Teicoplanin Versus Vancomycin in Children of Jordan: A Comparative Safety Study

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Abstract

Background and Aims: Vancomycin and teicoplanin are used frequently, and their use is variably associated with known mild to severe adverse events. The aim of this study was to evaluate and compare adverse event and toxicity profiles of vancomycin and teicoplanin in children at a university hospital in Jordan.

Methods: This prospective observational study evaluated 112 children aged 1 month to 15 years who received vancomycin (n = 69) or teicoplanin (n = 43). Baseline demographic, clinical and laboratory data were documented. Safety data during treatment were collected and analyzed, including adverse events and laboratory markers.

Results: Baseline characteristics of subjects were fairly balanced except for hemoglobin levels. More adverse events were observed in the vancomycin patients (64% vs. 44%; p = 0.02). Vancomycin was associated with a significantly higher rate of pyrexia (55% vs. 30%; p = 0.01) and a trend toward a higher rate of gastrointestinal adverse events. On the other hand, there was no significant difference in hemoglobin levels, white blood cell counts, neutrophils counts, and platelets counts between the two groups during treatment. Nephrotoxicity occurred in both vancomycin and teicoplanin arms, with no statistically significant difference (14% vs. 27%; p = 0.48).

Conclusion: Both drugs were fairly well-tolerated by children, with fewer serious adverse events than previously reported. Statistically, nephrotoxicity occurred equally in both arms. However, vancomycin was associated with a significantly higher rate of adverse events. Accordingly, and due to study limitations, there is a need for a large-scale, randomized study in children to better understand the safety profiles of both drugs.

Keywords: Vancomycin, Teicoplanin, Safety, Toxicity, Children, Jordan.

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Introduction

Vancomycin and teicoplanin are naturally occurring glycopeptide antibiotics used to treat resistant gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA).[1] However, vancomycin is associated with numerous adverse events, including red

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man syndrome, pruritus, rash, angioedema and nephrotoxicity. On the other hand, teicoplanin is not only considered equivalent to vancomycin in efficacy, but also found to have a better safety profile.[2,3]

Wood (1996) reviewed 11 comparative studies on the efficacy and safety of teicoplanin and vancomycin mostly in adults.[4] He concluded that patients treated with teicoplanin experienced significantly fewer adverse events compared to those treated with vancomycin (13.9% vs. 21.9%; $p = 0.0003$). Moreover, he reported that nephrotoxicity was significantly less likely, and red man syndrome extremely uncommon in patients who used teicoplanin.[2] Another review by Cavalcanti et al. (2010) reported that the relative risk of nephrotoxicity was reduced by 34% with the use of teicoplanin versus vancomycin, and that cutaneous rash, red man syndrome and other adverse events were less common with teicoplanin.[3]

These two studies focused on certain patient populations, such as those with febrile neutropenia or those in intensive care, rather than more diverse cohorts.[2,4] Moreover, other studies have reported cross-reactivity between the two drugs, including reactions such as maculopapular exanthems, vasculitis, neutropenia, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.[5,6] This would possibly complicate interpretation of comparison studies

While many studies have investigated the safety profiles of the two drugs, only a few studies have investigated the safety of vancomycin and teicoplanin in children. In a group of children with malignancy-associated neutropenia, Sidi et al. (2000) documented five cases of mild renal insufficiency in children treated with vancomycin, and no such cases in those treated with teicoplanin.[7]

Aims

The aim of this study was to evaluate and compare adverse event and toxicity profiles of vancomycin and teicoplanin in children at a major hospital in Jordan.

Methods

Study design and population

This was a prospective, clinical observational study conducted at the King Abdullah University Hospital in Ramtha, Jordan from March 2013 to February 2014. All eligible children (N = 112) during that time period were selected by daily screening of electronic and hard copy records of children admitted to the hospital by a master student.

Patients who satisfied the following criteria were included in the study: aged 1 month to 15 years, admitted to a regular pediatric floor (regardless of underlying diagnoses), and receiving at least one day of treatment with either vancomycin or teicoplanin using standard dosing. Children with abnormal serum creatinine (Cr) levels or permanent hearing loss were excluded from the study.

In most cases, treatment using vancomycin or teicoplanin were preapproved by an infectious diseases specialist. Therefore, authors did not make any active interventions, particularly in antibiotic selection, switching, or discontinuation. Antibiotic dosing and monitoring were performed by a clinical pharmacist according to standard guidelines. Vancomycin was typically initiated at a dose of 45 to 60 mg per kilogram per day divided in 3 to 4 daily doses depending on disease severity, patient status, and results of laboratory tests.

Teicoplanin was typically initiated at 10 mg per kilogram per dose every 12 hours intravenously for the first three doses, then once daily.

Data collection

Demographic and clinical data (such as gender, age, weight, length of hospital stay, diagnosis, and type of therapy) of the selected patients were retrieved by screening medical records, interviewing the patients and their legal guardians, and by daily clinical evaluations. This was performed by an experienced pediatrician.

Safety data were collected by standardized daily clinical evaluation of outcomes, including gastrointestinal symptoms (such as diarrhea and constipation), pyrexia (temperature ≥ $38C^0$), anaphylaxis, rash, pruritus, red man syndrome, fatigue, back pain, tremors, peripheral edema, headache, and discontinuation of antimicrobials. Standardized evaluation was formulated by the study team. All data collection was supervised by the same pediatrician. The occurrence of red man syndrome was confirmed in the same manner as published in a previous study.[8]

In addition, data on white blood cell (WBC) counts, neutrophil (NEU) counts, eosinophil (EOS) counts, hemoglobin (HB) levels, platelet (PLAT) counts, serum levels of alanine aminotransferase (ALT), Cr, and red blood cell counts in the urine were also collected. Reported laboratory values were those obtained just prior to therapy, and the highest or lowest values during the course of treatment with either antibiotic. The Harriet Lane Handbook was used to define abnormal laboratory values.[9] Hepatotoxicity was defined as meeting at least one of the following criteria: an ALT level at least twice the lower limit of normal, or a minimum of 100% increase in ALT from the baseline level. Nephrotoxicity was defined as meeting at least one of the following criteria: a serum creatinine level > 88 µmol/L (1 mg/dL), an absolute Cr increase of at least 44 µmol/L (0.5 mg/dL), or a minimum of 50% increase in Cr from the baseline level. Anaphylaxis, red man syndrome, nephrotoxicity, and hepatotoxicity were considered serious adverse events.

Patients switched from vancomycin to teicoplanin or vice versa were also included in the study, and all data collected from those patients were categorized as being part of the new treatment arm upon switching regardless of prior immediate management.

Statistical analysis

Descriptive statistics were used to analyze discrete variables, and medians, ranges and means were used to represent continuous variables. Safety variables for the categorical variables in two arms (vancomycin and teicoplanin) were compared by a two-tailed exact chi-square test. The Mann-Whitney U test and Wilcoxon signed-rank test were used to analyze continuous variables (for unpaired and paired data, respectively). Data were assumed to be non-parametric. Differences in means were calculated within and between arms for continuous variables. A *p*-value of 0.05 was considered to indicate statistical significance. Data were analyzed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethical Considerations

The study was approved by the Institutional Review Board of the King Abdullah University Hospital. The research objectives and methodologies were explained to all

participants' legal guardians and to participants if feasible. Written consent forms were obtained from legal guardians, including consent to publish results. All data were kept confidential, and all patient identifying information was removed.

Results

Of the 112 patients included in the study, 69 patients were in the vancomycin arm and 43 in the teicoplanin arm (Table 1). Male participants represented 60.7% of the whole cohort, and 66.7% of the vancomycin arm. However, the difference in gender distribution between both arms was not statistically significant ($p = 0.15$). The participants were classified into five age categories as shown in Table 1. Differences in age categories between treatment arms were not statistically significant ($p = 0.6$).

Admission diagnoses for all participants were recorded, and no participants met the exclusion criteria. Vancomycin was used for to treat central nervous system infections (44%), chest infections (22%), neoplastic disorders (20%), local infections (10%), and possible systemic infections (4%). Teicoplanin was used for local infections (50%), neoplastic disorders (21%), possible systemic infections (17%), and chest infections (12%). It is worth mentioning that teicoplanin is not approved for the treatment of central nervous system infections by manufacturers.

Other baseline characteristics, such as length of stay, weight, WBC count, absolute NEU count, PLAT count, serum Cr level and serum ALT level, were fairly balanced between both arms (Table 1). However, the median hemoglobin level was significantly lower in the teicoplanin arm (9.80 g/dL vs. 10.85 g/dL; $p = 0.02$). This corresponded to more cases of baseline anemia among teicoplanin subjects, although this difference did not reach statistical significance ($p = 0.23$).

More than half of the subjects (55%) developed at least one adverse event during treatment, which was observed more frequently in the vancomycin arm (64% vs. 44%; $p = 0.02$) (Table 2). Overall, pyrexia was the most common adverse event and observed in 46.4% of the subjects. Pyrexia was significantly more common in the vancomycin arm (55.1% vs. 30.2%; $p = 0.01$). This observation was consistent among all age categories. One patient in the vancomycin arm developed red man syndrome, but this did not necessitate a change in antibiotics. Rash was observed in 9.3% and 2.9% of patients receiving teicoplanin and vancomycin, respectively. However, this difference was not statistically significant ($p = 0.20$). Pruritus, headache and fatigue were uncommon and observed in only 5 patients total (3 in the vancomycin arm). Anaphylaxis was not observed in any of the patients.

Diarrhea and vomiting were the most frequent gastrointestinal adverse events in both vancomycin and teicoplanin arms (23.2% and 19% of patients, respectively). This difference was not statistically significant noting that a patient might have both symptoms. However, among vancomycin patients, diarrhea occurred significantly more in the age category of one to six months (33%; $p = 0.014$). This could be partially to difficult interpretation of bowel movements in this age group.

Both treatments were associated with changes in certain laboratory parameters. Treatment with either medication was associated with statistically significant reductions in hemoglobin levels, WBC counts, absolute NEU counts, and PLAT counts when

compared to immediate pretreatment levels (Table 3). However, comparison of the mean differences between both arms showed no significant differences in these values.

Table 1. Baseline characteristics of the study participants

Characteristic	Vancomycin arm (N = 69)	Teicoplanin arm (N = 43)	*p*-value
Age			
Median	1.9 years	1.9 years	
Range	1 month - 11 years	1 month - 13 years	
Age distribution, n (%)			0.6
1 month - 6 months	18 (26.1)	11 (25.6)	
7 months - 12 months	11 (15.9)	3 (7.0)	
13 months - 4 years	16 (23.2)	14 (32.6)	
5 years - 9 years	16 (23.2)	9 (20.9)	
10 years - 15 years	8 (11.6)	6 (14.0)	
Male sex, n (%)	46 (66.7)	22 (51.2)	0.15
Weight, kg			0.92
Median	11	11.8	
Range	3.4 - 36.8	1.2 - 46	
Length of hospital stay, days			0.19
Median	8	11	
Range	1 - 120	2 - 120	
Hemoglobin level, g/dL			0.02
Median	10.85	9.80	
Range	7.20 - 13.60	5.90 - 15.40	
Anemia cases, n (%)	32 (49)	22 (85)	0.23
White blood cell count, 10^3/µL			0.68
Median	11.4	10.5	
Range	0.8 - 43	0.9 - 34.5	
Absolute neutrophil count, 10^3/µL			0.57
Median	5.3	4.23	
Range	0 - 34.9	0.08 - 30.8	
Platelet count, 10^3/µL			0.99
Median	324	329	
Range	4 - 1,130	22 - 800	
Serum creatinine, µmol/L			0.87
Median	30	27.5	
Range	7 - 105	8 - 148	
Serum alanine aminotransferase, U/L			0.98
Median	20.9	21.2	
Range	5.8 - 365	7.7 - 116.8	

Table 2. Summary of clinical and other adverse events during the treatment period[a]

Characteristic	Vancomycin arm (N = 69)	Teicoplanin arm (N = 43)	*p*-value
Number of adverse events, n	69	30	NA
Patients with one or more adverse events, n (%)	44 (64)	19 (44)	0.02
Other adverse events, n (%)			
Pyrexia	38 (55.1)	13 (30.2)	0.01
Rash	2 (2.9)	4 (9.3)	0.20
Pruritus	2 (2.9)	1 (2.3)	1.00
Red man syndrome	1 (1.4)	0 (0)	1.00
Fatigue	0 (0)	1 (2.3)	0.38
Headache	1 (1.4)	0 (0)	1.00
Anaphylaxis	0 (0)	0 (0)	NA
Gastrointestinal adverse events, n (%)			
Vomiting	10 (14.6)	3 (7)	0.36
Diarrhea	8 (12)	5 (12)	1.00
Abdominal pain	3 (4.3)	1 (2.3)	1.00
Poor oral intake	2 (2.9)	1 (2.3)	1.00
Constipation	1 (1.4)	1 (2.3)	1.00
Nausea	1 (1.4)	0 (0)	1.00
Flatulence	0 (0)	0 (0)	NA
Discontinuation of antibiotic, n (%)	12 (17.3)	5 (11.6)	0.60
Nephrotoxicity, n (%)	4 (14)	3 (27)	0.48
Hepatotoxicity, n (%)	0 (0)	2 (27)	0.48
Antibiotic-related death, n (%)	0 (0)	0 (0)	NA

[a] NA: not applicable.

Table 3. Summary of laboratory values for vancomycin and teicoplanin study arms

	Teicoplanin arm			Vancomycin arm			*p*-value[a]
Laboratory parameter	Baseline mean	Mean of highest or lowest values during treatment[b]	*p*-value[d]	Baseline mean	Mean highest or lowest values during treatment[b]	*p*-value[c]	
Hemoglobin, g/dL	9.83	8.77	0.005	10.24	9.35	0.018	0.720
White blood cell count, 10^3/µL	11.25	7	0.001	13.43	7.28	0.001	0.753
Absolute neutrophil count, 10^3/µL	7.26	3.74	< 0.001	8.23	2.89	< 0.001	0.573
Platelet count, 10^3/µL	289	198	< 0.001	334	258	0.012	0.561
Serum creatinine, µmol/L	32.71	40.71	0.177	31.42	31.21	0.901	0.196
Serum alanine aminotransferase, U/L	51	63.44	0.313	92.78	50.08	0.625	0.171

[a] The *p*-value was calculated for the difference in means between the teicoplanin group and the vancomycin group during treatment. [b]The mean of the lowest values for each patient was calculated for the following parameters: hemoglobin level, white blood cell count, absolute neutrophil count, and platelet count; the mean of the highest values for each patient was calculated for serum creatinine and alanine aminotransferase level. [c]The *p*-value was calculated for the difference in means between baseline and treatment levels within the same group (either the teicoplanin group or the vancomycin group).

Neither vancomycin nor teicoplanin had significant impacts on serum Cr levels within or between both treatment arms (Table 3). However, both teicoplanin and vancomycin were associated with reversible nephrotoxicity, although this was not statistically significant (p=0.48) (Table 2). Vancomycin was associated with 4 proven cases of nephrotoxicity (13% of evaluated 31 cases) while teicoplanin was associated with 3 proven cases of nephrotoxicity (27% of evaluated 11 cases) (Table 2). There were no deaths related to the antibiotics in this study.

Discussion

Presently, there are few and inconclusive studies comparing the safety profiles of vancomycin and teicoplanin. Moreover, safety patterns observed in these studies were usually secondary outcomes. Previously published studies have reported that teicoplanin has a better safety profile than vancomycin. However, none of these studies explored safety in children. This observational, prospective study is a step towards filling the research gap on safety comparisons between vancomycin and teicoplanin in children with various clinical diagnoses.

Despite the heterogeneity of clinical diagnoses of the participants, the only group of patients that might have confounded the pattern

of adverse event outcomes was that of patients with neoplastic disorders. This is partly due to difficulty in deciding whether a given adverse event is secondary to the drug, the disease, or the chemotherapy. However, those patients represented almost equal proportions in both arms (20% and 21% for vancomycin and teicoplanin arms, respectively).

Interestingly, we observed that 55% of all subjects developed at least one clinical adverse event. This unexpectedly high rate of adverse events might have been related to the prospective nature of the study. Despite this difference in rate of adverse events, the relatively higher rate of adverse events in the vancomycin arm was consistent with previously published studies,[2] including Wood's meta-analysis (2000) in which he observed statistically fewer adverse events in patients treated with teicoplanin (13.9% versus 21.9%). Studies in mainly adults have also shown that vancomycin is associated with higher rates of total adverse events, nephrotoxicity, and red man syndrome.[3,10,11]

On the other hand, adverse events did not typically result in discontinuation of therapy, which occurred in only 17 patients total in both arms. Moreover, the higher rate of pyrexia among vancomycin subjects was the cause for the significantly higher rate of total adverse events with vancomycin.

Previous studies in mainly adult cohorts have shown significantly more nephrotoxicity with vancomycin,[3,12-14] reaching 10.7% versus 4.8% in one review. In our study, both drugs were associated with reversible nephrotoxicity (7 cases total, 4 of which occurred in the vancomycin group), with no statistically significant differences. This finding contradicts older studies that observed higher rates of nephrotoxicity in vancomycin-treated patients.[3,12-14] This could be explained by the increased use of drug therapeutic monitoring, cautious use of concomitant nephrotoxic medications, and availability of highly purified vancomycin preparations.[15] Our results are consistent with a more recent study that reported no significant difference in the occurrence of drug-related nephrotoxicity with the use of either drug in adults.[15]

Hepatotoxicity was reported in only two patients in the teicoplanin arm compared to none in the vancomycin arm, with no statistically significant difference. Hepatotoxicity was reversible in both cases.

There was no statistically significant difference regarding the occurrence of skin rash in this study. Previous studies have shown fewer cutaneous adverse events with teicoplanin use,[4] which may be explained by the current use of highly pure preparations of vancomycin as explained in one study.[16]

This study also observed that both drugs had significant reductions in hemoglobin levels, WBC counts, and PLAT counts. These laboratory values were not significantly different between the two study arms, which is in agreement with previously published studies in mainly adults cohorts.[4,17,18]

This study has several limitations. These include the practical difficulty in standardizing antibiotic dosing and selection, which were done by the physician and/or clinical pharmacist on a case-by-case basis. These dosing and selection differences, including those made depending on a patient's diagnoses and existing comorbidities, may have

confounded the clinical and laboratory results. In addition, adverse events such as nephrotoxicity and hepatotoxicity may have been related to drug doses, but this dosing information was not collected in this study. Data on concurrent medications and potential drug-drug interactions, which may have confounded the results, were also not collected. Another limitation is the fact that the identification of adverse events was subjective in nature, depending on the physician who made the diagnosis.

Conclusion

Despite the relatively high occurrence of adverse events, both vancomycin and teicoplanin were associated with less serious adverse events than those previously reported in children. Reversible nephrotoxicity was reported with both medications, with no significant difference between the two arms. Both drugs were associated with significant reductions in hemoglobin levels, WBC counts, and PLAT counts. However, there were no significant differences in these laboratory values between the two study arms. Vancomycin was associated with a significantly higher rate of pyrexia. In general, both drugs were fairly well-tolerated by children. Due to potentially significant limitations of this study, including those related to antibiotic dosing regimens and selection, a large-scale, randomized study in children would contribute toward better understanding of the safety profiles of both drugs.

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استخدام التيكوبلانين والفانكوميسين عند الأطفال في شمال الأردن: دراسة مقارنة السلامة والمأمونية

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الملخص

الخلفية والأهداف: تستعمل مضادات الفانكوميسين والتيكوبلانين بشكل متكرر حيث يقترن استعمالها بطيف من المضاعفات الجانبية المعتدلة والشديدة. تهدف هذه الدراسة الى تقييم ومقارنة المضاعفات الجانبية والسمية الناتجة عن استخدام هذين المضادين عند الأطفال في مستشفى جامعي في شمال الأردن.

الطرائق: شارك في هذه الدراسة المتقدمة والاستطلاعية مائة واثنا عشر طفلا تقع أعمارهم بين الشهر الواحد والخمسة عشر عاما منهم تسعة وتسعون في مجموعة الفانكوميسين وثلاثة وأربعون في ذراع التيكوبلانين. تم جمع المعلومات الديموغرافية والسريرية والمخبرية وتوثيقها. قام الباحثون بعد ذلك بمتابعة وتوثيق معلومات المضاعفات الجانبية والسمية السريرية والمخبرية أثناء تلقي العلاج.

النتائج: كنت خصائص المجموعتين الأساسية متشابهة باستثناء معدلات خضاب الدم. كانت المضاعفات الجانبية أكثر تكرارا لدى مجموعة الفانكوميسين ((64% vs. 44%; P = 0.02). كما تميزت مجموعة الفانكوميسين بحدوث أكثر تكرارا وذي دلالة احصائية لعرض الحرارة المرتفعة (55% vs. 30%; P = 0.01)، وباتجاه نحو معدل أعلى من المضاعفات في الجهاز الهضمي. تساوت المجموعتان في احداث انخفاض ملحوظ في مستويات خضاب الدم وكريات الدم البيضاء والصفائح. كما كان حصول السمية الكلوية لدى المجموعتين متشابها ودون أي دلالة احصائية (14% vs. 27%; P = 0.48).

الخلاصة: كان تحمل الأطفال تلقي المضادين بشكل عادل وبمعدلات أقل من المضاعفات الشديدة مقارنة بما هو موثق في الأدبيات الطبية السابقة كما كان حدوث السمية الكلوية متشابها بين المجموعتين. ومع ذلك فقد كان حدوث المضاعفات الجانبية أكثر لدى مجموعة الفانكوميسين وذا دلالة إحصائية. تبين الدراسة الحاجة الى دراسة أوسع نطاقا وأكثر ضبطا لفهم أفضل لخصائص السلامة والمأمونية المرتبطة باستخدام هذين المضادين.

الكلمات الدالة: فانكوميسين، تيكوبلانين، السلامة، السمية، الأطفال، الأردن.