Piperacillin penetration into tissue of critically ill patients with sepsis—Bolus versus continuous administration?

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Objective: **To describe a pharmacokinetic model of piperacillin concentrations in plasma and subcutaneous tissue when administered by bolus dosing and continuous infusion in critically ill patients with sepsis on days 1 and 2 of antibiotic therapy and to compare results against previous results for piperacillin from a cohort of patients with septic shock.**

Design: **Prospective randomized controlled trial.**

Setting: **Eighteen-bed intensive care unit at 918-bed tertiary referral hospital.**

Patients: **Thirteen critically ill adult patients with known or suspected sepsis in whom the treating physician deemed piperacillin–tazobactam appropriate therapy were conveniently sampled.**

Interventions: **Patients were randomized to receive different daily doses of piperacillin–tazobactam by bolus dosing or continuous infusion (continuous infusion—six patients; bolus dosing—seven patients). Serial plasma and tissue concentrations were determined on days 1 and 2 of treatment. Tissue concentrations of piperacillin were determined using a subcutaneously inserted microdialysis catheter. Separate pharmacokinetic models were developed for both bolus and continuous dosing.**

Measurements and Main Results: **This is the first known article to report concurrent plasma and subcutaneous tissue concentrations of a β-lactam antibiotic administered by bolus and continuous dosing in critically ill patients with sepsis. With a 25% lower piperacillin dose administered to the continuous infusion group, the infusion group had statistically significantly higher median plasma concentrations than the bolus group on day 2 (16.6 vs. 4.9 mg/L; $p = 0.007$). There was a trend to higher median plasma concentrations on day 1 in the bolus dosing group (8.9 vs. 4.9 mg/L; $p = 0.078$). Median tissue concentrations were not statistically different on day 1 (infusion group 2.4 mg/L vs. bolus group 2.2 mg/L; $p = 0.48$) and day 2 (infusion group 5.2 mg/L vs. bolus group 0.8 mg/L; $p = 0.45$). A two-compartment pharmacokinetic model was found to describe the data best. Tissue pharmacodynamic targets were achieved more successfully with infusion dosing.**

Conclusions: **Patients with sepsis do not seem to have the same level of impairment of tissue distribution as described for patients with septic shock. A 25% lower dose of piperacillin administered by continuous infusion seems to maintain higher trough concentrations compared with standard bolus dosing. It is likely that the clinical advantages of continuous infusion are most likely to be evident when treating pathogens with high minimum inhibitory concentration, although without therapeutic drug monitoring and subsequent dose adjustment, infusions may never achieve target concentrations of organisms with very high minimum inhibitory concentrations in a small number of patients. (Crit Care Med 2009; 37:926–933)**

Key Words: β-lactam; piperacillin; pharmacokinetics; continuous infusion; sepsis; microdialysis; target site

Treatment of sepsis remains a significant challenge to critical care physicians worldwide, with persisting high mortality and morbidity rates. With an incidence exceeding either colon or breast cancer and with mortality rates approaching 50% for severe sepsis and septic shock (1, 2), improved treatment strategies are necessary. Current evidence suggests that with source control of the pathogen, early and appropriate antibiotic therapy remains the most important intervention that the clinician can implement for such patients (3–8). Given the increasing incidence of sepsis (9), further research toward optimizing antibiotic therapy should be a priority (10).

A wide array of pathophysiologic changes can occur in patients with sepsis, which complicate antibiotic dosing (10). Changes in volume of distribution and clearance of antibiotics are well documented. Previous data from Joukhadar et al (11) have shown significantly reduced concentrations of piperacillin in peripheral tissues in critically ill patients with septic shock. Impaired antibiotic distribution into tissue, the target site where most infections occur (12), is a major concern for clinicians and may explain some of the persisting high morbidity and mortality in this patient population.

Many authors have suggested continuous infusion as a modality to optimize the time-dependent bacterial killing characteristics of β-lactam antibiotics (13–18). Indeed, preliminary data from the larger prospective and retrospective clinical studies suggest some clinical advantages of a β-lactam administration by continuous infusion in critically ill patients (19–21). Previous pharmacokinetic studies comparing both dosing modalities have focused on plasma concentrations (22), with little research

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into tissue distribution. Previous studies that have compared tissue and plasma pharmacokinetics of bolus and continuous administration have reported concentrations in peritoneal exudate (23) or other tissue (rat muscle and lung [24], volunteer blister fluid tissue [25, 26], and volunteer muscle and subcutis [27]).

Piperacillin is an ureidopenicillin β-lactam antibiotic that is commonly used as empirical therapy for nosocomial infections. It is commonly combined with the β-lactamase inhibitor, tazobactam, to increase its spectrum of activity. It is moderately protein bound and is eliminated by predominantly renal mechanisms (28). Use of piperacillin in critically ill patients with sepsis is common because of its broad spectrum and minimal adverse effect profile.

Our aim was to develop a pharmacokinetic model of piperacillin concentrations in plasma and subcutaneous tissue when administered by bolus dosing and continuous infusion in critically ill patients with sepsis on days 1 and 2 of antibiotic therapy. Furthermore, we aimed to compare our results against previous results for piperacillin administered by bolus dosing in a cohort of patients with septic shock (11).

MATERIALS AND METHODS

Patients. This study was performed in an 18-bed intensive care unit of a 918-bed tertiary referral hospital. Ethical approval to conduct the study was obtained from the local Institutional Ethics Committee (protocol 2005/028). Consent to participate was obtained from the patient's legally authorized representative.

Procedures. Critically ill adult patients with known or suspected sepsis in whom the treating physician deemed piperacillin–tazobactam appropriate therapy were conveniently sampled. Sepsis was diagnosed according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee (29). Patients with a known or suspected allergy to penicillin, piperacillin–tazobactam, or renal impairment (defined as plasma creatinine >120 μM/L) were excluded. In accordance with usual practice, all patients had an indwelling arterial cannula.

Antibiotic Administration. Patients were randomized using opaque sealed envelopes to receive piperacillin–tazobactam by bolus or continuous infusion. Continuous infusion dosing was as follows:

1. Day 1: 4 g/0.5 g piperacillin–tazobactam bolus infusion (by central line over 20 minutes) followed immediately by a continuous 24-hour infusion of 8 g piperacillin/1 g tazobactam (piperacillin 333 mg/hr).
2. Day 2 onward: 12 g/1.5 g piperacillin–tazobactam administered by 24-hour infusion (piperacillin 500 mg/hr).

Piperacillin–tazobactam solutions have previously been shown to be stable at 37°C for at least 24 hours (30). Bolus dosing for piperacillin–tazobactam was 4 g/0.5 g every 6 or 8 hours as prescribed by the treating critical care physician.

Sample Collection. On day 1, samples of arterial blood were collected at approximately 0, 3, 6, 15, and 20 minutes during the bolus infusion then postbolus infusion at 3, 6, 15, 20, 30, 45, 60, 90, 120, 210, 360, and 480 minutes. On day 2 (fifth piperacillin–tazobactam bolus dose or change of continuous infusion bag), arterial blood samples were taken before 0 minute and 5, 10, 20 30, 60, 120, 180, 240, and 480 minutes after commencement of the new infusion (continuous or bolus infusion dose). Specimens were centrifuged at 3000 rpm for 10 minutes and then frozen at −20°C for subsequent analysis. Recognizing that piperacillin has limited stability at this temperature, samples were assayed individually as soon as possible after collection (usually within 7 days).

Eight-hour creatinine clearance was calculated using the equation:

$$\text{Creatinine clearance (mL/min)} = (C_{\text{creatinine in urine}} \times \text{volume}_{\text{urine}})/(C_{\text{creatinine in plasma}} \times \text{urine collection time}).$$

No microbiological susceptibility testing was undertaken.

In Vivo Microdialysis. Microdialysis was the technique chosen to measure the free (or unbound) antibiotic concentration in subcutaneous tissue. Given that the free antibiotic concentration determines antibacterial effect (31), this information is particularly instructive. This technique is used by many intensivists who are interested in drug concentrations in muscle, subcutis, epithelial lining fluid, ascites, cerebrospinal fluid, and blood in case of remote infection (11, 32–41). The principles and details of microdialysis have been described previously (33). Briefly, microdialysis is based on the sampling of analytes from the extracellular space by diffusion across a semipermeable membrane. *In vivo*, this process is accomplished by constantly perfusing the microdialysis probe with a physiologic solution at a low flow rate. Once the probe is implanted in tissue, analytes diffuse across the membrane from the extracellular fluid into the perfusate and may be sampled and analyzed. In this study, a microdialysis probe (CMA 60, Microdialysis AB, Stockholm, Sweden) with a molecular weight cutoff of 20 kDa, an outer diameter of 0.6 mm, and a membrane length of 30 mm was aseptically placed in the subcutaneous tissue of the upper arm of each patient. The probe was perfused with penicillin G (2 mg/L; internal standard) in 0.9% sodium chloride at a flow rate of 1.6 μL/min (33). After commencement of the piperacillin–tazobactam infusion, microdialysis samples were collected at approximately 20-minute intervals on days 1 and 2 of antibiotic treatment. Samples were stored at −20°C for subsequent analysis. The recovery of piperacillin in the microdialysate solution was interpolated from the loss of internal standard (penicillin G) across the microdialysis membrane into tissue according to the retrodialysis method (42, 43):

$$\%\ \text{piperacillin recovery} = 100 \times (C_{in} - \text{mean}\ C_{out}/C_{in})$$

where C_{in} is penicillin G 2 mg/L (perfusate); C_{out} is the measured penicillin-G concentration in microdialysate.

Clinical Outcome. Clinical outcome from the antibiotic therapy was assessed by the treating intensivist using the definitions described in Table 1.

Determination of Unbound Piperacillin Fraction in Plasma. Five hundred microliters of 100 μg/mL piperacillin in plasma from patients was ultracentrifuged (12,000 rpm for 20 minutes) through 3 kDa nominal cutoff membrane devices (Amicon YM30, Millipore, Billerica, MA), giving an approximate filtrate yield of 25% original volume. One hundred-microliter filtrate plus 20 μL of 500 μg/mL penicillin G (internal standard) was analyzed by high-performance liquid chromatography.

Drug Assay. Plasma piperacillin concentrations were measured by reverse-phase high-performance liquid chromatography (HPLC) with UV detection (Waters 510 pump, 717 autosampler and 486 Tunable Absorbance Detector set at 218 nm λ) using a 150 mm × 4.6 mm Gemini 3-μm C18 column (Phenomenex,

Table 1. Definitions for classification of clinical outcome of antibiotic therapy

Clinical Outcome	Definition
Resolution	Disappearance of all signs and symptoms related to the infection
Improvement	A marked or moderate reduction in the severity and/or number of signs and symptoms of infection
Failure	Insufficient lessening of the signs and symptoms of infection to qualify as improvement, including death or indeterminant (no evaluation possible, for any reason)

Lane Cove, Australia) as previously described (44). Assay validation with pooled human plasma gave a limit of quantification (signal to noise ratio 10) of 2.5 mg/L and the reproducibility was acceptable: coefficient of variation (for 50 mg/L) was 2.2% (intraday) and 6.4% (interday).

Microdialysate concentrations of piperacillin were analyzed with a high-performance liquid chromatography system with electrospray mass spectrometer (MS) detector (LCMS) (Applied Biosystems API3000 Tandem MS System [Carlsbad, CA]; Shimadzu HPLC [Kyoto, Japan] with Phenomenex Gemini C18 column). Results were interpreted using Analyst software (45). The limit of quantification of the piperacillin LCMS assay was 0.125 mg/L and the reproducibility was acceptable: coefficient of variation (n = 6) was 2% and 3% at 2 and 0.2 mg/L, respectively.

Sample Size Calculation. A power calculation for independent patients with an alpha of 0.05 and a power of 90%, using a delta (difference of C_{min} between population means) of 4 and a sigma (SD) of 160% required a sample size of five patients (46).

Table 2. Demographic and clinical details of enrolled patients

	Patient															
	1	2	3	4	5	6	7	8	9	10	11	12	13	Bolus Group	Infusion Group	*p*
Administration method	B	I	B	I	B	B	I	B	I	I	B	I	B	7 patients	6 patients	—
Age (yrs)	75	35	20	25	42	23	20	65	36	17	65	24	40	42.0 (23.0–65.0)	24.5 (19.3–35.3)	0.04[a]
Sex	M	M	F	M	M	M	M	M	M	M	F	M	F	4 male, 3 female	6 male	0.19[b]
Indication for antibiotic	VAP	VAP	VAP	VAP	VAP	VAP	VAP	VAP	VAP	VAP	VAP	VAP	VAP	—	—	—
Piperacillin dose (0–30 hrs; mg/kg)	267	158	278	167	152	222	200	250	156	188	176	160	235	235 (176–267)	164 (158–191)	0.06[c]
Clinical outcome	Cure	Cure	Cure	Cure	Cure	Cure	Cure	Cure	Cure	Cure	Cure	Cure	Cure	7/7 cure	6/6 cure	—
Height (cm)	173	190	170	178	175	181	176	180	171	176	171	175	172	173 (171–180)	176 (174–181)	0.32[c]
Weight (kg)	75	95	72	90	132	90	48	45	64	80	85	75	85	85 (72–90)	78 (60–91)	0.77[c]
Body mass index (m^2)	25.1	26.3	24.9	28.4	43.1	27.5	24.2	24.7	28.0	25.8	29.1	24.5	28.7	27.5 (24.9–29.1)	26.1 (54.4–28.1)	0.32[c]
Plasma creatinine (μmol/L)	102	73	57	99	62	90	48	45	67	43	48	54	49	57 (48–90)	61 (47–80)	0.94[c]
Eight-hour creatinine clearance (mL/min)	91	221	91	97	325	165	105	231	284	159	199	174	233	199 (91–233)	166 (103–237)	0.84[c]
Vasopressors?	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	1/7	1/6	1.00[b]
Day 1 SOFA Score	2	3	4	4	3	2	1	3	3	4	3	7	3	3.0 (2.0–3.0)	3.5 (2.5–5.5)	0.26[c]
Day 2 SOFA Score	8	3	3	5	4	2	1	4	2	3	2	6	3	3.0 (2.0–4.0)	3.0 (1.8–4.5)	0.66[c]
Day 1 APACHE Score	15	10	23	21	24	27	16	26	19	16	16	26	31	24.0 (16.0–27.0)	17.5 (14.5–22.3)	0.17[c]
Day 2 APACHE II Score	9	11	24	26	20	22	18	34	20	5	11	26	26	22.0 (11.0–26.0)	19.0 (9.5–26.0)	0.56[c]

B, bolus group; I, infusion group; VAP, ventilator-associated pneumonia; SOFA, Sepsis Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

[a]*p* value determined using independent samples *t* test; [b]*p* value determined using Fisher's exact test; [c]*p* value determined using Mann-Whitney *U* test; Group data are presented as median (interquartile range).

Table 3. Pharmacokinetic properties or piperacillin administered by bolus dosing and continuous infusion on days 1 and 2 of antibiotic therapy

	Plasma PK		Tissue PK	
	Bolus Dosing	Continuous Infusion	Bolus Dosing	Continuous Infusion
AUC_{0-24} of modeled data (mg/hr/L)	802.8	464.1	168.5	93.8
Unbound C_{max} (mg/L)	266.6 (178.3–316.1)	151.5 (90.1–275.0)	40.57 (23.9–153.1)	11.9 (2.7–34.6)
Day 1 unbound C_{min} (mg/L)	8.9 (2.3–10.0)	4.9 (2.5–18.5)	2.2 (0.9–3.7)	2.4 (1.8–7.6)
Day 2 unbound C_{min} (mg/L)	2.0 (1.8–7.5)	16.6 (11.1–23.7)	0.8 (0.0–9.9)	5.2 (2.5–7.7)
Half-life (hrs)	0.56 (0.49–0.58)	0.28 (0.19–0.95)	—	—
Volume of central compartment (L)	14.7 (12.1–15.9)	9.2 (7.5–18.7)	—	—
Volume of peripheral compartment (L)	—	—	34.2 (24.2–50.9)	25.3 (15.53–382.5)
k_{el} (hrs^{-1})	1.24 (1.19–1.41)	2.48 (.43–3.65)	—	—
k_1 (hrs^{-1})	0.008 (0.003–0.022)	0.007 (0.005–0.009)	—	—
k_2 (hrs^{-1})	0.006 (0.003–0.01)	0.004 (0.0001–0.01)	—	—
A (mg/L)	272 (252–331)	315 (214–533)	—	—
Alpha (hrs^{-1})	1.8 (1.2–1.4)	2.5 (0.7–3.6)	—	—
B (mg/L)	0.004 (0.002–0.038)	0.001 (0.00003–0.036)	—	—
Beta (hrs^{-1})	0.006 (0.003–0.01)	0.004 (0.0001–0.01)	—	—

PK, pharmacokinetics; AUC_{0-24}, the area-under-the concentration time curve from 0 to 24 hours; C_{max}, maximum observed concentration; C_{min}, minimum observed concentration; k_1, constant for distribution from central into peripheral compartment; k_2, constant for distribution from peripheral into central compartment; A, alpha, B, and beta are microconstants derived during the integration process. The half-life and central and peripheral volumes for continuous infusions are apparent values.

Data are reported as median (interquartile range).

Pharmacokinetic and Statistical Analysis. Pharmacokinetic parameters for each patient were estimated for the plasma and subcutaneous microdialysis data by nonlinear regression applied to individual dosing regimens (Scientist 2.0, Micromath, St. Louis, MO). We applied various models to the data (one-, two-, and three-compartment linear and Michaelis-Menten models were attempted as part of the modeling process, as were different weightings [unweighted, $1/Y$, $1/Y^2$]). Area-under-the-concentration (AUC) time curve from 0 to 24 hours (AUC_{0-24}) was calculated using the linear trapezoidal rule. The mean pharmacokinetic parameter estimates for individual patients were then derived from the individual estimates from patients to describe the piperacillin distribution kinetics from plasma to subcutis, the volume of the central compartment and the rate of elimination. Graphing of data was undertaken using Prism version 4.0 (GraphPad Software, San Diego, CA). Statistical analysis of data was undertaken using SPSS 15.0 for Windows (SPSS, Chicago, IL).

Calculation of Time to Plasma-Tissue Concentration Equilibrium. Time to equilibrium ($T_{1/2eq,50}$) is defined as time to reach 50% tissue:plasma concentration ratio (47). $T_{1/2eq,50}$ is dependent on intravenous administration rate. When a loading dose has been administered and is immediately followed by a continuous infusion:

$$T_{1/2eq,50} = 0.693/k2$$

$$\text{Time to 90\% equilibrium } (T_{1/2eq,90}) = 3.3 \times T_{1/2eq}$$

Pharmacodynamic Analysis. A pharmacodynamic evaluation of bolus and continuous dosing methods was undertaken using the lower limit of the 95% confidence interval minimum concentration observed during the dosing period (C_{min}). Given the large pharmacokinetic variability between critically ill patients, we elected to use the lower limit 95% confidence interval concentrations as these are representative of 95% of the target population (as opposed to mean or median concentrations). For continuous infusion, time above the minimum inhibitory concentration ($T >$ MIC) of 100%, and bolus dosing $T >$ MIC of 60% of the dosing interval, were used as targets for pharmacodynamic success. These probability of target attainments were then compared against a MIC distribution. Given the lower dose of continuous infusion used in this study (12 g piperacillin/24 hrs), we measured probability of target attainment using the observed continuous infusion C_{min} (95% confidence interval) and a "dose-normalized C_{min}" where the calculation was based on the same dose used in bolus administration (16 g piperacillin/24 hrs).

RESULTS

Thirteen patients were enrolled, seven patients were randomized to receive piperacillin–tazobactam by bolus dosing and six by continuous infusion. Patients were each enrolled to the study within 5–10 days of admission to the intensive care

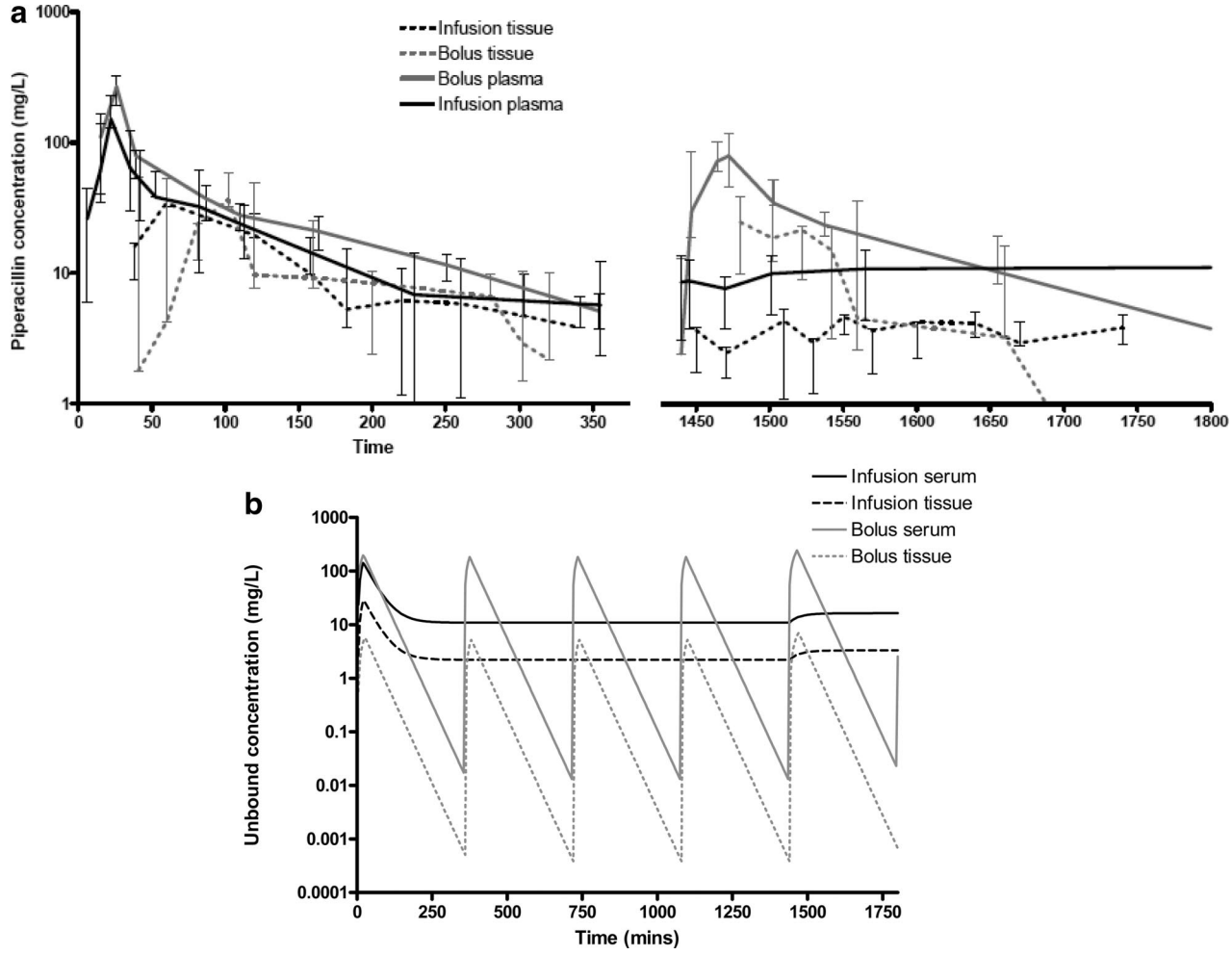

Figure 1. (*a*) Concentration–time profile of unbound piperacillin in plasma and subcutaneous tissue when administered by bolus administration (4 g over 20 minutes) or continuous infusion after initial loading dose (data represented as median and interquartile ranges); and (*b*) simulated plasma and subcutaneous concentrations of unbound piperacillin administered by bolus dosing (4 g/6 hrs; 16 g/24 hrs) or continuous infusion (12 g/24 hrs).

unit. Patient demographic and clinical details are described in Table 2. There were no statistically significant differences between groups in terms of patient weight, urine output, mean arterial pressure, body mass index, Sepsis Organ Failure Assessment Scores, or Acute Physiology and Chronic Health Evaluation II Scores (Mann-Whitney *U* tests). Patients in the bolus group were older than the infusion group (median age 42 years vs. 24 years; $p = 0.04$; independent samples Student's *t* test). The infusion group had statistically significantly higher median plasma concentrations on day 2 than the bolus group (16.6 vs. 4.9 mg/L; $p = 0.007$). There was a trend to higher median plasma concentrations on day 1 in the bolus dosing group (8.9 vs. 4.9 mg/L; $p = 0.078$). Median tissue concentrations were not statistically different on day 1 (infusion group 2.4 mg/L vs. bolus group 2.2 mg/L; $p = 0.48$) and day 2 (infusion group 5.2 mg/L vs. bolus group 0.8 mg/L; $p = 0.45$). The half-life of piperacillin determined in our patients (0.56 $hours^{-1}$ [interquartile range 0.50–0.58] bolus group and 0.28 $hours^{-1}$ [interquartile range 0.19–0.95] infusion group) was faster than that of healthy volunteers (0.6–1.1 $hours^{-1}$) (28, 48). Piperacillin was 30% protein bound in this cohort. The mean recovery rate of piperacillin from the microdialysis probes was 40%.

A two-stage pharmacokinetic approach was undertaken to model the plasma and tissue concentrations for each of the patients. Linear one-compartment, three-compartment, and various Michaelis-Menten models were also examined. An attempt to model bolus patients using a different linear compartmental model compared with the infusion group, which was modeled using a nonlinear model (because of previous data from Vinks et al [49]), was also undertaken. However, a two-compartment linear model was found to best describe the data. None of the data weighting strategies applied improved the individual models. The results of the individual pharmacokinetic models were then pooled together to simulate the plasma and subcutaneous tissue concentration profiles of piperacillin administered by bolus or continuous administration. The parameters for the individual pharmacokinetic models are described in Table 3. The observed plasma and tissue data are shown in Figure 1*a*, with the population simulations from the pharmacokinetic model shown in Figure 1*b*.

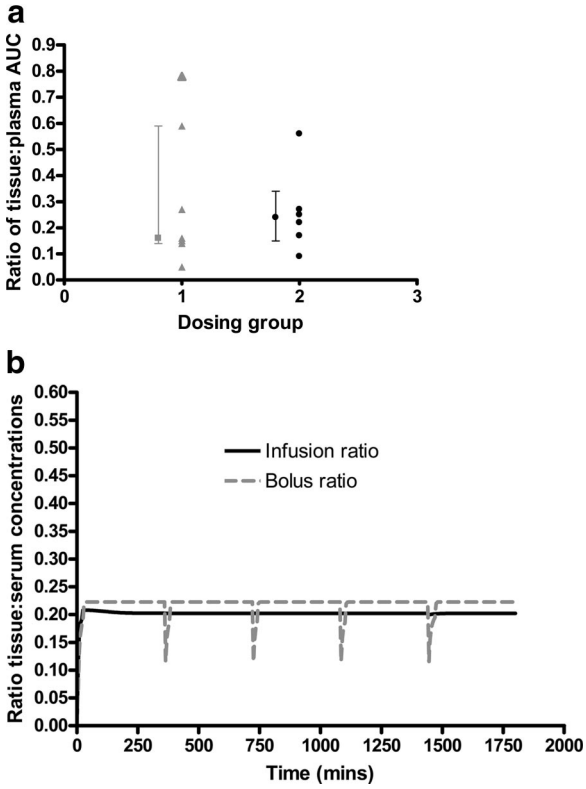

Figure 2. Tissue distribution: the extent of piperacillin penetration into subcutaneous tissue as described by: (*a*) the ratio of subcutaneous tissue to plasma piperacillin area under the concentration–time curve (*AUC*) for individual patients (median data with interquartile range are proximal to each group; group 1 is the bolus dosing group and group 2 is the infusion dosing group); and (*b*) time course of subcutaneous tissue to unbound plasma piperacillin concentration ratios using modeled data.

The extent of distribution of piperacillin from plasma to tissue from the actual data and modeled data are presented in Figure 2. We observed the ratio of piperacillin in tissue to be 1–5 times lower than plasma concentrations in our individual patients. When C_{min} was normalized to actual body weight, there was a significant decrease in the variability of C_{min} (bolus group SD decreased from 160% to 49% and infusion group 106% to 28%).

Using k_2 (Table 3), the $T_{1/2eq,50}$ for the continuous infusion group occurs after approximately 173 $hours^{-1}$. The $T_{1/2eq,90}$ occurs after 570 $hours^{-1}$. Therefore, tissue:plasma equilibrium was not achieved in this study.

Bolus dosing of piperacillin produced decreased $T >$ MIC compared with continuous administration in both tissue and plasma. It was not possible to compare 100% $T >$ MIC of both dosing methods as bolus administration rarely achieved adequate trough concentrations. The results of our probability of target attainment calculations that utilized the lower limit C_{min} using the 95% confidence intervals from each dosing method are shown in Figure 3*a* (plasma) and Figure 3*b* (tissue).

DISCUSSION

In critically ill patients with sepsis, the plasma and tissue pharmacokinetics of piperacillin are similar when administered by bolus dosing or continuous infusion. By using predefined pharmacodynamic end points, we have shown that a continuous infusion dose that is 25% smaller than the bolus dose can attain higher pharmacodynamic targets in subcutaneous tissue. Bolus dosing achieved marginally higher plasma pharmacodynamic targets than continuous infusion, although different pharmacodynamic targets were used for each dosing regimen. The concentration data obtained from tissues is particularly useful for predicting antibiotic efficacy, given that tissues are frequently the target site of infection (12).

Comparisons of bolus dosing and continuous infusion of β-lactam antibiotics in humans have been published primarily on plasma pharmacokinetics (13, 50, 51), with studies on bile (52) and peritoneal

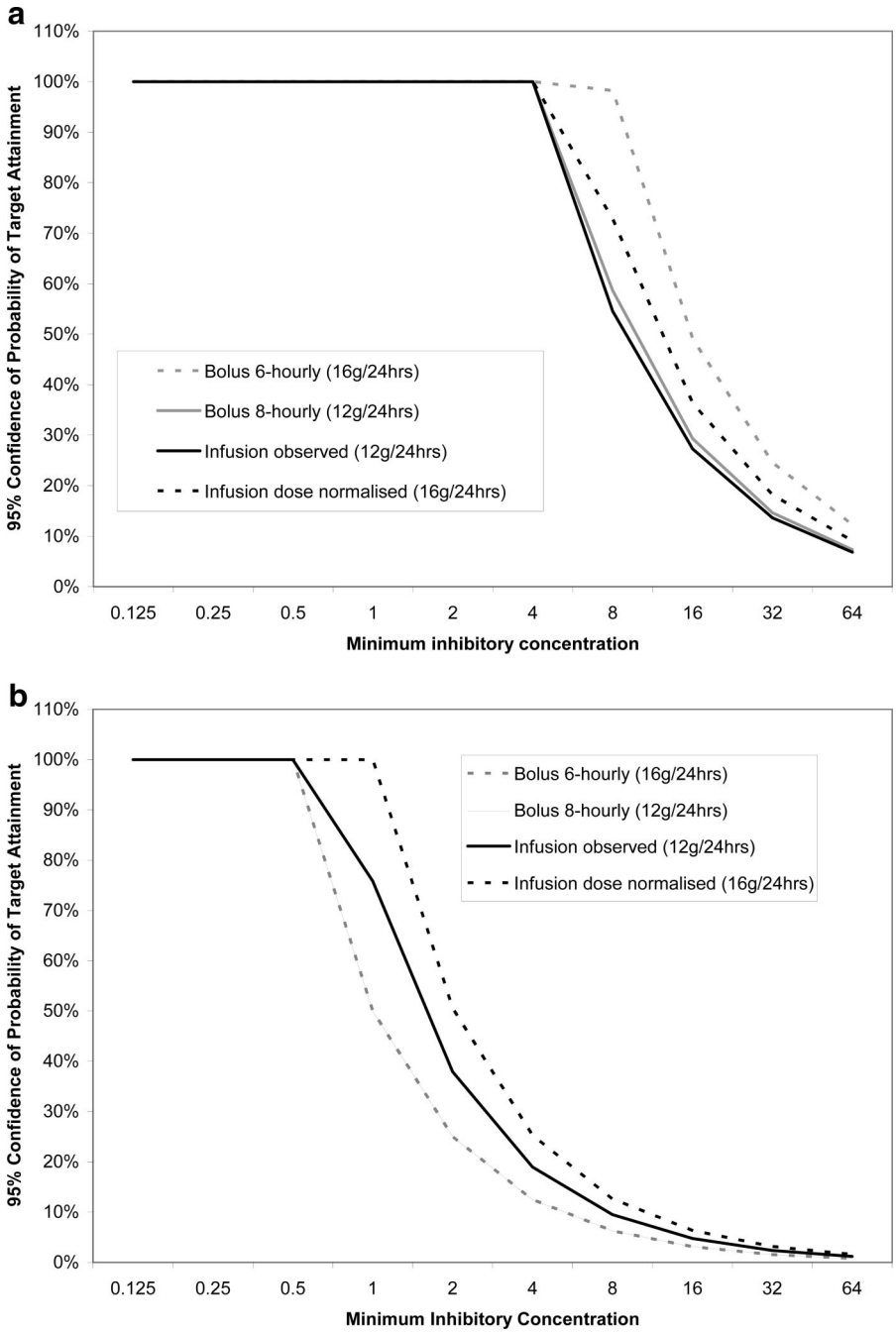

Figure 3. *a*, Probability of target attainment of pharmacodynamic indices in plasma for bolus (60% T > MIC) vs. continuous infusion (100% T > MIC). *b*, Probability of target attainment of pharmacodynamic indices in subcutaneous tissue for bolus (60% T > MIC) vs. continuous infusion (100% T > MIC). *MIC*, minimum inhibitory concentration.

exudate (23) also performed. To our knowledge, the information presented in this article is the first to describe subcutaneous extracellular fluid tissue concentrations of a β-lactam antibiotic administered by both continuous infusion and bolus dosing. Like previous authors, we used microdialysis because it measures the unbound (free) fraction of piperacillin that distributes into tissue (11, 35, 38, 53–55). Our data indicate improved tissue pharmacodynamics using continuous infusion. Although the clinical significance of this difference is likely to only be important when treating infections caused by susceptible pathogens with high MICs (2 or 4 mg/L).

We found that a two-compartment linear pharmacokinetic model best described the data from our cohort of patients. This contrasts with previous data that suggest that piperacillin elimination may have a significant saturable component. Landersdorfer has identified the conflicting data that exist on whether the reported saturable piperacillin pharmacokinetics arises from renal or nonrenal elimination or both (28, 49, 56–58). As stated by the author, the lack of agreement on the extent of piperacillin elimination is important in comparing short-term intravenous infusion vs. continuous infusion (56). In a dose-ranging crossover study in ten volunteers, the author concluded that piperacillin elimination was best described with saturable renal elimination (K_m 46.8 mg/L) and first-order nonrenal elimination. Given that the peak piperacillin concentrations observed here greatly exceed this value, renal saturation was likely in our cohort of patients. However, the shape of the profiles (Fig. 1) and a lack of model improvement when saturable renal elimination was used in the model, suggest this renal saturation may not be significant in this critical care population.

The $T_{1/2eq,90}$ in this study (570 hours^{-1}) was longer than that calculated from a sample of healthy volunteers (10 hours^{-1}) (56). The reason for the difference is unknown, although the altered microvascular perfusion that is common to critically ill patients with sepsis is a likely explanation.

Joukhadar et al (11) produced a landmark article in 2001 describing tissue piperacillin concentrations in critically ill patients with septic shock that were 5–10 times lower than that found in healthy volunteers. Reduced peripheral drug concentrations probably result from the peripheral microvascular failure that can occur with focused central organ perfusion observed in patients with septic shock (11). We observed subcutaneous tissue concentrations higher than those observed by Joukhadar et al in patients with septic shock. As the patients in the present study fulfilled the criteria for sepsis but did not qualify for septic shock, their likely increased cardiac output leading to increased capillary perfusion in the periphery may result in comparatively higher piperacillin concentrations throughout the body (59–61). Similar antibiotic tissue concentrations, which are also less than plasma concentrations, have also been reported for cefpirome in critically ill patients with sepsis (39). The first patient had tissue piperacillin concentrations comparable to those of other patients in the bolus group, whereas the second patient did have lower tissue con-

centrations than most of the other patients receiving the drug by continuous infusion. This information is inconclusive of the effect of vasopressors in potentially reducing peripheral drug perfusion but may provide some support for the article by Joukhadar et al (11).

The first dose and steady-state antibiotic data from this study are important because of the dynamic physiology common to critically ill patients, which can affect drug pharmacokinetics (10). The data in the present article show reduced variability of steady-state concentrations using continuous infusion, which enables the intensivist to dose the patient with greater confidence for achieving target concentrations. We also observed that the tissue:plasma concentration ratio of piperacillin is similar when administered by continuous infusion and bolus dosing. Interestingly, even at steady state, equal concentrations are not achieved in plasma and tissue, probably due to the altered peripheral blood flow observed in patients with sepsis.

Given the slightly improved probability of target attainment success of continuously infused piperacillin in tissue, this method of administration may be seen as advantageous. A caveat for use of continuous infusions exists when treating organisms with high MICs (>4 mg/L) because without therapeutic drug monitoring and subsequent dose adjustment, infusions may never achieve appropriate concentrations.

There are limitations with this study that we would like to declare. First, our patients with sepsis all met the inclusion criteria of a plasma creatinine concentration below 120 μM/L. Given that sepsis patients may often present with renal failure, the results of this study are applicable only to patients without renal dysfunction. Second, there was a statistically significantly younger cohort in the continuous infusion group, which may have enabled better peripheral antibiotic perfusion, although this would probably be balanced by the likely higher renal function and drug clearance of this group. Third, the median age of this cohort is younger than the typical sepsis population, which limits the generalizability of these results.

CONCLUSIONS

In summary, the present study shows that continuous infusion of piperacillin in critically ill patients attains pharmacodynamic targets in subcutaneous tissue more successfully than bolus dosing. These results were evident despite a 25% lower dose used in the continuous infusion group. This contrasts with data from a previous study in septic shock patients, which showed significantly lower tissue concentrations, but is consistent with the reduced peripheral perfusion observed in patients with septic shock. The difference between bolus dosing and continuous infusion is most likely only relevant to pathogens with high MICs. The results of this study support a need for a large multicentered trial comparing the clinical and bacteriologic outcomes of continuous infusion and bolus dosing of a β-lactam antibiotic in critically ill patients with sepsis.

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