Clinical effectiveness of generic vancomycin products compared to Vancocin CP® in patients with methicillin-resistant *Staphylococcus aureus* infections: A retrospective cohort

Juliana Castaño-Rendón MD, Sebastián Sánchez López MD, Andrés Felipe Barbosa Padierna MD, María Paulina Cortés Palacio MD, Laura María Mesa Tobon MD, María Sady Bustamante De La Ossa MD, Carolina Zapata Muriel MD, Johana Ascuntar Tello MD, Fabián Jaimes MD

ABSTRACT

Introduction: *Approval of generic drugs requires only bioequivalence studies. Some research suggests that generic vancomycin is not clinically equivalent to the branded drug, and this exposes patients to therapeutic failure and the development of microbial resistance.*

Aims: *Compare the rates of microbiological and clinical failure between generic vancomycin and Vancocin-CP®.*

Methods: *Retrospective cohort analysis of hospitalized adults with culture-proven methicillin-resistant* Staphylococcus aureus *infection, treated with vancomycin in a tertiary care hospital in Medellín, Colombia. General clinical variables, laboratory findings, severity and mortality scores, and type of vancomycin used were recorded. Logistical regression models, adjusted for potential confounders, were fitted to estimate the effect of vancomycin on clinical and microbiologic outcomes.*

Results: *Of 209 patients, 153 (73.2%) received generic vancomycin and 56 (26.8%) Vancocin-CP®. Systems more commonly affected were skin and soft tissues (28.5%), blood with involvement of catheters (27.6%) and blood without the involvement of catheters (23.3%). There were 62 clinical failures (29.5%) and 41(38%) microbiological failures. The hospital mortality rate was 15% (n = 31); only 7 (3.4%) episodes of adverse drug reactions were documented. No difference was found in the risk of clinical or microbiological failure between Vancocin-CP® and generic products with OR = 2.3 (95% CI = 0.8; 6.3) and 0.89 (95% CI = 0.4; 1.9), respectively.*

Conclusion: *There were no association between the use of generic vancomycin and the outcomes of clinical or microbiological failure. Sample size is an important limitation for these findings.*

Keywords: Vancomycin, bioequivalence, MRSA, clinical equivalence

INTRODUCTION

Staphylococcus aureus has an enormous ability to generate antibiotic resistance.[1] The current prevalence of penicillinase-producing *S. aureus* is approximately 80%[2], and, although the first methicillin-resistant *Staphylococcus aureus* (MRSA) was identified halfway through the 1950s,[3] its prevalence currently reaches 60% in some states in the United States.[4] Vancomycin became available in 1956, and approximately 30 years later, the first vancomycin generic products were introduced in the market.[5]

According to the World Health Organization (WHO), a generic medication is defined as a drug that has the same qualitative and quantitative composition

Corresponding author: **Sebastian Sanchez**
Contact Information: Sebastian.sanchez@ttuhsc.edu
DOI: 10.12746/swrccc.v10i45.1103

of the active component and whose bioequivalence with the innovator product has been demonstrated.[6] In the United States, after the approval of the Hatch-Waxman act in 1984, new generics will only require bioequivalence and quality control studies, with no efficacy or tolerance clinical trials. With the entry of generic drugs into the market, consumers benefit from price reductions with an accompanying rise in generic products sale.[7] However, several studies have found that some generic antibiotics are not bioequivalent when compared with the original product, exposing patients to high rates of clinical failure and the development of antimicrobial resistance.[8] Vancomycin is a large molecule with little penetrance into the respiratory epithelium which also has nephrotoxicity and ototoxicity; this leads to some clinicians to under dose patients, and thus serum levels are below the Minimum Inhibitory Concentration (MIC) against *S. aureus*.[9,10] In December 2004, Eli Lilly sold the original commercial rights of Vancocin CP® to Baxter laboratories of Latin America,[11] and 3 years later Baxter was able, in collaboration with Eli Lilly personnel, to produce a bioequivalent Vancomycin product sold as Vancocin CP®.[12]

Independent researchers have demonstrated that the 6 types of generic vancomycin products sold in the US were bioequivalent.[13–16] However, a series of experiments by Zuluaga et al, which compared the potency of different generic vancomycins against the Eli Lilly molecule, showed that equipotency was reached only at Active Principle (API) concentrations 25% higher.[17] In a subsequent study by the same group, the efficacy of various vancomycin products was measured using the Neutropenic Mouse Thigh infection model (NMTIM); in which the pharmacodynamic parameters of the generic products were completely different from the original.[18] Results from these studies agree with a case report in which a hepatic transplant patient, with a vancomycin-susceptible MRSA strain (*S. aureus* GRP-0109 with MIC = 1 mg/lt), had a therapeutic failure with the use of generic vancomycin, despite adequate dosing and serum levels, as well as exclusion of other sources of infection. A final favorable outcome in this patient was attributed to the switch made to the original Vancomycin product.[19,20]

Despite the fact that *in vitro* and *in vivo* models have appropriate methodological and experimental validation, they could be an excessive oversimplification of the complex interaction between medication, humans, and microorganisms. To our knowledge, there is no current evidence of this type of clinical studies. Considering absence of the innovator drug from Eli Lilly and the current availability of the non-innovator analogous vancomycin product by Baxter, the goal of this study was to determine if there are differences in the rates of clinical or microbiological failures with the use of generic vancomycin products when compared to Vancocin CP® from Baxter in a cohort of adult inpatients with MRSA infections.

Methods

Design and patients

This is a retrospective cohort study of patients 18 years or older hospitalized with culture-proven MRSA infection (oxacillin MIC ≥4 mg/L) (21) who received vancomycin as treatment. The study was carried out in Hospital San Vicente Fundación (HSVF), Medellín, Colombia, from the 1st march of 2011 to 31st December of 2016. Pregnant patients, patients who received other antibiotic active against MRSA (daptomycin, linezolid, trimethoprim-sulfamethoxazole, clindamycin, doxycycline, ceftaroline), and patients with no available clinical records or culture results were excluded. The study was approved by the ethics and research committee of HUSVF.

Source of data

The HSVF microbiology department traced the cases with MRSA positive-cultures. Afterwards, the researchers and auxiliary personnel, previously trained, reviewed the hospital records (Systems, applications, products in data processing; SAP®) using the national ID number. Demographic data, physiologic status, medication used, laboratory results, including cultures and antimicrobial susceptibility testing, and imaging were collected by the researchers and auxiliary personnel in a predesigned form. For each patient the following data were collected: age, gender, hospitalization date, comorbidities with an impact on the immune system as solid organ or hematological transplantation, use of

immunosuppressive medications, neutropenia, defined as an absolute neutrophil count below <500 cells/µL (22); chronic use of corticoids (>5 mg/day of prednisone or its equivalent for a month or longer), chronic hepatic disease or cirrhosis, chronic kidney disease (glomerular filtration rate <60 mL/min) with or without dialysis, solid or hematologic active malignancy, HIV infection with $CD4^+$ < 200 cells/µL, primary immunodeficiency; date of culture positivity, system(s) affected, infection associated with a prosthesis or medical device, health-care related infection, post-surgical infection, antimicrobial resistance pattern of the MRSA. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were calculated from laboratory and physiological records taken the day of the microbiological diagnosis. Since 87% of patients had no bilirubin measurement, a modified 5-domain SOFA score was developed (maximum value 20). The presence of cavitation, pleural effusion, consolidation, multilobar pneumonia, abscess, and osteomyelitis were assessed using the official radiology reading (IMPAX client, Afga Healthcare, Belgium). Concomitant infections, application and dates of other antibiotics used, control culture for MRSA and its corresponding antimicrobial resistance pattern, adverse drug reactions attributed to vancomycin use, completed treatment regimen, discharge date and vital status, were also recorded. Date of purchase, brand, and batches of vancomycin were provided by the commercial department of the hospital.

Outcomes

Main outcomes were assessed, according to the reports in the clinical records, by at least two researchers with clinical training and blinded to the type of vancomycin used:

- **Clinical failure:** persistence, increase, or recurrence of symptoms or signs related to the original infection occurring less or equal to 5 days after finishing antibiotic treatment; or antimicrobial change due to non-response, or death due to MRSA.
- **Microbiological failure:** persistence of MRSA growth in cultures despite 48 hours or more of appropriate antibiotic treatment.

As secondary outcomes, hospital mortality and adverse drug reactions attributed to vancomycin were assessed.

Statistical analysis

Continuous variables were reported as means with standard deviations and categorical variables were presented as proportions. As a formal sample size calculation was not possible, these results are considered exploratory in terms of statistical inference. Since the hospital codes all vancomycin with the same administrative ID number, exact vancomycin product received by each patient was unavailable. We matched the dates when the patient received the vancomycin with the brand of the batch bought by the hospital for that same period of time. To determine the association between the outcomes and the administration of Vancocin CP® or generic vancomycin, logistic regression models were used, non-adjusted and adjusted for confounders: immunosuppression (one or more of these: absolute neutrophil count below 500, use of systemic corticosteroids for a month or longer, solid organ or hematological transplantation, chemotherapy, use of biological medication, chronic kidney disease, solid or hematologic malignancy, $CD4^+$ < 200 cells/µL or a diagnosis of primary immunodeficiency), APACHE-II and SOFA scores, damage of 2 or more systems, vancomycin MIC, gender, and age. Finally, as a sensitivity analysis, logistic regression models were also fitted assuming the vancomycin batch was used up on the same week, one, two, or three weeks after the date of purchase. Also, patients were classified as receiving combined treatment, if batches from Baxter or other were bought during the same week. Association measures are reported as Odds Ratio (OR) with its corresponding 95% Confidence Interval (CI). All statistical analysis was made with STATA V.14 (StataCorp; 4905 Lakeway Drive. College Station, Texas 77845 USA)

Results

During the study period, 1350 patients with positive MRSA cultures were reported by the hospital microbiology department. Eighty-four percent (n = 1140)

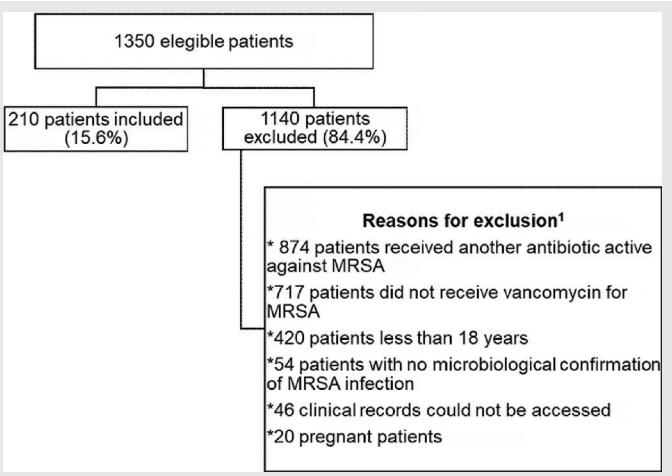

Figure 1. Flowchart of patient selection.
[1]some patients fulfilled more than one exclusion criteria.

were excluded for several reasons, the most common one being the co-administration of another antibiotic active against MRSA (Figure 1). Finally, 210 patients were analyzed.

Based on the date of vancomycin batch purchase, 153 patients (73.2%) received generic vancomycin, 56 (26.8%) received Vancocin CP® and 1 received both. Most of the patients were male (61.7%, n = 129), and mean age was 53 ± 18 years. Thirty-eight patients (18,1%) had some kind of associated immunosuppression other than HIV or primary immunodeficiency, 66 (31.4%) had chronic kidney disease, and 49 (23.3%) were diabetic. The most common sites of infection were skin and soft tissues (28.5%), vascular access sites with a catheter (27.6%), vascular sites with no catheter (23.3%), lower respiratory tract (17.1%), and musculoskeletal sides (10.1%). The sites with positive MRSA cultures included 103 blood cultures, 41 skin and soft tissue, and 20 bone samples; some patients had positive cultures in more than one site simultaneously. Most of the patients completed the planned therapy (n = 176, 83.8%), and there were 62 clinical failures (29.5%). One hundred and nine patients had follow-up cultures and MRSA growth was detected in 41 for a 38% rate of microbiological failure. In-hospital mortality was 15% (n = 31), and 7 (3.4%) adverse drug reactions associated with vancomycin use were documented (Table 1).

There were no differences between the risk of clinical or microbiological failure in patients treated with Vancocin CP®, compared with those receiving other vancomycin: OR = 2.3 (95% CI = 0.8; 6.3) and 0.89 (95% CI = 0.4; 1.9), respectively. These results were not modified after the sensitivity analysis (Table 2). In addition, no differences were found for secondary outcomes (Table 3).

Discussion

In this retrospective cohort study, no difference was observed in the occurrence of clinical or microbiological failure between patients treated either with generic vancomycin products or Vancocin CP®. This result remained after adjusting for confounding variables and also after a sensitivity analysis with different potential dates of Vancocin CP administration. Although a tendency towards mortality reduction was seen in patients receiving Vancocin CP®, this difference was not statistically significant.

Alert results do not agree with the in vivo studies by Vesga et al.[18] in which 3 generic vancomycin products show a maximal antibacterial effect (E_{max} 2.4, 2.5, y 3.48) lower than that seen with the innovator product (E_{max} 5.65), thus failing to eradicate MRSA infection in the NMTIM. Our study used Baxter's Vancocin CP® as the closest related innovator product, since Eli Lilly's original vancomycin is no longer produced. To date there are no human-based studies with the original product, hindering any definitive conclusions about the comparative effectiveness of generic and original vancomycin products.

Despite not being statistically significant, it is noteworthy the tendency for a reduction in mortality with the Vancocin CP® molecule. Since this drug is more similar and therapeutically equivalent to the original product, the question still persists if the so-called original product is better than other vancomycin products in the market. Clinical equivalency has to be the final goal of generic products, a goal that becomes more relevant for antimicrobial medication used in the critically ill or immunosuppressed patients,[19] in whom immune dysregulation creates a demand for drugs with high bactericidal power. Currently, the approval

Table 1. Study Population and Main Clinical Characteristics According to Provided Vancomycin Product

	Generic (n = 153; 73.2%)	Vancocin CP® (n = 56; 26.8%)	Total (n = 209)[1]
Age*	53.7 (17.7)	49.3 (17.7)	52.6 (17.8)
Male gender	92 (60.1%)	37 (66.1%)	129 (61.7%)
Comorbidity			
Chronic kidney disease	51 (33.3%)	15 (26.8%)	66 (31.6%)
Diabetes	38 (24.8%)	10 (17.9%)	48 (22.9%)
Non-HIV, non-primary immunodeficiency[2]	27 (17.7%)	10 (17.9%)	37 (17.7%)
Cancer[3]	23 (15%)	5 (8.9%)	28 (13.4%)
HIV[4]	2 (1.3%)	2 (3.6%)	4 (1.9%)
Liver disease	2 (1.3%)	1 (1.8%)	3 (1.4%)
Primary immunodeficiency	0 (0%)	1 (1.8%)	1 (0.5%)
Affected System			
Skin and soft tissues	36 (23.5%)	23 (41.1%)	59 (28.2%)
Intravascular associated with a catheter	47 (30.7%)	11 (19.6%)	58 (27.8%)
Intravascular	35 (22.9%)	14 (25%)	49 (23.4%)
Lower respiratory tract	21 (13.7%)	15 (26.8%)	36 (17.2%)
Osteomuscular	18 (11.8%)	3 (5.4%)	21 (10.1%)
Gastrointestinal	6 (3.9%)	2 (3.6%)	8 (3.8%)
Nervous system	6 (3.9%)	1 (1.8%)	7 (3.4%)
Urogenital	2 (1.3%)	2 (3.6%)	4 (1.9%)
Cardiac	1 (0.7%)	1 (1.8%)	2 (0.9%)
Upper respiratory tract	1 (0.7%)	1 (1.8%)	2 (0.9%)
Mediastinum	1 (0.7%)	0 (0%)	1 (0.5%)
2 or more systems affected	21 (13.8%)	16 (28.6%)	37 (17.7%)
Infection involving a medical-implanted device or prothesis	72 (47%)	21 (37.5%)	93 (44.5%)
Post-surgical infection	30 (19.6%)	11 (19.6%)	41 (19.6%)
APACHE-II*	10.9 (5.7)	10.8 (6.3)	10.8 (5.8)
SOFA*	2.8 (2.7)	2.8 (2.7)	2.8 (2.6)
Main Culture Site			
Blood	84 (54.9%)	24 (42.9%)	108 (51.7%)
Skin and soft tissues	22 (14.4%)	14 (25%)	36 (17.2%)
Bone	15 (9.8%)	2 (3.6%)	17 (8.1%)
Tracheal aspirate	5 (3.3%)	7 (12.5%)	12 (5.7%)

(*continued*)

Table 1. Study Population and Main Clinical Characteristics According to Provided Vancomycin Product (*Continued*)

	Generic (n = 153; 73.2%)	Vancocin CP® (n = 56; 26.8%)	Total (n = 209)
Others	27 (17.6%)	9 (16%)	36 (17.2%)
Two or more cultures	13 (8.5%)	9 (16%)	22 (10.5%)
Use of other antibiotics	59 (38.6%)	18 (32.1%)	77 (36.8%)

*Mean (standard deviation).
[1]one patient not included because he received 2 different vancomycin batches.
[2]Includes: Solid organ or hematopoietic transplantation, immunosuppressive medication, neutropenia defined as an absolute PMN count <500 cells/μL(22), chronic steroid use (>5 mg/day of prednisone or its equivalent for more than a month).
[3]solid or hematopoietic transplantation, according to clinical record.
[4]With $CD4^+$ <200 cells/μL.

of generic medications by the United States Food and Drug Administration (FDA) depends only on proving pharmacological equivalence and bioequivalence, judged by pharmacokinetic studies without the need of well-designed clinical trials.[23] This pharmacologic studies may not be suitable to demonstrate clinical equivalency, especially for drugs that can be altered by so many variables.[24] In the case of vancomycin, several in vitro and in vivo studies based on animal models,[15,18–20,25] pointed to the high content of impurities derived from fermentation, like the CDP-1 product, to be responsible for the antagonistic effect over the active components of the medication.[18,26]

We found a low percentage of adverse drug reactions, with nephrotoxicity the most common one, results similar to those seen in other studies.[27] The lower incidence in our population may reflect the

Table 2. Bivariate and Multivariate Logistical Regression for the Outcomes of Clinical Failure and Microbiological Failure

Time of Batch Administration	Variable	Microbiological Failure (n = 41/107)		Clinical Failure (n = 62/209)	
		OR (95% CI)	P Value	OR (95% CI)	P Value
Exact date	Vancocin CP®	2.0 (0.8; 4.8)	0.139	1.05 (0.5; 2.0)	0.895
	Vancocin CP® adjusted*	2.3 (0.8; 6.3)	0.109	0.89 (0.4; 1.9)	0.752
One week	Vancocin CP®	2.0 (0.8; 5.0)	0.120	1.4 (0.7; 2.6)	0.363
	Vancocin CP® adjusted*	2.5 (0.9; 6.8)	0.077	1.2 (0.6; 2.5)	0.643
Two weeks	Vancocin CP®	1.8 (0.7; 4.5)	0.198	1.2 (0.6; 2.3)	0.641
	Vancocin CP® adjusted*	2.0 (0.7; 5.6)	0.166	0.99 (0.5; 2.1)	0.974
Three weeks	Vancocin CP®	1.8 (0.8; 4.3)	0.183	1.1 (0.6; 2.2)	0.709
	Vancocin CP® adjusted*	1.8 (0.7; 4.7)	0.194	1.2 (0.6; 2.4)	0.621
Batch bought the same week	Vancocin CP®	1.6 (0.7; 4.1)	0.282	1.02 (0.5; 2)	0.958
	Combined vancomycin	0.5 (0.1; 4.2)	0.480	1.2 (0.3; 5.1)	0.795
	Vancocin CP® adjusted*	1.9 (0.7; 5.3)	0.233	0.9 (0.4; 1.9)	0.711
	Combined vancomycin	0.7 (0.1; 7.0)	0.732	1.4 (0.3; 7.0)	0.700

*adjusted for immunosuppression, APACHE-II, modified SOFA score, two or more systems affected, age, gender, and vancomycin MIC.

Table 3. Bivariate and Multivariate Logistical Regression for the Outcomes of In-hospital Mortality and Adverse Drug Reactions

Time of Batch Administration	Variable	In-Hospital Mortality		Adverse Drug Reactions	
		OR (95% CI) (n = 31/209)	P Value	OR (95% CI) (n = 7/209)	P Value
Exact date	Vancocin CP®	0.77 (0.3; 1.9)	0.567	0.45 (0.1; 3.8)	0.459
	Vancocin CP® adjusted*	0.44 (0.1; 1.5)	0.195	0.43 (0.1; 4.0)	0.454
One week	Vancocin CP®	0.94 (0.4; 2.2)	0.893	0.45 (0.1; 3.8)	0.459
	Vancocin CP® adjusted*	0.51 (0.2; 1.7)	0.267	0.41 (0.1; 3.7)	0.432
Two weeks	Vancocin CP®	0.75 (0.3; 1.8)	0.526	0.52 (0.1; 4.6)	0.560
	Vancocin CP® adjusted*	0.33 (0.1; 1.2)	0.089	0.51 (0.1; 4.8)	0.556
Three weeks	Vancocin CP®	0.43 (0.2; 1.2)	0.09	0.99 (0.2; 5.2)	0.987
	Vancocin CP® adjusted*	0.18 (0.04; 0.8)	0.021	1.1 (0.2; 6.4)	0.931
Batch bought the same week	Vancocin CP®	0.66 (0.3; 1.7)	0.401	0.44 (0.1; 3.7)	0.449
	Combined Vancomycin	1.5 (0.3; 7.8)	0.618	–	–
	Vancocin CP® adjusted*	0.39 (0.1; 1.4)	0.156	0.42 (0.1; 3.8)	0.439
	Combined Vancomycin adjusted*	2.1 (0.2; 20.6)	0.522	–	–

*adjusted for immunosuppression, APACHE-II, modified SOFA score, two or more systems affected, age, gender, and vancomycin MIC.

lack of serial creatinine or urinary output measurements, which allow a close follow-up of renal function to identify toxicity. Significant differences in adverse effects were not found between treatment groups, although a tendency for lower incidence was seen with Baxter's Vancocin CP®. In a retrospective study by Izuwa, renal function was assessed by serum creatinine measurements in 122 patients who received vancomycin for MRSA infections, defining "decreased renal function" when serum creatinine reached or surpassed 1.20 mg/dL and 0.96 mg/dL for men and women, respectively. In that study, no difference in the incidence of renal dysfunction was seen between brand vancomycin and generic vancomycin products (2/62 vs. 4/60; p = 0.436).[28]

To our knowledge, this is the first clinical study that compares the generic vancomycin products against the formula purchased by Baxter. To confirm this statement, we performed a systematic search in medical databases, at the beginning and at the end of the study. Only two results were found: the study by Izawa mentioned earlier, and another study performed at the Brigham and Women's Hospital. In this last study, using a nationwide drug prescription database, patients that had received a prescription for generic and an original form of the same medication were identified.[29] For vancomycin products, hospitalization due to *Clostridium difficile* infection was the outcome. After the introduction of the generic product, there was a fall in the incidence of *C. difficile* hospitalization, mostly due to widespread use and cheaper costs of vancomycin.

This study has several limitations. First, its retrospective nature, the limited number of patients, and the wide range of clinical infections limit the power of the study, and bigger prospective and more focused studies are needed. Other limitations include that the exact brand of the vancomycin product finally given to the patient is unknown due to coding system used by the commercial department of the hospital, as a consequence the decision of choosing between vancomycin product was based on availability, and, thus, the need to match patient´s hospitalization date to date of vancomycin batch bought by the hospital. The

most important limitation is the absence of the original Eli Lilly's molecule, Vancocin®. Even though this is the first clinical study in humans, the conclusions drawn here can be limited by the fact of not having the original molecule as comparator. However, the slight tendency for reduced mortality with Vancocin CP® calls for attention. Knowing that the original product will not be manufactured again, to carry out prospective clinical trials that test the efficacy of vancomycin generic products is a possible scenario. To determine the true efficacy and adverse effects of these products could have an important economic and public health impact, and might lead to changes in the laws for the approval of generic medications. An additional limitation was the hospital policy regarding distribution of vancomycin from the pharmacy using the same batch administrative ID number, not allowing to know the exact brand of vancomycin applied to the patient. Nonetheless, even after running the sensitivity analysis adjusted by date of batch purchase, no significant differences were found, granting consistency to the results shown. Finally, a major limitation was the reduced sample size, which hampers from drawing statistically significant conclusions.

Based on these findings, no statistically significant differences were found, either clinically or microbiologically, when comparing the use of generic vancomycin products against Baxter's Vancocin CP® in patients with MRSA infection. However, the analysis showed a slight tendency for lower mortality in patients using the last product. As exploratory research and being the first study of its kind, is clear the need for more randomized clinical trials, with greater number of patients, limited to a narrower spectrum of infections. For these studies, conditions similar to the ones required for the approval of innovator products must be used, to assess the safety and clinical effectiveness of the current generic vancomycin products.

Acknowledgments

We thank the San Vicente Fundación hospital (HSVF) microbiology department for providing the data on MRSA-positive cultures, and the commercial department for providing information on the vancomycin batches and suppliers.

Article citation: Castaño-Rendón J, Sánchez López S, Barbosa Padierna AF, Cortés Palacio MP, Mesa Tobon LM, Bustamante De La Ossa MS, Zapata Muriel C, Ascuntar Tello J, Jaimes F. Clinical effectiveness of generic vancomycin products compared to Vancocin CP® in patients with methicillin-resistant Staphylococcus aureus infections: A retrospective cohort. The Southwest Respiratory and Critical Care Chronicles 2022;10(45): 1–9
From: Internal Medicine Department (JC-R, SSL, FJ), Universidad de Antioquia. Medellín, Colombia; School of Medicine (AFBP, MPCP, LMMT, MSBO, CZM, JAT), Universidad de Antioquia. Medellín, Colombia; Hospital San Vicente Fundación (FJ) - Research Direction. Medellín, Colombia
Submitted: 1/27/2022
Accepted: 10/6/2022
Conflicts of interest: none

References

1. Lowy FD. Antimicrobial resistance: The example of Staphylococcus aureus. J Clin Invest. 2003;111(9):1265–73.
2. Nimmo GR, Bell JM, Mitchell D, et al. Antimicrobial resistance in Staphylococcus aureus in Australian teaching hospitals, 1989-1999. Microb Drug Resist. 2003;9(2):155–60.
3. Jevons M. Celbenin-resistant staphylococci. Br Med J. 1961; 1(5219):124–5.
4. Styers D, Sheehan DJ, Hogan P, et al. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among Staphylococcus aureus: 2005 status in the United States. Ann Clin Microbiol Antimicrob. 2006; 5(Feb 9):2.
5. Moran GJ, Krishnadasan A, Gorwitz RJ , et al. Methicillin-resistant S. aureus infections among patients in the emergency department. N Engl J Med. 2006;355(7):666–74.
6. World Health Organization (WHO). WHO Expert Committee on Specifications for Pharmaceutical Preparations [Internet]. 2013 [cited 2019 Mar 13]. Available from: http://www.who.int/bookorders
7. US Food And Drugs Administration. Abbreviated New Drug Application (ANDA): Generics [Internet]. Center for Drug

Evaluation and Research; 2016 [cited 2016 Dec 9]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrug-ApplicationANDAGenerics/

8. Tattevin P, Crémieux AC, Rabaud C, et al. Efficacy and quality of antibacterial generic products approved for human use: A systematic review. Clin Infect Dis. 2014;58(4): 458–69.
9. Sakoulas G, Moellering Jr. RC, Eliopoulos GM. Adaptation of methicillin-resistant Staphylococcus aureus in the face of vancomycin therapy. Clin Infec Dis. 2006;42 Suppl 1(1537–6591):S40–50.
10. Concia E, Novelli A, Schito GC, et al. Ideal microbiological and pharmacological characteristics of a quality antimicrobial agent: comparing original and generic molecules. J Chemother. 2007;19(6):609–19.
11. U.S Food and Drug administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [Internet]. 2019. Available from: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm
12. U.S Food and drug administration. Center for Drug Evaluation and Research | FDA [Internet]. 2019. Available from: https://www.fda.gov/about-fda/center-drug-evaluation-and-research/center-drug-evaluation-and-research
13. Nambiar S, Madurawe RD, Zuk SM, et al. Product quality of parenteral vancomycin products in the United States. Antimicrob Agents Chemother. 2012 Jun;56(6):2819–23.
14. Hadwiger ME, Sommers CD, Mans DJ, et al. Quality assessment of U.S. marketplace vancomycin for injection products using high-resolution liquid chromatography-mass spectrometry and potency assays. Antimicrob Agents Chemother. 2012 Jun;56(6):2824–30.
15. Jones RN, Watters AA, Flamm RK, et al. Comparative potencies of contemporary generic vancomycin lot: In vitro assay results from nine products and a reference reagent-grade sample. Diagn Microbiol Infect Dis. 2013;76(2): 237–8.
16. Tattevin P, Saleh-Mghir A, Davido B, et al. Comparison of six generic vancomycin products for treatment of methicillin-resistant staphylococcus aureus experimental endocarditis in rabbits. Antimicrob Agents Chemother. 2013;57(3): 1157–62.
17. Zuluaga AF, Agudelo M, Rodriguez C, et al. Application of microbiological assay to determine pharmaceutical equivalence of generic intravenous antibiotics. BMC Clin Pharmacol. 2009;9(16):1.
18. Vesga O, Agudelo M, Salazar BE, et al. Generic vancomycin products fail in vivo despite being pharmaceutical equivalents of the innovator. Antimicrob Agents Chemother. 2010; 54(8):3271–9.
19. Rodriguez CA, Agudelo M, Catano JC,et al. Potential therapeutic failure of generic vancomycin in a liver transplant patient with MRSA peritonitis and bacteremia. J Infect. 2009 Oct;59(4):277–80.
20. Rodriguez CA, Agudelo M, Zuluaga AF, et al. Generic vancomycin enriches resistant subpopulations of Staphylococcus aureus after exposure in a neutropenic mouse thigh infection model. Antimicrob Agents Chemother. 2012 Jan;56(1): 243–7.
21. Wayne P. CLSI Performance Standards for Antimicrobial Susceptibility Testing. 28th ed. Clinical and Laboratory Standards Institute; 2018.
22. Lingaratnam S, Slavin MA, Koczwara B, et al. Introduction to the Australian consensus guidelines for the management of neutropenic fever in adult cancer patients, 2010/2011. Intern Med J. 2011 Jan;41(1b):75–81.
23. Davit BM, Nwakama PE, Buehler GJ, et al. Comparing generic and innovator drugs: A review of 12 years of bioequivalence data from the United States Food and Drug Administration. Ann Pharmacother. 2009;43(10):1583–97.
24. Kesselheim AS, Gagne JJ. Product-specific regulatory pathways to approve generic drugs: the need for follow-up studies to ensure safety and effectiveness. Drug Saf. 2015;38(10): 849–53.
25. Fujimura S, Watanabe A, Fuse K, et al. In vitro susceptibility of clinical isolates of methicillin-resistant Staphylococcus aureus (MRSA) to manufactured generic drugs compared with the brand vancomycin. Int J Antimicrob Agents. 2008 Apr; 31(4):391–2.
26. Lewis PO, Kirk LM, Brown SD. Comparison of three generic vancomycin products using liquid chromatography-mass spectrometry and an online tool. Am J Heal Pharm. 2014;71(12):1029–38.
27. Filippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. Clin Pharmacol Ther. 2017;102(3):459–69.
28. Izuwa Y, Ueshima S, Sato T, et al. [Frequency of decreased renal function between patients treated with brand and generic products of vancomycin hydrochloride injection]. Yakugaku Zasshi. 2008;128(10):1493–8.
29. Gagne JJ, Polinski JM, Jiang W, et al. Outcomes associated with generic drugs approved using product-specific determinations of therapeutic equivalence. Drugs. 2017;77(4): 427–33.