Efficacy and Safety of Piperacillin-Tazobactam: Systematic Review and Metaanalysis

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Abstract

Introduction: Piperacillin-tazobactam (PTZ), although contested, is frequently utilized for empirical treatment of Gram-negative bacteria treatment.

Objective: Systematic review to evaluate if PTZ is associated with lower rates of treatment failure and less adverse effects than other comparators.

Material and Methods: Literature search in Embase, and MEDLINE databases using “piperacillin tazobactam” as leading term. A study qualified, when a properly randomized control trial (RCT) compared the efficacy and safety of PTZ with other antibacterial agents in an “intention to treat analysis” of clinically evaluable patients.

Results: Eleven studies fulfilled inclusion criteria. Pooled RR of failure risk rate was 25% less using PTZ than other comparators (0.75; CI 95% 0.59-0.95). Adverse effects were similar.

Conclusions: PTZ can be adequately considered for empirical treatment of patients with Gram-negative bacteria infections

Keywords: Piperacillin-Tazobactan; Efficacy; Bacterial Infections; Safety; Gram Negative; Empiric Therapy; Systematic Review; Failure

Introduction

Piperacillin-tazobactam (PTZ) is one of the most frequently utilized antibiotic agents for empirical Gram-negative bacteria coverage and remains active against a large proportion of extended-spectrum-beta-lactamase-producing Gram-negative bacteria [1] (ESBL-GN.). The efficacy of PTZ, its similar safety profile and the possibility of its use as monotherapy decreasing the need for combined antibiotic treatments, make the drug an attractive option in clinical practice [1,2].

Carbapenems have been considered the most effective therapy for serious infections caused by resistant Gram negative bacteria; however, increased use has selection pressure for carbapenem resistance, an emerging threat which has contributed to increased selective pressure of multi-resistant Enterobacteriaceae [2-5]. To counterbalance this, PTZ is proposed as a carbapenem-sparing agent to reduce the incidence of multidrug-resistant bacteria and super infections [2].
With all these previous considerations, physicians have to prescribe the most appropriate empirical antibiotic therapy for Gram-negative infections.

To clarify this, we carried out a systematic review (SR) to evaluate if PTZ is associated with a lower rate of treatment failure compared with other antibiotics.

**Material and Methods**

**Search Strategies**

A literature search was carried out in Embase and MEDLINE databases using the search terms "piperacillin tazobactam" with the following filters: Clinical Trial, Review, Comparative Study, Systematic Reviews, Randomized Controlled Trial (RCT), Controlled Clinical Trial, Practice Guideline, Meta-Analysis and Guidelines, and Use in Human Studies. The International Clinical Trials Registry Platform (WHO) and The Cochrane Library were also searched. Articles published in English, Spanish, or French till September 2019 was reviewed and articles reference lists were manually searched for additional relevant studies. See Table 1 Search strategy results.

| Database            | Access platform | Inicial date | Access date     | Results |
|---------------------|-----------------|--------------|-----------------|---------|
| MEDLINE             | Ovid SP         | 1946         | 30/09/2019      | 957     |
| EMBASE              | Elsevier        | 1974         | 30/09/2019      | 1133    |
| COCHRANE LIBRARY    | Clarivate Analytics | 1995   | 30/09/2019      | 142     |
| TOTAL               |                 |              |                 | 2232    |
| DUPLICATED          |                 |              |                 | 607     |
| TOTAL               |                 |              |                 | 1625    |

**Study Selection**

Data extraction and qualitative assessment were performed independently by two reviewers (MTR and DB). In case of disagreement, a third reviewer (RL) analyzed the data and managed the scientific discussion until consensus was reached.

Studies qualified if RCT assigned testing interventions by randomization procedures (non violable) with proper allocation concealment (non predictable); assessed the efficacy and safety of PTZ versus other antibacterial agent in an "intention to treat analyses" of clinically evaluable patients and had a loss-to-follow-up rate ≤15%. Trials were included regardless their blinded or open-label design. Only trials in which the research unit were patients were considered.

**Data Analysis and Statistical Methods**

Efficacy end points were based on clinical evaluable (CE) populations of each study. Pooled risk ratio (RR) and 95% confidence intervals (CIs) were calculated for treatment failure and safety outcomes using the random-effects model (Der-Simmonian-Laird) for more conservative analysis irrespective heterogeneity results. Calculations were carried out using the Metaanalysis calculator by EPIDATA software (WHO) ver. 3.1. Heterogeneity bias was estimated according to the Q-test and \( I^2 \) index. Publication bias was estimated by the Egger’s test. A subgroup analysis was performed to assess bias associated to double blind or open label RCT related bias using J Primo, Sagunto Hospital, Spain software, applying the Mantel-Haenszel procedure. In any stage, the null hypothesis was rejected if \( p<0.05 \). This study complies with the suggestions of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6].

**Results**

Literature search identified a total of 2264 related papers of which only 11 fulfilled inclusion criteria; and thus, were included in the SR. Figure 1 shows the results of the articles’ selection process and Table 2 summarizes the main characteristics of the included articles.
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Table 2: Treatment failures and Safety of PTZ vs comparator in included studies.
Exper: Pip-taz; Control: comparator.

| Author Year | Indication                           | Intervention       | Failure / Total | AE / Total |
|-------------|--------------------------------------|--------------------|-----------------|------------|
|             |                                      | exper | control       | Exper:     | Control:   | Exper:     | Control:   |
| Eklund, 1993 | Intra-abdominal infections           | pip-taz | imipipinem / cilastin | 4 / 55 | 18 / 58 | 13 / 55 | 14 / 58 |
| Marra, 1997  | Serious bacterial infections         | pip-taz | imipinem       | 24 / 75 | 23 / 75 | 4 / 75  | 12 / 75 |
| Jaccard, 1998 | Nosocomial pneumonia or peritonitis  | pip-taz | imipinem / cilastatin | 17 / 151 | 29 / 162 | 22 / 151 | 24 / 162 |
| Ohlin, 1999  | Intra-abdominal infections           | pip-taz | cefuroxime / metronidazole | 37 / 140 | 39 / 1298 | 13 / 105 | 9 / 100 |
| Alvarez, 2000 | Nosocomial Pneumonia                | pip-taz / amikacin | ceftazidime / amikacin | 10 / 88 | 10 / 36 | 21 / 88 | 5 / 36 |
| Naber, 2002  | Complicated urinary tract infections | pip-taz | imipenem / cilastatin | 25 / 147 | 31 / 152 | 20 / 147 | 16 / 152 |
| Roy, 2003    | Acute pelvic infection               | pip-taz | etarpenem      | 12 / 153 | 8 / 163  | 43 / 192 | 48 / 214 |
| Erasmo, 2004 | Intra-abdominal infections           | pip-taz | imipipinem / cilastin | 3 / 111 | 3 / 103 | 16 / 111 | 19 / 103 |
| Saltoglu, 2010 | Diabetic foot infections             | pip-taz | imipenem / cilastatin | 16 / 30 | 23 / 32 | 9 / 30  | 3 / 32  |
| Aamir, 2015  | Febrile neutropenia                  | pip-taz | ceftazidime      | 5 / 20  | 4 / 20   | 5 / 20  | 6 / 20   |
| Zhang, 2016  | Diabetic foot infections             | pip-taz | etarnepem       | 6 / 224 | 14 / 219 | 1 / 275 | 3 / 275 |

Figure 1: Flowchart of included studies.
Only 4 trials out of 11 were double-blind [7-10]. The rest were open-label, single blind or no blindness. Two RCT included patients treated for diabetic foot infections [8,11] four comprised patients with intra-abdominal infections [10,12-14] one focused on oncology patients with treated for febrile neutropenia [15] and four compared patients treated for other types of infections [9,7,16,17].

The pooled incidence of treatment failure of the PTZ group was 13.32% and of the comparator group, 17.55%. Table 3 shows the pooled RR (CI95%) for the risk of failure, the effect size of each study and the results of the sensitivity analysis.

| Author  | Year | N patients | RR  | CI 95%          | Sensitivity analysis |
|---------|------|------------|-----|-----------------|----------------------|
| Eklund  | 1993 | 113        | 0.23| 0.08-0.64       | 5.56                 |
| Marra   | 1997 | 150        | 1.04| 0.64-1.67       | -5.02                |
| Jaccard | 1998 | 313        | 0.62| 0.36-1.09       | 1.88                 |
| Ohlin   | 1999 | 269        | 0.87| 0.59-1.27       | -3.53                |
| Alvarez | 2000 | 124        | 0.4 | 0.18-0.89       | 5.14                 |
| Naber   | 2002 | 301        | 0.84| 0.52-1.35       | -2.46                |
| Roy     | 2003 | 316        | 1.59| 0.67-3.80       | -3.79                |
| Erasmo  | 2004 | 214        | 0.92| 0.19-4.49       | -0.85                |
| Saltoglu| 2010 | 62         | 0.74| 0.49-1.10       | -0.89                |
| Aamir   | 2015 | 40         | 1.25| 0.39-3.98       | -2.18                |
| Zhang   | 2016 | 443        | 0.41| 0.16-1.07       | 3.51                 |

**Table 3:** Risk of treatment failure in individual studies and pooled results.

No relevant heterogeneity was detected (Q-test 14.93; DF 9; p 0.09. F 35%). Pooled RR failure risk rate was 25% less using PTZ than other comparators (0.75; CI 95% 0.59-0.95) (Graphic 1).

**Graphic 1:** Forest plot: Treatment failure risk in individual and combined studies.
Cumulative metaanalysis (Graphic 2) illustrates that as the sample size increases, the effect size achieves more relevance and accuracy, showing a consistent trend toward less risk of treatment failure using PTZ.

The sensitivity analysis shows that [12] (5.56%) is the most influential study and the least, [14] (-0.85%). Both used the same comparator (imipinem-cilastin) and for the same indication (intraabdominal infections). The planned subgroup analyses according blindness, reveals that the pooled RR in double blind studies (n 1 210 patients), is 0.91; CI 95% 0.61 to 1.35, while that of the open label studies (n 1 135), 0.67; CI 95% 0.49 to 0.90. The difference between them was not statistically significant, yielding a p value of 0.23 (Z statistic 1.20). No risk of bias of publication was detected (Graphic 3).

Adverse events: Nor heterogeneity nor publication bias was detected in this comparison. Treatment groups had similar rates of adverse events (15.75% vs. 14.28%) (Pooled RR 1.02; CI95% 0.81-1.29).

Discussion

We conducted this SR to assess in children and adults, with all sorts of bacterial infections, the comparative
effectiveness and safety of PTZ against available comparators.

Some authors state that PTZ is another treatment option to carbapenems, but limited to mild infections or urinary tract infections [6,18,19].

This SR analyzed PTZ vs another antibiotic comparator in a wide type of infections, including intra-abdominal infections, febrile neutropenia, infections in diabetic patients, nosocomial pneumonia, all of which cannot be considered minor clinical threats.

Our results suggest that PTZ leads to a lower rates of treatment failure and is well tolerated, consistent with the good safety profile of the beta-lactam class [1-5]. The cumulative metaanalysis showed a clear trend that the risk of treatment failure is lower for PTZ than for comparators, and that the incidence of adverse events was not different.

A strength of our study is that, to the best of our knowledge, this is the first systematic review and metaanalysis on the efficacy and safety of PTZ that includes only properly randomized controlled trials minimizing selection bias. This means that given the precautions taken to minimize selection bias by including only properly RCT, the clinician, who must often prescribe antibiotic treatments before having the microbiological results, can be confident that the risk of failure with empirical PTZ is lower than if another antibiotic is indicated.

Concerns arose, when it was found that all RCT studies were conducted in a diversity of underlying diseases, with some antibiotic comparators that are not typically indicated in clinical practice for treatment of these pathologies, using different doses and follow-up periods, with some infections not being microbiologically documented or in absence of ESBL-GN, some studies with few participants and mostly having treated adults. However, no significant heterogeneity was identified in the study.

On the other hand, it is not possible to totally rule out that the obtained results are not linked to the bias protection grade of the adopted design.

Further studies are needed to better understand the role of PTZ in empiric treatment of patients in intensive care settings, with ESBL-GN microbiologically documented infections and particularly, in children.

Conclusions

PTZ can be considered an adequate antibiotic option for empirical treatment of serious infections due to gram negative bacteria.

Summary points

Piperacillin tazobactan (PTZ) is an antibiotic frequently used in medical practice for the treatment of Gram negative infections. The present SR suggests that PTZ has a lower risk of therapeutic failure than other antibiotics, while the safety profiles are the same.

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