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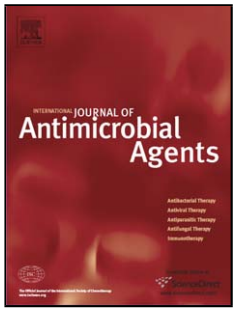

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Daily serum piperacillin monitoring is advisable in critically ill patients

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ABSTRACT

The aim of the present study was to evaluate the benefit of monitoring serum piperacillin concentrations in critically ill patients. This was an 11-month, prospective, observational study in a 30-bed Intensive Care Unit in a teaching hospital, involving 24 critically ill patients with evidence of bacterial sepsis. All patients received a 66 mg/kg intravenous bolus of piperacillin in combination with tazobactam (ratio 1:0.125) followed by continuous infusion of 200 mg/kg/24 h. The dosage was adjusted when the serum piperacillin concentration either fell below 4× the drug's minimum inhibitory concentration (MIC) for the causative agent or exceeded the toxic threshold of 150 mg/L. With the initial regimen, serum piperacillin concentrations were within the therapeutic target range in only 50.0% of patients (*n* = 12). This proportion increased to 75.0% (18 patients) (*P* = 0.006) following dosage adjustment. For patients with low initial serum piperacillin concentrations (*n* = 8), the percentage of time during which the concentration remained above 4× MIC (%*T*>4× MIC) was 7.1 ± 5.9% before dosage adjustment and 27.3 ± 8.6% afterwards. In conclusion, in critically ill patients, monitoring and adjustment of serum piperacillin levels is required to prevent overdosing and might also help to correct underdosing, an important cause of antibiotic therapy failure.

1. Introduction

Broad-spectrum β-lactams are commonly used to treat severe infections (either alone or combined with other antibiotics), especially in the Intensive Care Unit (ICU) setting. The bactericidal effects of these antibiotics are mostly time-dependent. Laboratory and clinical evidence indicates that to achieve effective bactericidal levels, a serum concentration of at least 4× times the minimum inhibitory concentration (MIC) for the pathogen involved may be required [1,2]. A related determinant of β-lactam efficacy is the time during which the drug's serum concentration remains above the MIC threshold (*T*>MIC) [3]. Continuous infusion of these antimicrobial agents facilitates the optimisation of their pharmacodynamic profiles [4,5].

In ICU patients, it is more difficult to maintain stable serum antibiotic levels. Apart from the excretory impairments observed in these patients, several other phenomena can significantly alter drug distribution and/or elimination profiles [6]. Furthermore, ICU patients show great interindividual variability in their pharmacokinetic parameters [7], which can also change quickly in response to improvements in or worsening of the clinical condition. Monitoring of serum antibiotic concentrations and subsequent dosage adjustment can avoid underdosing or overdosing and limit the risk of therapeutic failure and toxicity.

Piperacillin/tazobactam (PIP/TAZ) is a β-lactam/β-lactamase inhibitor combination with activity both against Gram-negative and Gram-positive bacteria (including β-lactamase

producers). The broad spectrum of action of PIP/TAZ makes it an appropriate choice in the ICU.

Over the last decade, new modes of administration have significantly optimised the antimicrobial activity of PIP/TAZ. In several pharmacokinetic studies, continuous infusion of PIP/TAZ was superior to intermittent injection (despite the use of lower doses) [8,9] and also appeared to be a better pharmacoeconomic option [10]. Under these supposedly optimal pharmacokinetic conditions, the objective of this study was to assess the utility of daily serum piperacillin monitoring to achieve pharmacodynamic targets associated with optimal piperacillin activity.

2. Patients and methods

2.1. Subjects

Study subjects were adult patients admitted to the Department of Respiratory Emergencies and Intensive Care at Lille University Medical Center (Lille, France) with various pathologies (Table 1). The study's main inclusion criterion was the presence of a community- or hospital-acquired infection requiring antibiotic therapy with PIP/TAZ. Patients with known hypersensitivity/intolerance to penicillins or a previous infection with PIP/TAZ-resistant bacteria were excluded from the study.

2.2. Antibiotic administration

All patients received PIP/TAZ via continuous infusion. The regimen consisted of a loading bolus of 66 mg/kg piperacillin and 8.25 mg/kg tazobactam (Tazocilline®; Wyeth Pharmaceuticals, Paris, France) injected over 30 min followed by constant-rate infusion of 200 mg/kg/24 h piperacillin and 25 mg/kg/24 h tazobactam. Although this dosage may not be adapted to patients weighing more than 120 kg, we did not use daily doses above 24/3 g of PIP/TAZ because they are not recommended by the manufacturer. Furthermore, none of the enrolled patients weighed more than 105 kg. In patients with impaired renal function [creatinine clearance (CL_{Cr}) ≤ 30 mL/min, calculated according to the Cockcroft and Gault formula], the maintenance dose was halved.

2.3. Target serum concentrations

Dosage adjustment was performed when the serum piperacillin concentration was below 4× MIC for the identified pathogen or >150 mg/L (defined as the toxicity threshold, based on empirical data). Above this concentration, the likelihood of neurological adverse events increased (personal data). When the pathogen was not known, the lower target value was defined as 4× the critical concentration above which all bacterial strains are considered to be resistant to piperacillin, i.e. 4 × 16 mg/L = 64 mg/L (according to guidelines issued by the French Microbiology Society's Antibiotics Committee).

2.4. Analytical method

Serum piperacillin concentrations were determined by high-pressure liquid chromatography using a 322-A pump, an autoinjector, a 332 variable ultraviolet wavelength detector (all from Serlabo Technologies, Entraigues-sur-la-Sorgue, France) and a C18 Resolve column (4 μm, 3.9 × 150 mm; Waters Associates, Milford, MA). The mobile phase consisted of 0.02 M ammonium acetate buffer and acetonitrile in a 76:24 ratio (v/v) at pH 5.0. The flow rate was 1 mL/min. Pooled human serum was used to prepare standards, to check samples and to dilute serum samples, as required. The assay was linear over the range 1 mg/L to 200 mg/L. Only the free fraction of piperacillin was measured, as an initial step of protein precipitation with acetonitrile was carried out [11].

2.5. Blood sampling

Blood samples for pharmacokinetic analysis were obtained from a peripheral venous catheter placed in the arm not used for drug infusion. Blood was collected before starting drug administration (t = 0) and 1.5 h afterwards (t = 1.5) to ensure that the bolus injection had been completed. A sample was then taken each morning at steady state until the end of the course of treatment.

2.6. Adverse events

Convulsions, changes in white blood cell count, modification of CL_{Cr} and signs of cutaneous intolerance were monitored throughout the study.

2.7. Statistical analysis

A paired Student's *t*-test was used to check for statistical significance.

3. Results and discussion

In total, 24 patients [22 males and 2 females; mean ± standard deviation (S.D.) age, 62.5 ± 14.3 years; mean ± S.D. weight, 78.7 ± 16.8 kg] were initially included. Patient characteristics and PIP/TAZ dosage management are presented in Table 1. Seven patients (2, 3, 8,12, A, E and F; Table 1) displayed severe renal function impairments (CL_{Cr} ≤ 30 mL/min) The infecting pathogen was only documented in 9 of the 24 cases (Table 1b) and included *Pseudomonas aeruginosa* (Patients A and B), *Escherichia coli* (Patients C and D), *Klebsiella pneumoniae* (Patients E and F), *Acinetobacter baumannii* (Patient G), meticillin-susceptible *Staphylococcus aureus* (Patient H) and *Enterobacter aerogenes* (Patient I). In these strains, the MIC of piperacillin (when combined with tazobactam) ranged from 4 mg/L to 16 mg/L (mean value 7.6 ± 5.1 mg/L).

The serum piperacillin concentration was monitored in 4 to 21 samples per patient (mean ± S.D., 10 ± 4.6). With the initial regimen, the serum piperacillin concentrations were above the previously defined target value (i.e. >4× MIC) in 12 (50.0%) of the patients (Patients 1–6, 9, C, D, G, H and I) (Table 1). This goal was achieved in six additional patients (Patients 7, 8, 10, A, E and F) following dosage adjustment (P = 0.006). In four patients (Patients 8, A, E and F), antibiotic levels were considered toxic

(>150 mg/L), thus the dosage was reduced and no adverse events were observed. Conversely, a dosage increase in two patients (Patients 7 and 10) of the eight patients with below-target serum piperacillin concentrations enabled achievement of the therapeutic value. Dosage adjustment was not efficient in the six remaining patients (Patients 11–15 and B). Despite many dosage changes (with up to 18 g of piperacillin per day in some cases), serum piperacillin concentrations >4× MIC were never achieved. Interestingly, all but one (Patient B) of these subjects had extensive cellulitis, which might have influenced the pharmacokinetics of the antibiotic [12]. In this clinical setting, subcutaneous inflammation might generate an additional distribution compartment and could be responsible for extracellular and extraplasmatic leakage of the antibiotic. This hypothesis is supported by the substantial increase in the volume of distribution of PIP/TAZ seen in burns victims compared with healthy individuals (indicating translesional diffusion of the antibiotic) [13]. Further investigation is now required to establish suitable antibiotic regimens in this setting; nevertheless, daily monitoring of serum piperacillin concentrations significantly increased achievement of the therapeutic target concentration.

By contrast to that shown for fluoroquinolones [14], the possibility of selecting resistant mutants at serum piperacillin concentrations <4× MIC is not supported by experimental data. However, several authors have suggested that prolonged percentage of time during which the concentration remains above 4× MIC (*T*>4× MIC), instead of *T*>MIC, is an important pharmacokinetic/pharmacodynamic (PK/PD) parameter that better predicts treatment outcome with β-lactams (especially for critically ill patients) [2,5,15]. Here,

serum piperacillin concentrations were monitored daily for between 3 days and 20 days (mean ± S.D., 9 ± 5.2 days). For the eight patients (Patients 7, 10–15 and B) with low initial serum piperacillin concentrations, the mean percentage $T>4\times$ MIC was 7.1 ± 5.9% before antibiotic dosage adjustment and 27.3 ± 8.6% afterwards (Fig. 1). This significant difference (P = 0.03) demonstrates the beneficial impact of regular serum piperacillin monitoring on these important therapeutic PK/PD parameters.

4. Conclusion

In critically ill patients, monitoring and adjustment of serum piperacillin levels are warranted to prevent overdosing and to help correct underdosing, an important cause of antibiotic therapy failure. Additional trials in a more homogeneous patient population are required to underpin these preliminary findings.

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Competing interests

None declared.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients or their legal guardians.

References

[1] Craig WA, Ebert SC. Continuous infusion of β-lactam antibiotics. Antimicrob Agents Chemother 1992;36:2577–83.

[2] MacGowan AP, Bowker KE. Pharmacodynamics of antimicrobial agents and rationale for their dosing. J Chemother 1997;9(Suppl 1):64–73.

[3] Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1–10.

[4] Kasiakou SK, Sermaides GJ, Michalopoulos A, Soteriades ES, Falagas ME. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect Dis 2005;5:581–9.

[5] Roberts JA, Paratz J, Paratz E, Krueger WA, Lipman J. Continuous infusion of β-lactam antibiotics in severe infections: a review of its role. Int J Antimicrob Agents 2007;30:11–8.

[6] Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet 2005;44:1009–34.

[7] Mehrotra R, De Gaudio R, Palazzo M. Antibiotic pharmacokinetic and pharmacodynamic considerations in critical illness. Intensive Care Med 2004;30:2145–56.

[8] Buck C, Bertram N, Ackermann T, Sauerbruch T, Derendorf H, Paar WD. Pharmacokinetics of piperacillin–tazobactam: intermittent dosing versus continuous infusion. Int J Antimicrob Agents 2005;25:62–7.

[9] Rafati MR, Rouini MR, Mojtahedzadeh M, Najafi A, Tavakoli H, Gholami K, et al. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. Int J Antimicrob Agents 2006;28:122–7.

[10] Kotapati S, Kuti JL, Geissler EC, Nightingale CH, Nicolau DP. The clinical and economic benefits of administering piperacillin–tazobactam by continuous infusion. Intensive Crit Care Nurs 2005;21:87–93.

[11] Rudrik JT, Bawdon RE. Determination of penicillinase-resistant penicillins in serum using high pressure liquid chromatography. J Liq Chromatogr 1981;4:1525–45.

[12] Gould IM, Ansari A, Harvey G, Douglas JG, Smith CC, Reid TM. Piperacillin/tazobactam in the treatment of serious acute soft tissue infection. Drugs Exp Clin Res 1991;17:187–90.

[13] Bourget P, Lesne-Hulin A, Le Reveille R, Le Bever H, Carsin H. Clinical pharmacokinetics of piperacillin–tazobactam combination in patients with major burns and signs of infection. Antimicrob Agents Chemother 1996;40:139–45.

[14] Drlica K, Zhao X. Mutant selection window hypothesis updated. Clin Infect Dis 2007;44:681–8.

[15] Mouton JW, den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother 1994;38:931–6.

Fig. 1. Impact of piperacillin/tazobactam dosage changes on pharmacokinetic/pharmacodynamic parameters. Change in %*T*>4× MIC for patients who received dosage adjustment due to below-target serum concentrations. Horizontal bars represent the mean %*T*>4× MIC. %*T*>4× MIC, percentage of time during which the concentration remained above 4× the minimum inhibitory concentration.

Table 1

Characteristics of the 24 patients treated with piperacillin/tazobactam (PIP/TAZ)

(a) Characteristics of the 15 patients with non-documented infection (no pathogen isolated). The lower target value was defined as 4× the critical concentration above which all bacterial species are considered to be resistant to PIP, i.e. 4 × 16 mg/L = 64 mg/L (according to guidelines issued by the French Microbiology Society's Antibiotics Committee). For these patients, target values are between 64 mg/L and 150 mg/L (toxicity threshold); otherwise dosage was changed

Patient no.	Age (years)	Weight (kg)	Gender	Renal function impairment [a]	Indication for antibiotic therapy	Initial dosage (g/day) [b]	Dosage change (g/day) [b]	PIP concentration (mg/L) [c]		*n* × PIP MIC	
								Before dosage adjustment	After dosage adjustment	Before dosage adjustment	After dosage adjustment
1	75	90	M	No	HAP	18/2.25	No	80.5 ± 2.1	–	5.03 ± 0.13	–
2	46	70	M	Yes	HAP	7/0.875	No	105.9 ± 3.8	–	6.62 ± 0.24	–
3	69	90	M	Yes	HAP	9/1.125	No	97.5 ± 22.5	–	6.10 ± 1.41	–
4	68	59	M	No	HAP	12/1.5	No	95.4 ± 13.0	–	5.96 ± 0.81	–

5	80	70	M	No	HAP	14/1.75	No	70.1 ± 5.4	–	4.38 ± 0.34	–
6	67	102	M	No	HAP	20/2	No	77.0 ± 8.4	–	4.81 ± 0.53	–
7	74	71	M	No	HAP	14/1.75	Yes: 16/2	3.3 ± 1.6	64.9 ± 4.3	0.20 ± 0.10	4.06 ± 0.27
8	56	80	M	Yes	HAP	8/1	Yes: 4/0.5	320.6 ± 19.4	92.7 ± 54.9	20.03 ± 1.21	5.79 ± 3.43
9	81	54	F	No	Cellulitis	10/1.25	No	78.9 ± 12.2	–	4.93 ± 0.73	–
10	53	87	M	No	Cellulitis	18/2.25	Yes: 20/2.5	44.8 ± 9.2	66.7 ± 6.1	2.80 ± 0.58	4.17 ± 0.38
11	60	70	M	No	Cellulitis	14/1.75	Yes: 16/2, then 18/2.25	51.9 ± 18.0	55.3 ± 17.1	3.24 ± 1.13	3.46 ± 1.07
12	61	65	M	Yes	Cellulitis	7/0.875	Yes: 9/1.125	35.6 ± 0.6	39.8 ± 3.2	2.21 ± 0.04	2.49 ± 0.20

13	58	80	M	No	Cellulitis	16/2	Yes: 18/2.25	54.3 ± 3.3	59.0 ± 4.6	3.39 ± 0.21	3.69 ± 0.29
14	34	80	M	No	Cellulitis	16/2	Yes: 18/2.25, then 20/2.5	42.6 ± 5.3	50.0 ± 6.2	2.66 ± 0.33	3.13 ± 0.39
15	43	100	M	No	Cellulitis	20/2.5	Yes: 24/3	25.9 ± 5.4	30.6 ± 2.9	1.62 ± 0.34	1.91 ± 0.18

(b) Characteristics of the 9 patients with documented infection. The lower target value was defined as 4× the PIP MIC for the identified pathogen. For these patients target values are between 4× the PIP MIC and 150 mg/L

Patient no.	Age (years)	Weight (kg)	Gender	Renal function Impairment [a]	Indication for antibiotic therapy	Isolates/ PIP MIC (mg/L)	Initial dosage (g/day)	Dosage change (g/day)	PIP concentration (mg/L) [c]		*n* × PIP MIC	
									Before dosage adjustment	After dosage adjustment	Before dosage adjustment	After dosage adjustment

A	74	90	M	Yes	HAP	P.a./4	9/1.125	Yes: 7/0.875	147.9 ± 8.8	109.9 ± 28.2	36.98 ± 2.20	27.48 ± 7.05
B	48	50	F	No	HAP	P.a./16	10/1.25	Yes: 12/1.5	55.2 ± 3.4	46.5 ± 2.0	3.45 ± 0.21	2.91 ± 0.12
C	71	105	M	No	HAP	E.c./4	20/2.5	No	102.0 ± 9.0	–	25.50 ± 2.25	–
D	29	90	M	No	HAP	E.c./8	18/2.25	No	69.9 ± 26.5	–	8.74 ± 3.31	–
E	69	90	M	Yes	HAP	K.p./4	9/1.125	Yes: 4/0.5	224.1 ± 30.4	54.6 ± 25.2	56.02 ± 7.60	13.65 ± 6.30
F	74	80	M	Yes	Septic shock	K.p./8	8/1	Yes: 6/0.75	181.8 ± 34.5	140.8 ± 17.6	22.72 ± 4.31	11.51 ± 2.20
G	65	46	M	No	HAP	A.b./4	10/1.25	No	25.0 ± 2.8	–	6.26 ± 0.70	–
H	80	72	M	No	HAP	S.a./4	14/1.75	No	87.5 ± 17.7	–	21.87 ± 4.43	–
I	64	80	M	No	sUTI	E.a./16	16/2	No	65.6 ± 2.4	–	4.10 ± 0.15	–

HAP, hospital-acquired pneumonia; sUTI, severe urinary tract infection; P.a., *Pseudomonas aeruginosa*; E.c., *Escherichia coli*; K.p., *Klebsiella pneumoniae*; A.b., *Acinetobacter baumannii*; S.a., *Staphylococcus aureus*; E.a., *Enterobacter aerogenes.*

[a] Creatinine clearance ≤30 mL/min, calculated according to the Cockcroft and Gault formula.

[b] PIP/TAZ combination.

[c] Serum PIP concentration (free fraction): mean ± S.D. of 2 to 17 samples according to the patient.