More Potency Assay Results for EX-USA Generic Piperacillin/Tazobactam Lots and Initial Meropenem Generic Lots Marketed in the USA

P1413
ECCMID 2012

RN JONES, HS SADER, AA WATTERS, GJ MOET, RK FLAMM, DJ FARRELL
JMI Laboratories, North Liberty, Iowa, USA

JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

Abstract

Objective: To further assess piperacillin/tazobactam (P/T) generic lots in EX-USA nations and to initiate screening of meropenem (MER) generic lots recently (2011) marketed in the USA. P/T potency results expand prior experience reported in 2008 and 2009, performed by a precise, incremental MIC assay as published by Jones et al, (2008).

Methods: An additional 15 P/T generic lots (8 manufacturers; marketed in India, Chile, United Kingdom, and Sweden) were analyzed as part of an ongoing worldwide (EX-USA) screen that now includes results from 61 generic product lots (through 12/2010). Each lot was directly compared to a reference branded (Zosyn; Pfizer) lot or RBL using a previously described and validated assay method. MER lots (Hospira and Sandoz) from the USA were also tested and compared to a Merrem reference branded lot (TM0052; expirations of lots ranged from 06/2012-02/2013).

Results: The results (in 2010) of 15 P/T generic lots supplement reports of 46 other lots tested from EX-USA nations published in 2008 and 2009. Vials ranged from 2.25-4.5 gm each and all were tested within labeled expiration dates. Orchid (3 lots), Aurobindo (1 lot), Libra (1 lot), Wockhardt (2 lots), Hospira (2 lots), Sandoz (2 lots), Fresenius-Kabi (2 lots) and Stragen (2 lots) generic products were assayed. Variations compared to P/T RBL were -23% to +3% (average, -10%; prior 46 lot experience was -16%). USA MER generic lots (Hospira [4 lots], Sandoz [2 lots]) exhibited potencies equal to Merrem RBL, without any significant variation, see Table.

Conclusions: P/T generic lots marketed outside of the USA continue to demonstrate sub-optimal activity averaging 10 to 16% less activity when compared to the RBLs. Some lots, however, show comparable or acceptable activity. MER lots, FDA-approved for use in USA, exhibited equal activity compared to Merrem via this validated in-vitro assay method. Hospital formulary practices should consider these documented differences between lots as well as between generic and branded products when making therapeutic choices.

Introduction

Piperacillin combined with the β-lactamase inhibitor tazobactam, as a parenteral broad-spectrum antimicrobial, was approved by the United States (USA) Food and Drug Administration in 1993. The introduction of piperacillin/tazobactam into the market was coupled with numerous clinical indications. Piperacillin/tazobactam has become a very widely used intravenous penicillin/β-lactamase inhibitor combination, generally delivered as an 8:1 ratio (4 g of piperacillin and 0.5 g of tazobactam every 6 h), directed by the product Package Insert (2007). Alternative dosing vials contain 2 or 3 g of piperacillin and with corresponding 0.25 or 0.375 g of tazobactam, respectively.

The original worldwide sponsor/developer of this product (Zosyn® or Tazocin®) was Wyeth (now Pfizer Inc.) Pharmaceuticals of Philadelphia, Pennsylvania, and the patent rights to produce and market this combination now vary geographically. Generic formulations containing piperacillin/tazobactam have been approved in several global markets but have been questioned as to their potencies and clinical efficiency when compared with the branded product (Jones et al., 2008 Moet et al., 2009; Ye et al., 2006).

Problems with generic formulations related to excessive impurities and subpotent activity performance in various monitoring systems have occurred among other β-lactam agents as well as among lots of azole antifungal agents and glycopeptides. Furthermore, the original sponsor's product (Zosyn®) has been reformulated using proprietary methods to maximize quality and establish more uniform potencies.

The objective of this study was two-fold: 1) to expand the quality assurance evaluation of "nonbranded" generic piperacillin/tazobactam lots (now numbering 61 lots from 33 manufacturers) using the incremental MIC antimicrobial assay method as previously described (Jones et al., 2008), and 2) to compare 5 samples of generic meropenem available in the USA to the branded product Merrem®, all tested in 2011.

Materials and Methods

Assay method and lots:
An updated analysis of piperacillin/tazobactam ex-USA generic formulations (see Figure 1, prior data) was performed on 15 additional lots (8 manufacturers; Table 1). In the reference laboratory (JMI Laboratories, North Liberty, Iowa, USA) those samples were tested by the incremental MIC assay method of Jones et al. (2008) in a broth microdilution test performed as described by the Clinical and Laboratory Standards Institute (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 0.188 mg/L. The complete dilution schedule was 32, 28, 24, 20, 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 and 0.188 mg/L and a growth control.

Four well-characterized strains were used to assay the piperacillin/tazobactam activity, each having a reference MIC dilution end points specified as CLSI quality control ranges: *Escherichia coli* ATCC 25922 at 1 to 4 mg/L, *E. coli* ATCC 35218 at 0.5 to 2 mg/L, *Pseudomonas aeruginosa* ATCC 27853 at 1 to 8 mg/L, and *Staphylococcus aureus* ATCC 29213 at 0.25 to 2 mg/L. All strains were tested in triplicate on the same day from fresh stock solutions, and the lowest reproducible MIC value was applied to calculations of product lot potency compared with the Zosyn® (Pfizer) contemporary reference branded lot (RBL) control. The same assay method was applied to meropenem using four strains: *P. aeruginosa* ATCC 27853 and three clinical isolates. The tested generic products of meropenem were marketed by Hospira (3 lots) and Sandoz (2 lots); see Table 2.

Results

- Prior reports for generic piperacillin/tazobactam lots marketed outside of the USA showed (Figure 1):
  - Initial report of 23 lots averaged 16% less potent than RBL
  - Second report of 23 additional lots averaged 15% less potent than RBL
  - Branded Zosyn® lots were only 6% less compared to the RBL in a reproducibility experiment.
- This current expanded study of 15 more piperacillin/tazobactam lots (includes 4 unique producers) from 8 manufacturers showed a potency compared to the RBL ranging from +3% to -23% (average, -10%).
- USA meropenem generic lots (Hospira [4 lots] and Sandoz [2 lots]) achieved absolute parity to the RBL across all assayed products and organisms.
- This assay technique has been used successfully to make local hospital formulary additions of generic products in Europe (Sutter, Frei and Widmer; 2011).

Table 1. Potencies of 15 generic lots of piperacillin/tazobactam tested against a reference branded lot (Zosyn®; Pfizer/Wyeth 066871).

Manufacturer (lot. no.)	Vial strength	Expiration date	Country of origin	Variation (%)
Orchid (B059003)	4.5gm	6/2011	India	-10
Orchid (B059004)	4.5gm	6/2011	India	-7
Orchid (B059005)	4.5gm	7/2011	India	-2[a]
Aurobindo (AZNPB9005)	4.5gm	4/2011	Chile	-22
Libra (119092)	4.5gm	7/2011	Chile	-19
Wockhardt (C026)	4.5gm	4/2012	United Kingdom	-10
Wockhardt (C001)	2.25gm	3/2012	United Kingdom	-4
Hospira (B028009Z)	4.5gm	7/2010	United Kingdom	-17
Hospira (B018003W)	2.25gm	7/2010	United Kingdom	-7
Sandoz (AJ4598)	4.5gm	7/2011	United Kingdom	-23
Sandoz (AJ4542)	2.25gm	7/2011	United Kingdom	+3
Fresenius-Kabi (0005701)	4.5gm	5/2011	Sweden	-16
Fresenius-Kabi (18C0617)	4.5gm	7/2011	Sweden	-1
Stragen (1PT0803S)	2.25gm	10/2010	Sweden	-6
Stragen (1PT0909S)	4.5gm	12/2010	Sweden	-3

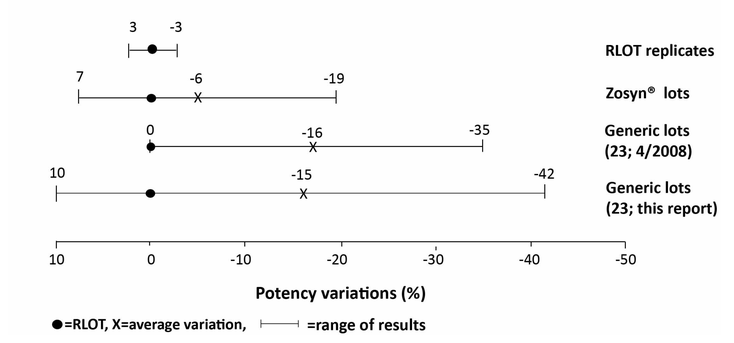
a. Average of two assays.

Table 2. Meropenem assay (MIC) results for tested organisms using branded (Merrem®) and five generic lots marketed in the USA.[a]

Meropenem sample (expires)	Replicate MIC (mg/L) for *P. aeruginosa* ATCC 27853	*P. aeruginosa* 4-48716A	*E. cloacae* 106-49157A	*S. aureus* 104-37827A
Merrem TM0052 (06/2012)[b]	0.313	0.156	0.045/0.038[c]	0.045
Hospira 609A029 (06/2012)	0.313	0.156	0.045	0.045
Hospira 609A013 (12/2012)	0.313	0.156	0.038	0.045
Hospira 609A020 (12/2012)	0.313	0.156	0.038	0.045
Sandoz CA0710027A (04/2012)	0.313	0.156	0.038	0.045
Sandoz BN1589 (02/2013)	0.313	0.156	0.038	0.045
Variation (%)[b]	(0.0)	(0.0)	(0.0)	(0.0)

a. Triplicate testing of four assay strains by methods described earlier [Jones et al. 2008, Moet et al., 2010 and Sutter et al., 2011]. Vial strength was 0.5 or 1.0 gram for each product.
b. Branded lot used as benchmark for variation calculations.
c. Results from two separate triplicate assay determinations.

Figure 1. Extent of potency variations among four groups of experiments with piperacillin/tazobactam intravenous injection lots from Moet et al (2009), DMID 65:319-322.



Conclusions

- Ex-USA generic piperacillin/tazobactam lots generally remain subpotent (-10 to -16%, assayed over three reports of 61 lots) compared to branded product (Zosyn®) using a simple, 4 organism reproducible in vitro assay.
- In contrast, USA generic lots of meropenem (Hospira and Sandoz) were acceptable by this in vitro assay method.
- Some generic antimicrobials continue to be variable and suboptimal in the inhibitory activity demonstrated by this assay method. Hospitals in all parts of the world should be cautious of generic products until qualified by regulators and/or local microbiological/chemical testing.

Acknowledgment

The initial assays reported by Jones et al (2008) and Moet et al (2009) were funded by Pfizer (Wyeth) Inc. These presented results were funded by the co-authors and JMI Laboratories; and the co-authors are without conflicts of interest.

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