three times higher for the intermittent infusion.

The higher differences between the resistant strain and those with MIC $\leq$ 16 mg/L for intermittent versus continuous administration can be attributed to the fact that $t>MIC$ (which favours continuous infusion) is the pharmacodynamic parameter linked to efficacy, since AUC_{0-24}/MIC are similar for both regimens and IQs favour intermittent administration (which against the resistant strain showed lower initial inocula reduction). IQs seem to have significance in continuous infusion (when $t>MIC$ is 100% against all strains) at least in relation to regrowth after 24 h. In this simulation, when IQs (C_{ss}/MIC) are above 2.5, no regrowth occurred (as with strains 1, 2 and 3). IQ (C_{max}/MIC) has no such relevance in the experiment with an intermittent bolus, because despite the IQs being always higher than those for continuous infusion, regrowth (higher than with continuous infusion) occurred only when $t>MIC$ was very low ($<50\%$) as with strain 4. Maintenance of $t>MIC$ for 100% of the dosing interval, even at peri-MIC concentrations against highly resistant strains, is important to predict therapeutic efficacy with empirical treatments taking into account the possibility of resistant strains in critically ill patients. Continuous infusion is a good method for optimizing $t>MIC$. Other authors have reported efficacy in experimental endocarditis using ceftazidime continuous infusion (with or without amikacin) provided that the C_{ss} reached $4\times MIC$ of the susceptible strains used (MIC $\leq$ 8 mg/L).[19] Further studies are needed to explore whether the addition of amikacin to the ceftazidime continuous infusion regimen could eliminate the difference between the resistant and intermediate or susceptible strains at the end of the simulation, as well as the relative regrowth obtained after 24 h.

The results of this study showed that intermittent infusion produced bactericidal activity over time against the susceptible and intermediate strains but not against the resistant strain. The resistance prevalence of 15% in previous surveillance studies[1] justifies electing for continuous infusion of ceftazidime because of its higher bactericidal activity and capability for regrowth prevention against the strains used: susceptible, intermediate and resistant in a clinical environment where continuous infusion has been at least as effective as intermittent administration in severe infections.[7,13]

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