# Optimization of Continuous Infusion of Piperacillin–Tazobactam in Children With Fever and Neutropenia

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**Abstract:** The study through Monte Carlo simulation of β-lactam pharmacokinetic/pharmacodynamic target attainment and determination of subsequent serum concentrations of piperacillin–tazobactam administered through continuous infusion to children treated for fever and neutropenia shows that 400 mg/kg/day has the highest probability of target attainment against *Pseudomonas aeurginosa* in our oncology ward compared with the standard regimen of 300 mg/kg/day.

**Key Words:** fever neutropenia, piperacillin–tazobactam, continuous infusion, pharmacokinetic and pharmacodynamic optimization

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Fever and neutropenia (FN) is a major potentially life-threatening complication of myelosuppressive chemotherapy for hematologic cancer partly due to translocation of opportunistic bacteria.[1] Large-spectrum β-lactams, among which piperacillin/tazobactam (PIP/TAZ), are recommended as first-line empiric therapy in FN based on pharmacokinetic and pharmacodynamic (PK/PD) characteristics, that is, bactericidal activity at low minimal inhibitory concentration (MIC) against a large spectrum of bacteria[2] save for local, institutional and/or geographic situations of high incidence of multidrug resistant strains.

Data from animal models and human studies strongly suggest that the time during which β-lactam concentrations are above the MIC, or time above MIC (T>MIC), is the best PK/PD predictor of bacterial killing in vivo and of clinical efficacy.[3] In fact, time above 4- to 5-fold MIC is considered as a minimal target.[3–7] However, specific pathogen/antimicrobial pairings is required. Indeed, Kuti et al[8] demonstrated that in the case of PIP/TAZ and *Pseudomonas aeruginosa*, a time above 6-fold MIC was the target required for immune-compromised adults. Most studies have described that the time above MIC targets for β-lactams vary from 40% to 70%. Moreover, several authors suggest, based on data from neutropenic animals, that in profound neutropenia, penicillin and cephalosporin levels should exceed MIC for 90%–100% of the dosing interval to increase efficacy against gram-negative bacilli.[9,10] Early animal and human adult studies have shown that continuous infusion of β-lactams leading to 100% T>MIC were at least similar to intermittent dosing or better in the case of immune-compromised hosts.[11–18]

In the present study, in a cohort of children with FN treated by continuous infusion of PIP/TAZ, we investigated whether a 300 mg/kg standard dosing regimen recommended for children administered through continuous infusion allowed successful attainment of the 100% time above 6-fold MIC target (100% T > 6 MIC).

## MATERIALS AND METHODS

In children over 12, the French Health Agency recommends 240–320 mg/kg of PIP/TAZ over 24 hours in 3–4 injections. After approval by our institutional review board (Eudract number 2008-005131-15) and informed child/parental consent, we prospectively enrolled children with FN to be treated with continuous infusions of 300 mg/kg of piperacillin (and 37.5 mg/kg tazobactam) over 24 hours following a loading dose of 30% total daily dose. Free PIP steady-state serum concentrations ($C_{SS}$) were assessed by high pressure liquid chromatography, as described elsewhere,[19] at 30 minutes (peak) and 24 hours (steady state) after infusion onset in venous blood samples (<1.5 mL) obtained from an indwelling peripheral intravenous catheter (not used for PIP/TAZ infusions) before PIP/TAZ administration. Monte Carlo simulation (@Risk software v.5.7, Palisade co., Ithaca, NY) was used to assess antimicrobial dosing regimens. This method calculates the probability of achieving a defined PK/PD target, resulting from a specific drug dose/regimen and population PK parameters such as drug clearance ($C_L$) and volume of distribution ($V_D$). Values of $C_L$ and $V_D$ used in our simulation were calculated from the measured $C_{SS}$ in our patients according to the following equations:

$$C_L = R \cdot C_{SS}^{-1}$$

$$V_D = R \cdot \left(1 - e^{-kt}\right) \cdot \left(C_{SS} \cdot k\right)^{-1}$$

For Monte Carlo simulation, drug concentration was calculated as follows as previously described[20]: $C = D_L \cdot V_D^{-1} \cdot e^{-kt} + R \cdot V_D \cdot k^{-1} \cdot \left(1 - e^{-kt}\right)$, with $k = C_L \cdot V_D^{-1}$, where C indicates plasma drug concentration; $D_L$, leading initial dose; $V_D$, volume of distribution; R, infusion rate; k, overall volume rate constant; t, dosing interval; $C_L$, clearance of drug.

In our study, the predefined PK/PD target was attaining free PIP serum concentration 100% of the time above 6-fold MIC (100% T > 6 MIC). In FN, *P. aeruginosa* must be taken into account in the empiric antimicrobial spectrum.[2] Indeed, in our pediatric hematological department, 14 strains of *P. aeruginosa* were isolated from blood cultures since 2008. Of these, 8 were PIP/TAZ susceptible and 6 resistant. However, these 6 PIP/TAZ-resistant strains were from breakthrough infections acquired while undergoing empirical treatment by either PIP/TAZ or ceftazidime. Because our goal was

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not optimizing therapy of breakthrough infections, these resistant strains were excluded. Thus, target MIC in our model was established by E-test results of PIP/TAZ against the 8 susceptible strains, equal to 4 mg/L for 2 strains and 2 mg/L for 6 strains. Therefore, our PK/PD target was 100% T > 6-fold MIC of 24 mg/L.

Using Monte Carlo simulation, we calculated theoretical minimal necessary $C_{SS}$ to achieve maximal PK/PD target attainment probability at various continuous infusion regimens (300, 350 and 400 mg/kg/24h), loading doses (50, 100 and 150 mg/kg over 1 hour) and *P. aeruginosa* MICs for PIP (2, 4 and 8 mg/L). We then confronted PIP $C_{SS}$ measured in our patients with the minimal necessary $C_{SS}$ to achieve maximal target attainment from the Monte Carlo simulation. The study was designed to subsequently administer PIP/TAZ in children with FN according to the dose/regimen with the highest probability of target attainment to assess by measured PIP $C_{SS}$ in these patients. During this subsequent use of "optimized" PIP/TAZ regimens, our study was not powered nor designed for collecting extensive standardized safety data other than routinely collected clinical and biological data.

## RESULTS

Nineteen children presenting with FN and treated by continuous infusion of 300 mg/kg/day of PIP/TAZ were enrolled. The median age was 10 years (7–14.5). The sex ratio was 8.4 boys to girls. FN occurred during immunosuppressive chemotherapy for acute lymphoid leukemia (n = 12), acute myeloid leukemia (n = 3) and lymphoma (n = 4). All patients had an absolute neutrophil count <500 cells/mm$^3$ and neutropenia duration exceeded 7 days. Median plasma protein was 58 g/L (52.5–64). No renal failure was observed. Median body weight was 31 kg (20–49).

Drug assay showed a median PIP $C_{SS}$ of 22.5 mg/L (19.3–33.6). Based on these results, $V_D$ was calculated at 0.56 L/kg (±0.2) and $C_L$ was calculated at 8.9 mL/min/kg (±3.8). Noteworthy, among the 19 patients tested, 8 had a PIP $C_{SS}$ lower than the defined serum target of 24 mg/L 24 hours after perfusion initiation. We next used the Monte Carlo simulation to assess predefined PK/PD target attainment probability by integrating PIP $V_D$ and $C_L$ calculated from our cohort (Table 1). A $C_{SS}$ of 26.7 mg/L corresponding to the standard regimen of 300 mg/kg/day following a loading dose of 100 or 150 mg/kg led to a target attainment probability of only 86.7% for a MIC of 4 mg/L (Table 1). Using this standard regimen, 100% target attainment probability was only achieved for a lower MIC of 2 mg/L (Table 1). However, increasing dosing regimen to 400 mg/kg/day allowed 100% target attainment probability overall, with a $C_{SS}$ at 24 hours of 35.6 mg/L. Indeed, PIP/TAZ was subsequently administered continuously to 6 children with FN following a 100 mg/kg bolus. With this regimen, the $C_{SS}$ of PIP was increased and reached a median of 35.85 mg/L (33.95–47.55).

## DISCUSSION

Our data show that continuous infusion of PIP/TAZ at the recommended dose of 300 mg/kg/day does not reach the optimal PK/PD target for antibiotic efficacy in our population of children with febrile neutropenia. Compared with non-neutropenic children,[21,22] both $V_D$ and $C_L$ were increased in our population as observed in adult oncology patients.[9] Moreover, serum protein is often decreased in children with hematological malignancy leading to increased free fraction of antibiotics more rapidly distributed and cleared, resulting in lower serum concentrations. These observations support the use of prolonged infusions of β-lactams in this population of children to compensate for these PK/PD modifications due to disease. Moreover, a benefit of prolonged β-lactam infusions was previously demonstrated in healthy children aged 2 to 12 without such PK/PD modifications.[22] Because patients included were all high-risk patients (recent intensive chemotherapy, predicted prolonged and profound neutropenia, fever over 39°C), we opted for the use of PIP/TAZ in continuous infusion at 6-fold MIC, rather than the minimal target of 4- to 5-fold MIC consistent with expert views based upon studies in immunocompromised adults.[23] Consensual dosing recommendations for prolonged infusion of β-lactams are also lacking for children. However, our data show that 400 mg/kg/day of PIP/TAZ after 100 mg/kg loading dose is appropriate for the *P. aeruginosa* MICs encountered in our pediatric hematology department. Although 350 mg/kg/day did achieve 99.9% target attainment probability in our model, we would be cautious in using this regimen. Indeed, using 400 mg/kg/day led to a variation of real steady-state PIP concentrations ($C_{SS}$) of more than 5% from the satisfactory average of 35.8 mg/L very close to the modeled $C_{SS}$ of 35.6 mg/L. If the same interindividual variation around real $C_{SS}$ close to modeled $C_{SS}$ occurred using 350 mg/kg/day, it could lead to steady-state PIP concentrations more than 5% lower than the average modeled $C_{SS}$ of 31.2 mg/L. Such a $C_{SS}$ of about 29.6 mg/L in certain individuals would have a target attainment probability between 86.7% and 99.9%, with a probably significant risk of treatment failure. Given the stakes of antimicrobial treatment of FN in high-risk pediatric patients, any significant treatment failure risk was unreasonable and led us to optimize the regimen with 400 mg/kg/day. This regimen has since been implemented in our pediatric hematology department without any observed adverse events.

**TABLE 1.** Probability of Target Attainment of Continuous Piperacillin–Tazobactam Administration Based on PKs Parameters From our Cohort

| Drug Dose (mg/kg) | | Probability (%) of Target Attainment* of Piperacillin–Tazobactam | | | Minimal Serum Antibiotic Concentration for Target Attainment (mg/L) | |
|---|---|---|---|---|---|---|
| Continuous | Bolus | MIC = 2 mg/L | MIC = 4 mg/L | MIC = 8 mg/L | At Peak | At Steady State |
| 400 | 150 | 100 | 100 | 0.5 | 258.9 | 35.6 |
| | 100 | 100 | 100 | 0.5 | 180.2 | 35.6 |
| | 50 | 100 | 100 | 0.0 | 102.3 | 35.6 |
| 350 | 150 | 100 | 99.9 | 0.0 | 255.3 | 31.2 |
| | 100 | 100 | 99.9 | 0.0 | 177.2 | 31.2 |
| | 50 | 100 | 99.9 | 0.0 | 99 | 31.2 |
| 300 | 150 | 100 | 86.7 | 0.0 | 252.7 | 26.7 |
| | 100 | 100 | 86.7 | 0.0 | 174.6 | 26.7 |
| | 50 | 100 | 82 | 0.0 | 96.3 | 26.7 |

*The target of PK/PD indices was 6×MIC and T>MIC = 100% over the 24 hours.

This study highlights that Monte Carlo modeling of PK/PD target attainment probabilities may allow optimization of β-lactam continuous infusion, which can be successfully implemented in the real-life setting of pediatric patients with febrile neutropenia.

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