

# A pilot study on pharmacokinetic/pharmacodynamic target attainment in critically ill patients receiving piperacillin/tazobactam

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## Abstract

**Background:** In critically ill patients, multi-trauma and intensive therapy can influence the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics with time-dependent bacterial killing. Consequently, PK/PD targets ( $\%fT_{>MIC}$ ) — crucial for antimicrobial effects — may not be attained.

**Methods:** Two patients admitted to the surgical ICU of the University Hospital in Hradec Králové for multiple-trauma were given piperacillin/tazobactam by 1-hour IV infusion 4/0.5 g every 8h. PK variables: total and renal clearance ( $CL_{tot}$ ,  $CL_R$ ), volume of distribution ( $V_d$ ), and elimination half-life ( $T_{1/2}$ ) were calculated, followed by glomerular filtration rate (MDRD) and cumulative fluid balance (CFB-total fluid volume based on 24-h registered fluid intake minus output). The PK/PD target attainment ( $100\%fT_{>MIC}$ ) was defined as free ( $f$ ) piperacillin plasma concentrations that remain, during the entire dosing interval ( $T$ ), above the minimum inhibitory concentration ( $100\%fT_{>MIC}$ ) within days 4–8 (when CFB culminates and disappears). Piperacillin concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and corrected for unbound fraction (22%).

**Results:** CFB culminated over days 2–5 reaching 15–30 L and was associated with a large  $V_d$  (29–42 L). While MDRD in patient 1 was low ( $0.3–0.4 \text{ mL s}^{-1} 1.7 \text{ m}^{-2}$ ), that of patient 2 was increasing ( $> 3.1 \text{ mL s}^{-1} 1.7 \text{ m}^{-2}$ ), which was associated with augmented  $CL_R$ . In patient 2, the  $fT$  reached only 62, 52, and 44% on days 4, 6, and 8, respectively. In patient 1, the  $\%fT$  was much higher, attaining values four to fivefold greater than that targeted.

**Conclusions:** Critically ill patients are at risk of drug under- or overdosing without dose up-titration with regard to covariate effects and individual drug pharmacokinetics.

**Key words:** PK/PD target attainment, body fluid retention, pharmacokinetics, pharmacodynamics, piperacillin, critically ill patients, personalised therapy

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Antibiotic dosing regimens are usually based on healthy volunteers with normal physiology or non-critically ill patients. In critically ill hospitalized patients, pathophysiological changes may have profound effects on the primary determinants of the pharmacokinetics (PK) of hydrophilic antibiotics which are distributed to interstitial fluid and are predominantly excreted via the kidneys ( $\beta$ -lactams, amino-

glycosides, glycopeptides). Extravascular volume expansion with fluid loading and capillary leak may alter their low volume of distribution ( $V_d$ ), while changes in renal function can significantly influence drug clearance (Cl) [1].

The  $\beta$ -lactams are the most commonly prescribed antibiotics in the critically ill. Since bacterial killing is considered time-dependent, the PD parameter of interest is the

fraction of time that the free drug's concentration exceeds a minimum inhibitory concentration (MIC tested *in vitro*) of the causative microorganism — the  $fT_{>MIC}$ .

It is traditionally accepted that maintaining concentrations above the MIC of the causative organisms around 40–70% of the time (during each dosing interval) is adequate (40–70%  $fT_{>MIC}$ ) [2]. However, recent studies suggest that higher targets are needed in critically ill patients to improve clinical outcome whilst minimizing the development of resistance. Concentrations four to fivefold greater than the MIC are associated with maximum bactericidal activity [3, 4]. The PK/PD target was set at 100%  $fT_{>4-5 \times MIC}$ .

In this prospective, observational, pharmacokinetic report, the PK/PD target was set at 100%  $fT_{>MIC}$  (the piperacillin breakpoint for *Pseudomonas aeruginosa* being 16  $\mu\text{g mL}^{-1}$  — according to EUCAST). The primary endpoint of this pilot study is the documentation of differences within and between subjects in reaching the target PK/PD attainment in two intensive care unit (ICU) trauma patients who developed a positive cumulative fluid balance (CFB) during treatment with a standard dose of piperacillin. Intensive crystalloid fluid loading in ICU patients according to Rivers "early goal-directed therapy" [5] is one possible cause of a positive CFB during the first posttraumatic days. Moreover, the PK/PD target needs to be analysed throughout the ICU stay because of the dynamic nature of critical illness. In the past, a positive CFB and glomerular filtration rate were the main pathophysiological variables monitored in relation to PK/PD. Secondary endpoints were maximum absolute values of  $fT_{>MIC}$  attained.

## METHODS

Patient 1 (male) and patient 2 (female), were admitted in the ICU of the Surgical Clinic, at the Teaching Hospital, Hradec Krlov, the Czech Republic, for multiple-trauma. The demographic characteristics for patient 1 were as follows: age 32 years, weight 70 kg, serum creatinine 158  $\mu\text{mol L}^{-1}$ , with MDRD 0.74  $\text{mL s}^{-1} 1.73 \text{ m}^{-2}$ , ISS 54, and affected, apart from skeletal injuries, with left kidney disruption needing acute nephrectomy. Those for patient 2 were as follows: age 59 years, weight 60 kg, serum creatinine 57  $\mu\text{mol L}^{-1}$ , with MDRD 1.57  $\text{mL s}^{-1} 1.73 \text{ m}^{-2}$ , ISS 54. They were both treated with piperacillin/tazobactam as a 1-hour IV infusion of 4/0.5 g given every 8 hours according to the standard protocol for empiric antibiotic treatment of suspected hospital-associated infections and/or ventilator-associated pneumonia during the first week of stay in a surgical ICU, University Hospital in Hradec Kralove (the Czech Republic). All patients were given IV volume-therapy per protocol in order to prevent hypotension [5].

## SAMPLING AND $\beta$ -LACTAM ASSAY

Four serial plasma concentrations were obtained on days 6 and 8 (patient 1) and 4, 6, and 8 (patient 2). Blood samples were taken at the baseline (0.5 h prior to the dose) and 1, 2.5, and 4.5 hours post-administration. In patient 1, blood samples were taken 1.5, 3, and 5.5 hours post-administration on day 6. Specimens were centrifuged at 3000 rpm for 10 minutes within 30 minutes of sampling and frozen at  $-80^\circ\text{C}$ . Determination of piperacillin in plasma samples was performed using the liquid chromatography-tandem mass spectrometry (LC-MS/MS) modified method [6]. Unbound concentrations were calculated using published studies on the fraction of protein binding for the study drug [7]. Urine samples were taken from a 1–8 hour and 24-hour urine collection in order to calculate cumulative renal excretion of piperacillin and creatinine clearance ( $Cl_{cr}$ ), respectively.

## PHARMACOKINETIC ANALYSIS

Each plasma concentration-time plot was based on four points of piperacillin plasma concentrations obtained within the 1–8 hour dosing intervals. Three concentrations were detected using LC-MS/M, the fourth concentration ( $C_{min}$ ) was calculated using the following equation:  $C_t = C_0 \times e^{-kt}$  [8].  $C_0$  was the y-intercept of a plot of piperacillin plasma concentration versus time on the semilog scale. Area under the curve ( $AUC_{1-8}$ ) was estimated using the trapezoidal rule. Elimination half-life was calculated as follows:  $(T_{1/2}) = \ln 2/k_e$ , where  $k_e$  is elimination rate constant. The  $k_e$  was calculated as the negative slope of the non-weighted squares curve fit of three sampling points during post-administration. The apparent volume of distribution ( $V_d$ ) was calculated from the equations:  $V_d = Cl/k_e$ . The total clearance ( $Cl_{tot, pip}$ ) values were estimated as follows:  $Cl_{tot} = \text{dose}/AUC_{1-8}$ , and renal clearance ( $Cl_{R, pip}$ ) =  $TADU_{1-8}/AUC_{1-8}$ .  $TADU_{1-8}$  is the amount of piperacillin excreted in the urine collected over 1–8 hour post-administration, while  $AUC_{1-8}$  is the area under the plasma concentration-time curve within the timespan  $t_1$  (after termination of the 1-hour infusion) to  $t_8$  (at the end of a dosing interval). Renal function was defined in the Central Laboratory University Hospital, Hradec Krlov as a glomerular filtration rate (eGFR) assessed by a value of MDRD [9] and creatinine clearance ( $Cl_{cr}$ ).

## PHARMACODYNAMIC ANALYSIS

The  $fT_{>MIC}$  was calculated for both the total and unbound (free) piperacillin by observing the time during the dosing interval that the log-linear least squares regression profile of drug concentrations intersected the target MIC for *Pseudomonas aeruginosa*, based on EUCAST breakpoints (16  $\mu\text{g mL}^{-1}$  for piperacillin) [10]. The target was 100%  $fT_{>MIC}$ , i.e. free piperacillin concentration maintained above the breakpoint value throughout the entire dosing interval. CFB was evalu-

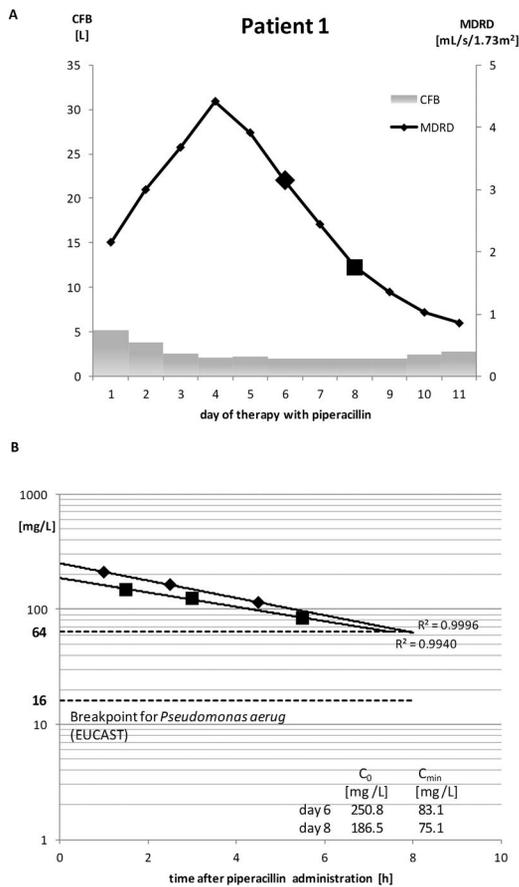


Figure 1. Patient 1  
 Panel A. Cumulative fluid balance (CFB) and glomerular filtration rate (MDRD).  
 Panel B. Total piperacillin plasma concentration • time plots on day 6, and 8 of therapy.

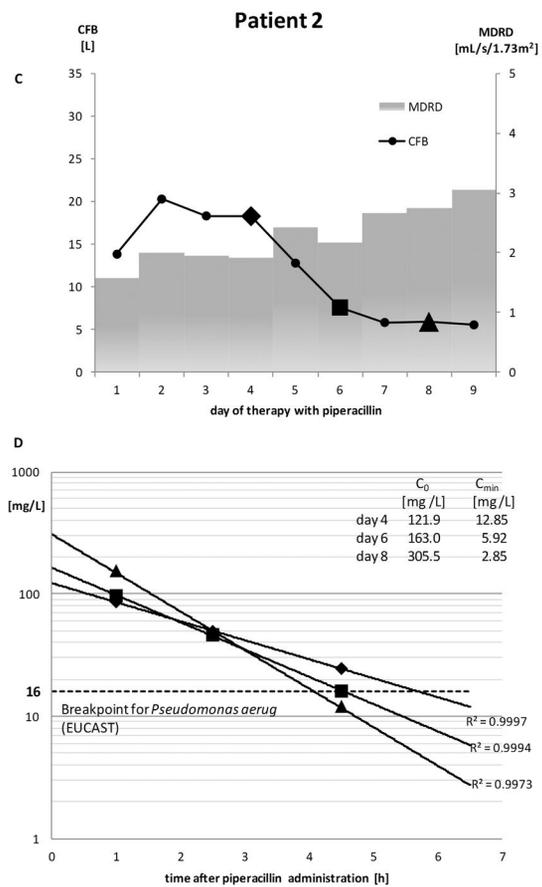


Figure 2. Patient 2  
 Panel C. Cumulative fluid balance (CFB) and glomerular filtration rate (MDRD).  
 Panel D. Total piperacillin plasma concentration • time plots on day 4, 6, and 8 of therapy.

**Figure 1.** Cumulative fluid balance and glomerular filtration rate (MDRD) in relation to the target PK/PD attainment in patient 1 (panel A, B) and patient 2 (panel C, D). The volume of CFB culminated over days 2–5 (patient 1 and 2) of antibiotic treatment. While glomerular filtration rate (GFR) in patient 2 is high (as a sign of augmented renal clearance syndrome), that in patient 1 is very low as a consequence of severe renal injury. Attainment of the  $fT$  is based on a plasma-concentration-time plot in the semi-log graph and its intersection with the line of  $16 \text{ mg L}^{-1}$  (the piperacillin breakpoint for *Pseudomonas aeruginosa* based on EUCAST). Piperacillin plasma concentrations were measured on days 6 and 8 (patient 1) and days 4, 6, and 8 (patient 2). Patient 2 failed to attain the maximum PK/PD target ( $100\%fT_{>MIC}$  ( $16 \text{ mg mL}^{-1}$ )). Moreover, the  $fT$  decreases with the number of days of treatment. On the x-axis of the semi-log graph, this value is gradually shifted to the left. In contrast, in patient 1 an unexpected  $100\% fT_{>4 \times MIC}$  ( $64 \text{ mg L}^{-1}$ ) was achieved with the increasing value over days 6–8. The  $fT$  is shifted to the right.

ated daily as the difference between fluid intake and output. Free piperacillin concentration maintaining a level above  $16 \text{ } \mu\text{g mL}^{-1}$  during a dosing interval was considered the target attainment. The glomerular filtration rate was assessed by the MDRD equation [9], while every  $Cl_{cr}$  was examined on days when PK parameters were estimated, as follows:

24-hour  $Cl_{cr} = U_v \times U_{cr} / (1.440 \times S_{cr})$ , where  $U_v$  is urinary volume (L),  $U_{cr}$  the urinary creatinine concentration ( $\mu\text{mol L}^{-1}$ ), and  $S_{cr}$  the serum creatinine concentration ( $\mu\text{mol L}^{-1}$ ) [11].

**RESULTS**

The sampling method used allowed one to describe a mono-exponential, first-order elimination process [5].

Patient 1 had a low GFR as demonstrated with MDRD (Fig. 1, Panel A) and a very positive CFB. The estimated  $Cl_{cr}$  was 9 and  $15 \text{ mL min}^{-1}$  on days 6 and 8, respectively. On those days, a  $100\% fT_{>MIC}$ , as well as a  $100\% fT_{>4 \times MIC}$  ( $64 \text{ mg L}^{-1}$ ) was reached (Fig.1, Panel B). The slope of total piperacillin plasma concentration indicates a very low  $k_e$  value (Table 1).

In contrast, the results obtained from patient 2 demonstrated increasing GFR presented as daily MDRD, and positive values of CFB (Fig. 1, Panel C). The estimated  $Cl_{cr}$  was 112, 124, and  $145 \text{ mL min}^{-1}$  on days 4, 6, and 8, respectively.

Patient 2 failed to attain the maximum PK/PD target ( $100\%fT_{>MIC}$ ) (Fig. 1, Panel D). The  $fT$  attained 80, 65, and 55% if derived from total piperacillin plasma concentration-time plots on days 4, 6, and 8, respectively (Fig. 1, Panel D).

**Table 1.** Piperacillin pharmacokinetics in intensive care unit patients Nos.1 and 2

PK parameters of unbound drug*	$V_d$ [L]	$k_e$ [ $h^{-1}$ ]	Clearance <sub>tot,pip</sub> [ $L h^{-1}$ ]	Clearance <sub>R,pip</sub> [ $L h^{-1}$ ]	$t_{1/2}$ [h]
<b>Patient 1</b>					
Day 6	27.5	0.157	7.17	4.6	4.4
Day 8	21.1	0.178	6.50	4.9	3.9
<b>Patient 2</b>					
Day 4	42.1	0.333	16.2	7.1	2.1
Day 6	27.6	0.498	15.4	11.5	1.4
Day 8	11.3	0.736	11.3	10.2	0.9

PK — pharmacokinetic; Clearance<sub>tot,pip</sub> — total plasma clearance; Clearance<sub>R,pip</sub> — renal clearance; \* observed plasma concentrations of piperacillin were corrected for binding with plasma protein (22%);  $V_d$  — volume of distribution;  $k_e$  — elimination rate constant;  $t_{1/2}$  — elimination half time

Total piperacillin plasma concentration plots (days 4, 6, and 8) differ with regard to the slope, as demonstrated by the  $k_e$  value (Table 1).

The  $fT$  estimated for unbound piperacillin plasma concentrations in patient 1 maintained a value of 100%  $fT_{>4 \times MIC}$  ( $64 \text{ mg mL}^{-1}$ ), while in patient 2 the  $fT$  achieved 62, 52, and 44%  $fT_{>MIC}$  on days 4, 6, and 8, respectively. In this patient, the pharmacokinetic variables of piperacillin show increasing values of  $Cl_{R,pip}$  in accordance with  $Cl_{cr}$  while decreasing values were observed for  $Cl_{tot,pip}$ ,  $V_d$ , and  $t_{1/2}$  over days 4–8 of treatment (Table 1).

## DISCUSSION

This pilot study reports the results on the first two typical patients studied in our institution. In order to describe intra-individual variability in the target PK/PD attainment, we have studied these 2 patients whose clinical status mainly differed with regard to renal function, while CFB was similar.

The dynamic nature of critical illness does not allow one to achieve a predictable “steady state”.  $Cl_{tot}$  and apparent  $V_d$  are considered two PK parameters that closely correlate with adequate drug dosing.  $V_d$  determines the initial drug dose, whereas the maintenance dose (in order to maintain a “steady state” — plasma concentration) is based on clearance.

$V_d$  is the factor that relates the amount of a drug in the body to the concentration of the drug in the sampling site. This hypothetical volume is determined by the drug’s distribution behaviour. For hydrophilic drugs, this value is thought to be variable in critically ill patients with acute kidney injury and sepsis. Sepsis can lead to the development of endothelial damage followed by increased capillary permeability, which results in the displacement of intravascular fluid from the systemic circulation into the interstitium [12]. These fluid shifts into the interstitial space can be substantial owing to the large fluid volumes often administered to septic patients as a part of resuscitation (fluid overload) [13].

Extravascular volume can be even more marked in patients who have a decreased urine output secondary to acute kidney injury [14–16]. This fluid related weight gain correlates closely with increased mortality [14]. Moreover, an increase in fluid volume can dilute serum creatinine concentration, resulting in inappropriately low measures, and delay diagnosis of acute kidney insufficiency (AKI) [17].

These changes in PK variables were first described for hydrophilic aminoglycosides whose bactericidal activity is concentration dependent. Maximum concentration ( $C_{max}$ ) of gentamicin detected 1 hour after a 30-minute IV infusion should be 8 to 12 times higher than the MIC tested *in vitro* [18, 19]. In ICU patients with sepsis the  $V_d$  of gentamicin was  $0.48 \text{ L kg}^{-1}$ , compared to  $0.29 \text{ L kg}^{-1}$  in postoperative non-septic patients [20]. With respect to dosing, an increase in  $V_d$  should be taken into account with an adapted (increased) loading dose to achieve a concentration within the therapeutic range and to avoid underdosing. On the other hand, a maintenance dose dependent on the clearance of a drug is necessary to maintain a “steady state”. As the patient’s clinical status improves and the degree of tissue oedema disappears, the value of  $V_d$  can decrease dramatically within days. The drug dosage should be adjusted again in order to prevent drug accumulation and overdosing. This was shown during treatment with gentamicin in critically ill patients with suspected or confirmed sepsis related to a Gram-negative bacterial infection. Over days 2–7 of treatment (after aggressive fluid loading), the  $V_d$  of gentamicin decreased from  $0.43 \text{ L kg}^{-1}$  to  $0.29 \text{ L kg}^{-1}$ . The required dosage was reduced from  $5.14 \text{ mg kg}^{-1}$  every 24 h to  $3.98 \text{ mg}$  every 24 h despite the patient’s renal functions remaining stable [21].

Comparable changes in PK variables in critically ill ICU patients have also been described in clinical studies using hydrophilic time-dependent piperacillin (a beta-lactam), and meropenem (carbapenem). Time-dependency is based on the PK/PD target attainment, i.e. on the time (percentage of the dosing interval) covered by antibiotic plasma

concentration exceeding the MIC tested *in vitro*. Recently, it was found that many ICU patients experienced an augmented renal clearance syndrome (ARC) characterized by  $Cl_{cr} > 130 \text{ mL min}^{-1}$  [11]. For such patients, standard dosing of antibiotics eliminated predominantly “via the kidneys”, was not adequate [10, 22–24]. In spite of the fact, that the mechanisms for ARC have not been fully clarified yet, it is considered an independent predictor for not achieving the PK/PD target [6]. This implies that more aggressive dosing regimens should be used in such patients. On the other hand, low  $Cl_{cr}$  may be predictive for insufficient renal excretion of piperacillin and risk of drug toxicity.

Within this respect, future techniques (like bio-electrical impedance analysis, BIA) to assess fluid overload and volume excess may be of special interest in critically ill patients [25].

Our findings are in good agreement with the clinical outcomes mentioned above. Patient 2 did not reach the predefined PK target ( $100\% fT_{>MIC}$ ) probably related to his high  $Cl_{cr}$  ( $\geq 112 \text{ mL min}^{-1}$ ). In addition, over time the  $fT$  was decreasing. For this patient, standard dosing was not adequate and resulted in subtherapeutic plasma concentrations (drug underdosing). In contrast, patient 1 had a low  $Cl_{cr}$  and attained unexpected values of  $100\% fT_{>4 \times MIC}$ . At a standard dosing regimen, the target  $100\% fT_{>4 \times MIC}$  can only be attained in case of a low  $Cl_{cr}$  and consequently a low  $Cl_{R,pip}$ . Hence, this patient was at risk of drug toxicity [26]. Although considered safe, beta-lactam antibiotics have a number of adverse effects including neurotoxicity, liver damage and bone marrow suppression [26]. Moreover, it should be stressed that piperacillin dosing for this patient should have been reduced at the beginning of treatment and individually adjusted afterwards [27]. We have noticed that with repeated standard piperacillin doses given in multiple trauma patients having a low  $Cl_{cr}$  due to acute kidney injury, the  $fT_{>MIC}$  expressed on x-axis on the semi-log graph will be shifted to the right while in a multiple trauma patient with ARC, the  $fT_{>MIC}$  will be shifted to the left. This is important in clinical practice, as intra-individual changes in PK variables during treatment imply that dose adjustment may be warranted.

In addition, critically ill patients with fluid overload and AKI often experience larger  $V_d$  for hydrophilic antibiotics related to decreased binding of the drug to serum proteins (not analysed in this report). Although this can be explained not only by the reduced albumin synthesis, it could also be a result from the accumulation of certain uremic molecules that may compete with other drugs for the same albumin binding sites. An increase in  $V_d$  in patients with AKI has been also documented for hydrophilic amikacin, meropenem, and vancomycin [27].

Changes in PK parameters are related to changes in the PK/PD target.  $Cl_{R,pip}$  increases in accordance with  $Cl_{cr}$  [5],

while  $Cl_{tot,pip}$  decreases when there is a rapid fall in  $V_d$  and a slow decrease in  $T_{1/2}$ , as indicated by  $Cl_{tot} = \ln 2 \times V_d / T_{1/2}$ .

## CONCLUSION

Without individual dose adjustment, critically ill patients are at risk of either treatment failure (underdosing), or drug toxicity (overdosing). Thus, a dosing regimen should be based on repeated therapeutic drug monitoring and personalised antibiotic treatment.

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