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Critical Evaluations of Generic Piperacillin/Tazobactam Compared to the Branded Product: A Worldwide Sampling of 26 Intravenous Formulations

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ABSTRACT

Objective: To evaluate generic P/T intravenous product activity by diffusion and MIC assays compared to branded product (Zosyn® or Tazocin®; Wyeth). P/T is a widely used penicillin/beta-lactamase inhibitor combination (8:1 ratio). Recently, generic formulations have been introduced into various global markets said to possess bioequivalence and the original brand was reformulated using proprietary methods to enhance quality.

Methods: We studied "non-branded" generic lots for antimicrobial potency against 4 assay organisms (triplicate testing; P/T MICs, 1-4 mg/L), and directly compared to current branded agent. Generic P/T products (26 samples from 23 lots) were from Greece (3 lots), India (5), Philippines (10), Portugal (1), Taiwan (2), China (2), Jordan (1) and Spain (2). CLSI susceptibility testing applied reconstituted product sample vial contents to prepare panels having 20 dilution steps between 0.5-8 mg/L. Each strain was tested and the lowest reproducible MIC value was used for calculating lot potency compared to control (Zosyn® lot B75011).

Results: All tests were performed on the same day from fresh stock solutions. 4 manufacturers (Astral, Meditrina, YSS and Zuventus) had 2 or more lots. The branded formulation consistently produced the lowest MIC results (range, 1.0-3.5 mg/L) and generic products had MIC results that were consistently elevated, indicating reduced activity varying from -3 to -35% (ave. -16%; only Orchid Piptamate was equal). Largest differences were observed with Zopercin (1517018; -21%), Tazidron (07077; -27%) and Vigocid (8001C; -35%), and the tazobactam effect also appeared diminished. A second sampling of 3 lots (PIPTAZ AUPM-601 and AUPI-601; Vigocid 8002C) exhibited consistently decreased activity that varied from -3 to -20%, demonstrating reproducibility of the MIC-based assay.

Table

Product (no. lots)	Assay organism MIC (mg/L)			
	E. coli (2)	*P. aeruginosa*	*S. aureus*	% variation
Zosyn control (1)	1.75-4.0	2.0-3.5	1.0-1.25	NA
STADA (2)	2.5-5.0	2.5-3.5	1.25-1.5	-15 to -23
Tazorex (1)	2.5-5.0	2.5	1.25	-23
Tazotum (2)	2.5-5.0	3.0	1.25-1.5	-11 to -16
Tazidron (2)	1.25-5.0	2.5	1.25	-13 to -27
Piptamate (1)	1.75-3.5	2.0	1.25	0

Conclusions: In vitro activities of various formulations of intravenous P/T products can vary significantly as assessed by this incremental MIC assay system when applying product vial content to reference dilution testing. Per-label activity was noted for the branded formulation and all but one generic lot (among 26 sampled from 15 manufacturers) had decreased potencies. Hospital formularies should be cautious when applying generic products without well-documented equivalence by chemical parameters, biologic tests related to in vivo bioavailability or clinical outcomes and direct in vitro potency assays.

INTRODUCTION

Piperacillin combined with the ß-lactamase inhibitor tazobactam, was developed by Wyeth Pharmaceuticals and approved in 1993 by the United States Food and Drug Administration (USA-FDA). The introduction of piperacillin/tazobactam (Zosyn®) into the market was for the following indications 1) to treat nosocomial pneumonia (moderate to severe), 2) community-acquired pneumonia (moderate severity only caused by ß-lactamase producing *H. influenzae*), 3) appendicitis (complicated by rupture or abscess) or peritonitis, 4) uncomplicated and complicated skin and skin structure infections, and 5) postpartum endometritis or pelvic inflammatory disease caused by ß-lactamase producing *E. coli*.

Piperacillin/tazobactam became a very widely used intravenous penicillin/ß-lactamase inhibitor combination delivered as an 8:1 ratio, usually 4 grams of piperacillin and 0.5 grams of tazobactam every six hours as directed by the package insert. Alternative dosing vials may contain 2 or 3 grams of piperacillin and 0.25 or 0.375 grams of tazobactam, respectively. The original worldwide sponsor/developer of this product (trade name Zosyn® or Tazocin®) was Wyeth Pharmaceuticals (Philadelphia, PA) and the patent rights to produce this combination varies geographically. Recently, generic formulations containing piperacillin/tazobactam have been introduced into various global markets, but have been questioned as to their bioequivalence when compared to the branded product. Also, the original sponsor's product (Zosyn®) has been reformulated to provide improved quality using proprietary techniques.

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 wholesale distributor in the USA. Generic piperacillin/tazobactam products (26 samples from 23 lots) were forwarded to JMI Laboratories (North Liberty, Iowa, USA) from China (two samples), Greece (three), India (five), Jordan (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) 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 incremental dilution schedules over the MIC 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, 0.188 mg/L 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 mg/L, *E. coli* ATCC 35218 at 0.5 to 2 mg/L, *P. aeruginosa* ATCC 27853 at 1 to 8 mg/L and *S. aureus* ATCC 29213 at 0.25 to 2 mg/L. All strains were tested in triplicate on the same day from fresh stock solutions (five 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.

RESULTS

- Twenty-three lots of generic intravenous piperacillin/tazobactam formulations were tested with multiple lots sampled from five manufacturers; Astral Phamaceuticals Industries (3), Meditrina Pharmaceuticals (2), STADA (2), YSS Laboratories Co., INC. (4) and Zuventus (2); Table 1.
- "Non-branded" disk diffusion and BMD MIC tests were from fresh stock solutions prepared on each of five testing days compared with a the Zosyn® product control.
- 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.
- The MIC test results for the 23 lots of generic piperacillin/tazobactam compounds against the four ATCC assay strains are listed in Table 2. The amount of potency variation as compared to the Zosyn® control ranged from equivalent (Piptamate, Orchid Healthcare, India) to -35% (Vigocid, YSS Laboratories Co., INC., Philippines).

Table 1. Listing of Zosyn® and 23 lots of generic intravenous piperacillin/tazobactam screened.

Manufacturer	Product name	Vial strength	Lot no.	Dates[a]		Country of origin
				Expiration	DOT	
Wyeth	Zosyn®	3.375 grams	B75011	06/2008	Five dates	USA
Astral Pharmaceuticals Industries	PIPTAZ™	2.25 grams	AUPM-601	10/2008	06/07/07	Philippines[b]
Astral Pharmaceuticals Industries	PIPTAZ™	4.5 grams	AUPI-601	10/2008	06/07/07	Philippines[b]
Astral Pharmaceuticals Industries	PIPTAZ™	4.5 grams	AUPI-701	03/2009	08/22/07	Philippines[b]
Aurobindo Pharma Limited	Zobactin	4.5 grams	ZBNPB7048	07/2008	10/05/07	India
China Chemical & Pharmaceutical Co., Ltd.	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
FARMA-APS	-	4.5 grams	A005	05/2009	08/23/07	Portugal
Shanghai Asia Pioneer Pharmaceuticals Co., Ltd.	Fengtailing	4.5 grams	070302	02/2009	11/29/07	China
Hikma	Prizma	4.5 grams	A001	07/2009	11/29/07	Jordan
United Laboratories Zhuhai	Pip/Tazo	4.5 grams	70808401	07/2009	11/29/07	China
Meditrina Pharmaceuticals	Tazidron®	4.5 grams	07076	02/2009	08/22/07	Greece
Meditrina Pharmaceuticals	Tazidron®	4.5 grams	07077	02/2009	08/22/07	Greece
Orchid/Zeiss Pharmaceuticals	Zopercin®	4.5 grams	1517018	04/2009	10/05/07	India
Orchid Healthcare	Piptamate	4.5 grams	1517004	01/2009	08/23/07	India
STADA	-	4.5 grams	A001	02/2009	06/07/07	Spain
STADA	-	4.5 grams	A013	06/2009	10/05/07	Spain
YSS Laboratories Co., INC.	Vigocid	2.25 grams	8001C	10/2008	06/07/07	Philippines[c]
YSS Laboratories Co., INC.	Vigocid	4.5 grams	8002C	10/2008	08/23/07	Philippines[c]
YSS Laboratories Co., INC.	Vigocid	4.5 grams	8003C	01/2009	08/23/07	Philippines[c]
YSS Laboratories Co., INC.	Vigocid	2.25 grams	8004C	02/2009	08/23/07	Philippines[c]
Yung Shin	Tapimycin	2.25 grams	TY12T039	05/2010	11/29/07	Taiwan
Zuventus	Tazotum®	4.5 grams	(GZC 07003)	02/2009	10/05/07	India
Zuventus	Tazotum®	4.5 grams	(GZC 07001)	01/2009	10/05/07	India

a. DOT =date of test; five dates.
b. From Astral Pharmaceutical Industries (India) via United Laboratories, Inc. (Mandaluyong City).
c. From YSS Laboratories, Co., via The Cathay Drug Co. Inc. (Makati City).

Table 2. Lowest reproducible, replicate MIC derived from the generic product vial (23 product lots, 15 manufacturers) compared to a randomly selected contemporary lot of Wyeth-produced piperacillin/tazobactam (Zosyn® [B75011]).

Product (lot no.)	Assay organism MIC (mg/L):				Variation (%)[a]
	E. coli		*P. aeruginosa*	*S. aureus*	
	ATCC 25922	ATCC 35218	ATCC 27853	ATCC 29213	
Zosyn® control	1.75-2.5[b]	3.5-4.0[c]	2.0-3.5[d]	1.0-1.25[e]	NA
PIPTAZ™ (AUPM-601)	2.0-2.5	4.0-5.0	2.5	1.25	-22[f]
PIPTAZ™ (AUPI-601)	1.75-2.0	4.0	2.5	1.25	-13[f]
PIPTAZ™ (AUPI-701)	2.0	4.0	2.5	1.25	-20
Vigocid (8001C)	2.5	5.0	3.0	1.5	-35
Vigocid (8002C)	2.0-2.5	3.5-5.0	2.0-2.5	1.25	-13[f]
Vigocid (8003C)	2.0	3.5	2.5	1.25	-10
Vigocid (8004C)	1.75	3.5	2.5	1.25	-6
Tazidron® (07076)	1.75	3.5	2.5	1.25	-13
Tazidron® (07077)	2.0	5.0	2.5	1.25	-27
STADA (A001)	2.5	5.0	2.5	1.25	-23
STADA (A013)	2.5	4.0	3.5	1.5	-15
Tazotum® (GZC 07003)	2.5	5.0	3.0	1.25	-11
Tazotum® (GZC 07001)	2.5	5.0	3.0	1.5	-16
Pip/Tazo (70808401)	2.5	5.0	2.5	1.25	-13
Fengtailing (070302)	2.0	4.0	3.0	1.25	-5
Tazorex (0701172)	2.5	5.0	2.5	1.25	-23
FARMA-APS (A005)	2.0	3.5	2.5	1.25	-10
Zobactin (ZBNPB7048)	2.5	5.0	3.0	1.25	-11
Zopercin® (1517018)	2.5	5.0	3.5	1.5	-21
Tapimycin (TY12T039)	2.5	5.0	3.0	1.25	-18
Pisutam (58P713)	2.5	4.0	3.0	1.5	-16
Prizma (A001)	2.5	6.0	3.0	1.25	-24
Piptamate (1517004)	1.75	3.5	2.0	1.25	EQ

a. Overall % change (four assay organisms) compared to control potency, NA = not applicable (control) and EQ = equivalent.
b. CLSI control range at 1-4 mg/L.
c. CLSI control range at 0.5-2 mg/L, 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 mg/L.
e. CLSI control range at 0.25-2 mg/L.
f. Averages of replicate testing of these lots (AUPM-601, AUPI-601, 8002C).

- The average reduction in potency of the 23 generic lots of piperacillin/tazobactam was -16%. Only three lots demonstrated <10% reduced potency, 13 lots showed 10-20% reduced potency and seven 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 mg/L; *E. coli* ATCC 35218, 3.5-4.0 mg/L; *P. aeruginosa* ATCC 27853, 2.0-3.5 mg/L and *S. aureus* ATCC 29213, 1.0-1.25 mg/L).

CONCLUSIONS

- The 23 lots of generic intravenous piperacillin/tazobactam compounds from 15 manufacturers showed an average decrease in potency of 16%.
- The use of incremental BMD MIC susceptibility values between the standard $\log_2$ 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 due to the under dosing by 2-3 grams daily.

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