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Results of the effectiveness of two piperacillin–tazobactam molecules in the real world

Jorge Enrique Machado-Alba[a,*], Andres Gaviria-Mendoza[b], Manuel E. Machado-Duque[b]

[a] Grupo de Investigación en Farmacoepidemiología y Farmacovigilancia, Universidad Tecnológica de Pereira-Audifarma S.A., Pereira, Risaralda, Colombia
[b] Fundación Universitaria de las Americas, Pereira, Colombia

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ABSTRACT

Objective: The objective was to determine the effectiveness of two piperacillin–tazobactam molecules in terms of all-cause mortality, mortality by infection, and hospital stay.
Methods: A cohort study was performed involving patients treated with piperacillin–tazobactam at a clinic in Colombia. The patients were divided into those who received the innovator piperacillin–tazobactam (from July to December 2014) and those who received the generic piperacillin–tazobactam (from January to June 2015). Socio-demographic, clinical (all-cause mortality, death by infection, days of hospitalization), microbiological, pharmacological, and comorbidity variables were evaluated. Multivariate analyses were performed.
Results: A total of 279 patients were included: 140 treated with the innovator piperacillin–tazobactam and 139 with the generic piperacillin–tazobactam. The median age was 63 years, and 56% of the patients were male. There was no statistically significant difference in death from all causes (22.9% vs. 14.4%, $p = 0.069$), death by infection (7.9 vs. 10.8%, $p = 0.399$), or hospital stay (18.1 ± 16.2 vs. 15.7 ± 11.6 days, $p = 0.178$) between the innovator and generic piperacillin–tazobactam, respectively.
Conclusions: The generic piperacillin–tazobactam was equivalent to the innovator piperacillin–tazobactam with regards to all-cause mortality, mortality by infection, hospital stay, and safety, and at a lower cost, which may be useful for decision-makers in hospitals.

Introduction

There is growing concern over severe community-acquired and nosocomial infections that require management within an intensive care unit (ICU), especially due to the steady increase in bacteria that are resistant to multiple antibiotics (Luna et al., 2014). This observed resistance includes that involving the most novel and broad-spectrum drugs, such as carbapenems, extended-spectrum penicillins, and antipseudomonal penicillins (Luna et al., 2014; Cotta et al., 2014; Curcio, 2013).

Piperacillin–tazobactam is one of the broadest spectrum antimicrobials available, covering Gram-positive, Gram-negative, and anaerobic bacteria. It has been shown to be effective in the treatment of moderate and severe infections, such as complicated urinary tract infections, intra-abdominal infections, soft tissue infections, gynecological infections, and pneumonia (Gin et al., 2007). The innovator antibiotic, which is highly effective and safe in critically ill patients, has been marketed since 1993 (Gin et al., 2007), but due to its increasingly frequent use in the ICU, concern has been raised about the high costs of health care for these patients (Grau and Alvarez-Lerma, 2008).

Generic drugs should prove their bioequivalence with regard to the innovator molecules, demonstrating the same effectiveness and safety, and the use of such drugs may represent a considerable reduction in treatment costs (McCormack and Chmelicek, 2014). Health systems with limited resources invest between 20% and 60% of their resources in drugs. Hence, the World Health Organization has called for their rational use since 1985, striving for patients to receive the proper medication, at the appropriate dose and in the appropriate regimen, at the lowest cost possible for them and the community. A rational practice is achieved by using equally effective drugs at the lowest possible cost (World Health Organization (WHO), 2011a, 2011b).

Through in vitro studies, murine models, and observational investigations, it has been shown that the generic form of piperacillin–tazobactam is bioequivalent to the innovator

* Corresponding author at: Grupo de Investigación en Farmcoepidemiología y Farmacovigilancia, Universidad Tecnológica de Pereira-Audifarma S.A., Paraje la Julita, Pereira, Risaralda, 660003, Colombia.
E-mail address: machado@utp.edu.co (J.E. Machado-Alba).

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molecules, with no significant difference in pharmacokinetic, effectiveness, or safety parameters (Agudelo et al., 2015; Tschudin-Sutter et al., 2011; Charoenpong et al., 2013; Araya et al., 2015). However, the quality of the generic presentations has been questioned, with some studies reporting that they present lower in vitro activity (Jones et al., 2008; Jones et al., 2013). Furthermore, a lack of therapeutic equivalence in murine models for a specific generic molecule of piperacillin–tazobactam was reported recently (Rodriguez et al., 2016).

In December 2014, there was a shortage of innovator piperacillin–tazobactam (Tazocin, Pfizer (Wyeth), USA) in Colombia. As a result, some hospital centers had to change to using the generic molecule. This study sought to determine the effectiveness in terms of all-cause mortality, mortality by infection, and hospital stay of both molecules in patients with infections treated during a period of 12 months at a tertiary clinic in the city of Cali, Colombia.

Methods

A cohort study was conducted that included patients of both sexes, older than 18 years of age, who received piperacillin–tazobactam therapy at Clínica Nuestra in Cali, Colombia. The patients were divided into two groups covering two 6-month time periods: the first group included those patients who had been treated with the innovator piperacillin–tazobactam (Tazocin) between July 1, 2014 and December 31, 2014; the second group consisted of patients who had received the generic presentation (Vitalis Laboratory, Colombia) between January 1, 2015 and June 30, 2015, because of a shortage of the innovator molecule in Colombia. The same safety techniques were used for both molecules in the application of the drugs.

All variables were retrieved from the patients' medical records, and the information was tabulated in a database using Microsoft Excel. The data were reviewed by two trained physicians and validated by another researcher. The following variables were included: (1) Socio-demographic: age, sex, urban or rural origin. (2) Clinical: type of infection (community-acquired, nosocomial), infection site (respiratory, genitourinary, skin and soft tissue, intra-abdominal, catheter-related, osteoarticular, bacteremia), and evidence of infection (microbiological documentation, clinical documentation). (3) Comorbidities: (a) debilitating diseases or diseases affecting the immune system (HIV, cancer), (b) cardiovascular diseases, (c) diabetes mellitus, and (d) other infections. Each patient was assessed using their scores on the Charlson age–comorbidity index scale. (4) Microbiological: bacterial agent isolated in the patient's cultures. (5) Pharmacological: use of piperacillin–tazobactam (innovator or generic, dose and dosage interval, and duration of use in days), antibiotic used previously, switch to another antibiotic and number of days until the change. (6) Safety: adverse events reported with regard to the use of piperacillin–tazobactam.

The main objective of effectiveness was measured by the status at discharge: alive, death as a result of infection, or death of any cause. The stay in the hospital and in the ICU was also calculated (in days).

This study was endorsed by the Bioethics Committee of the Universidad Tecnológica de Pereira under the category of 'research without risk', and the principles of the Declaration of Helsinki were respected.

The data were analyzed using SPSS Statistics v. 23.0 for Windows (IBM, USA). Univariate analyses were performed with proportions, means, and standard deviations. Variables that did not present a normal distribution were identified through the Kolmogorov–Smirnov test. The Student *t*-test or Mann–Whitney *U*-test was used for the comparison of quantitative variables, and the Chi-square test was used for categorical variables; variables for which there were fewer than five subjects were assessed using Fisher's exact test. Differences in the duration of hospital stay and number of days of antibiotic use from admission until the outcome were established. First, bivariate analyses were performed in which all of the established variables were included compared with the dependent variables (death by infection and death from any cause). Subsequently binary logistic regression models were applied using death from any cause and death by infection as dependent variables and the following as independent variables: all those that were significantly associated with this outcome in the bivariate analyses, including the use of the two molecules of piperacillin–tazobactam; also, according to a literature review, all those that may be related or those that due to plausibility could have some association, including age, sex, admission to the ICU or general hospitalization rooms; others associated with the use of drugs such as the dosing interval, days of use, change or addition of another antibiotic, de-escalation according to antibiogram results, and whether or not the patient completed the therapy with piperacillin–tazobactam. An adjustment multivariate model was used to find possible variables associated with mortality and hospital stay and not a comparison between the two molecules. A p-value of <0.05 was determined as the level of statistical significance.

Results

A total of 279 patients treated with piperacillin–tazobactam were evaluated: 140 patients were in the innovator molecule group and 139 in the generic molecule group. The median age was 63 years, with an interquartile range of 46–77 years. There was a slight predominance of males (155 patients, 55.6%). The majority came from urban areas (99.3%), and only 1.4% were elderly patients institutionalized in a nursing home.

The clinical variables of the patients evaluated are shown in Table 1, including comorbidities, surgical history, ICU admission, severity at admission, diagnoses, and site of infection, and are presented according to the piperacillin–tazobactam molecule used. Table 1 also shows details of the paraclinical examination results and the scores on the Charlson comorbidity index scale. In each case, it is shown whether there was a statistically significant difference between the patients who received the innovator molecule and the patients who received the generic molecule. There was a change in the pattern of drug use following the shortage of the original molecule, which, for example, was more commonly used in the ICU, in older patients, and in respiratory infections, but less frequently in surgical patients (Table 1).

Cultures of the agent of infection were performed in less than half of the patients. *Pseudomonas aeruginosa* was the microorganism most often isolated ($n = 31$, 11.1%), followed by *Escherichia coli* ($n = 26$, 9.3%). Other bacteria isolated, resistance results, and antibiotics used prior to the prescription of piperacillin–tazobactam are listed in Table 2.

Table 3 shows the median dose used, dosage intervals, the service in which antibiotic treatment was started, the duration of the therapy, reasons for the change to another antimicrobial, and outcomes for the total population and by type of molecule employed. Only four patients received continuous infusion of piperacillin–tazobactam, and only half were administered a complete regimen (68 patients with the innovator piperacillin–tazobactam and 73 with the generic piperacillin–tazobactam). There was no statistically significant difference in the duration of hospitalization, but the patients treated with the innovator drug remained in the ICU longer ($p = 0.035$) (Table 3). There were no reports of adverse reactions or safety concerns for either product.