Dosing of piperacillin/tazobactam in a morbidly obese patient

Hanna Deman¹*, Jan Verhaegen², Ludo Willems¹ and Isabel Spriet³

¹Pharmacy Department, Research Centre for Clinical Pharmacy, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium; ²Medical Diagnostic Sciences Department, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium

*Corresponding author. Tel: +0032-16-34-30-80; Fax: +0032-16-34-30-85; E-mail: hanna.deman@uzleuven.be

Keywords: β-lactams, PK/PD, therapeutic drug monitoring

Sir,
The combination of piperacillin and tazobactam has been shown to be efficacious for the treatment of intra-abdominal infections, skin and soft tissue infections, bacteraemia and pneumonia. The pharmacokinetics (PK) of piperacillin/tazobactam have been extensively investigated in both healthy volunteers and in distinct patient settings.¹ Like other β-lactams, piperacillin/tazobactam displays time-dependent pharmacodynamics (PD), whereby duration of time that concentrations remain above the MIC correlates best with bacterial kill and efficacy. The PK/PD target associated with a high probability of therapeutic success is defined as free concentrations above the MIC for 50% of the dosing interval (50% T > MIC).² In case of more severe infections or when poor penetration into infected tissues is expected, 30%–40% T > 4–5 × MIC should ideally be attained.³ It is not clear whether these targets are reached in morbidly obese patients as published information on optimal dosing in this subset of patients is rare.

A 33-year-old morbidly obese patient (220 kg, 1.9 m and body mass index 55 kg/m²) was transferred to our orthopaedic ward with a surgical site infection following a transfemoral amputation of the left leg following a car accident. He has provided written, informed consent for the details given here to be published. The patient had been empirically started on amoxicillin/clavulanic acid; however, despite 8 days of treatment, necrosis increased and markers of infection were still raised (C-reactive protein 217 mg/L, white blood cell count 18×10⁹/L). An urgent surgical debridement was performed, deep tissue cultures were obtained and a vacuum-assisted closure (VAC) was installed.

Enterobacter cloacae, cultured from tissue biopsy, was resistant to amoxicillin/clavulanic acid, but susceptible to piperacillin/tazobactam, which was started at a dose of 4 g/500 mg every 6 h as a 30 min infusion. This regimen, along with VAC, was continued for a total of 15 days, and was then safely stopped as culture results remained negative and markers of infection normalized. The wound was eventually closed by reconstructive surgery.

Blood samples were obtained in lithium–heparin tubes at steady state (after the 40th dose) from a peripheral venous catheter at the end of the infusion (0.5 h, peak level) and just before the succeeding dose (6 h, pre-dose level). Plasma piperacillin levels were quantified at the Université Catholique de Louvain (UCL; Brussels, Belgium) by validated HPLC followed by UV detection, as published previously.³ The area under the curve was calculated by integration. The elimination rate constant, half-life, volume of distribution and clearance were calculated with conventional PK equations. The percentage of time that the concentration exceeded the MIC (%T > MIC) was calculated by using the clinical breakpoint of Enterobacteriaceae for susceptibility to piperacillin/tazobactam as defined by EUCAST (8 mg/L).⁴ A free fraction of 70% was used, as piperacillin/tazobactam is known to be approximately 30% bound to plasma proteins.⁵ The PK results, as calculated in our patient, were compared with the parameters determined at the same dose at steady state in healthy volunteers, as provided in the package insert.⁵

The peak and trough concentrations in our patient were 86.5 and 2.5 mg/L, respectively. Based on these values, the area under the curve (181 mg·h/L), volume of distribution (33 L), half-life (1.07 h) and clearance (21 L/h) were calculated. These values differ substantially from those obtained in healthy volunteers, which are 281 mg·h/L, 8.24 L, 0.71 h and 8.03 L/h, respectively.⁶ As shown in Figure 1, %T > 4×MIC and %T > MIC were found to be 25% and 60% in our patient, respectively.

The PK parameters in this morbidly obese patient were substantially different when compared with the product information.⁵ The increased volume of distribution led to a substantially lower peak level and diminished AUC; these results are in line with previous results reported in a morbidly obese patient weighing 167 kg.⁶ Despite these significant differences, as illustrated in Figure 1, the PK/PD targets are approximately attained, depending on the chosen target, which is in line with the positive clinical response in our patient. Moreover, as the clinical breakpoint for susceptibility (8 mg/L) was used to calculate the magnitude of the PK/PD target, the attainment would probably even be better when the individual MIC value for the infecting strain is lower than this breakpoint. On the other hand, in morbidly obese patients infected with more resistant strains, PK/PD target attainment could be enhanced by administering piperacillin/tazobactam as an extended infusion.

Despite the fact that our results should ideally be confirmed in larger case series with several morbidly obese patients, our results are reassuring in terms of PK/PD target attainment, which is consistent with the hydrophilic nature of piperacillin/tazobactam, leading to relatively moderate alterations in morbidly obese patients. Extending the dosing interval in order to maximize the PK/PD target might, however, contribute to better efficacy in morbidly obese patients infected with more resistant strains, or in the case of immunosuppression. Therapeutic drug monitoring of piperacillin/tazobactam in these special...
settings could contribute to evaluating and optimizing the PK exposure and guaranteeing antimicrobial efficacy.

**Funding**
This work was supported by internal funding.

**Transparency declarations**
None to declare.

**References**