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International Journal of Antimicrobial Agents 26 (2005) 22–27

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

# Piperacillin–sulbactam versus piperacillin–tazobactam: a multicentre, randomised, single-blind, controlled clinical trial

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Received 12 August 2004; accepted 18 February 2005

**Abstract**

The objective of this study was to compare the efficacy and safety of piperacillin–sulbactam (PIP–SBT) and piperacillin–tazobactam (PIP–TAZ) in the treatment of bacterial respiratory and urinary tract infections. A randomised, single-blind, controlled clinical trial was performed. Differences in clinical efficacy, bacteriology and safety between the two groups were subjected to statistical analysis, including intent-to-treat (ITT) analysis. A total of 215 cases were enrolled, with 203 complete cases (99 PIP–SBT, 104 PIP–TAZ). A total of 209 cases (103 PIP–SBT, 106 PIP–TAZ) were included in the ITT analysis and a total of 212 cases (104 PIP–SBT, 108 PIP–TAZ) were included in the safety analysis. Overall efficacy rates of PIP–SBT and PIP–TAZ were 93.2% and 93.4%, respectively. Overall bacterial eradication rates of the two groups were 95% and 97.59%, respectively. Among the PIP–SBT group, eight patients (7.69%) had adverse events, including four probable drug-related events. Among the PIP–TAZ group, nine patients (8.33%) had adverse events, including one definitely drug-related and four probable drug-related events. All differences between the two groups were insignificant. PIP–SBT could be a suitable replacement for PIP–TAZ in the therapy of community-acquired respiratory and urinary tract infections caused by β-lactamase-producing bacterial isolates.


*Keywords:* Piperacillin; Sulbactam; Tazobactam; RCT; Bacterial infection

## 1. Introduction

Piperacillin is a potent antimicrobial agent against many Gram-positive and Gram-negative bacteria, but is unstable to hydrolysis by most conventional-spectrum β-lactamases and all extended-spectrum β-lactamases [1,2]. β-Lactamase inhibitors, including clavulanic acid, sulbactam and tazobactam, can protect piperacillin from inactivation by β-lactamase-producing bacteria [3]. Thus, piperacillin–β-lactamase inhibitor combinations can significantly enhance the antimicrobial spectrum of piperacillin. Piperacillin–tazobactam has been widely used to treat various bacterial infections for many years and has exhibited excellent clinical efficacy and safety [4]. Sulbactam is usually combined with ampicillin or cefoperazone in clinical practice. Recently, sulbactam has been approved in some countries (Germany, Austria, Switzerland and China) as a single substance to be combined with piperacillin or other β-lactams [1]. However, no randomised controlled clinical trial is available to compare the clinical efficacy and safety between piperacillin–tazobactam and piperacillin–sulbactam in the treatment of bacterial infections. We describe the results from this pre-market trial of piperacillin and sulbactam.

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0924-8579/$ – see front matter 
doi:10.1016/j.ijantimicag.2005.02.018

## 2. Patients and methods

### 2.1. Study design and criteria for eligibility

This randomised, single-blind, controlled clinical trial was designed to compare the efficacy and safety of piperacillin–sulbactam and piperacillin–tazobactam in the treatment of bacterial respiratory and urinary tract infections. The trial was conducted in three Chinese University hospitals. Hospitalised male and female patients 18 years of age or older with a clinical or bacteriological diagnosis of suppurative tonsillitis, or acute lower respiratory or urinary tract infections (including acute episodes of chronic infections) caused by bacteria were eligible for the study. They must not have received effective antimicrobial therapy within 48 h of study enrollment.

Patients with any of the following conditions were excluded: a history of hypersensitivity to β-lactams; serum creatinine level >200 μmol/L or creatinine clearance <40 mL/min; serum alanine aminotransferase (ALT) >80 U/L; severe cardiac or haematological abnormalities; terminal malignancy; pregnant or lactating woman; or non-bacterial infections.

### 2.2. Ethics

The study was conducted in accordance with the updated Declaration of Helsinki. The ethical committee in West China Hospital, the principal investigating institution, approved the study protocol. Patients or their guardians provided written informed consent to participate in the study prior to enrollment.

### 2.3. Randomisation and antimicrobial treatment

Patients were randomly allocated to one of the antibiotics in the trial, stratified by centre, by consecutive opening of computer-yielded sealed envelopes. Patients received either piperacillin–sulbactam (4 g/1 g, every 8 h) or piperacillin–tazobactam (4 g/500 mg, every 8 h) by 30 min intravenous drip. The duration of therapy was 7–14 days.

### 2.4. Evaluation and monitoring

At baseline, a complete medical history and physical examination, as well as a complete blood cell and differential count, urinalysis, routine chemistry and at least two cultures of swab, sputum or urine were performed before initiating antimicrobial therapy. Chest radiography was necessary for patients with a lower respiratory tract infection at baseline and at the termination.

Patients were monitored daily for clinical signs, symptoms and adverse events during the treatment. Complete blood cell counts, chemistry parameters and urinalysis were repeatedly performed on the fourth day during therapy and at the end of treatment. Culture of swab, sputum (if present) or urine was necessary at the end of treatment.

Following isolation and identification, all bacterial isolates were tested for in vitro susceptibility to piperacillin–sulbactam, piperacillin–tazobactam, piperacillin, ceftazidime, amikacin and levofloxacin by the Kirby–Bauer disc diffusion method, and β-lactamase production was identified by nitrocefin as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [5].

The clinical response was categorised as cure, marked improvement, improvement or failure. The classification into four categories was based on four criteria, including: (1) complete resolution of signs; (2) complete recovery of symptoms; (3) eradication of the pathogens; and (4) normal laboratory findings and chest radiography. Cure means that the patient met all four criteria. Marked improvement means that the patient met three criteria. Improvement indicates that the patient met only one or two criteria. Failure means that the clinical signs and symptoms of infection persisted or worsened after 72 h of treatment. The overall efficacy rate was defined as the proportion of patients cured and markedly improvement.

Safety analysis was performed as follows. All clinical adverse experiences and any changes in laboratory test results were classified as definitely drug related, probably drug related, probably not drug related, definitely not drug related or not assessable. The side-effect rate was defined as the proportion of patients in each treatment group who were considered to have definitely drug-related or possibly drug-related events.

### 2.5. Statistical analysis

All data were carefully checked at the end of the study by the principal investigators of each centre. Each case report form was then systematically reviewed by two of the authors (Lü XJ and Liu YB). All data were entered into a computerised database by EpiData software and analysed using Statistical Analysis System (SAS).

Student's *t*-test, Chi-square ($\chi^2$) test or Fisher's exact test were used to test the hypotheses (type I error level 5%; power 90%), according to the type of variables and purpose of studies. $\chi^2_{CMH}$ test was used to compare the clinical efficacies between the two groups for controlling the confounding factors of each centre. The hypotheses were designed to demonstrate the differences between the two groups. An intent-to-treat (ITT) analysis was used to assess efficacy rates.

### 2.6. Approval

The clinical trial was approved by China SFDA (State Food and Drug Administration; approval document 2002HL0577).