A-079

Worldwide Generic Piperacillin/Tazobactam (P/T) Comparison to Branded Product: A Contemporary Assessment of 31 Intravenous Formulations

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ASM 2008
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AMENDED ABSTRACT

Background: P/T (Zosyn®, Wyeth) is a widely used ß-lactamase inhibitor combination, but generic formulations were recently introduced into several global markets that were stated to possess bioequivalence. The Zosyn® brand was also reformulated using proprietary methods to enhance antimicrobial quality.

Methods: The generic P/T activity was assessed by disk diffusion and MIC assays for antimicrobial potency against 4 assay organisms (P/T MICs, 1-4 µg/ml), compared to branded product. Thirty-one (28 lots) generic P/T products were from Brazil (4 lots), Greece (3), India (5), Mexico (1), Philippines (10), Portugal (1), Taiwan (2), China (2), Jordan (1) and Spain (2). CLSI susceptibility testing utilized reconstituted vial contents when preparing panels with 20 dilutions between 0.5-8 µg/ml. Each strain was tested and the lowest triplicate MIC was used to calculate lot potency compared to the control (Zosyn®).

Results: The branded formulation consistently produced the lowest MIC results (range, 1.25-3.5 µg/ml; Table) and generic products had MIC results that were consistently elevated, indicating reduced product vial activity varying from -4 to -35% (ave. -16%; only Orchid Piptamate from India was comparable). Greatest differences were observed with Tazidron, Novafarma and Cellofarm (-27%) and Vigocid (-35%). Tazobactam effect was diminished using *Acinetobacter* and ATCC 35118 control strains. A second sampling of 3 lots exhibited consistent low activity that varied from -3 to -20%, demonstrating reproducibility of the MIC-based assay. Within and between lot variations for Zosyn® was acceptably low.

	ATCC Assay Organism MICs (µg/ml)				
Product (lot no.)	25922	35218	27853	29213	% variation
Zosyn control (B75011)	2.0	3.5	2.5	1.25	NA
Novafarma (0760076)[1]	2.5	5.0	3.0	1.5	-27
Cellofarm (7100789)[1]	2.5	5.0	3.0	1.5	-27
Eurofarma (121609C)[1]	2.0	4.0	2.5	1.25	-4
Eurofarma (117968B)[1]	2.0	5.0	2.5	1.25	-11
Kendrick (6JB030)[2]	2.0	4.0	2.5	1.25	-4

1. Brazil
2. Mexico

Conclusions: Activities of generic intravenous P/T products can significantly vary as determined by our incremental MIC assay system. Labeled activity was highest for the branded product and nearly all 31 sampled (19 manufacturers) lots had decreased potencies (-16% overall). Hospital formularies should be warned that using generic products without well-documented equivalences by chemical parameters, biologic tests related to in vivo bioavailability or direct in vitro potency assays, could lead to poor clinical responses.

INTRODUCTION

The combination of the ß-lactamase inhibitor tazobactam with piperacillin was approved by the United States Food and Drug Administration (USA-FDA) in 1993. The original worldwide sponsor/developer of this product (trade name Zosyn® or Tazocin®) was Wyeth Pharmaceuticals (Philadelphia, PA), while the patent rights to this combination varies geographically. Piperacillin/tazobactam is a widely used intravenous penicillin/ß-lactamase inhibitor combination delivered as a 8:1 ratio, usually 4 grams of piperacillin and 0.5 grams of tazobactam every six to eight hours. Alternative dosing vials may contain 2 or 3 grams of piperacillin and 0.25 or 0.375 grams of tazobactam, respectively.

The introduction of piperacillin/tazobactam (Zosyn®) into the market was to treat 1) nosocomial pneumonia and community-acquired pneumonia (moderate severity only caused by ß-lactamase producing *H. influenzae*), 2) appendicitis (complicated by rupture or abscess) or peritonitis, 3) uncomplicated and complicated skin and skin structure infections, and 4) postpartum endometritis or pelvic inflammatory disease.

Recently, generic formulations containing piperacillin/tazobactam have been introduced into various global markets. There have been questions about bioequivalence of these generics when compared to the branded product. Also, the original sponsor's product (Zosyn®) has been reformulated to provide improved quality using proprietary techniques.

The objective of the present study was to evaluate "non-branded" generic formulation samples of piperacillin/tazobactam (31 samples from 28 lots) for antimicrobial potency against four selected assay organisms (replicate testing), and directly compare them to the current Zosyn® formulation purchased from a drug wholesale distributor in the United States.

MATERIALS AND METHODS

Antimicrobial compounds: "Non-branded" generic formulation samples of piperacillin/tazobactam for antimicrobial potency against four selected assay organisms (replicate testing) were directly compared to the current Zosyn® formulation purchased from a drug distributor in the USA. Generic piperacillin/tazobactam products (31 samples from 28 lots) were forwarded to JMI Laboratories (North Liberty, Iowa, USA) from Brazil (four samples), China (two), Greece (three), India (five), Jordan (one), Mexico (one), Philippines (10), Portugal (one), Spain (two), and Taiwan (two).

Susceptibility testing: Reference susceptibility testing methods were performed as described by the Clinical and Laboratory Standards Institute (CLSI) documents M2-A9, M7-A7 and M100-S18. Broth microdilution tests used reconstituted product sample vial contents as the stock solution to prepare panels having expanded $\log_2$ dilution schedules over the MIC range of 32 to 0.188 µg/ml. 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, 0.188 µg/ml and a growth control. Four strains (Table 2) were utilized to assay the piperacillin/tazobactam activity, each having a reference MIC dilution specified by the CLSI quality control ranges; *E. coli* ATCC 25922 at 1 to 4 µg/ml, *E. coli* ATCC 35218 at 0.5 to 2 µg/ml, *P. aeruginosa* ATCC 27853 at 1 to 8 µg/ml and *S. aureus* ATCC 29213 at 0.25 to 2 µg/ml. All strains were tested in triplicate on the same day from fresh stock solutions (six separate testing events) and the lowest reproducible MIC value was used for calculation of the product lot potency compared to the Zosyn® (Wyeth) contemporary product control (lot B75011).

Disk diffusion testing: The CLSI disk diffusion test was performed to compare commercially prepared 100/10-µg piperacillin/tazobactam disk (Becton-Dickinson [BBL], Sparks, MD) zone diameters to the zones of inhibition produced from vial contents of generic products diluted to produce a disk containing 100/12.5-µg (8:1 ratio). All disk diffusion tests were performed in triplicate and the modal zone of inhibition (in mm) was used for screening analysis to detect gross differences in product potencies. All strains were tested in triplicate on the same day from fresh stock solutions (six separate test events).

RESULTS

- Twenty-eight lots of generic intravenous piperacillin/tazobactam formulations were tested with multiple lots sampled from six manufacturers; Astral Phamaceuticals Industries (3), Meditrina Pharmaceuticals (2), STADA (2), YSS Laboratories (4), Zuventus (2) and Eurofarma (2); Table 1.
- No significant variations in zones of inhibition (≤1 mm) were observed between commercial disks (100/10 µg) and disks prepared from vial contents (100/12.5 µg); data not shown due to prior sensitivity of this method.

Table 1. Listing of Zosyn® and 28 lots of generic intravenous piperacillin/tazobactam screened.

				Dates[a]		
Manufacturer	Product name	Vial strength	Lot no.	Expiration	DOT	Country of origin
Wyeth	Zosyn®	3.375 grams	B75011	06/2008	Six dates	USA
Astral Pharmaceuticals Industries[b]	PIPTAZ™	2.25 grams	AUPM-601	10/2008	06/07/07	Philippines[c]
Astral Pharmaceuticals Industries[b]	PIPTAZ™	4.5 grams	AUPI-601	10/2008	06/07/07	Philippines[c]
Astral Pharmaceuticals Industries[b]	PIPTAZ™	4.5 grams	AUPI-701	03/2009	08/22/07	Philippines[c]
Aurobindo Pharma Limited[b]	Zobactin	4.5 grams	ZBNPB7048	07/2008	10/05/07	India
Cellofarm	Tazpen®	4.5 grams	7100789	01/2009	1/31/2008	Brazil
China Chemical & Pharmaceutical[b]	Pisutam	2.25 grams	58P713	08/2008	11/29/07	Taiwan
Demo S.A.	Tazorex	4.5 grams	0701172	08/2008	06/07/07	Greece
Eurofarma	Pip/Tazo	4.5 grams	121609C	09/2009	1/31/2008	Brazil
Eurofarma	Pip/Tazo	2.25 grams	117968B	08/2009	1/31/2008	Brazil
FARMA-APS[b]	Pip/Tazo	4.5 grams	A005	05/2009	08/23/07	Portugal
Shanghai Asia Pioneer Pharmaceuticals	Fengtailing	4.5 grams	070302	06/2009	11/29/07	China
Hikma	Prizma®	4.5 grams	A001	07/2009	11/29/07	Jordan
United Laboratories Zhuahi[b]	Pip/Tazo	4.5 grams	70808401	07/2009	11/29/07	China
Kendrick Laboratories	Tasovak	4.5 grams	6JB030	08/2008	1/31/2008	Mexico
Meditrina Pharmaceuticals[b]	Tazidron®	4.5 grams	07076	02/2009	08/22/07	Greece
Meditrina Pharmaceuticals[b]	Tazidron®	4.5 grams	07077	02/2009	08/22/07	Greece
Novafarma	Pip/Tazo	4.5 grams	0760076	12/2009	1/31/2008	Brazil
Orchid/Zeiss Pharmaceuticals[b]	Zopercin®	4.5 grams	1517018	04/2009	10/05/07	India
Orchid Healthcare[b]	Piptamate	4.5 grams	1517004	01/2009	08/23/07	India
STADA[b]	Pip/Tazo	4.5 grams	A001	02/2009	06/07/07	Spain
STADA[b]	Pip/Tazo	4.5 grams	A013	06/2009	10/05/07	Spain
YSS Laboratories[b]	Vigocid	2.25 grams	8001C	10/2008	06/07/07	Philippines[d]
YSS Laboratories[b]	Vigocid	4.5 grams	8002C	10/2008	08/23/07	Philippines[d]
YSS Laboratories[b]	Vigocid	4.5 grams	8003C	01/2009	08/23/07	Philippines[d]
YSS Laboratories[b]	Vigocid	2.25 grams	8004C	02/2009	08/23/07	Philippines[d]
Yung Shin[b]	Tapimycin	2.25 grams	TY12T039	05/2010	11/29/07	Taiwan
Zuventus[b]	Tazotum®	4.5 grams	GZC 07003	02/2009	10/05/07	India
Zuventus[b]	Tazotum®	4.5 grams	GZC 07001	01/2009	10/05/07	India

a. DOT =date of test; six dates.
b. From Jones et al. *Diagn Microbiol Infect Dis* 2008; 61: 76-79.
c. From Astral Pharmaceutical Industries (India) via United Laboratories, Inc. (Mandaluyong City).
d. From YSS Laboratories, Co., via The Cathay Drug Co. Inc. (Makati City).

- The MIC results for the 28 lots of generic piperacillin/tazobactam compounds tested against the four ATCC assay strains are listed in Table 2. The potency variation as compared to the Zosyn® control ranged from equivalent (Piptamate, Orchid Healthcare, India) to -35% (Vigocid, YSS Laboratories, Philippines).
- The average reduction in potency of the 28 generic lots of piperacillin/tazobactam was -16%. Only four lots demonstrated <10% reduced potency, 14 lots showed 10-20% reduced potency and nine lots had a reduced activity of >20%.
- Minor intra-lot variation for the branded Zosyn® lot was observed with the four assay strains (*E. coli* ATCC 25922, 1.75-2.5 µg/ml; *E. coli* ATCC 35218, 3.5-4.0 µg/ml; *P. aeruginosa* ATCC 27853, 2.0-3.5 µg/ml and *S. aureus* ATCC 29213, 1.0-1.25 µg/ml).

Table 2. Lowest reproducible, replicate MIC derived from the generic product vial (28 product lots, 19 manufacturers) compared to a randomly selected contemporary lot of Wyeth-produced piperacillin/tazobactam (Zosyn® [B75011]).

	Assay organism MIC (µg/ml):				
	E. coli		*P. aeruginosa*	*S. aureus*	
Manufacturer (lot no.)	ATCC 25922	ATCC 35218	ATCC 27853	ATCC 29213	Variation (%)[a]
Wyeth Control (B75011)	1.75-2.5[b]	3.5-4.0[c]	2.0-3.5[d]	1.0-1.25[e]	NA
Astral Pharmaceuticals Industries (AUPM-601)[f]	2.0-2.5	4.0-5.0	2.5	1.25	-22[g]
Astral Pharmaceuticals Industries (AUPI-601)[f]	1.75-2.0	4.0	2.5	1.25	-13[g]
Astral Pharmaceuticals Industries (AUPI-701)[f]	2.0	4.0	2.5	1.25	-20
YSS Laboratories (8001C)[f]	2.5	5.0	3.0	1.5	-35
YSS Laboratories (8002C)[f]	2.0-2.5	3.5-5.0	2.0-2.5	1.25	-13[g]
YSS Laboratories (8003C)[f]	2.0	3.5	2.5	1.25	-10
YSS Laboratories (8004C)[f]	1.75	3.5	2.5	1.25	-6
Meditrina Pharmaceuticals (07076)[f]	1.75	3.5	2.5	1.25	-13
Meditrina Pharmaceuticals (07077)[f]	2.0	5.0	2.5	1.25	-27
STADA (A001)[f]	2.5	5.0	2.5	1.25	-23
STADA (A013)[f]	2.5	4.0	3.5	1.5	-15
Zuventus (GZC 07003)[f]	2.5	5.0	3.0	1.25	-11
Zuventus (GZC 07001)[f]	2.5	5.0	3.0	1.5	-16
Zhuahi United Laboratories (70808401)[f]	2.5	5.0	2.5	1.25	-13
Shanghai Asia Pioneer Pharmaceuticals (070302)[f]	2.0	4.0	3.0	1.25	-5
Demo S.A. (0701172)[f]	2.5	5.0	2.5	1.25	-23
FARMA-APS (A005)[f]	2.0	3.5	2.5	1.25	-10
Aurobindo Pharma Limited (ZBNPB7048)[f]	2.5	5.0	3.0	1.25	-11
Orchid/Zeiss Pharmaceuticals (1517018)[f]	2.5	5.0	3.5	1.5	-21
Yung Shin (TY12T039)[f]	2.5	5.0	3.0	1.25	-18
China Chemical & Pharmaceuticals (58P713)[f]	2.5	4.0	3.0	1.5	-16
Hikma (A001)[f]	2.5	6.0	3.0	1.25	-24
Orchid Healthcare (1517004)[f]	1.75	3.5	2.0	1.25	EQ
Novafarma (0760076)	2.5	5.0	3.0	1.5	-27
Cellofarm (7100789)	2.5	5.0	3.0	1.5	-27
Eurofarma (121609C)	2.0	4.0	2.5	1.25	-4
Eurofarma (117968B)	2.0	5.0	2.5	1.25	-11
Kendrick Laboratories (6JB030)	2.0	4.0	2.5	1.25	-4

a. Overall % change (four assay organisms) compared to control potency, NA = not applicable (control) and EQ = equivalent.
b. CLSI control range at 1-4 µg/ml.
c. CLSI control range at 0.5-2 µg/ml, however this is an MIC produced using fixed 4 µg/ml of tazobactam not an 8:1 ratio which would be expected to be at least two-fold higher.
d. CLSI control range at 1-8 µg/ml.
e. CLSI control range at 0.25-2 µg/ml.
f. From Jones et al. *Diagn Microbiol Infect Dis* 2008; 61: 76-79.
g. Averages of replicate testing of these lots (AUPM-601, AUPI-601, 8002C).

CONCLUSIONS

- The 28 lots of generic intravenous piperacillin/tazobactam compounds from 19 manufacturers showed an average decreased potency of -16%.
- The use of discreet broth microdilution MIC susceptibility test values between the standard $\log_2$ test values was critical to determining the amount of potency loss for the tested generic products.
- The use of piperacillin/tazobactam antimicrobial product lots from some generic manufacturers to treat clinical infections could place patients at serious risk of poor outcome due to the under-dosing by 2-3 grams of the piperacillin component alone each day.
- Further investigations should address the level of particulate matter and by-products in generic piperacillin/tazobactam formulations, a problem observed before with other generic broad-spectrum ß-lactam agents.

ACKNOWLEDGEMENTS

This project was funded in part by an educational/research grant from Wyeth Pharmaceuticals (Collegeville, PA).

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