Comparative Study between Teicoplanin and Vancomycin in Methicillin-Resistant Staphylococcus Aureus (MRSA) Infectious of Toxicological Intensive Care Unit (TICU) Patients- Tehran- Iran

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Abstract: *Methicillin-resistant staphylococcus aureus* (MRSA) a leading cause of invasive infections is one of the most important causes of nosocomial pneumonia with high morbidity and mortality**.** Vancomycin and teicoplanin are used in clinical practice with bactericidal activity by interfering cell wall peptidoglycan synthesis. Our objective is to compare efficacy and safety of vancomycin versus teicoplanin in MRSA infections among poisoned patients of toxicological ICU of Loghman Hakim hospital. **Material and Method:** Safety and efficacy of vancomycin versus teicoplanin has been assessed in 104 patients consisted of 54 patients treated by teicoplanin and 50 patients treated by vancomycin. Blood, urine and tracheal samples were cultured. Chest X-ray and routine Para clinical studies have been done in all cases. The study populations were assessed during 3 visits and one month follow up. Patients with fever and positive tracheal cultures (TC) ± abnormal WBC at the end of treatment, have been reported as failure of treatment. **Results:** seventy eight (75%) out of the 104 eligible patients, were male. The mean age± SD of patients was 36.1±16.8 and 39±13.4 in teicoplanin and vancomycin groups, respectively. Most common drug toxicities were opium, TCA (tricyclic antidepressant), methadone. Mortality rate in teicoplanin group was 16.6%but in vancomycin was 22%. Treatment failure in vancomycin group was 10% and in teicoplanin group was 8.5%and all of them with positive TC were polymicrobial, too. Nephrotoxicity and bicytopenia, as the adverse effects had significant differences between two groups. (P value< 0.05). **Conclusion:** Teicoplanin should be considered as an effective alternative to vancomycin in Methicillin-resistant staphylococcus aureus (MRSA) infections treatment. Adverse effects such as nephrotoxicity and bicytopenia significantly were decreased in teicoplanin therapy.
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Key words: Teicoplanin, Vancomycin, Methicillin-Resistant Staphylococcus Aureus, Toxicological ICU

Introduction

Methicillin-resistant staphylococcus aureus (MRSA) a leading cause of invasive infections is one of the most important causes of nosocomial pneumonia which increases morbidity, mortality and healthcare resources usage. MRSA bacteraemia leads to longer hospital stay and increased treatment cost. (1-6)Glycopeptides have been choice of the treatment for invasive MRSA infections along time. (1-3, 7-9). Currently and commonly, two agents being used in clinical practice are vancomycin and teicoplanin whose bactericidal activity is by interfering cell wall peptidoglycan synthesis. (1, 8, 10) Vancomycin (a glycopeptide) remains the drug of choice for serious MRSA infections since 1980. (1, 6, 12) It was approved by USA FDA in 1988 and has been in clinical use for more than 37years and it is administered by IV (Intravenous) rout. (13, 14)

Teicoplanin (alipoglycopeptid) previously known as teichmycin is produced by Actinoplanesteichomyceticus and is active against gram positive infections caused by both MSSA and MRSA. (11, 15). Its main rout of administration is IV or IM with a bioavailability of 90-95 %.(11 Teicoplanin is used commonly as vancomycin in Europe while is not approved for clinical use in USA.(6) Teicoplanin has some advantages over vancomycin such as longer half-life (as long as 100 hrs. in patients with normal renal function) that allows once-daily dose administration, IM use, out of hospital treatment possibility and not needed routine serum level monitoring, but teicoplanin is more expensive. (1, 11, 15) However, there is uncertainty regarding the safety of vancomycin versus teicoplanin (1). Several studies suggest lower total adverse effects for teicoplanin including skin

reactions, redman syndrome (RMS) and nephrotoxicity. (1, 16-18) Phlebitis, neutropenia and thrombocytopenia although not frequent have been reported with vancomycin administration. (13, 18, 19) As with vancomycin, neutropenia or thrombocytopenia has occasionally been reported during teicoplanin therapy. (20) Hearing loss, tinnitus, vertigo and dizziness have been reported with vancomycin, but appear to be quite uncommon with teicoplanin. (13, 20) In fact nephrotoxicity (Cr> 1.1-1.5 mg/dl or 0.5mg/dl increase or 50-100 % increase from baseline) has been much more reported after vancomycin versus teicoplanin therapy .(1) Objective: our objective is to compare efficacy and safety of vancomycin versus teicoplanin in MRSA infections among poisoned patients of toxicological ICU of Loghman Hakim hospital.

Materials and Methods

Subjects

This study was approved by ethical committee of SBMU, Iran (Trial registration: No.122). This prospective study was conducted during 7 months period from May 2013 to Nov 2013 at Toxicological ICU of Loghman Hakim hospital, the unique referral poison center of Shahid Beheshti University of Medical sciences (SBMU). Safety and efficacy of vancomycin versus teicoplanin has been assessed in 104 patients consisted of 54 patients treated by teicoplanin and 50 patients treated by vancomycin. Inclusion criteria consist of age ≥ 14 years, positive culture for MRSA. Colony count $> 10^5$ was considered significantly positive. Also patients with teicoplanin hypersensitivity, pregnancy and prior antibiotic treatment in last 2 weeks were excluded from the study. All intubated (at least for 48 hrs) poisoned patients under mechanical ventilation with fever, leukocytosis, bronchial hyperactivity and respiratory discharge, new infiltration in CXR and decreasing of respiratory sound or existence of fine rales were selected. Informed consent was obtained from their family prior to enrollment in the study. Demographic data such as age, sex and weight in both groups were compatible. Blood (BC), urine (UC) and tracheal (TC) culture samples were obtained. CXR (Chest X-ray) and routine Para clinical studies (CBC, ESR, CRP, CPK, Creatinin, LFT and biochemistry) have been done in all cases. Brain and lung CT-scan have been done if only necessary. Based on the manufacturer's instruction and kidney function in each patient, drug dose was adjusted (22) Teicoplanin was administered at a loading dose of 6mg/kg (400mg maximum dose) for three loading doses every 12 hrs and then every 24 hrs for 7 to 10 days. Vancomycin was administered at a loading dose of 20 mg/kg every 12 hrs (maximum dose 2gr/day). Vancomycin level was measured after 48 hours of treatment.

Study outcomes

Patient's health statues, sequence of treatment, response to treatment were assessed during 3 visits and one month follow up. Patients were observed in the admission day, the first day of treatment after positive cultures, end of treatment and one month follow up from the day of admission. Patients with fever and positive tracheal cultures (TC) ± abnormal WBC at the end of study, have been reported as failure of treatment. A tympanic temperature (TT) more than 37.8 C was considered as fever. Leukocyte count >11000 or <4000 is mentioned as abnormal WBC.

Statistical Analysis

The statistical analysis was performed with Statistical Product and Service Solutions (SPSS)version 16 (SPSS Inc., Chicago, IL, USA). Data of the participants were analyzed through appropriate statistical testes, such as Chi-square test ($\chi 2$) for categorical and Student's t-test. P-values equal to or less than 0.05 considered significant.

Results

Of the 104 eligible patients, 78 (75%) were male and 26 (25%) were female. The meanage±SD of patients was 36.1±16.8 and 39±13.4 in teicoplanin and vancomycin groups, respectively. There were no significant differences between teicoplanin and vancomycin groups according to the age and sex. (P value>0.05). Most common drug toxicities between two groups were opium, TCA (tricyclic antidepressant) and methadone. History of underlying diseases was recorded in11 patients (22%) of vancomycin group and 6 patients (11.1%) of teicoplanin group. (Table 1) Demographic characteristics, comorbid conditions and kind of toxicity are shown in Table 1. At the end of the treatment, in84%of patients in vancomycin group and 48.9% of teicoplanin group CXR were cleared. Positive TC in vancomycin group was detected in 5/50(10%) and in teicoplanin group 4/50 (8.5%). (Table2, 3) Seven (14%) patients in vancomycin group and 17(31.5%) patients in teicoplanin group needed chest CT scan, which in 5 (29.4%) patients of teicoplanin group was normal, 8 patients had pleural effusion (47.1%) and remaining 4 patients (23.6%) had empyema, empyema and effusion, effusion and consolidation and abscess formation, in order to. All 7 (100%) patients in vancomycin group had effusion in chest CT scan. Also from 20 (40%) patients in vancomycin group and 41(75.9%) patients in teicoplanin group brain CT scan was obtained. Brain CT was normal in 31/41 of teicoplanin group and 11/20 of vancomycin group. Brain edema in 10/41 of

teicoplanin group versus 8/20 in vancomycin group was seen and in 1/20 patient of vancomycin group infarct was detected. Mortality rate in teicoplanin group was 9/54 (16.6%). Lack of clinical response to teicoplanin was the reason for the 3 patients' death. Mortality rate of vancomycin group was 11/50(22%).The results of BC, UC and TC are shown in Table 3. Complications during respiratory infection process were seen in 5/50 and 9/54 in vancomycin and teicoplanin groups respectively, including ARDS 2 (40%) in vancomycin group and 7 (77.8%) in teicoplanin group, pleural effusion in 2 (40%) in vancomycin group versus 1 patient (11.1%) in teicoplanin group.1 patient in teicoplanin group had empyema and 1 (20%) in vancomycin group had chronic obstructive pulmonary disease (COPD).

Treatment failure in vancomycin group was 5/50 (10%) and in teicoplanin group was 4/47(8.5%) (P value>0.05) and all positive TC in both groups were polymicrobial. The adverse effects of both groups are shown in table4. Nephrotoxicity and bicytopenia, had significant differences between these two groups, as adverse effects. (P value< 0.05) No cases of RMS, hypotension, ototoxicity, severe thrombocytopenia or pancytopenia were detected in both groups.

Table 1. Demographic characteristics, kind of toxicity and comorbid conditions

Variable	Vancomycin N (%) T=50	Teicoplanin N (%) T=54	P value
Sex			
Male	37(74%)	41(75.9%)	0.825
Female	13(26%)	13(24.1%)	
Drug overdose			
Syanor	0	0	-
Organophosphorea	4(8%)	0	0.050
Acetaminophen	1(2%)	0	0.481
BZD	2(4%)	7(13%)	0.163
TCA	1(2%)	9(16.7%)	0.017
Lithium	1(2%)	0	0.481
Alp	3(6%)	0	0.108
Opium	15(30%)	5(9.3%)	0.012
Tramadol	2(4%)	8(14.8%)	0.095
Methadone	7(14%)	7(13%)	0.877
MDT	2(4%)	1(1.9%)	0.607
Co	2(4%)	1(1.9%)	0.607
Phenobarbital	2(4%)	1(1.9%)	0.607
Unknown	5(10%)	3(5.6%)	0.477
Alcohol	0	0	----
Substance + drug overdose	3(6%)	12(22.5%)	0.025
Suicidal Yes	46(92%)	34(63%)	0.000
History of underlying disease (Yes)	11(22%)	6(11.1%)	0.185
Kind of underlying disease			
CVA	1(9.1%)	0	0.481
Cardiac disease	2(18.2%)	2(33.3%)	0.937
Epilepsy	0	2(33.3%)	0.495
HTN	1(9.1%)	1(16.7%)	0.956
Psychosis	2(18.2%)	1(16.7%)	0.607
Cancer	1(9.1%)	0	0.481
Hydrocephaly	1(9.1%)	0	0.481
IHD	0	0	---
Multi organ disease	3(27.3%)	0	0.108

Discussion

The glycopeptide antibacterial drugs, vancomycin and teicoplanin, are widely used for therapy of infections caused by severe or multi drug-resistant gram-positive bacteria. Vancomycin has a narrow therapeutic range and its pharmacokinetics, volume of distribution and clearance are considerably affected by patient's condition and kidney function.

Therefore, to determine the optimal drug dosage TDM (therapeutic drug monitoring) is necessary that decreases the incidence of side effects and enhances cost-effectiveness.

Table 2. Comparison of clinical and paraclinical data between the two groups.

Variables	Initiation day(day 0)			End day (day 10)		
	Vancomycin Mean(SD)	Teicoplanin Mean(SD)	P value	Vancomycin Mean(SD)	Teicoplanin Mean(SD)	P value
***TT**	38.08(0.61)	37.82(0.69)	0.048	37.17(0.48)	37.37(0.37)	0.021
SBP	114.68(21.96)	117.15(19.39)	0.543	116.26(23.12)	111.50(13.26)	0.221
HR	94.74(19.83)	106.92(41.04)	0.06	91.24(14.77)	87.17(10.54)	0.124
GCS	8.44(3.16)	7.94(2.61)	0.384	12.7(3.74)	12.63(3.52)	0.926
WBC	11286(3524.2)	11185.18(3972.09)	0.892	10809.32(8869.6)	8202.13(2924.15)	0.043
PMN	77.46(11.69)	78.35(10.48)	0.681	76.32(10.64)	73.085(10.16)	0.129
ESR	25.5(27.94)	54.57(27.8)	0.000	96(29.70)	47.4(23.76)	0.007
HBG	10.89 (1.88)	12.37 (1.34)	0.000	10.1 (1.28)	10.85 (1.74)	0.008
HCT	34.502(6.09)	38.11 (6.65)	0.005	31.77 (3.91)	34.25 (5.19)	0.009
PLT	173360(84627.5)	173592 (65327.4)	0.987	237140(116691.1)	219531(105141.4)	0.438
Cr	1.408 (1.8)	1.425 (1.34)	0.954	1.292 (1.63)	1.010 (0.84)	0.293
K	4.146 (0.64)	3.966 (0.68)	0.168	4.106 (0.56)	4.74 (0.5.41)	0.412
CPK	1939.5(3514.8)	2132.3 (4288.03)	0.803	987.34 (3200.09)	432.51 (768.56)	0.25
ALT	115.46(201.87)	71.70 (125.47)	0.955	66.82 (66.81)	54.91 (107.32)	0.549
AST	109.18(122.42)	107.40 (189.85)	0.955	64.102 (34.03))	53.059 (57.07)	0.292
ALP	222.62(145.85)	184.24 (54.88)	0.075	238.31 (171.32)	164.28 (60.45)	0.007
Bili T	1.438(2.697)	.806 (.473)	0.93	1.15 (1.11)	0.87 (0.38)	0.107
Bili D	0.53(1.44)	.254 (.180)	0.165	0.477 (0.60)	0.325 (0.19)	0.105
PH	7.40(0.1145)	7.379 (.083)	0.284	7.43(0.10)	7.35(0.05)	0.000
Po2	55.89(29.38)	98.052 (19.618)	0.000	71.34 (42.51)	96.44 (18.31)	0.000
Pco2	38.75(8.771)	42.759 (11.669)	0.051	39.93 (12.29)	41.75 (7.63)	0.388
HCO3	26.02(6.17)	25.009 (7.212)	0.000	28.32 (12.03)	23.05 (3.29)	0.005
O2sat	80.44(13.70)	85.111 (10.892)	0.056	84.9 (15.84)	91.20 (10.43)	0.025
Auscultation	**N (%)**	**N (%)**		**N (%)**	**N (%)**	Pvalue
Clear	7(14%)	22(40.7%)	0.00	38(76%)	19(40.4%)	0.001
Coarse rales	37(74%)	17(31.5%)		10(20%)	15(31.9%)	
Fine rales	0	2(3.7%)		0	5(10.6%)	
Ronchy	2(4%)	11(20.4%)		1(2%)	8(17%)	
**DRS	1(2%)	1(1.9%)		1(2%)	0	
CXR			0.367			0.00
Clear	5(10%)	9(16.7%)		42(84%)	23(48.9%)	
Infiltrative	45(90%)	44(81.5%)		8(16%)	24(51.1%)	
Blunt angel	0	0		0	0	
Consolidation	0	0		0	0	
Infiltration+ consolidation	0	1(1.9%)		0	0	

*Tympanic Temperature
**Decreased Respiratory sound

Teicoplanin, a narrow spectrum antibiotic, has some advantages over vancomycin such as longer half-life, possibility of IM use, serum level monitoring only needed in hemodynamically unstable patients or those with serious infections. (21) The studies have found no differences between vancomycin and teicoplanin regarding clinical and bacteriological efficacy and antimicrobial spectrum coverage except for vanB (vancomycin resistant enterococci) which is sensitive to teicoplanin. (6-8, 15-17)While in this study the teicoplanin showed better antibacterial coverage for its less failure and mortality. In this study all 104 cases were intubated poisoned patients and under mechanical ventilation. According to kinds of drug toxicity, some patients had fever on admission day, since some drugs like

lithium and TCA may lead to hyperthermia while some others like alcohol and barbiturates can reduce the body temperature. (22) Two percent of vancomycin group and 10.6% of teicoplanin group had fever as drug adverse effect but it was not significantly different between two groups.

Table 3: Antibiogram of tracheal cultures (TC), blood cultures (BC), urine cultures(UC)

	Day0		Day10	
Cultures	vancomycin N (%)	teicoplanin N (%)	vancomycin N (%)	teicoplanin N (%)
TC				
Positive	50(100%)	54(100%)	5(10%)	4(8.5%)
Negative	0	0	45(90%)	43(91.5%)
Microorganisms (if positive)				
MRSA	23(46%)	23(43.4%)	0	0
MSSA	5(10%)	1(1.9%)	0	0
Staphylococcus areus	0	0	0	0
Staphylococcus Epidermidis	0	0	0	0
Klebsiela	0	2(3.8%)	0	0
Pseudomona	0	0		
Acinetobacter	0	2(3.8%)	0	0
Entrobacter	0	0	0	0
Ecoli	0	0	0	0
MRSA combination with other bacteria	20(40%)	25(47.4%)	5(100%)	4(100%)
BC				
Positive	10(20%)	7(13%)	0	0
Negative	40(80%)	47(87%)	50(100%)	54(100%)
MRSA	3(30%)	5(71.4%)		
MSSA	0	0		
Staphylococcus areus	0	0		
Staphylococcus epidermidis	5(50%)	1(14.3%)		
Staphylococcus pneumonia	2(20%)	0		
Ecoli	0	0		
Klebsiela	0	1(14.3%)		
Pseudomona	0	0		
Acinetobacter	0	0		
Entrobacter	0	0		
UC				
Positive	7(14%)	11(20.3%)	0	0
Negative	43(86%)	43(79.6%)	50(100%)	54(100%)
Staphylococcus epidermidis	1(14.3%)	0		
Ecoli	4(57.1%)	3(27.3%)		
Klebsiela	0	3(27.3%)		
Pseudomona	1(14.3%)	0		
Acinetobacter	0	4(36.4%)		
Entrobacter	0	1(9.1%)		
Citrobacter	1(14.3%)			

According to definition of anemia in“up to date 21.1”(a HGB <13.5 g/dL (<135 g/L) or a HCT <41.0 % in men anda value <12.0 g/dL (<120 g/L) or <36.0%, in women), most of the patients in this study were anemic in the first day of treatment in both groups (mean HB in the first day, vancomycin:10.89, teicoplanin: 12.37, P value: 0.000). On day 10, the Mean of HB was 10.1 in vancomycin and 10.85 in teicoplanin groups (P value<0.05). However anemia is a common transient event in poisoned patients. According to this definition there was no significant difference between anemic patients in two groups on day 10. (P value= 0.499). Three of fifty patients in vancomycin group and 6/54 in teicoplanin group had rash during treatment without flashing or pruritus, which does not necessitate discontinuation of

treatment, while in Bibler et al. study, the most significant adverse reaction to teicoplanin was an urticarial rash. (23) Nephrotoxicity was defined heterogeneously as creatinin levels above the normal range (1.1 to 1.5 mg/dl), by an absolute increase of 0.5 mg/dl or as a 50% to 100% increase from the baseline level which showed in the meta-analysis survey by ShuliSvetitsky et al. (8) Patients with creatinin levels upper than normal values in the first day of treatment were excluded and others showing a 50% to 100% increase in creatinin values are reported as adverse event (vancomycin:16/50 teicoplanin 4/47P value<0.005).

Table 4: Comparison of adverse effects between the two groups.

Kind of adverse effect	Vancomycin group N (%) T=50	Teicoplanin group N (%) =47	P value
Anemia	15(30%)	11(23.4%)	0.499
Nephrotoxicity	16(32%)	4(8.5%)	0.005
Fever	1(2%)	5(10.56%)	0.105
Ototoxicity	0	0	-
Thrombocytopenia	12(24%)	10(21.2%)	0.811
Leukopenia	1	0	0.330
Bicytopenia	10	0	0.003
Pancytopenia	0	0	-
Hypotension	0	0	-
Rash	3	6/54	0.354
Red Man Syndrome	0	0	-

According to the rhabdomyolysis definition by CPK greater than 10000, 3.7% patients in teicoplanin group and 6% in vancomycin group fit this category on admission day. At the end of treatment, only 3 patients in teicoplanin group and1patient in vancomycin group had elevated CPK. (P value: 0.330) Rhabdomyolysis is a common event in poisoned patients, which elevates creatinin levels. As it was shown in our pervious study in poison induced rhabdomyolysis and acute renal failure, 3 out of 180 patients acquired persistent renal failure which needed hemoperfussion dialysis. (24,25) In present study, rabdomyolysis and increased creatinin levels are detected in both groups. Therefore elevation of creatinin values can be related to both rabdomyolysis and drug adverse effects and we cannot disregard drug induced nephrotoxicity as a side effect in else groups but as mentioned above teicoplanin showed less nephrotoxicity than vancomycin. (P value<0.05) A lower frequency of nephrotoxicity was reported as characteristic advantages of teicoplanin over vancomycin and likewise our findings; nephrotoxicity was described as asymptomatic and self-limited in 8% of patients in several surveys. (26-29) Other adverse events such as RMS, hypotension, pancytopenia and ototoxicity were not detected. Cavanlcanti et al have done a randomized clinical trial (RCT), in 24 studies and in 2610 patients. (1) They have shown similar clinical and microbiological cure and mortality rate for teicoplanin and vancomycin. We detected a similar clinical and microbiological cure rate between teicoplanin and vancomycin, too. Blood cultures were positive in 10 (20%) patients in vancomycin group and 7 (13%) patients in teicoplanin group. Tracheal cultures were positive in all 50 (100%) patients in vancomycin group and 53 (98.1%) in teicoplanin group in the first day of treatment. Also MRSA has been reported in most cases(positive TC or BC was 92% in vancomycin group and 98% in teicoplanin).On day 10, 10% in vancomycin group and 8.5% in teicoplanin group hadpositive culture and all were polymicrobial. In this study, using other antibiotics such as meropenem and ciprofloxacin as empirical therapy of VAP (Ventilator Associated Pneumonia) could not be avoided. Portolés A et al have reported more total adverse effects by vancomycin which was phlebitis in all cases that was not detected in our study.(17) Likewise this study, they reported no cases of diarrhea, RMS or significant changes in baseline Creatinin. They also showed some economic advantages for vancomycin in acquisition, administration and monitoring which is not assessed in this study. Michael J. et al (14) in a double-blind, randomized, clinical efficacy trial assessed 25 patients receiving vancomycin or high dose teicoplanin to evaluate RMS between groups. They showed incidence of RMS after vancomycin or teicoplanin treatment is low and seems not to be dose related.

Conclusion

Teicoplanin should be considered as an effective alternative to vancomycin in Methicillin-

resistant staphylococcus aureus (MRSA) infectious treatment. Adverse effects such as nephrotoxicity and bicytopeniamay be decreased in teicoplanin therapy.

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