Comparison of Six Generic Vancomycin Products for Treatment of Methicillin-Resistant *Staphylococcus aureus* Experimental Endocarditis in Rabbits

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Concerns have recently emerged about the potency and the quality of generic vancomycin (VAN) products approved for use in humans, based on experiments in a neutropenic mouse thigh infection model. However, other animal models may be more appropriate to decipher the bactericidal activities of VAN generics *in vivo* and to predict their efficacy in humans. We aimed to compare the bactericidal activities of six generic VAN products currently used in France (Mylan and Sandoz), Spain (Hospira), Switzerland (Teva), and the United States (Akorn-Strides and American Pharmaceutical Products [APP]) in a rabbit model of aortic valve endocarditis induced by 8×10^7 CFU of methicillin-resistant *Staphylococcus aureus* (MRSA) strain COL (VAN MIC, 1.5 $\mu\text{g/ml}$). *In vitro*, there were no significant differences in the time-kill curve studies performed with the six generic VAN products. Ten rabbits in each group were treated with intravenous (i.v.) VAN, 60 mg/kg of body weight twice a day (b.i.d.) for 4 days. Mean peak serum VAN levels, measured 45 min after the last injection, ranged from 35.5 (APP) to 45.9 $\mu\text{g/ml}$ (Teva). Mean trough serum VAN levels, measured 12 h after the last injection, ranged from 2.3 (Hospira) to 9.2 (APP) $\mu\text{g/ml}$. All generic VAN products were superior to controls (no treatment) in terms of residual organisms in vegetations ($P < 0.02$ for each comparison) and in the spleen ($P < 0.005$ for each comparison). Pairwise comparisons of generic VAN products found no significant differences. In conclusion, a stringent MRSA endocarditis model found no significant differences in the bactericidal activities of six generic VAN products currently used in Europe and America.

More than 50 years after its approval in the United States, vancomycin (VAN) remains the first choice for the treatment of most severe methicillin-resistant *Staphylococcus aureus* (MRSA) infections in humans (1). VAN is a fermentation product of *Amycolatopsis orientalis*, an actinomycete. As such, industrial production of the active pharmaceutical product involves complex processes for biosynthesis, purification, and manufacture: even within the same manufacturer, differences in composition and in degradation products have been documented (2). As the innovator, Eli Lilly, discontinued VAN production at the end of 2004, all the VAN products currently used are generics. Over the last decade, the efficacy of VAN has been challenged for a number of reasons, including emergence of VAN resistance in a few clinical isolates of *S. aureus* (3), a gradual increase in VAN MICs in some institutions (4), and high rates of clinical failure for treatment of MRSA infections when VAN MICs are above 1.5 $\mu\text{g/ml}$ (5).

On this background, a recently published study performed with generic VAN products manufactured between 2002 and 2008 reported that, despite similar pharmacokinetic parameters and *in vitro* antibacterial activities, some generic VAN products were less bactericidal *in vivo* in a neutropenic mouse thigh infection model (6) and could induce more resistant subpopulations than the innovator, still available at the time the study was conducted (7). Those results have been the subject of intense debate worldwide, involving the scientific communities, drug regulatory agencies, and the public (8). Concerns have been expressed regarding current assumptions by the World Health Organization (WHO) and drug regulatory agencies that two products for parenteral use are

therapeutically equivalent if they are pharmaceutically equivalent (9). This issue is of great concern, as (i) it would imply that patients may be currently treated with suboptimal anti-MRSA agents, depending on the VAN generics they receive, and (ii) major changes would be required in the generic antibacterial approval process, including the need for more studies on efficacy, which would, in turn, translate into increased costs.

At present, data suggesting suboptimal *in vivo* bactericidal efficacy of some VAN generics are limited. Additional experimental studies are needed. We aimed to compare the efficacies of six VAN generic products currently used in humans in Europe and in America in the rabbit model of aortic valve MRSA endocarditis, a stringent model with longstanding records for evaluation of antibacterial agents, which has demonstrated its capacity to predict clinical efficacy in humans and to discriminate antibacterial agents as a function of their *in vivo* bactericidal activities (10).

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TABLE 1 Characteristics of generic vancomycin products

Manufacturer	Country of purchase	Form ^a	Treatment group
Mylan S.A.S.	France	1 g powder for i.v. injection	T1
Sandoz	France	1 g powder for i.v. injection	T2
Teva Pharma	Switzerland	1 g powder for i.v. injection	T3
American Pharmaceutical Products (APP)	USA	1 g powder for i.v. injection	T4
Akorn-Strides	USA	1 g powder for i.v. injection	T5
Hospira	Spain	1 g powder for i.v. injection	T6

^a i.v., intravenous.

MATERIALS AND METHODS

Bacterial strain. *S. aureus* strain COL is a homogeneous, β -lactamase-producing, highly methicillin-resistant clinical isolate (nafcillin MIC = 256 μ g/ml) (11). The VAN MIC was determined by the Etest method (bioMérieux, La Balme-les-Grottes, France), as recommended by the manufacturer. A single inoculum adjusted to a McFarland standard of 0.5 in distilled water was used. Mueller-Hinton agar plates (Bio-Rad, Marnes-La-Coquette, France) were inoculated with swabs saturated with a suspension of the test organism and incubated for 18 h at 37°C. The MIC was defined as the value at which the inhibition zone intersected the scale of the Etest strip.

Antibacterial agents. VAN generics were bought from local drug companies and prepared following label instructions for clinical use in humans (Table 1).

Time-kill curve studies. The bactericidal activity of VAN generic powder was determined. Overnight cultures were diluted in 10 ml of fresh Mueller-Hinton broth to yield an inoculum of 10^7 CFU/ml. The antibiotic concentrations used were equivalent to $10\times$ MIC for vancomycin (15 μ g/ml). After 0, 3, 6, and 24 h of incubation in a shaking water bath at 37°C, serial dilutions of 0.1-ml samples were subcultured onto Mueller-Hinton or Mueller-Hinton II agar plates (Becton, Dickinson, Rungis, France) and incubated at 37°C for 24 h before CFU were counted. Bactericidal effect was defined as a ≥ 3 -log₁₀-unit decrease of the initial inoculum.

Rabbit endocarditis model. New Zealand White rabbits, each weighing between 2.5 and 3 kg, were used. They were housed in individual cages with a natural light-dark cycle. The experimental protocol was in keeping with French legislation on animal experimentation and was approved by the Animal Use Committee of Maison Alfort Veterinary School, France. To establish endocarditis, anesthesia was induced by intramuscular (i.m.) injection of ketamine (25 mg/kg of body weight) and then by continuous inhalation of 1% isoflurane. A cut-down over the right carotid artery was performed, and a polyethylene catheter was positioned across the aortic valve. The catheter was secured in place for the duration of the experiment. Twenty-four hours after the positioning of the catheter, 1 ml of 0.9% saline containing approximately 8×10^7 CFU of COL was injected intravenously. The rabbits were randomized to one of seven groups of 10 rabbits each: (i) an untreated control group (T0), the members of which were euthanized 5 days after inoculation to determine the bacterial burdens in aortic valve vegetations and spleens, and (ii) six groups (T1 to T6) treated with VAN generics at a dose of 60 mg/kg i.m. every 12 h for 4 days. Antibiotic treatment was started 24 h after infection, and the treated rabbits were euthanized 12 h after the last dose of vancomycin. Aortic valve vegetations and spleens were removed. Blood culture was performed before sacrifice in all animals. Tissues were homogenized in 0.5 ml of 0.9% saline, and 100- μ l volumes were quantitatively cultured on blood agar to determine the number of bacteria present.

Serum vancomycin levels. Concentrations of VAN in serum were determined for all infected rabbits from blood samples obtained 45 min (peak) and 12 h (trough) after the last injection. In addition, to determine the area under the concentration-time curve (AUC)/MIC ratio obtained with the 60-mg/kg twice a day (b.i.d.) dose, we measured the VAN AUC from 0 to 12 h (AUC₀₋₁₂) in 4 noninfected rabbits from blood samples obtained 15 min and 1, 2, 6, and 12 h after one injection of VAN (Sandoz) at 60 mg/kg. VAN concentrations were measured with a fluorescence polarization immunoassay (AxSym; Abbott Laboratories, IL). The quantification limit was 2.0 μ g/ml, and the interday variation coefficient was <7% for all standards.

Data analysis. The bacterial titers in the aortic valve vegetations and spleen from each rabbit were expressed as log₁₀ CFU per gram of tissue. Cultures yielding no growth after incubation for 48 h at 37°C were scored as sterile and assigned a value of 2.7 log₁₀ CFU, the limit of detection with this method (12). All pairwise comparisons of titers between treatment groups were tested for statistical significance using a general linear regression model, with the robust sandwich estimator for the covariance matrix estimate. We used Tukey's multiple-comparison procedure to ensure that the overall type 1 error remained below 0.05. A sensitivity analysis using a nonparametric Kruskal-Wallis test was performed, with Bonferroni correction to take into account the multiple comparisons. We compared rates of sterilization between treatment groups using Fisher's exact test and Bonferroni correction methods to estimate adjusted *P* values. Analyses were performed using R Development Core Team software (13) and the multcomp software package (14).

RESULTS

In vitro antibiotic susceptibility testing. The vancomycin MIC against MRSA COL was 1.5 μ g/ml.

In vitro bactericidal effect. In time-kill curves obtained at $10\times$ VAN MIC (i.e., 15 μ g/ml), all generic products exerted bactericidal activity as defined by at least a 3-log₁₀-unit decrease compared with the control. No significant differences were found between the six generics tested (Fig. 1).

Serum vancomycin concentrations in rabbits. In infected animals, following the 8th injection of VAN, there were no significant differences between groups in terms of peak and trough serum concentrations for all VAN generics tested, except that the VAN generic product from American Pharmaceutical Products (APP) yielded a lower mean peak concentration (*P* = 0.001) and a higher mean trough concentration (*P* = 0.05) than other compounds (Table 2). The mean VAN AUC₀₋₁₂ in the 4 noninfected rabbits treated with VAN at 60 mg/kg b.i.d. was 296.7 $\pm$ 34 μ g/ml, which translates into a mean AUC₀₋₂₄/MIC ratio of 396 with the MRSA COL strain.

Therapeutic studies. All control animals infected with MRSA COL had positive blood, spleen, and vegetation cultures, with a mean bacterial count of 5.4 ± 1.4 log₁₀ CFU/g in spleens and 9.1 ± 0.8 log₁₀ CFU/g in vegetations and median values (interquartile range) of 5.4 log₁₀ CFU/g (4.5 to 6.5) in spleens and 9.4 log₁₀ CFU/g (8.6 to 9.8) in vegetations (Fig. 2). In comparison to untreated rabbits, each group of VAN-treated rabbits had lower titers of the organism in vegetations (*P* < 0.02 for each comparison) and in spleens (*P* < 0.005 for each comparison). Face-to-face comparisons between treatment groups found no significant differences in terms of organism titers in vegetations (Fig. 3) and in spleens (Fig. 4). In comparison to untreated controls, each group achieved a higher proportion of spleen sterilization (*P* < 0.001 for each comparison), but no significant differences were observed in terms of vegetation sterilization. There were no significant differ-

FIG 1 Time-kill curve studies. Vancomycin concentrations were equivalent to $10\times$ MIC (i.e., $15\text{ }\mu\text{g/ml}$). After 0, 3, 6, and 24 h of incubation in a shaking water bath at 37°C , serial dilutions of 0.1-ml samples were subcultured onto Mueller-Hinton agar plates and incubated at 37°C for 24 h before CFU were counted.

ences between proportions of spleens and vegetations sterilized in each group.

DISCUSSION

We found no significant differences in the levels of *in vitro* and *in vivo* bactericidal activity for the six generic products of VAN evaluated in the treatment of MRSA experimental endocarditis in rabbits in this study in terms of organisms titers in cardiac vegetations and in the spleens after 4 days of intravenous treatment. None of the generic VAN products evaluated could achieve a 100% proportion of vegetation sterilization after 4 days of VAN treatment, but this is in accordance with previous studies of VAN in the rabbit endocarditis model, including those performed with the

innovator of VAN (15, 16). These data do not support recent results obtained in the neutropenic mouse thigh infection model, where most generic products of VAN failed to achieve the expected bactericidal activity, with very significant disparity from one product to another (6). Of note, this *in vivo* failure of VAN generics in the neutropenic mouse model was observed even though their *in vitro* antibacterial effects determined by minimal inhibitory or bactericidal concentrations and time-kill curves were indistinguishable from those of the innovator, as were their serum pharmacokinetic parameters. The authors postulated that the suboptimal efficacy of generic VAN products observed *in vivo*, compared to the innovator, could be related to an excess of impurities. More specifically, crystalline degradation product (CDP-1)

TABLE 2 Concentrations in serum of six generic vancomycin products from blood samples obtained 45 min (peak) and 12 h (trough) after the last injection in treated rabbits

Sample	Mean serum vancomycin concn $\pm$ SD ($\mu\text{g/ml}$)					
	T1 (Mylan)	T2 (Sandoz)	T3 (TEVA)	T4 (APP)	T5 (Akorn)	T6 (Hospira)
Peak	39.2 ± 7.3	37.4 ± 5.7	45.9 ± 7.3	35.5 ± 3.2	42.4 ± 11.9	36.8 ± 11.7
Trough	3.8 ± 1.8	3.5 ± 2.9	4.8 ± 1.6	9.2 ± 3.3	6.9 ± 4.9	2.3 ± 1.8

FIG 2 Organism titers ($\log_{10}$ CFU/g) in vegetations for untreated (T0) and antibiotic-treated (T1 to T6) rabbits. For each group (T0 to T6), individual data for each rabbit are represented by a dot, and the median is represented by a horizontal bar. Means (and standard deviations [sd]) and the proportion of sterile vegetations are indicated below the diagram. T0, untreated rabbits; T1, vancomycin generic, Mylan; T2, vancomycin generic, Sandoz; T3, vancomycin generic, Teva; T4, vancomycin generic, APP; T5, vancomycin generic, Akorn Strides; T6, vancomycin generic, Hospira.

would exert an antagonistic effect on factor B, the compound responsible for the antibacterial effect of VAN (6). In response to those concerns, the U.S. Food and Drug Administration (FDA) investigated factor B and CDP-1 quantities in all VAN products

FIG 3 Differences between treatment groups in terms of organism titers in vegetations ($\log_{10}$ CFU/g). Dots are mean differences between treatment groups, and parentheses are the upper and lower bounds of their 95% confidence interval. Analysis was performed using the Tukey method, taking into account multiple comparisons, with corrected α risk. Differences between two groups are statistically significant if the confidence interval does not include the zero value. T0, untreated rabbits; T1, vancomycin generic, Mylan; T2, vancomycin generic, Sandoz; T3, vancomycin generic, Teva; T4, vancomycin generic, APP; T5, vancomycin generic, Akorn Strides; T6, vancomycin generic, Hospira.

FIG 4 Differences between treatment groups in terms of organism titers in spleens ($\log_{10}$ CFU/g). Analysis was performed using the Tukey method, taking into account multiple comparisons, with corrected α risk. Differences between two groups are statistically significant if the confidence interval does not include the zero value. T0, untreated rabbits; T1, vancomycin generic, Mylan; T2, vancomycin generic, Sandoz; T3, vancomycin generic, Teva; T4, vancomycin generic, APP; T5, vancomycin generic, Akorn Strides; T6, vancomycin generic, Hospira.

marketed in the United States (18, 19), including four generics evaluated in the current study (i.e., Sandoz, Hospira, APP, and Akorn Strides) and two generics studied by Vesga et al. (6). All of them met the quality specifications outlined in the U.S. pharmacopeia of not more than 9% of any one impurity, with CDP-1 being less than 2% (wt/wt) in all cases (18, 19).

The rabbit model of experimental endocarditis was among the first animal models to be validated and remains the gold standard to evaluate the bactericidal activity of antimicrobial therapy almost 40 years after the first descriptions (16). Its assets include its reproducibility, with little interobserver or intraobserver variability, and its power to precisely discriminate antibacterial regimens as a function of their bactericidal effects (10, 20). This stringent model was used in the validation of most regimens currently recommended for the treatment of infective endocarditis in humans (21, 22) and contributed to the evaluation of various antistaphylococcal drugs (12, 23, 24).

Our study has limitations. First, we could not compare generic VAN products with the innovator, as Eli-Lilly halted its production in 2005 and no remaining stocks are currently available (O. Vesga, personal communication). However, the generic VAN products that we evaluated were carefully selected, and all are approved for use in humans by the National Medicine Agencies in North America and/or Western Europe. One of them, the generic VAN produced by Hospira in Spain, was classified among the “effective” VAN generics in the landmark study performed in the neutropenic mouse thigh infection model, with *in vivo* bactericidal activity similar to that of the innovator (6). Contrary to what was observed in the mouse model, we found no significant differences in terms of bactericidal activity between the six VAN generics evaluated in the model of rabbit MRSA endocarditis. This is in agreement with (i) *in vitro* comparative studies, including time-

kill curves, as performed by us and others; (ii) population pharmacokinetics of various generic VAN products in mice (6) and in rabbits; and (iii) analysis of the qualities and potencies of the six generic VAN products recently tested (18, 19). The second limitation of our study lies in the 60-mg/kg b.i.d. dose of VAN evaluated in the rabbits, which achieved mean peak serum concentrations above 35 µg/ml and trough serum concentrations below 10 µg/ml in all treatment groups. Although these pharmacokinetic parameters are in accordance with past recommendations (25), more recent guidelines recommend targeting trough serum concentrations of VAN between 15 and 20 µg/ml for the treatment of severe infectious diseases in humans (26). The mean AUC_{0-12} was 296.7 ± 34 µg/ml in rabbits receiving a regimen of 60 mg/kg b.i.d., which translates into an AUC_{0-24}/MIC ratio of 396 with the MRSA COL strain. This is marginally below the target of ≥ 400 that has been recommended for clinical effectiveness (26). However, the optimal VAN pharmacokinetic target is still a matter of controversy. In addition, the use of suboptimal VAN concentrations in the rabbit model of MRSA endocarditis, associated with a high inoculum in difficult-to-reach sanctuaries (i.e., vegetations [17]), could be considered the perfect experimental setting to identify suboptimal drugs in terms of sterilization rates or the risk for selection of resistant subpopulations during treatment. The third limitation of our study is the sample size. The differences we observed between the generic Hospira and APP products in terms of organism titers in vegetations (median, 2.5 versus 6.6 CFU/g) or the proportion of sterile vegetations (70% versus 20%) were not statistically significant, but one could argue that significance could be reached with a higher number of animals per group. Ten rabbits were evaluated for each VAN generic product, a typical sample size for experimental studies designed to detect *in vivo* differences in antibiotic efficacies. Indeed, the suboptimal bactericidal effect of linezolid (12, 23) or tigecycline (24) for the treatment of human endocarditis was detected in the same experimental model with less than 10 rabbits per treatment arm. As noninferiority studies would require hundreds of rabbits, they are not performed with this discriminating experimental model, close to human infection, due to practical and ethical considerations. It should be noticed that in the Vesga et al. study, significant differences between the *in vivo* bactericidal activities of different VAN generic products were observed with even smaller sample sizes.

The current controversy over the equivalence of generic drugs is of paramount importance for at least two reasons: (i) the issue extends to many other therapeutic classes, including antiepileptic (27) and cardiovascular (28) drugs; (ii) the volume of generic drug use surpasses that of branded drugs and is continuously increasing, accounting for two-thirds of the worldwide consumption of antibiotics in 2010 (IMS Health, Falls Church, VA). The promotion of generic drug use aims to decrease the cost of drugs all over the world. It was one of the most important factors behind the dramatic increase in the number of HIV-infected patients who have access to effective combinations of antiretroviral agents in developing countries. However, these economic considerations should not occur at the price of lower quality of care for patients, including the use of less effective antibacterial agents. Pioneering work performed by Vesga et al. in the evaluation of the activities of various generic antimicrobial drugs in their experimental model of neutropenic mice is to be commended (29), as it provided stimulating data and paved the way for additional investigations, including by the FDA (18, 19). Our study does not support the

findings of Vesga et al. We found no significant differences in the levels of bactericidal activity in the gold standard model of experimental endocarditis in rabbits for six generic VAN products currently used in humans in Europe and America. Although recently suggested by some experts (9), and in the media, the refinement of the marketing authorization process for injectable anti-infective generic drugs appears premature at this stage.

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