Population Pharmacokinetics of Doripenem in Critically Ill Patients with Sepsis in a Malaysian Intensive Care Unit

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Abstract

Doripenem has been recently introduced in Malaysia and is used for several infections in the intensive care unit. However, limited data currently exist to guide optimal dosing in this scenario. We aimed to describe the pharmacokinetics of doripenem in Malaysian critically ill patients with sepsis and use Monte Carlo dosing simulations to develop clinically relevant dosing guidelines for these patients. In this pharmacokinetic study, 12 critically ill adult patients with sepsis requiring 600 mg of doripenem daily 3 to 4-hourly were enrolled. Serial blood samples were collected on 2 different days, and population pharmacokinetic analysis was performed using a nonlinear mixed-effects modeling approach. A two-compartment linear model with between-subject and betweenoccasion variability on clearance was used. The typical value of clearance and interindividual variability in this compartment were 0.41 L/hr and 0.14 (lognormal, respectively). Doripenem clearance was significantly influenced by patients' creatinine clearance (CLCR), such that a 30% decrease in the estimated CLCR would increase doripenem CL to 62%. Monte Carlo dosing simulations suggested that, for patients with a CLCR of less than 50 mL/min, a dose of 1,600 mg every 8 hr as a 6-hr infusion or 3,200 mg every 12 hr as a 4-hr infusion is optimal for patients with a CLCR of 30 to 100 mL/min, while a dose of 1,000 mg every 8 hr as a 6-hr infusion is best for patients manifesting a CLCR of < 10 mL/min. Findings from this study suggest that doripenem usage in Malaysian critically ill patients, an alternative dosing approach may be needed, particularly when robust data related to patient populations are lacking.

Keywords:
- Pharmacokinetics
- Critically Ill Patients
- Sepsis
- Intensive Care Unit
- Doripenem
- Pharmacokinetic

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Population pharmacokinetics of doripenem in critically ill patients with sepsis in a Malaysian intensive care unit.


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Abstract

Doripenem has been recently introduced in Malaysia and is used for severe infections in the intensive care unit. However, limited data currently exist to guide optimal dosing in this scenario. We aimed to describe the population pharmacokinetics of doripenem in Malaysian critically ill patients with sepsis and use Monte Carlo dosing simulations to develop clinically relevant dosing guidelines for these patients. In this pharmaco kinetic study of 12 critically ill adult patients with sepsis receiving 500 mg of doripenem every 8 h for 48 h, blood samples were collected on 2 different days, and population pharmacokinetic analysis was performed using a nonlinear mixed-effects modeling approach. A two-compartment linear model, with between-subject and betweenoccasion variability on clearance was adequate in describing the data. The typical volume of distribution and clearance of doripenem in this cohort were 6.47 L/kg and 0.14 L/hr/kg, respectively. Doripenem clearance was significantly influenced by patients’ creatinine clearance (CLCR), such that a 30-mL/min increase in the estimated CLCR would increase doripenem CL by 2%. Monte Carlo dosing simulations suggested that, for patients with a 30-mL/min CLCR or a dose of 1,000 mg every 8 h (fixed-dose administration is optimal for patients with a CLCR of 30 to 100 mL/min), while a dose of 2,300 mg every 8 h is a 4-h infusion is best for patients manifesting a CLCR of < 60 mL/min. Findings from this study suggest that, for doripenem usage in Malaysian critically ill patients, an alternative dosing approach may be meritorious, particularly when neutropenic or resistant pathogens are involved. Copyright © 2010, American Society for Microbiology. All Rights Reserved.

Indexed Keywords

- ENTER: drug terms: doripenem
- ENTER: medical terms: adult; aged; adult; blood sampling; central volume of distribution; clinical article; creatinine clearance; critically ill patient; drug clearance; female; human; intensive care unit; Malaysian; male; middle aged; minimum inhibitory concentration; Monte Carlo method; multivariate resistance; open study; peripheral volume of distribution; practice guideline; priority journal; prospective study; sepsis; ventilator associated pneumonia; volume of distribution; young adult

Chemicals and CAS Registry Numbers: doripenem, 149316-81-3

Drug brand name: doripenem.


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References (53)