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 pharmacokinetic study, 12 critically ill adult patients with sepsis receiving 500 mg of doripenem every 8 h as a 1-hour infusion 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 between-occasion variability on clearance was adequate in describing the data. The typical volume of distribution and clearance of doripenem in this cohort were 0.47 liters/kg and 0.14 liters/kg/h, 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 52%. Monte Carlo dosing simulations suggested that, for pathogens with a MIC of 8 mg/liter, a dose of 1,000 mg every 8 h as a 4-h infusion is optimal for patients with a CLCR of 30 to 100 ml/min, while a dose of 2,000 mg every 8 h as a 4-h infusion is best for patients manifesting a CLCR of > 100 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 multidrug resistance pathogens are involved.

Keywords

KeyWords Plus: AUGMENTED RENAL CLEARANCE; BETA-LACTAM ANTIBIOTICS; ASIA-PACIFIC REGION; IN-VITRO ACTIVITY; NOSOCOMIAL PNEUMONIA; TARGET ATTAINMENT; MEROPENEM; CARBAPENEMS; PATHOGENS; PHARMACODYNAMICS

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Population pharmacokinetics of doripenem in critically ill patients with sepsis in a Malaysian intensive care unit (Article)

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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 pharmacokinetic study, 12 **critically ill** adult **patients** with **sepsis** receiving 500 mg of **doripenem** every 8 h as a1-hour infusion 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 between-occasion variability on clearance was adequate **in** describing the data. The typical volume of distribution and clearance of **doripenem in** this cohort were 0.47 liters/kg and 0.14 liters/kg/h, respectively. **Doripenem** clearance was significantly influenced by **patients'** creatinine clearance (CL_{CR}), such that **a** 30-ml/min increase **in** the estimated CL_{CR} would increase **doripenem** CL by 52%. Monte Carlo dosing simulations suggested that, for pathogens with **a** MIC of 8 mg/liter, a dose of 1,000 mg every8hasa4-hinfusion is optimal for **patients** with a CL_{CR} of 30 to 100 ml/min, while **a** dose of 2,000 mg every 8 h as **a** 4-h infusion is best for **patients** manifesting **a** CL_{CR} of >100 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 multidrug resistance pathogens are involved.

Indexed keywords

EMTREE drug terms: doripenem

EMTREE medical terms: adult; aged; Article; blood sampling; central volume of distribution; clinical article; cohort analysis; creatinine clearance; **critically ill** patient; drug clearance; female; human; **intensive care unit; Malaysian**; male; middle aged; minimum inhibitory concentration; Monte Carlo method; multidrug 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, 148016-81-3

Drug tradename: doribax, Janssen Cilag, United States;doribax, Raritan, United States.

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