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In vitro potency evaluations of various piperacillin/tazobactam generic products compared with the contemporary branded (Zosyn®, Wyeth) formulation

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Abstract

Twenty-three generic intravenous piperacillin/tazobactam products were compared for in vitro activity to the branded formulation (Zosyn®, Wyeth, Philadelphia, PA) by disk diffusion and incremental broth microdilution assay methods. All but 1 lot demonstrated significantly decreased activity (−5 to −35%), necessitating further investigations regarding the chemical purity, potency, and therapeutic equivalence of these products worldwide. The average −16% activity across all generic lots was equivalent to underdosing piperacillin/tazobactam by 2.6 g daily for serious clinical infections (4.5 g Q6 h).

Keywords: Piperacillin/tazobactam; Generics; Branded agents; Activity in vitro

Piperacillin/tazobactam is a widely used intravenous penicillin/β-lactamase inhibitor combination delivered as an 8:1 ratio, usually 4 g of piperacillin and 0.5 g of tazobactam every 6 h (Jones and Barry, 1989; Kuck et al., 1989; Package Insert, 2007). Alternative dosing vials may contain 2 or 3 g of piperacillin and 0.25 or 0.375 g of tazobactam (Package Insert, 2007). The original worldwide sponsor/developer of this product (trade name Zosyn® or Tazocin®) was Wyeth Pharmaceuticals, Philadelphia, PA, and the patent rights to this combination vary geographically. Recently, generic formulations containing piperacillin/tazobactam have been introduced into various global markets but have been questioned as to bioequivalence when compared with the branded product (Ye et al., 2006). Also, the original sponsor's product (Zosyn®) has been reformulated to provide improved quality using proprietary techniques (Package Insert, 2007).

We studied "nonbranded" generic formulation samples of piperacillin/tazobactam for antimicrobial potency against 4 selected assay organisms (replicate testing) and directly compared them with the current Zosyn® formulation (Package Insert, 2007) purchased from a drug wholesale distributor in the United States. Generic piperacillin/tazobactam products (26 samples from 23 lots) were forwarded to JMI Laboratories, North Liberty, IA, from China (2 samples), Greece (3), India (5), Jordan (1), Philippines (10), Portugal (1), Spain (2), and Taiwan (2).

Reference susceptibility testing methods were applied as described by the Clinical and Laboratory Standards Institute (CLSI) M2-A9, M7-A7, and M100-S17 (CLSI, 2006a, 2006b, 2007). Broth microdilution tests (CLSI, 2006a) 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, and a growth control. Four assay strains were used (Table 2), each having a reference piperacillin/tazobactam MIC between 1 and 4 μg/mL, 0.25 to 8 μg/mL using CLSI quality control

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ranges (CLSI, 2007). All strains were tested in triplicate, and the lowest reproducible MIC value was used for calculation of the product lot potency compared with the Zosyn® (Wyeth) contemporary product control (lot B75011).

The CLSI disk diffusion test was used only 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) (CLSI, 2006b, 2007). Only gross differences in potency (±4-fold) would be expected to appear as zone diameter changes in this screening assay for the following reasons: 1) all assay strains were highly susceptible (MIC, ≤16 μg/mL; susceptible) to piperacillin/tazobactam and would produce zone diameters of ≥21 mm (CLSI and US Food and Drug Administration [US-FDA] criteria for susceptible); 2) zone diameters of ≥25 mm are positioned in the parabolic (nonlinear) portion of the MIC versus zone diameter regression line; therefore, minimal zone changes would be expected when associated with significant MIC potency changes; and 3) lower disk concentrations would be required to assay the potency differences, that is, in the linear range of MIC values by regression analysis (Jones and Barry, 1989; Kuck et al., 1989). The 8:1 ratio MIC values correlate well to fixed concentration (4 μg/mL) tazobactam MIC results and to the categorical accuracy of piperacillin/tazobactam breakpoints as published in the Zosyn® package insert (US-FDA) and CLSI document M100-S17 (CLSI, 2007; Jones and Barry, 1989; Kuck et al., 1989; Package Insert, 2007). All disk diffusion tests were performed in triplicate, and the modal zone of inhibition (in mm) was used for screening analysis.

The listing of all tested piperacillin/tazobactam intravenous formulation products is found in Table 1. Five manufacturers (Astral Pharmaceutical Industries, Vadodara, India; Meditrina Pharmaceuticals, Athens, Greece; STADA, Barcelona, Spain; YSS Laboratories, Makati City, Philippines; and Zuventus, Mumbai, India) had 2 or more sampled lots, some varying in drug content (2.25 or 4.5 g). Wyeth and the remaining manufacturers' vials contained 2.25 or 3.375 or 4.5 g. All comparative tests were performed on the same day from fresh stock solutions (5 separate testing events).

Disk diffusion results for zones of inhibition (100/12.5-μg disks prepared from vial content) were compared with a commercial disk (BBL) that contained 100/10 μg of piperacillin/tazobactam (internationally used diagnostic product content). Zone diameter results showed no significant variation in the measured potencies of the generic lots when

Table 1
Listing of 13 screened piperacillin/tazobactam intravenous generic formulations

Manufacturer	Product name	Vial strength (g)	Lot no.	Dates [a]		Country of origin
				Expiration	DOT	
Wyeth	Zosyn®	3.375	B75011	06/2008	5 dates	United States
Astral Pharmaceuticals Industries	PIPTAZ	2.25	AUPM-601	10/2008	06/07/07	Philippines [b]
Astral Pharmaceuticals Industries	PIPTAZ	4.5	AUPI-601	10/2008	06/07/07	Philippines [b]
Astral Pharmaceuticals Industries	PIPTAZ	4.5	AUPI-701	03/2009	08/22/07	Philippines [b]
Aurobindo	Zobactin	4.5	ZBNPB7048	07/2008	10/05/07	India
China Chem	Pisutam	2.25	58P713	08/2008	11/29/07	Taiwan
Demo	Tazorex	4.5	0701172	08/2008	06/07/07	Greece [c]
FARMA-APS	–	4.5	A005	05/2009	08/23/07	Portugal
Hainan Sanyang	Pip/Tazo	4.5	70703	06/2009	11/29/07	China
Hikma	Prizmai	4.5	A001	07/2009	11/29/07	Jordan
Hong Kong United	Pip/Tazo	4.5	7080401	07/2009	11/29/07	China
Meditrina Pharmaceuticals	Tazidron	4.5	07076	02/2009	08/22/07	Greece
Meditrina Pharmaceuticals	Tazidron	4.5	07077	02/2009	08/22/07	Greece
Orchid/Aeiss	Zopercin	4.5	151018	04/2009	10/05/07	India
Orchid Healthcare	Piptamate	4.5	1517004	01/2009	08/23/07	India
STADA	–	4.5	A001	02/2009	06/07/07	Spain [d]
STADA	–	4.5	A013	06/2009	10/05/07	Spain
YSS Laboratories	Vigocid	4.5	8002C	10/2008	08/23/07	Philippines [e]
YSS Laboratories	Vigocid	4.5	8003C	01/2009	08/23/07	Philippines [e]
YSS Laboratories	Vigocid	2.25	8004C	02/2009	08/23/07	Philippines [e]
YSS Laboratories	Vigocid	2.25	8501C	10/2008	06/07/07	Philippines [e]
Yung Shin	Tapimycin	2.25	TY12T039	05/2010	11/29/07	Taiwan
Zuventus	Tazotum	4.5	7003	02/2009	10/05/07	India
Zuventus	Tazotum	4.5	7001	01/2009	10/05/07	India

DOT = date of test.

[a] Three dates = 06/07/07, 08/22/07, and 08/23/07.

[b] From Astral Pharmaceutical Industries via United Laboratories, Mandaluyong City, Philippines.

[c] From DEMO, Athens.

[d] From Laboratorio STADA.

[e] From YSS Laboratories, via The Cathay Drug, Makati City, Philippines.