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A meta-analysis of efficacy and safety of doripenem for treating bacterial infections

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ABSTRACT

Objective: The aim of this article is to compare the efficacy and safety of doripenem for bacterial infections.
Methods: We included six randomized clinical trials identified from PubMed and Embase up to July 31, 2014. The included trials compared efficacy and safety of doripenem for complicated intra-abdominal infections, complicated urinary tract infection, nosocomial pneumonia, and acute biliary tract infection. The meta-analysis was carried on by the statistical software of Review Manager, version 5.2.
Results: Compared with empirical antimicrobial agents on overall treatment efficacy, doripenem was associated with similar clinical and microbiological treatment success rates (for the clinical evaluable population, odds ratio [OR] = 1.26, 95% confidence interval [CI] 0.93–1.69, $p = 0.13$; for clinical modified intent-to-treatment population, OR = 0.88, 95% CI 0.55–1.41, $p = 0.60$; for microbiology evaluable population, OR = 1.16, 95% CI 0.90–1.50, $p = 0.26$; for microbiological modified intent-to-treatment (m-mITT), OR = 0.98, 95% CI 0.81–1.20, $p = 0.87$). We compared incidence of adverse events and all-cause mortality to analyze treatment safety. The outcomes suggested that doripenem was similar to comparators in terms of incidence of adverse events and all-cause mortality on modified intent-to-treatment population (for incidence of AEs, OR = 1.10, 95% CI 0.90–1.35, $p = 0.33$; for all-cause mortality, OR = 1.08, 95% CI 0.77–1.51, $p = 0.67$). In nosocomial pneumonia and ventilator-associated pneumonia treatment, doripenem was not inferior to other antibacterial agents in terms of efficacy and safety.
Conclusion: From this meta-analysis, we can conclude that doripenem is as valuable and well-tolerated than empirical antimicrobial agents for complicated intra-abdominal infections, complicated urinary tract infection, acute biliary tract infection and nosocomial pneumonia treatment.

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Introduction

Antibacterial agents of the carbapenem class are assuming a more important role in the treatment of severe bacterial infections. Doripenem, a new parenteral carbapenem, has been recognized as a valuable addition to the currently available carbapenems in the treatment of serious infections. Doripenem has a broad spectrum of in vitro activity against Gram-positive and Gram-negative bacteria, including multi-drug resistant bacteria that have been a significant cause of morbidity and mortality.[1] In the USA, doripenem is the most recent US Food and Drug Administration (FDA)-approved carbapenem for the treatment of patients with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and pyelonephritis. Doripenem is approved in Europe and in other countries for the treatment of patients with cIAI, cUTI and nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP).[2] However, a statement about doripenem was issued from the FDA, in May 2012, stating that the clinical trial for VAP treatment with doripenem had been terminated early due to significant safety concerns. The trial initiated by Kollef et al. was aimed at evaluating the effects of doripenem on treatment of patients with VAP, demonstrated excess mortality and a numerically poorer clinical cure rate among doripenem-treated subjects compared to those treated with imipenem–cilastatin.[3,4] In March 2014, the FDA issued further safety information stating the approved doripenem label changes for highlighting the increased risk of death for ventilator patients with pneumonia.[5] By now, several randomized controlled trials (RCTs) have assessed doripenem efficacy and safety compared to some empirical antimicrobial agents, including three trials evaluating NP and VAP treatment. So far, however, there is no systematic review and meta-analysis comparing the efficacy and safety of doripenem and comparators for treating bacterial infections. Although a meta-analysis was published by Jenkins in 2009, it was limited to patients with *Pseudomonas* infections enrolled in four clinical trials.[6] Therefore, we performed a comprehensive and updated meta-analysis to provide better evidence of the efficacy and safety doripenem on treating bacterial infections, especially focused on treatment efficacy and safety for NP and VAP patients.

Methods

Eligibility criteria

To be eligible a study would have to be designed as a RCT that directly compared efficacy or safety of doripenem with any other active antimicrobial agents for treating bacterial infections.

Retrospective studies were excluded, as well as those focused on in vitro susceptibility testing, experimental animal studies or pharmacokinetic–pharmacodynamic evaluations.

Outcome measures

The primary outcome measure was clinical treatment efficacy on clinical evaluable (CE) population and clinical modified intent-to-treatment (c-mITT) population. The secondary outcomes were microbiological treatment success rates on microbiology evaluable (ME) population and microbiological modified intent-to-treatment (m-mITT) population. At last, AEs and all-cause mortality on modified intent-to-treatment (m-ITT) population were assessed.

The details and definitions for study populations were demonstrated as followed: (i) mITT: patients who received at least one dose of study drugs; (ii) c-mITT: patients who met minimum disease criteria on mITT population; (iii) CE: patients who did not receive confounding doses of prior or concomitant study drugs, received sufficient therapeutic doses, and had a test-of-cure (TOC) efficacy assessment per protocol on c-mITT population. (iv) m-mITT: patients who had at least one baseline isolate on c-mITT population; and (vi) ME: patients who had at least one baseline isolate susceptible to each regimen and had a microbiologic response assigned on CE population.

Information sources and literature search

Publications at PubMed and Embase data sets up to July 31, 2014 were reviewed with the search strategies “doripenem” or “Doribax” and “efficacy”, “safety”, “infection” or “randomized controlled trials”.

Study selection and data extraction

Two reviewers (Qu and Hu) searched and examined the publications independently. The included studies were examined separately according to the eligibility criteria described above. Evaluation of the methodological quality of the RCTs was performed by two reviewers independently according to the Jadad scoring system.[7] The high quality trials were awarded three or more points with a maximum of five points. When disagreement occurred, a third author (Zhou) resolved the problem in time. The following data were extracted from every included study: year of publication, type of infection, patient population, drug information, clinical and microbiological outcomes of treatment, incidence of AEs, and all-cause mortality.

Statistical analysis

The software Review Manager, version 5.2 was used to conduct the statistical analyses. Heterogeneity was evaluated with Q statistic generated from the χ^2 test and inconsistency with I^2 measure.[8] Heterogeneity was considered significant when p-value was less than 0.10 or I^2 more than 50%. A Mantel–Haenszel fixed-effect model (FEM) with pooled odds ratio (OR) and 95% confidence interval (CI) was used for outcome analyses when heterogeneity was not significant. When heterogeneity was obvious DerSimonian and Laird random-effects model (REM) was used for outcome analysis.