A2 – 554
51st ICAAC

Vancomycin (Van), Ceftaroline (Cef), Daptomycin (Dap) and Linezolid (Lin) Pharmacodynamics against Methicillin-Resistant *Staphylococcus aureus* (MRSA) with Van MICs of 2 mg/L

S. A. Zelenitsky*, R. E. Ariano, G. G. Zhanel

University of Manitoba, Winnipeg, CANADA

Dr. S. Zelenitsky (PharmD)
Faculty of Pharmacy
University of Manitoba
Winnipeg, MB CANADA
s_zelenitsky@umanitoba.ca

ABSTRACT

BACKGROUND: There is mounting evidence that Van therapy is inadequate for MRSA with MICs of 2 mg/L ($MRSA_{VMIC=2}$). Although alternatives are recommended, antimicrobial PD data for this subset of isolates are limited.

METHODS: Using 2007-2010 CANWARD surveillance data from Canadian hospitals, MRSA pathogens were identified and antimicrobial activity (broth microdilution) was determined. Van (1 g q8-12h), Cef (600 mg q12h), Dap [4, 6, 10 (off-label) mg/kg q24h] and Lin (600 mg q12h) were evaluated using Monte Carlo simulations. Population pharmacokinetics with variances were applied to patient cohorts (n=5000): 75.0 + 10.4 kg, Cl_{cr} 60-120 mL/min. MIC distributions were used to determine cumulative target attainment (CTA) or % achieving AUC/MIC >400 for Van, fT>MIC >50% and >75% for Cef, AUC/MIC >400-2000 for Dap and AUC/MIC >80 for Lin. CTA for MRSA with Van MICs ≤1mg/L ($MRSA_{VMIC\leq1}$) was compared with $MRSA_{VMIC=2}$.

RESULTS: Of 1110 MRSA, 2.4% had Van MICs (broth microdilution) of 2 mg/L. A majority of $MRSA_{VMIC=2}$ were isolated from respiratory (56%), wound (22%) and blood (22%) specimens. Most (93%) were health-care associated genotypes, primarily USA100/800. Van CTA of 94% (1g q8h) and 55% (1g q12h) for $MRSA_{VMIC\leq1}$ was significantly reduced to 20% (1g q8h) and 3% (1g q12h) for $MRSA_{VMIC=2}$. Dap CTA was also notably lower for $MRSA_{VMIC=2}$. Dap 4 mg/kg produced AUC/MICs >400, >1200 and >2000 in 100%, 84% and 54% of $MRSA_{VMIC\leq1}$ cases compared with 100%, 65% and 20% of $MRSA_{VMIC=2}$ cases. Dap 6 mg/kg showed similar significant trends, whereas 10 mg/kg more effectively achieved all targets in >90% of cases with minimal differences between $MRSA_{VMIC\leq1}$ and $MRSA_{VMIC=2}$. Cef CTA was not affected by Van MICs with 100% achieving >50% fT>MIC and >90% attaining >75% fT>MIC. Lin CTA for $MRSA_{VMIC\leq1}$ and $MRSA_{VMIC=2}$ were similar, however only 63% reached AUC/MICs >80–100.

CONCLUSIONS: This study showed that Dap target attainment, like Van, was significantly compromised for MRSA with Van MICs of 2 mg/L. Cef and Lin maintained PD activity against this subset of isolates as did Dap at the higher, 10 mg/kg q24h (off-label) dose.

BACKGROUND

- There are indications that MRSA treatment failure is more likely when Van MICs exceed 1 mg/L. [1–4]
- Increasing concern that Van is inadequate for MRSA with Van MICs at the CSLI susceptible breakpoint of 2 mg/L has led to further study to predict such cases in the clinical setting. [5,6]
- Although the use of alternative therapies is being suggested, antimicrobial pharmacodynamic (PD) data for the subset of MRSA with Van MICs of 2 mg/L are limited.
- **GOAL:** To investigate the pharmacodynamics of Cef, Dap and Lin against MRSA, and characterize the effects of isolates with Van MICs of 2 mg/L.

REFERENCES: [1] Homes, JID 2011; [2] Choi, ICM 2011; [3] Takesue JID 2011; [4] Hague, Chest 2010; [5] Lubin, CID 2011; [6] Satola, JCM 2011; [7] Wu, IJAA 2011; [8] Rodvold, AAC 1998; [9] Zhanel, Drugs 2009; [10] Drusano, JAC 2010; [11] Dvorchik, AAC 2004; [12] Meager, AAC 2003

METHODS

- Monte Carlo Simulations (MCS) in SYSTAT® (Version 12) were used to construct cohorts of 5 000 study subjects with normally distributed body weights (75.0 ± 10.4 kg, range 50–100 kg) and uniformly distributed creatinine clearances (Cl_{cr} 60–120 mL/min). Predicted PD target attainment of Van and alternative therapies including Cef, Dap and Lin were compared for MRSA with Van MICs ≤1mg/L ($MRSA_{VMIC\leq1}$) and the subset of isolates with Van MICs of 2 mg/L ($MRSA_{VMIC=2}$).
- MRSA isolates:
  - MRSA pathogens from CANWARD (2007–2010), national surveillance conducted by the Canadian Antimicrobial Resistance Alliance (CARA), were included.
  - MIC data based on broth microdilution methods (as per the CLSI) were collected, and isolates were grouped according to $MRSA_{VMIC\leq1}$ and $MRSA_{VMIC=2}$.
  - hVISA status based on the Etest® macromethod (MM) and population analysis profile–area under the curve (PAP) was recorded.
- Antimicrobial dosing, pharmacokinetics & pharmacodynamics:
  - Relevant clinical antimicrobial dosing regimens were tested: Van 2 g/d (1 g iv q12h), 3 g/d (1 g iv q8h) and 4 g/d (2 g iv q12h); Cef 600 mg iv q12h (1h infusion); Dap 4 mg/kg iv q24h, 6 mg/kg iv q24h and 10 mg/kg iv q24h (off-label) [7] and Lin 600 mg iv q12h.
  - Available pharmacokinetic (PK) data and population-PK models were reviewed for each antimicrobial, and the best methods for simulating serum concs in the relevant patient population (75.0 ± 10.4 kg, Cl_{cr} 60–120 mL/min) were selected. MCS-generated PK and conc profiles for each antimicrobial regimen were examined for appropriateness. Initial PK data/formulae used in the simulations were:

    Van CL = [(Cl_{cr} x 0.79 + 15.7) x 0.06] ± 30% (cov) [8]
    Cef V_{ss} = [0.37 x TBW] ± 15%; $t_{½}$ = [2.6] ± 15%; CL = V_{ss} x ke; f = 0.80 ± 0.02 [9,10]
    Dap CL = (0.807 + 0.00154 x (Cl_{cr} – 91.2)) ± 30% [11]
    Lin CL = [6.85] ± 30% [12]

    where CL (L/h) is total drug clearance, cov is coefficient of variation, V_{ss} (L) is steady-state volume of distribution, TBW (kg) is total body weight, $t_{½}$ (h) is half-life, ke (h^{-1}) is elimination rate constant and f is free fraction (unbound).
  - The relevant PD index for each antimicrobial was calculated, and clinical targets were selected based on best available evidence:

    Van AUC/MIC >400 where AUC/MIC = AUC_{24} / MIC
    Cef %$fT_{>MIC}$ >50%, >75%, 100% where %$fT_{>MIC}$ = [$fT_{>MIC}$ (during t') + $fT_{>MIC}$ (during T-t')] x 100 / T
    Dap AUC/MIC >400–2000
    Lin AUC/MIC >80, >100

    where AUC_{24} (mg x h/L) is steady-state area under the conc-time curve over 24 h, t' (h) is infusion time and **T** (h) is dosing interval.
  - The probability of target attainment (PTA) for each antimicrobial regimen and MIC was calculated as the fraction of 5 000 subjects achieving the PD target.
  - Cumulative target attainment (CTA), also reported as a fraction of the population, was determined by integrating PTA and MIC data. CTA was calculated by multiplying the PTA at each MIC by the fraction of isolates at that MIC (as per the surveillance data) and adding the values.
  - CTA was compared among antimicrobials and between $MRSA_{VMIC\leq1}$ and $MRSA_{VMIC=2}$.

RESULTS

- 1 110 MRSA were identified, and 2.4% (27) were classified as $MRSA_{VMIC=2}$ based on broth microdilution MICs.
  - $MRSA_{VMIC=2}$ infections were more likely to be healthcare-associated *(P=0.002)* and involve the respiratory tract *(P=0.005)*.
  - hVISA was identified in 55.6% (15/27) and 25.9% (7/27) of $MRSA_{VMIC=2}$ by Etest® MM and PAP, respectively.
  - Isolate characteristics are summarized in **Table 1** and antimicrobial MIC distributions for $MRSA_{VMIC\leq1}$ compared with $MRSA_{VMIC=2}$ are shown in **Figure 1**.
- MCS-generated PK and conc data for each antimicrobial regimen are detailed in **Table 2**.
- CTA results are presented in **Figure 2**.
  - Van CTA of 55% (2 g/d) and 94% (3 g/d) for $MRSA_{VMIC\leq1}$ was significantly reduced to 3% (2 g/d) and 20% (3 g/d) for $MRSA_{VMIC=2}$ with the highest dose (4 g/d) reaching AUC/MICs >400 in only 50% of the population.
  - Cef CTA was not affected by Van MICs with 100% achieving >50% $fT_{>MIC}$ and >90% attaining >75% $fT_{>MIC}$.
  - Dap CTA was significant reduced for AUC/MIC targets ≥800 against $MRSA_{VMIC=2}$. Dap 4 mg/kg produced AUC/MICs >400, >1200 and >2000 in 100%, 84% and 54% of $MRSA_{VMIC\leq1}$ cases compared with 100%, 65% and 20% of $MRSA_{VMIC=2}$ cases. Dap 6 mg/kg showed similar trends for AUC/MIC targets ≥1200. Dap 10 mg/kg effectively achieved even the highest target in at least 88% of cases with minimal differences between $MRSA_{VMIC\leq1}$ and $MRSA_{VMIC=2}$.
  - Lin CTA for $MRSA_{VMIC\leq1}$ and $MRSA_{VMIC=2}$ were similar with 70% of cases reaching AUC/MICs >80 but only 56% achieving >100. Less than 1% of cases exceeded an AUC/MIC of 400, the suggested threshold for increased toxicity.

CONCLUSIONS

- ✓ Daptomycin pharmacodynamic target attainment at standard doses was significantly reduced for MRSA isolates with Van MICs at the CLSI susceptible breakpoint of 2 mg/L.
- ✓ Ceftaroline and linezolid maintained pharmacodynamic activity against the subset of MRSA with Van MICs of 2 mg/L, as did daptomycin at the higher, 10 mg/kg q24h (off–label) dose.

TABLE 1: Characteristics of MRSA isolates

		MRSA (n = 1 083)	$MRSA_{VMIC=2}$ (n=27)	$MRSA_{VMIC=2}$ & hVISA$_{PAP}$ (n=7)
Age (y)		57.7 ± 22.5	67.3 ± 13.5	57.6 ± 7.8
Male		634 (58.5%)	16 (59.3%)	5 (71.4%)
Healthcare-associated		732 (67.6%)	25 (92.6%)	7 (100%)
Specimen	respiratory	333 (30.7%)	15 (55.6%)	2 (28.6%)
	blood	431 (39.8%)	6 (22.2%)	3 (42.9%)
	wound	276 (25.5%)	6 (22.2%)	2 (28.6%)
	urine	42 (3.9%)	0	0
Isolated in ICU		188 (17.4%)	4 (14.8%)	2 (28.6%)
Isolated in Eastern region[1]		681 (62.9%)	20 (74.1%)	6 (85.7%)
Susceptibility Data[2]				
	Van	1 083 (100%)	27 (100%)	7 (100%)
	Cef	435/438 (99.3%)	26 (96.3%)	6 (85.7%)
	Dap	1 083 (100%)	27 (100%)	7 (100%)
	Lin	1 083 (100%)	27 (100%)	7 (100%)

[1] Includes Ontario, Quebec and the Atlantic provinces
[2] Based on broth microdilution MICs and CSLI breakpoints of ≤2 mg/L for Van, ≤1for Cef, ≤1for Dap, ≤4 for Lin
[Highlights indicate statistical significance with p-values <0.002, 0.005 and 0.03, respectively.]

TABLE 2: Monte Carlo simulation data

Van 2, 3 or 4 g iv / d		
CL (L/h)		5.0 ± 1.4
AUC_{24} (mg x L/h)	1 g q12h	436 ± 150
	1 g q8h	653 ± 224
	2 g q12h	871 ± 299
Cef 600 mg iv q12h		
V_{ss} (L)		27.8 ± 5.7
$t_{½}$ (h)		2.6 ± 0.4
CL (L/h)		7.6 ± 2.1
$fAUC_{24}$ (mg x L/h)		67.6 ± 18.3
fC_{max} (mg/L)		16.5 ± 3.7
fC_{min} (mg/L)		0.9 ± 0.5
Dap 4, 6 or 10 mg/kg iv q24h		
CL (L/h)		0.81 ± 0.24
Dose (mg)	4 mg/kg q24h	300 ± 42
	6 mg/kg q24h	450 ± 62
	10 mg/kg q24h	750 ± 104
AUC_{24} (mg x L/h)	4 mg/kg q24h	413 ± 163
	6 mg/kg q24h	620 ± 245
	10 mg/kg q24h	1033 ± 409
Lin 600 mg iv q12h		
CL (L/h)		6.8 ± 1.8
AUC_{24} (mg x L/h)		192 ± 62

Data presented as mean ± sd

FIGURE 1:
MIC distributions for $MRSA_{VMIC\leq1}$ (n=1083) and $MRSA_{VMIC=2}$ (n=27)

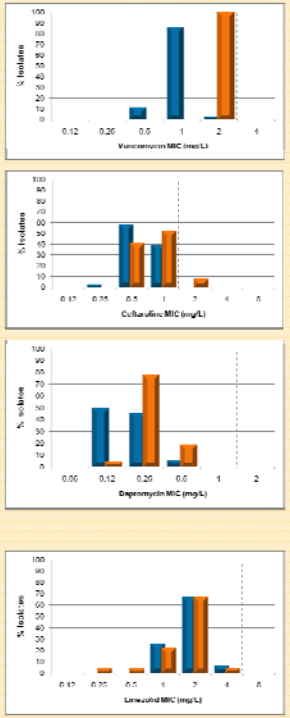

FIGURE 2:
PD cumulative target attainment (CTA) for $MRSA_{VMIC\leq1}$ and $MRSA_{VMIC=2}$