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Comparative Potencies of Contemporary Generic Vancomycin Lots; *In-vitro* Assay Results from Nine Products and a Reference Reagent-Grade Sample

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AMENDED ABSTRACT

Background: Numerous studies of generic vancomycin (GV) lots have emerged since the 1980's, casting some doubt on product quality. Publications question the *in-vivo* activity, even when concurrent *in-vitro* and chemical assays meet regulatory guidelines. This study assessed contemporary (2011) lots of GV by an *in-vitro* assay capable of measuring small variations from target-benchmark (BM) activity.

Methods: Nine GV lots (Hospira [6 lots; 0.5 or 1.0g vials], Akorn [1 lot; 1.0g vial], APP [2 lots; 1.0g vials]) were obtained from local USA distributors; each having expiration dates ranging from 11/2011 to 04/2013. A reagent-grade lot (Sigma lot 080M1341V) was tested as BM component due to the inability to purchase branded product vials (Vancocin®, Eli Lilly) in the USA. The previously published method of Jones et al. (2008) was utilized applying 4 Gram-positive assay strains.

Results: All lots of GV did not vary significantly from the BM when testing the 3 *S. aureus* (wild-type 4B25, ATCC 25923 and 29213) and *E. faecalis* (ATCC 29212) strains. These MIC endpoints were read at 18 h incubation and Hospira lots averaged +3.5% potency (range, -3% to +8%), Akorn at 0% and APP at 0% variance, e.g. acceptable performance (see Table 2). Note the between lot variation was only 11% and between manufacturer range was <4% of BM target potency.

Conclusions: Using a validated, precise multi-organism assay, current GV lots from 3 manufacturers marketing in the USA showed minimal activity variations from a selected BM lot. Branded product remains unavailable, not allowing direct comparisons to GV products used in USA hospitals. Generic antimicrobial products, in general, should be regularly monitored for potency, chemical purity and *in-vivo* activity.

INTRODUCTION

Generic vancomycin products have been available in the United States (USA) for over 30 years and Clinical and Laboratory Standards Institute (CLSI) susceptibility testing methods have been used to assess the quality of these products (Lederle and Lyphomed) dating from 1987. Generally, the quality of USA-Food and Drug Administration (FDA)-approved generic products has been comparable to those of branded agent; however, concerns have been voiced by numerous investigators about generic vancomycin lots used outside of the USA. Furthermore, our experience with non-USA generic lots of piperacillin/tazobactam documents significant trends toward reduced potencies (61 lots from 33 manufacturers). In contrast, USA-FDA-approved lots of generic meropenem have been equivalent to branded Merrem® (AstraZeneca) by our *in-vitro* assay methods.

Recently, several investigators in Colombia and Japan have shared study results that question generic vancomycin quality when determining activity with bioassays, *in-vivo* animal models and in human clinical cases. The objectives of this study were two-fold: 1.) to expand the quality assurance evaluation of "nonbranded" generics to vancomycin lots (now including meropenem and piperacillin/tazobactam) using our incremental MIC antimicrobial assay method as previously described (Jones et al., 2008), and 2.) to compare nine contemporary samples of generic vancomycin available in the USA to a reference analytical standard.

MATERIALS AND METHODS

Assay method and lots: Well-characterized Gram-positive control strains were used to assay vancomycin activity, three having a reference MIC dilution or zone diameter end-point specified by the CLSI (2012) quality control tables (range): *S. aureus* ATCC 29213 (0.5 - 2 µg/ml), *S. aureus* ATCC 25923 (17 - 21 mm) and *Enterococcus faecalis* ATCC 29212 (1 - 4 µg/ml). An additional wildtype (WT) MRSA was selected exhibiting a modal MIC at 1 µg/ml. These MIC values were determined via a $\log_2$ dilution scale from unity (1), e.g. 0.25, 0.5, 1, 2, 4, 8, 16 etc. All strains were tested in triplicate on the same day from fresh stock solutions derived from generic and the reference analytical vancomycin lot (RVL) and the lowest reproducible MIC result was applied to calculations of product lot potency compared to RVL values.

The lots tested are listed in Table 1, each obtained directly from the manufacturer (Sigma Chemical, St. Louis, Missouri, USA) or via domestic pharmaceutical distributors (all generic products; 9 lots from 3 manufacturers).

Antimicrobial susceptibility method: In the reference laboratory (JMI Laboratories, North Liberty, Iowa, USA) the samples were tested by the incremental MIC assay method of Jones et al. (2008) in a broth microdilution test performed as described by the CLSI documents M07-A9 and M100-S22. Broth microdilution tests used reconstituted product vial contents as the stock solution to prepare reference MIC panels having expanded doubling dilution schedules over the range of 32 to 0.094 µg/ml. The complete dilution schedule was 16,14,12,10, 8, 7, 6, 5, 4, 3.5, 3, 2.5, 2, 1.75, 1.5, 1.25, 1, 0.875, 0.75, 0.625, 0.5, 0.438, 0.375, 0.313, 0.25, 0.219, 0.188, 0.156, 0.125, 0.109 and 0.094 plus a growth control.

RESULTS

- Due to lack of branded vancomycin availability, a reagent-grade RVL (Sigma Chemical) was utilized and compared by assay to nine generic products (three manufacturers; 1-6 lots per product), see Table 1.
- Reference or RVL and generic lot reproducibility in the assay system was quite high (one or two applied dilution steps; Table 2 and Figure 1).
- Direct comparisons of generic vancomycin (GV) lot potencies showed very slight differences across the four utilized assay organisms (GV/RVL as a %):
  - SA 29213 (100.0%)
  - SA 25923 (101.6%)
  - WT-MRSA (90.8%)
  - EF 29212 (98.4%)
  - Overall (97.7%; e.g. - 2.3%; Table 2)
- Only three assay results among GV and RVL determination differed between lots, thus being declared not significant.

Table 1. List of assayed samples of generic and reference vancomycin.

Reference lot (source and lot number [expiration date])

- Sigma Chemical, 080M1341V (6/2013)

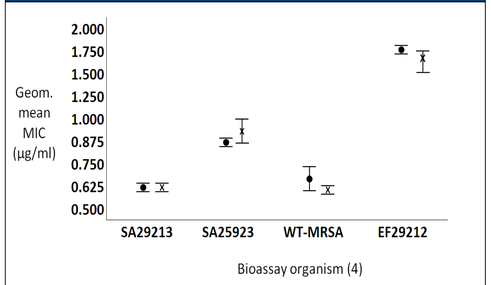
Generic lots (source and lot number [expiration dates])

- Akorn, 1.0 gram 7600462 (2/2013)
- APP, 1.0 gram 205207 (11/2011)
- APP, 1.0 gram 205234 (11/2011)
- Hospira, 0.5 gram 822528E04 (1/2011)
- Hospira, 1.0 gram 91165DD (1/2012)
- Hospira, 1.0 gram 95188E02 (11/2012)
- Hospira, 1.0 gram 011898E02 (1/2013)
- Hospira, 0.5 gram 022748E02 (2/2013)
- Hospira, 0.5 gram 044068E02 (4/2013)

Table 2. Replicate vancomycin assay MIC results (18 hours) for the reference and generic lots of vancomycin (10 total lots from four manufacturers).

	MIC in µg/ml by assay strain			
Lots	SA29213	SA25923	WT-MRSA	EF29212
Generic lots MICs (occurrences)	0.625 (9)	0.875 (8),1.000 (1)	0.625 (9)	1.500 (1), 1.750 (8)
Geometric mean	0.625	0.889	0.625	1.722
Reference MICs (occurrences)	0.625 (2)	0.875 (2)	0.625 (1), 0.750 (1)	1.750 (2)
Geometric mean	0.625	0.875	0.688	1.750

Figure 1. Geometric mean and variations in assay results for the reference lot (●) and nine generic lots (x) produced by three different manufacturers.



CONCLUSIONS

- Microbiologic activity of GV intravenous lots currently being marketed in the USA do not significantly differ from each other or from the RVL (Sigma Chemical).
- These results coupled with *in-vivo* bioavailability analysis and chemical assays appears to confirm the quality of the GV products (Akorn, APP, Hospira; Table 1) as approved by the USA-FDA.

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