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Comprehensive Investigations of Piperacillin/tazobactam Generic Formulations Compared to Branded Lots: Studies of 46 lots from 29 Manufacturers

GJ MOET, AA WATTERS, HS SADER, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

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

ABSTRACT

Background: Piperacillin/tazobactam (P/T), a widely used beta-lactamase inhibitor combination, has many generic products available needing careful evaluation/comparisons to recently reformulated branded product (Zosyn®). This presentation updates potency results (2007-2009) on 46 generic lots compared to branded lots.

Methods: Expanded analysis was performed as follows; 1.) MIC assay variations of reference branded lot (RLOT B75011; 13 replicates); 2.) 8 branded lots compared to RLOT; and 3.) tests of 46 generic lots. MIC assays used 4 organisms (P/T MIC range, 1-4 µg/ml) with triplicate processing compared to RLOT. 29 manufacturers of generic P/T were evaluated (17 nations). Assay susceptibility tests used CLSI M07-A8 methods with 20 incremental dilutions between 0.5-8 µg/ml, increasing precision.

Results: Assays (4 strains X triplicates X 17 events) of RLOT showed consistent results varying ±3% from averaged MIC results by strain. When other P/T branded lots were tested, potencies varied from +7 to -19% (average, -6%). This compares to generic lot results with potency variations of 0 to -35% (average, -16%) in earlier testing (ECCMID, 2008). 23 newer lots showed similar data (average, -15%; Figure 1). Only 17% of generic lots had a potency ≥ to average of Zosyn® lots and 7% vs RLOT. All values were based on demonstrated antimicrobial activity of vial contents, where only 2 generic lots (4%) had activity > RLOT.

Conclusion: The activity of P/T generic products can vary and significant decreases (-15% average) were documented by a precise MIC assay. RLOT test variations were minor and branded lots had greater activity correlations (-6%) compared to results from 46 generic lots (average, -15% of labeled potency). Generic product use should consider formulation quality measured by in vitro activity plus chemical-based tests.

INTRODUCTION

Piperacillin combined with the β-lactamase inhibitor tazobactam, as a parenteral broad-spectrum antimicrobial, was approved by the United States Food and Drug Administration (USA-FDA) in 1993. The introduction of piperacillin/tazobactam into the market was coupled with several indications: 1) nosocomial pneumonia (moderate to severe), 2) community-acquired pneumonia (moderate severity only), 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.

Piperacillin/tazobactam has become a very widely used intravenous penicillin/β-lactamase inhibitor combination delivered as an 8:1 ratio (4 grams of piperacillin and 0.5 grams of tazobactam every six hours) as directed by the product package insert (2007). Two alternative dosing vials contain 2 or 3 grams of piperacillin and corresponding 0.25 or 0.375 grams of tazobactam, respectively. The original worldwide sponsor/developer of this product (Zosyn® or Tazocin®) was Wyeth Pharmaceuticals Inc., (Philadelphia, Pennsylvania, USA); and the patent rights to produce and market this combination now varies geographically. Generic formulations containing piperacillin/tazobactam have been approved in several global markets, but have been questioned as to their potencies when compared to the branded product. 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 azole antifungal agents and glycopeptides. Furthermore, the original sponsor's product (Zosyn®) has been reformulated to maximize quality and establish more uniform potencies using proprietary methods.

The objective of this expanded study was three-fold: 1) to enlarge the quality assurance evaluation of "non-branded" generic piperacillin/tazobactam lots (now numbering 46 lots from 29 manufacturers) using the incremental MIC antimicrobial assay method as previously described, 2) to assess the reproducibility of the assay method via replicate tests of the reference Zosyn® lot (RLOT; B75011), and 3) to compare eight samples of other branded lots to the RLOT, all tests performed in 2007 through early 2009.

MATERIALS AND METHODS

An updated analysis of piperacillin/tazobactam generic formulations was performed on 23 additional lots (14 manufacturers, see Table 1) in the reference laboratories of the Jones Microbiology Institute (North Liberty, Iowa, USA). Those samples supplement the experience reported before using 23 other lots (15 manufacturers) and with products in eight other nations (Jones et al., 2008). The current generic products were forwarded from Brazil (eight lots), Colombia (three), Mexico (two), Australia (two), Czech Republic (two), Norway (two), and one lot each from Canada, Germany, India and Switzerland. Only samples from India had been assessed before (Jones et al., 2008).

The incremental MIC assay method of Jones et al. (2008), was applied with the broth microdilution tests performed as described by the Clinical and Laboratory Standards Institute (CLSI) documents M07-A8, and M100-S19 (CLSI, 2009a and CLSI, 2009b). 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 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 well characterized strains were utilized to assay the piperacillin/tazobactam activity, each having reference MIC dilution endpoints specified as CLSI quality control ranges; *E. coli* ATCC 25922 at 1 – 4 µg/ml, *E. coli* ATCC 35218 at 0.5 – 2 µg/ml, *Pseudomonas aeruginosa* ATCC 27853 at 1 – 8 µg/ml and *Staphylococcus aureus* ATCC 29213 at 0.25 – 2 µg/ml. 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 to the Zosyn® (Wyeth) contemporary RLOT control.

Additional branded lots (eight) were obtained from various wholesale distributors in the USA for comparison assay against the RLOT. These products were in the 2.25 (three), 3.375 (two) and 4.5 gram (three) vial formats. Also, the reproducibility of the RLOT results from 13 different replicate tests over 22 months was determined. The latter exercise showed high levels of reproducible incremental MICs results for all four assay organisms and replicate results at ±3% (Figure 1).

RESULTS

- Potency test results of 23 generic lots reported in 2008 (Jones et al., 2008) showed results ranging from RLOT equivalence to -35% (average, -16%; see Figure 1). This indicated a systematic level of decreased piperacillin/tazobactam activity among generic manufacturers that represented an average therapeutic underdosing of 2.6 grams of piperacillin daily compared to the RLOT

- The current report of an additional 23 lots, expanded the generics testing to 46 lots overall from 29 manufacturers/17 countries and confirmed that the shortfall in potency was similar at +10 to -42% (range) and an average of -15% (Table 1 and Figure 1). Only 3 of 46 generic lots possessed an activity equal to or greater than the RLOT. The organism indicting the greatest in vitro loss of activity was *P.* aeruginosa ATCC 27853, a strain expressing wildtype susceptibility for piperacillin ± tazobactam.

- In the comparisons of eight branded lots to the RLOT, the range of Zosyn® potencies varied from +7% to -19% (average, -6%). These results showed that only 22% of generic lots had vial strengths at least equal to the average of all branded lots tested (Figure 1).

- Not only were generic lots usually deficient in drug potency, between lot activities for some manufacturers could vary by 22 to 30% (Table 1), although replicates of of some lots (Europharma, 121609C) only varied from 0 to 6% (average, -4%; consistent with RLOT reproducibility statistics).

- Acceptable limits for generic potency variation have been quoted by some regulators at 25% (+15 to -10%), but the central tendency of these monitored piperacillin/tazobactam generic products rests below the acceptable -10% lower limit, e.g. -15% overall.

Figure 1. Extent of potency variations among four groups of experiments with piperacillin/tazobactam intravenous injection lots.

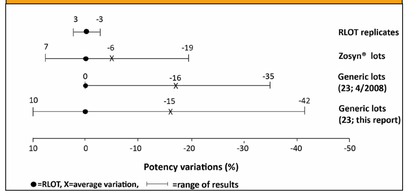

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Table 1. Listing of 23 additional (14 manufacturers) lots of generic intravenous piperacillin/tazobactam formulations screened by a multi-organism in vitro MIC assay[a].

Manufacturer (lot no.)	Product name	Vial strength	Dates: Expiration	Dates: DOT[b]	Country of origin	Assay Variation (%)[c]
Cellofarm (7100789)	Tazpen	4.5 grams	01/2009	01/2008	Brazil	-27
Cellofarm (7100794)	Tazpen	4.5 grams	01/2009	03/2008	Brazil	-5
Eurofarma (121609C)	Pip/Tazo	4.5 grams	09/2009	01/2008	Brazil	-4[d]
Eurofarma (117968B)	Pip/Tazo	2.25 grams	08/2009	01/2008	Brazil	-11
Eurofarma (126133A)	Pip/Tazo	2.25 grams	12/2009	03/2008	Brazil	-26
Eurofarma (124032E)	**Pip/Tazo**	**4.5 grams**	**12/2009**	**03/2008**	**Brazil**	**4[e]**
Novafarma (0760088)	Pip/Tazo	4.5 grams	12/2009	03/2008	Brazil	-18
Novafarma (0760076)	Pip/Tazo	4.5 grams	12/2009	01/2008	Brazil	-27
Farmalogica (11704-1)	Pip/Tazo	4.5 grams	06/2009	09/2008	Colombia	-16
Vitrofarma (B050822)	Vitalis®	4.5 grams	05/2010	09/2008	Colombia	-13
SUMI Med (08050434	Pip/Tazo	4.5 grams	01/2010	09/2009	Colombia	-10
Kendrick (6JB030)	Tasovak®	4.5 grams	08/2008	01/2008	Mexico	-3
Kendrick (7LB016)	Tasovak®	4.5 grams	08/2009	09/2008	Mexico	-13
Teva (A002)	Pip/Tazo (Teva®)	4.5 grams	12/2009	03/2008	Switzerland	-11
Ratiopharm (H22498)	Pip/Tazo	4.5 grams	02/2010	09/2008	Germany	-18
Hospira (B058004)	DBL®	4.5 grams	02/2010	03/2009	Australia (India)	-42
Hospira (B088001)	DBL®	4.5 grams	10/2010	04/2009	Australia (India)	-14
Orchid (B058005)	Zopercin®	4.5 grams	02/2010	03/2009	India	-26
Ibigen (8F06TR)	Ibigen®	4.5 grams	05/2010	03/2009	Czech Republic (Italy)	-21
Ibigen (8L12TR)	Ibigen®	4.5 grams	07/2010	03/2009	Czech Republic (Italy)	-26
Sandos (155534)	**Pip/Tazo**	**3.375 grams**	**03/2010**	**03/2009**	**Canada**	**10**
Stragen (1PT0803D)	Pip/Tazo	2.25 grams	10/2010	03/2009	Norway	-15
Stragen (1PT0801D)	Pip/Tazo	4.5 grams	10/2010	03/2009	Norway	-16

a. From Jones et al. [2008].
b. DOT = date of test.
c. Overall % change (four assay organisms) compared to control potency.
d. Average of three replicate assays on three different dates.
e. Bolded results are the only generic lots performing superior to RLOT.

CONCLUSIONS

- Piperacillin/tazobactam has demonstrated excellent broad-spectrum antimicrobial activity at the selected formulation ratio and dosing schedules for more than 15 years. A recent report from more than a decade of piperacillin/tazobactam in vitro surveillance experience tested against *P. aeruginosa* isolates (25,460), demonstrated a sustained high-level of activity (83.6% susceptible) and only a slight decrease in susceptibility rates over time (10 years).

- The experience with analyzing the potency of piperacillin/tazobactam generic formulations by a precise multi-organism in vitro assay was expanded to 46 lots (29 manufacturers, 17 countries). Across all generic lots the range of activity compared to a reference branded lot (Zosyn® ;RLOT) was +10% to -42%, average -16%. Eight lots of Zosyn® were also tested with a range of +7 to -19 (average, only -6%) and the reproducibility (13 replicates) of the RLOT assay was confirmed (±3%).

- This ongoing quality assurance project demonstrated wide activity variations for piperacillin/tazobactam generic lots with a consistent trend toward subpotent performance (-16%) compared to the branded product.

- Generic substitutions within hospital formularies should consider parameters of in vitro activity, in addition to applied chemical analyses and measures of bioavailability to avoid potential adverse clinical consequences.

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