Extended-infusion Piperacillin–tazobactam versus Intermittent-Infusion Dosing Strategy in Critically Ill Patients with suspected or confirmed bacterial Infections.

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Presented By

Christina Medhat Naiim

Teaching Assistant in Clinical Pharmacy Department

Faculty of Pharmacy

British University in Egypt (BUE)

Supervised By

Dr. Nagwaa Sabry

Head of Clinical Pharmacy Department

Ain Shams University

Prof.Dr. Mohey Elmazar

Head of Clinical Toxicology & Pharmacology Department

Dean of Faculty of Pharmacy

The British University in Egypt (BUE)

Dr.Naglaa Bazan

Fellow (Lecturer) and Head of Clinical Pharmacy

Critical Care Medicine Department

Cairo University Hospitals

Introduction

Treating gram-negative infections is becoming increasingly difficult due to the emergence of resistant pathogens. Studies have demonstrated worse outcomes for patients with resistant pathogens based on the premise of inappropriate antimicrobial therapy. The use of currently available antimicrobial agents can be optimized through pharmacodynamic parameters to improve treatment efficacy and patient outcomes **(Winstead et al., 2016).**

Piperacillin–tazobactam, is a beta-lactam beta-lactamase inhibitor combination antibiotic widely used in the treatment of complicated and hospital-acquired infections. It's a time-dependent antibiotic, that is widely used in the treatment of serious gram-negative healthcare-associated infections **(Winstead et al., 2016).**

The authorized mode of administration described in the product insert is by 30-min intermittent infusions. Nonetheless, some authors recommended continuous infusion to optimize treatment of infections due to multiresistant bacteria and those for which the minimum inhibitory concentration (MIC) of antibiotic is high (effectiveness has direct relationship with the percentage of time that the antibiotic levels are above the MIC). MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation **(Luque et al., 2015)**

Therefore, Continuous infusions of beta-lactam antibiotics have been employed in an attempt to maximize the time that free drug concentrations exceed the bacterial MIC. Several studies have shown beneficial outcomes associated with continuous infusion piperacillin–tazobactam, including higher antibiotic concentrations, improvement in clinical cure rates, and quicker time to defervescence **(Grant et al., 2002)**.

One retrospective cohort study comparing extended versus intermittent infusions of piperacillin–tazobactam in Pseudomonas aeruginosa infections found the 14-day mortality rate to be significantly lower among patients who received extended-infusion therapy (4-h infusion of piperacillin–tazobactam 3.375 g administered IV every 8 h) compared with patients who received

intermittent-infusions (infused over 30 min), but this reduction in 14-day mortality was only observed in patients with Acute Physiological and Chronic Health Evaluation-II (APACHE-II) scores of 17 or more **(Lodise et al., 2007)**.

A separate retrospective, two-site trial was conducted in an attempt to replicate these results using extended-infusion piperacillin–tazobactamin gram-negative infections and found no difference in 30-day mortality or length of stay **(Patel et al., 2009).**

A multicenter, retrospective trial was conducted in 14 hospitals to compare 4-h extended-infusion piperacillin–tazobactam to intermittent infusions of comparator antibiotics in gram-negative infections **(Patel et al., 2009)**. In-hospital mortality was significantly reduced in the extended-infusion piperacillin–tazobactamarm compared with intermittent- infusion piperacillin–tazobactam **(Yost et al., 2011).** Additional retrospective studies have been conducted using 4-h infusions of piperacillin–tazobactam 3.375 g administered IV every 8 h and have demonstrated reductions in both mortality and length of stay **(Lee et al., 2012).**

Continuous infusion of other beta-lactam drugs has been successfully used (clinical cure was achieved) in several clinical situations, such as neutropenia, cystic fibrosis, Pseudomonas aeruginosa infection in which intermittent administration failed. **(Dulhunty et al., 2013).** There are, however, few randomized studies comparing the efficacy of intermittent versus continuous infusion in this group of antibiotics **(Ashima Lal et al., 2016).**

Findings from meta-analyses and reviews have not provided conclusive data on the comparative effectiveness of the two modes of administration intermittent versus continuous. **(Roberts et al., 2007)** although one prospective, open-label controlled study reported a significantly shorter time to defervescence, higher clinical cure rate, and lower cost with continuous administration. The lower dose continuous regimen has been shown to provide serum concentrations above the levels reached by intermittent infusion in the steady-state **(Grant et al., 2002).**

Aim of the study

Evaluating the effectiveness and safety of extended-infusion piperacillin–tazobactam dosing strategy versus intermittent-infusion dosing in critically ill patients with suspected or proved bacterial infections.

Patients and Methods

Study Design

A prospective randomized comparative study will be conducted at Critical Care Medicine Department - Cairo University Hospitals

Patients:

A total of 52 patients will be recruited from ICU- Cairo University Hospitals. All adult critically ill patients admitted to Critical Care Medicine Department with suspected or confirmed bacterial infections on admission or during their ICU stay will be assessed for inclusion into the study.

Inclusion criteria

- Adults aged 18-74 years
- Expected ICU stay more than 24 hours

Exclusion Criteria:

- Allergy or potential allergy to the study medications
- Pregnancy
- Patients with CrCl< 20 ml/min or on dialysis
- Cancer patients

Recruited patients will be randomly assigned to either of two groups as follows:

Group I (n=26) will receive pipracillin/tazobactam as intermittent infusion (over 30min) every 8 hours. **(Kim etal., 2002)**

Group II (n=26) will receive piperacillin/tazobactam as extended infusion (over 4 hours) every 8 hours. **(Kim etal., 2007)** .

Calculation of sample size:

To achieve a power of 80% and a significant level of 5% based on an effect size conventions of 0.8 and the expected comparison of the difference between two independent means using G power program (3.010). The number of patients per arm was found to be 26.

Recruited patients' demographics, comorbidities, current medications and laboratory parameters will be recorded from patients' files. APACHE II scores will be determined during the first 24 hours of inclusion into the study and on day of stopping antibiotic, discharge and/or death of the patient. Microbiological cultures from suspected site of infection and blood cultures will be withdrawn from all patients before starting antibiotic therapy.

All patients will be subjected to the following:

A. Patient's full history:

1) Age
2) Sex
3) Medical history
4) Concurrent diseases
5) Concurrent medications

B. Patient evaluation and assessment:

The following will be evaluated at baseline and periodically thereafter until day of stopping antibiotic, discharge and/or death :

1) Kidney functions (Serum creatinine, blood urea nitrogen)

2) Liver functions (ALT, AST, Bil D, Bil T, Albumin)

3) Complete blood count

4) Microbiological Evaluation: Cultures and sensitivity tests from suspected site of infection will be withdrawn from all patients at baseline (before starting antibiotic) and at end of therapy

5) Clinical signs and symptoms of infection documented by the attending physician on patient's medical record

6) APACHE II Variables:

- Partial pressure of O2 in arterial blood (PaO2)
- Mean arterial pressure (MAP)
- Temperature
- Heart rate
- Respiratory rate
- Arterial pH
- Sodium plasma levels
- Potassium plasma levels.
- Serum Creatinine
- Hematocrit
- White blood count
- Glasgow coma score (The GCS is the summation of scores for eye, verbal, and motor responses. The minimum score is a 3 which indicates deep coma or a brain-dead state. The maximum is 15 which indicates a fully awake patient (the original maximum was 14, but the score has since been modified)
- Lactate, serum blood glucose, AST, ALT, BUN will be detected

Outcomes

Effectiveness

- Clinical cure: defined as complete resolution of the clinical signs and symptoms of infection (Physical assessment, white blood cells with differential, temperature)
- Composite endpoint of 30 day mortality or readmission within 30 days of discharge.
- Length of stay at the ICU

➢ Safety:

Any adverse events occurring during study period will be recorded

➢ Pharmacoeconomic Analysis

A cost-effectiveness analysis will be performed for level-1 and level-2 costs from the health care provider perspective, comparing treatment with continuous infusion *versus* intermittent infusion. The level-1 analysis will be limited to acquisition prices of drugs, whereas the level-2 analysis will encompass all costs directly related to antibiotic use: supplies, preparation, administration, daily hospital stay cost, treatment of adverse events, concomitant antibiotics, and expenditures for treating failures.

A decision tree categorizing each case as a treatment success or failure will be employed to compare the cost-effectiveness of intermittent versus continuous infusion with regard to average level-1 and level-2 costs. A sensitivity analysis will be performed to determine which study conditions or variables, if changed, will alter the economic outcome. One-way sensitivity analyses will be performed by varying each treatment arm's probability of success from 50–95%.

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