Standard Dosage Regimens of Broad-Spectrum β-Lactams Are Inadequate to Treat "Difficult-to-Treat" Pathogens in Obese Noncritically Ill Patients

Written by Phil Vinall

Results of a large case series of broad spectrum β-lactam agents in obese noncritically ill patients with infection treated using standard dose regimens showed insufficient measured serum concentrations to treat difficult-to-treat pathogens. Maya Hites, MD, Hôpital Erasme, Brussels, Belgium, presented a poster [Hites et al. ICAAC 2012 a-637] that suggested altered pharmacokinetics (PKs) in obese patients may be responsible.

This prospective study was conducted between October 2011 and May 2012 at a single institution. All consecutive adult (>18 years of age) obese (body mass index [BMI] ≥30 kg/m^2) patients with acute infection treated with standard doses of broad spectrum β-lactams (cefepime or ceftazidime [CEF], piperacillin-tazobactam [TZP], or meropenem [MEM]) were enrolled (Table 1).

Table 1. Standard Doses of β-lactams Adapted to Renal Function.

	Creatinine Clearance		
	>50 mL/min	10-50 mL/min	<10 mL/min
Meropenem	1 g TID	1 g BID	500 mg QD
Piperacillin-tazobactam	4 g QID	4 g TID	4 g BID
Ceftazidime	2 g TID	2 g BID	500 mg QD
Cefepime	2 g TID	2 g QD	500 mg QD

QID=four times a day; TID=three times a day; BID=twice a day; QD=every day.

Two serum samples were taken during the elimination phase after 30 minutes of intravenous β-lactam infusion to estimate PK and calculate the percentage of time spent above minimum inhibitory concentration (MIC). Serum drug concentrations were measured with high-pressure liquid chromatography. Adequate therapy was defined as a serum concentration 4 to 8 times the MIC for difficult-to-treat Gram-negative bacteria (eg, for *Pseudomonas aeruginosa,* optimal time>MIC: >70% for CEF, >50% for TZP, or >40% for MEM).

Thirteen men and 16 women were enrolled in the study. Subjects were a mean age of 64 years. Mean BMI and creatinine clearance were 35 kg/m^2 and 91.5 mL/min, respectively. Comorbidities included chronic obstructive pulmonary disease (13.8%), diabetes (41%), cardiomyopathy (48%), renal insufficiency (21%), and neoplasia (41%); 28% of patients reported no comorbidities. The sites of infection included the abdomen (48%), skin (21%), urinary tract (17%), lung (10%), and other (4%).

Thirty-eight drug levels were obtained from the 29 patients treated with standard-dose regimens; 10 serum drug concentrations were obtained in 5 of these patients who were treated with an increased dose regimen (1 g every 6 hours of MEM as a 3-hour infusion and a median of 22 g/day TZP as a continuous infusion). Twenty-nine of 38 serum drug concentrations (3/5 CEF, 10/11 MEM, 16/22 TZP) were insufficient to treat difficult-to-treat pathogens. Four of 10 serum drug concentrations in 5 patients treated with increased drug regimens were adequate (1/2 MEM, 3/8 TZP).

Prof. Hites concluded that recommended dosage regimens of broad spectrum β-lactam agents for obese noncritically ill patients needs to be reconsidered.

Comparison of Tedizolid Phosphate Versus Linezolid in a Phase 3 Study in Patients with ABSSSI

Written by Phil Vinall

In a Phase 3 study comparing tedizolid, a second generation oxazolidinone, to linezolid in patients with acute bacterial skin and skin structure infections (ABSSSI), tedizolid phosphate was noninferior and demonstrated high microbiological efficacy compared with linezolid. Carisa De Anda, PharmD, Trius Therapeutics, San Diego, California, USA, presented a poster [De Anda et al. ICAAC 2012 L1-1665] on the outcomes using the the new Food and Drug Administration (FDA) method for assessing clinical response, programmatic assessment, and the traditional post-treatment investigator assessment.

This was a randomized (1:1), double-blind, multicenter study of oral tedizolid phosphate (TDZ) 200 mg QD administered for 6 days versus oral linezolid 600 mg BID for 10 days in adult patients (mean age 43.4 years) with ABSSSI consisting of cellulitis/erysipelas (41%), infected wounds (29%), and major cutaneous abscesses (30%). Men and women aged ≥18 years with ABSSSI that started at least 7 days before screening were included. To be eligible, patients also had to have at least 1 of the following syndromes: cellulitis with erythema surface

area of at least 75 cm^2 and at least 1 local sign and symptom (induration, warmth, pain/tenderness, or swelling), major cutaneous abscess with erythema surface area of at least 75 cm^2 and extending at least 5 cm from margin of pus collection and at least 1 local sign and symptom (fluctuance, incision and drainage required, warmth, pain/tenderness), or wound infection including surgical site infection and trauma with erythema surface area of at least 75 cm^2 extending at least 5 cm from margin and purulent drainage. All syndromes required at least 1 regional or systemic sign of infection (lymph node tenderness and increase in volume, fever ≥ 38°C, WBC ≥10,000 or <4000 or >10% immature neutrophils) and suspected or documented Gram-positive infection.

A total of 667 patients from North American, Europe, and South America were enrolled in the study. Demographics as well as surface area of lesion (188.3 cm^2 in the tedizolid phosphate group vs 190.0 cm^2 in the linezolid group) were comparable between the treatment groups.

Tedizolid phosphate once a day for 6 days was noninferior to linezolid administered twice a day for 10 days for both programmatic outcome (79.5% vs 79.4%; 95% CI, –6.1 to 6.2), defined as cessation of spread and no fever at the 48 to 72 hour visit after the first dose of study drug, and investigator's assessment performed at the 7 to 14 day post-therapy evaluation. In the intention-to-treat population, clinical success (defined by the investigator's assessment) was 85.5% in the tedizolid group and 86.0% in the linezolid group. There was >80% concordance between the programmatic outcome at the 48 to 72 hour visit and the investigator's assessment of clinical response at the post-therapy evaluation point.

The Biomarker Consortium of the Foundation for the National Institute of Health [Talbot GH et al. *Clin Infect Dis* 2012] recommended to the FDA that clinical success be defined as ≥20% decrease in lesion size from baseline at the 48 to 72 hour visit without fever included in the endpoint. The results were consistent with the primary outcome with a responder rate of 78% in the tedizolid arm and 76.1 % in the linezolid arm.

The most common baseline infection site pathogen was Gram-positive (63% of patients in both groups). In the tedizolid treatment group, methicillin-resistant *Staphylococcus aureus* (MRSA; 42.1%) and methicillin-sensitive *S. aureus* (MSSA; 39.7%) were the most common isolated pathogens. In the linezolid treatment group, similar percentages were reported for MRSA (43.1%) and MSSA (41.6%). The per-patient microbiological response at the post-therapy evaluation is shown in Table 1.

Table 1. Per-Patient Microbiological Response at PTE in the mITT and ME Populations.

Response	Tedizolid Phosphate n (%)	Linezolid n (%)
mITT Population		
Favorable	179 (85.6)	181 (86.6)
Eradication	1 (0.5)	0
Presumed eradication	178 (85.2)	181 (86.6)
Unfavorable	7(3.3)	2 (1.0)
Persistence	0	0
Presumed persistence	7 (3.3)	2 (1.0)
Indeterminate	23 (11.0)	26 (12.4)
Microbiologically Evaluable Population		
Favorable	164 (95.9)	169 (98.8)
Eradication	0	0
Presumed eradication	164 (95.9)	169 (98.8)
Unfavorable	7 (4.1)	2 (1.2)
Persistence	0	0
Presumed persistence	7 (4.1)	2 (1.2)

ME=microbiologically evaluable; mITT=modified intention-to-treat; PTE=post-therapy evaluation.