Inhibiteurs de β-lactamases
Pharmacokinetics-Pharmacodynamics of Tazobactam in Combination with Ceftolozane in an In Vitro Infection Model

Brian VanScyoc,a Rodrigo E. Mendes,b Anthony M. Nicasio,c Mariana Castanheira,d Catharine C. Bulik,e Olanrewaju O. Okusanya,e Sujata M. Bhavnani,a Alan Forrest,a Ronald N. Jones,b Lawrence V. Friedrich,d Judith N. Steenbergen,d Paul G. Ambrosea,e

Institute for Clinical Pharmacodynamics, Latham, New York, USAa; JMI Laboratories, North Liberty, Iowa, USA; Albany College of Pharmacy and Health Sciences, Albany, New York, USA; Cubist Pharmaceuticals, Lexington, Massachusetts, USA; University of Oxford, Oxford, United Kingdom

Objectives:

1. identify the exposure measure (e.g., area under the concentration-time curve[AUC], maximal concentration [C\text{\text{max}}], or the percentage of the dosing interval that the drug concentration remains above a threshold concentration [%\text{Timethreshold}]) that best predicts tazobactam efficacy in combination with ceftolozane

2. determine the magnitude of the exposure measure associated with net bacterial stasis and a 1- and 2-log10 CFU reduction in bacteria at 24 h.

3. determine the impact of various -lactamase transcription levels on the magnitude of the exposure measure associated with efficacy.
Un des premiers articles...
Pharmacocinétique/pharmacodynamie (PK/PD) des antibiotiques

Un des premiers articles…

TABLE 1 Susceptibility testing results and hydrolytic activity rates for ceftolozane alone and in combination with tazobactam at 4 μg/ml against E. coli strains producing different levels of CTX-M-15

<table>
<thead>
<tr>
<th>E. coli strain</th>
<th>MIC (μg/ml)</th>
<th>Hydrolytic activity</th>
<th>qRT-PCRd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftolozane alone</td>
<td>Ceftolozane + TAZb (4 μg/ml)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.25</td>
<td>0.25</td>
<td>-3</td>
</tr>
<tr>
<td>Low producer</td>
<td>4</td>
<td>0.25</td>
<td>36</td>
</tr>
<tr>
<td>Moderate producer</td>
<td>16</td>
<td>0.25</td>
<td>120</td>
</tr>
<tr>
<td>High producer</td>
<td>64</td>
<td>0.25</td>
<td>580</td>
</tr>
</tbody>
</table>

a The transcription levels of blaCTX-M-15 are also shown.
b TAZ, tazobactam.
c Hydrolytic activity rates expressed as the amount (mg) of ceftolozane hydrolyzed per minute per milligram of protein.
d Expression of blaCTX-M-15 relative to the E. coli strain demonstrating the lowest CTX-M-15 production based upon MIC results and hydrolysis assays for β-lactams. ND, not detected.
Pharmacokinetics-Pharmacodynamics of Tazobactam with Ceftolozane in an In Vitro Infection Model

Brian VanScoy, Rodrigo E. Mendes, Anthony M. Nicasio, Mariana Castanheira, Sujata M. Bhavnani, Alan Forrest, Ronald N. Jones, Lawrence V. Friedrich, Judy J. O'Sullivan

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<th>Ceftolozane alone</th>
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<tbody>
<tr>
<td>Control</td>
<td>0.25</td>
<td>0.25</td>
<td>−3</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Low producer</td>
<td>4</td>
<td>0.25</td>
<td>36</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moderate producer</td>
<td>16</td>
<td>0.25</td>
<td>120</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>High producer</td>
<td>64</td>
<td>0.25</td>
<td>580</td>
<td>43.9</td>
<td></td>
</tr>
</tbody>
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d Expression of blaCTX-M-15 relative to the E. coli strain demonstrating the lowest CTX-M-15 production based upon MIC results and hydrolysis assays for β-lactams. ND, not detected.

FIG 2 Dose fractionation study results for the low- (A), medium- (B) and high-level (C) CTX-M-15-producing E. coli. The effect of each active regimen is shown relative to the no-treatment controls. CXA-101, ceftolozane; Tazo, tazobactam; Q8h, every 8 h.
Un des premiers articles...

Antimicrob Agents Chemother
2013;57:2809–2814

**FIG 3** Relationships between three tazobactam exposure measures, AUC, $C_{\text{max}}$, and %Time>$\text{threshold}$, and the change in log$_{10}$ CFU of isogenic CTX-M-15-producing *E. coli* after 24 h of therapy in a PK-PD *in vitro* infection model. The color of the symbols represent the different dose fractionation schedules, while the shape of the symbol represents the level of β-lactamase production. $C_{\text{max}}$ is shown in micrograms per milliliter. $^1$, the threshold concentration was 0.05 μg/ml for the low- and moderate-β-lactamase genetic constructs and 0.25 μg/ml for the high-β-lactamase genetic construct.
Un des premiers articles...

Antimicrob Agents Chemother
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FIG 4 Relationships between tazobactam %Time > threshold and the change in log₁₀ CFU of low-, medium- and high-level CTX-M-15-producing *E. coli* after 24 h of therapy in a PK-PD *in vitro* infection model. The threshold concentrations are given in micrograms per milliliter.
Observations:

1. The exposure measure associated with efficacy was the percentage of the dosing interval that tazobactam concentrations remained above a threshold (%Time>threshold), regardless of enzyme expression.

2. The threshold concentrations identified were 0.05 µg/ml for low and moderate, and 0.25 µg/ml for the high-β-lactamase expression strain constructs.

3. The magnitudes of %Time>threshold for tazobactam associated with net bacterial stasis and a 1- and 2-log10 CFU reduction in bacteria at 24 h were approximately 35, 50, and 70%, respectively.
Objectives:

1. to characterize the relationship between tazobactam %Time>threshold and efficacy for 4 β-lactamase-producing clinical *E. coli* isolates.

2. identify a translational relationship that would allow for comodeling of the relationship between %Time>threshold and efficacy.

3. to evaluate the translational relationship to other ESBL-producing Enterobactriaceae by including 3 well-characterized β-lactamase-producing clinical *Klebsiella pneumoniae* isolates.

4. to allow for the forecasting of effective and noneffective clinical regimens from preclinical models systems based upon in vitro susceptibility test results.
Un deuxième article ... avec des souches cliniques...

**TABLE 1** Susceptibility testing results for ceftolozane and ceftolozane combined with tazobactam against an *E. coli* ATCC control strain and seven clinical isolates

<table>
<thead>
<tr>
<th>Species and isolate</th>
<th>Microtiter MIC (mg/liter)</th>
<th>MBC (mg/liter), ceftolozane-tazobactam (4 mg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftolozane alone</td>
<td>Ceftolozane-tazobactam (4 mg/liter)</td>
</tr>
<tr>
<td><strong>E. coli</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATCC 25922</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>4643A</td>
<td>128</td>
<td>0.5</td>
</tr>
<tr>
<td>1801A</td>
<td>128</td>
<td>0.5</td>
</tr>
<tr>
<td>21711R</td>
<td>256</td>
<td>2</td>
</tr>
<tr>
<td>13319R</td>
<td>512</td>
<td>4</td>
</tr>
<tr>
<td><strong>K. pneumoniae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>604C</td>
<td>256</td>
<td>1</td>
</tr>
<tr>
<td>21904E</td>
<td>512</td>
<td>2</td>
</tr>
<tr>
<td>4812E</td>
<td>512</td>
<td>4</td>
</tr>
</tbody>
</table>
FIG 2 Dose-ranging study results for each of the four *E. coli* (A to D) clinical isolates. The effect of each active regimen relative to the no-treatment controls is shown. TOL, ceftolozane; TAZ, tazobactam. Error bars represent the range of data over two studies.
FIG 2 Dose-ranging study results for each of the three *K. pneumoniae* (Kp) (E to G) clinical isolates. The effect of each active regimen relative to the no-treatment controls is shown. TOL, ceftolozane; TAZ, tazobactam. Error bars represent the range of data over two studies.
Un deuxième article ... avec des souches cliniques...

**Pharmacological Basis of β-Lactamase Inhibitor Tazobactam in Combination**

Brian VanScy, a Rodrigo E. Mendes, b Jennifer McCaul, a Alan Forrest, a Ronald N. Jones, b Lawrence V. Friedrich b

Institute for Clinical Pharmacodynamics, Latham, New York, USA a, J
University of Oxford, Oxford, United Kingdom b

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**FIG 3** Relationships between tazobactam %Time>threshold and change in log_{10} CFU from baseline at 24 h for the four *E. coli* clinical isolates in a PK-PD *in vitro* infection model. Data points and fitted functions for each isolate are represented by different colors. The threshold for each isolate was identified using an iterative process which allowed for evaluation of dispersion of data along the %Time>threshold axis and optimization of $r^2$ values.

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all *E. coli* individually
Un deuxième article ... avec des souches cliniques...

Pharmacological Basis of β-Lactamase Inhibitor Tazobactam in Combination with Antimicrobial Agents

Brian VanScoy, Rodrigo E. Mendes, Jennifer McCauley, S. Alan Forrest, Ronald N. Jones, Lawrence V. Friedrich, Judy Kay

Institute for Clinical Pharmacodynamics, Latham, New York, USA; JMI Laboratories, University of Oxford, Oxford, United Kingdom

all *E. coli* together with threshold = MIC x 0.5

FIG 4 Relationship between tazobactam %Time>threshold and change in log_{10} CFU from baseline at 24 h for the four *E. coli* clinical isolates in a PK-PD *in vitro* infection model. Isolates are represented by different colors. The black line represents the fitted function for the pooled data across isolates. The threshold for each isolate represented the product of the ceftolozane-tazobactam MIC for the individual isolate and 0.5.
Un deuxième article … avec des souches cliniques…

all *E. coli* together with treshold = MIC x 0.5

**FIG 4** Relationship between tazobactam %Time>threshold and change in log_{10} CFU from baseline at 24 h for the four *E. coli* clinical isolates in a PK-PD *in vitro* infection model. Isolates are represented by different colors. The black line represents the fitted function for the pooled data across isolates. The threshold for each isolate represented the product of the ceftolozane-tazobactam MIC for the individual isolate and 0.5.
Un deuxième article ... avec des souches cliniques...

**Pharmacological Basis for the Antimicrobial Activity of Tazobactam in Combination with Ceftolozane**

Brian VanScoy, a Rodrigo E. Mendes, b Alan Forrest, a Ronald N. Jones, b Laura P. Boysa, a
Institute for Clinical Pharmacodynamics, LabCorp, Durham, North Carolina, United States

**FIG 5** Relationship between tazobactam %Time>threshold and change in log_{10} CFU from baseline at 24 h for the four *E. coli* and three *K. pneumoniae* clinical isolates in a PK-PD *in vitro* infection model. Isolates are represented by different colors. The black line represents the fitted function for the pooled data across isolates. The threshold for each isolate represented the product of the ceftolozane-tazobactam MIC for the individual isolate and 0.5.

All *E. coli* and *K. pneumoniae* with threshold = MIC x 0.5
Observations:

1. The data were well described by fitted functions describing the relationship between the tazobactam %Time>threshold and change in log_{10} CFU from baseline.

2. We identified an enabling translational relationship for the tazobactam threshold that allowed comodeling of all four clinical isolates, which was the product of the individual isolate’s ceftolozane-tazobactam MIC value and 0.5.

3. The translational relationship for the tazobactam threshold performed well for the expanded data set (seven isolates in total; four E. coli and three K. pneumoniae).

4. This simple translational relationship is especially useful as it is directly linked to in vitro susceptibility test results, which are used to guide the clinician’s choice of drug and dosing regimen.
Objectives and means:

1. to use the neutropenic mouse infection models (thigh infection and pneumonia) with ceftazidime-resistant Pseudomonas aeruginosa to determine the exposure-response relationship of ceftazidime alone and to derive estimates of pharmacodynamic indices (PDI) over 24 h for avibactam in combination with ceftazidime.

2. Use the the notional threshold concentration (CT), that represents an approximation of the threshold concentration of avibactam during a declining concentration-time curve, below which β-lactamase is no longer effectively inhibited *in vivo* (determined to be 1 mg/L in previous studies)
Un modèle animal (souris neutropénique)

TABLE 1 P. aeruginosa strains used for pharmacodynamic studies of ceftazidime and avibactam, including magnitude of the PDI %T>MIC of monotherapy ceftazidime

<table>
<thead>
<tr>
<th>Isolate no.</th>
<th>Resistance summary$^a$</th>
<th>MIC (mg/liter)</th>
<th>Static % T&gt;MIC (ceftazidime)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td>Ceftazidime-avibactam$^b$</td>
</tr>
<tr>
<td>1</td>
<td>Nitrocefinase activity, +++; AmpC transcript, overexpressed; β-lactamase genotype, blaAmpC; class A, class B</td>
<td>128</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Nitrocefinase activity, baseline; AmpC transcript, basal; β-lactamase genotype, blaAmpC, blaTEM-24 (CAZ-6); class B</td>
<td>64</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Nitrocefinase activity, +++; AmpC transcript, overexpressed; β-lactamase genotype, blaAmpC; class A, class B</td>
<td>128</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Nitrocefinase activity, +++; AmpC transcript, overexpressed; β-lactamase genotype, blaAmpC; class A, class B</td>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>OprD, AmpC$^{con}$, class A, class B</td>
<td>128</td>
<td>16</td>
</tr>
<tr>
<td>18</td>
<td>OprD, AmpC$^{ind}$, class A, class B</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>19</td>
<td>OprD, AmpC$^{con}$, class A, class B</td>
<td>64</td>
<td>4</td>
</tr>
</tbody>
</table>

$^a$ con, constitutive; ind, inducible; OprD, outer membrane protein deficiency causing resistance to carbapenems in Pseudomonas species; blaAmpC, possesses β-lactamase gene coding for AmpC; blaTEM-24, possesses β-lactamase gene coding for TEM-24.

$^b$ The MIC of ceftazidime-avibactam was the value of the ceftazidime MIC measured in the presence of a fixed concentration of avibactam of 4 mg/liter.

$^c$ The highest dose used did not result in a bacteriostatic effect.
Pharmacodynamics of Ceftazidime and Avibactam in Neutropenic Mice with Thigh or Lung Infection

FIG 1 Change in log_{10} CFU in lung-infected mice treated with ceftazidime dosing q2h and avibactam q2h or q8h. = ceftazidime; AVI, avibactam; ΔlogCFU, change in log_{10} CFU compared to the initial inoculum The ΔlogCFU values for controls treated with ceftazidime for 24 h but with zero avibactam are plotted on the vertical axis.
Un modèle animal (souris neutropénique)

*P. aeruginosa* 18 thigh  CAZ 27.2 mg/kg q2h

**FIG 2** Example of exposure-response, dose fractionation studies of avibactam in thigh-infected neutropenic mice treated with ceftazidime q2h. CAZ, ceftazi-dime; AVI, avibactam; ΔlogCFU, change in log$_{10}$ CFU compared to the initial inoculum.
Un modèle animal (souris neutropénique)

Pharmacodynamics of Ceftazidime and Avibactam in Neutropenic Mice with Thigh or Lung Infection

FIG 3 Example of exposure response of avibactam in neutropenic thigh- and lung-infected mice treated with ceftazidime and various doses of avibactam q2h. CAZ, ceftazidime; AVI, avibactam; ∆log CFU, change in log_{10} CFU compared to the initial inoculum. MIC of ceftazidime-avibactam versus this strain, 4 mg/liter.
Observations and conclusions:

1. Dose fractionation studies of avibactam in both the thigh and lung models indicated that the effect of avibactam correlated well with %fT>CT 1 mg/liter.

2. Addition of avibactam enhanced the effect of ceftazidime, which was more pronounced at frequent dosing and well related with %fT>CT 1 mg/liter.

3. The thigh model appeared more stringent, with higher values, ranging up to 62.5% fT>CT 1 mg/liter, required for a static effect.
Analyse d'une population spéciale: patients atteints de mucoviscidose

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses To Determine Optimal Dosing of Ceftazidime-Avibactam for the Treatment of Acute Pulmonary Exacerbations in Patients with Cystic Fibrosis

Timothy J. Bensman, a Joshua Wang, b Jordanna Jayne, a Lynn Fukushima, c Adupa P. Rao, c David Z. D’Argenio, a Paul M. Beringer b

Biomedical Simulations Resource, Department of Biomedical Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, California, USA a; Department of Clinical Pharmacy, School of Pharmacy, University of Southern California, Los Angeles, California, USA b; Division of Pulmonary and Critical Care Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA c
Background, objectives and means:

1. Altered pharmacokinetics (PK) of several beta-lactam antibiotics have been reported in CF patients.
2. The aim was to characterize the PK of ceftazidime-avibactam (CZA) and perform target attainment analyses to determine the optimal treatment regimen.
3. The PK of ceftazidime and of avibactam in 12 adult CF patients administered 3 intravenous doses of 2.5 g every 8 h infused over 2 h were determined.
4. Population modeling utilized the maximum likelihood expectation method. Monte Carlo simulations determined the probability of target attainment (PTA).
5. Criteria: For ceftazidime: fT>MIC = 50% – For avibactam: fT>1 mg/L = 100%
Analyse d'une population spéciale: patients atteints de mucoviscidose

1. ceftazidime

Pharmacokinetic-Pharmacodynamic Target Attainment Analysis: Optimal Dosing of Ceftazidime for the Treatment of Acute Exacerbations in Patients with Fibrosis

Timothy J. Bensman, Joshua Wang, Jordanna J. Adupa P. Rao, David Z. D'Argenio, Paul M. Bertrad

Biomedical Simulations Resource, Department of Biomedical Engineering, University of Southern California, Los Angeles, California, USA; Department of Pharmacy, University of Southern California, Los Angeles, California. Care Medicine, Keck School of Medicine, University of Southern California

1. ceftazidime

FIG 1 Observed CAZ plasma concentrations, model-predicted CAZ plasma concentrations, and goodness-of-fit of CAZ plasma concentrations after multiple administrations of CZA i.v. via a 2-h infusion in adults with CF. (A) Spaghetti plot of CAZ concentrations. (B) Summary of observed CAZ concentration-time profiles after the 3rd dose overlaid with the mean of the individual model predictions (Model Pred). (C to F) Goodness-of-fit plots of final population PK model: Individual measured CAZ concentrations versus population prediction (C) or individual prediction (D), conditional standardized residuals (Cond. Std. Resid.) versus time after dose (E), and conditional standardized residuals versus individual prediction (F). Drug concentrations are plotted on a log_{10} scale. Summarized observed data are presented as the mean ± SD (n = 12).
Pharmacokinetic-Pharmacodynamic Target Attainment Analysis for the Treatment of Acute Exacerbations in Patients with CF.  

2. avibactam

FIG 2 Observed AVI plasma concentrations, model-predicted AVI plasma concentrations, and goodness-of-fit of AVI plasma concentrations after multiple administrations of CZA I.v. with a 2-h infusion in adults with CF. (A) Spaghetti plot of AVI concentrations. (B) Summary of observed AVI concentration-time profiles after the 3rd dose overlaid with the mean of the individual model predictions (Model Pred). (C to F) Goodness-of-fit plots of final population PK model: individual measured AVI concentrations versus population prediction (C) or individual prediction (D), conditional standardized residuals (Cond. Std. Resid.) versus time after dose (E), and conditional standardized residuals versus individual prediction (F). Drug concentrations are plotted on a log_{10} scale. Summarized observed data are represented as the mean ± SD (n = 12).
FIG 3 Probability of target attainment for discrete CZA MICs for *Pseudomonas aeruginosa* isolates recovered from CF patients under steady-state conditions. (A) Probability of target attainment and cumulative response of *P. aeruginosa* to CZA over the MIC distribution for CZA at 2.5 g infused over 2 h every 8 h. (B) Probability of target attainment dependent on infusion time for discrete MICs of 8, 16, and 32 mg/liter using a 1,000-patient Monte Carlo simulation trial incorporating PK variability from a one-compartment base model derived from data for 12 adult CF patients. The target was defined as an $fT_{>\text{MIC}}$ of 50% for CAZ and an $fT_{>1\text{mg/liter}}$ of 50% for AVI. The distribution of the CZA MICs for *P. aeruginosa* isolates from patients with CF was digitized from previously published data (10).
Pharmacokinetic-Pharmacodynamic Target Attainment Analysis to Inform Optimal Dosing of Ceftazidime for the Treatment of Acute Exacerbations in Patients with Cystic Fibrosis

Timothy J. Bensman, a Joshua Wang, b Jordanna Jayne Adupa, P. Rao, c David Z. D’Argenio, a Paul M. Beringer

Biomedical Simulations Resource, Department of Biomedical Engineering, University of Southern California, Los Angeles, California, USA; Department of Pharmacy, University of Southern California, Los Angeles, California, USA; Division of Pulmonary, Allergy and Critical Care Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Analyse d'une population spéciale: patients atteints de mucoviscidose: 3. PTA / CRP

2017;61:e00988-17.

Cumulative response probability: overall likelihood of a therapeutic effect:

1. A PTA of $\geq 0.9$ is selected as threshold for optimal treatment.

2. The cumulative response probability (CRP) tells about the overall likelihood of a therapeutic effect in a population given
   - the empirical dosing regimen of CZA (2.5 g q8h infused over 2 h),
   - the pharmacokinetic variability, and
   - the susceptibility of \textit{P. aeruginosa} isolates obtained from a representative population of patients with CF.

3. Briefly, CRP was calculated as the product of the probability of target attainment and isolate frequency at each discrete MIC and the values obtained for each MIC then summed