ABSTRACT

Background: Doripenem (DORI), an investigational parenteral carbapenem, inhibits a great number of Gram-positive and -negative pathogens, as well as P. aeruginosa (PSA), among non-fermentative bacilli with acquired and intrinsic resistances (R). DORI was compared to imipenem (IMP) and meropenem (MERO) tested against contemporary (2003-2005) PSA isolated from patients in North America (NA), Latin America (LA), and Europe (EU) using a validated, reference, broth microdilution method in cation-adjusted Mueller-Hinton broth (CA-MHB). CLSI broth microdilution minimum inhibitory concentration (MIC) breakpoints were used for comparison purposes and because of similar pharmacokinetic and pharmacodynamic features with short infusion times (1 hour). Results were analyzed by geographic region (continents) due to initially recognized differences in resistance rates. IMP was the only carbapenem with a rank order of activity (A) favoring DORI > IMP > MERO.

RESULTS

• Doripenem (DORI), an investigational parenteral carbapenem, inhibits a great number of Gram-positive and -negative pathogens, as well as P. aeruginosa (PSA), among non-fermentative bacilli with acquired and intrinsic resistances (R). DORI was compared to imipenem (IMP) and meropenem (MERO) tested against contemporary (2003-2005) PSA isolated from patients in North America (NA), Latin America (LA), and Europe (EU) using a validated, reference, broth microdilution method in cation-adjusted Mueller-Hinton broth (CA-MHB). CLSI broth microdilution minimum inhibitory concentration (MIC) breakpoints were used for comparison purposes and because of similar pharmacokinetic and pharmacodynamic features with short infusion times (1 hour). Results were analyzed by geographic region (continents) due to initially recognized differences in resistance rates. IMP was the only carbapenem with a rank order of activity (A) favoring DORI > IMP > MERO.

• In Latin America, imipenem had 3% greater coverage at 2 mg/L, than meropenem. Whereas meropenem had 3% greater coverage at 4 mg/L, than imipenem (Table 1 and Figure 3).

• In some North American medical centers (17%), imipenem had a greater susceptibility rate than meropenem (data not shown). However, susceptibility to doripenem remained 4-1.5% greater than imipenem in these institutions. The cause of these variations appears to be strain and resistance mechanisms (efflux, OMP alterations, chromosomal AmpC expression).

• In Latin America, doripenem had the lowest rate of spontaneously occurring resistance. The enhanced doripenem activity was not altered by site or geographic variations in resistance mechanisms.

INTRODUCTION

Pseudomonas aeruginosa can be difficult to treat because of intrinsic resistance, caused by efflux systems and chromosomal β-lactamase, or emergent multidrug-resistance (MDR) patterns. Combination therapy has long been applied when treating patients with this pathogen, and early studies documented in vitro synergistic and additive effects when various antimicrobial agents were tested in combination. β-Lactams used in combination with aminoglycosides can be synergistic against Gram-negative organisms, including P. aeruginosa, and patients have improved clinically on such regimens. More recently, carbapenems have been prescribed for patients with P. aeruginosa infections, because of the high rates of resistance to other antimicrobial classes often encountered. However, rapid development of resistance to carbapenems, even with combination therapies, has been documented, and some studies suggest that antimicrobial penicillinil may inactivate aminoglycosides.

Doripenem (formerly S-4661[Shionogi]) is a broad-spectrum parenteral carbapenem being developed by Johnson & Johnson that is in the late stages of clinical development. The microbiological and pharmacokinetic/pharmacodynamic features of doripenem have been described previously and clinical success in human trials has been reported in Japan. Further development of clinical and pharmacological studies of doripenem confirmed the uniformly broader coverage of P. aeruginosa strains compared with imipenem and meropenem.

In Latin America, doripenem had the lowest rate of spontaneously occurring resistance. The enhanced doripenem activity was not altered by site or geographic variations in resistance mechanisms.

MATERIALS AND METHODS

A total of 3330 non-duplicate P. aeruginosa strains were collected from significant infections in patients hospitalized in Europe (29 sites, 1343 strains), North America (34 sites, 1199 strains), and Latin America (12 sites, 798 strains). Organisms were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), where the identification was confirmed and reference susceptibility testing performed. Doripenem, imipenem, and meropenem were tested in validated microdilution tests in cation-adjusted Mueller-Hinton broth using the Clinical and Laboratory Standards Institute (CLSI) methods (MT-AT, 2006). All interpretations were by CLSI M100-S16 breakpoint criteria. Doripenem was assigned the same susceptible breakpoint MIC (≤4 mg/L) for comparison purposes and because of similar pharmacokinetic and pharmacodynamic features with short infusion times (1 hour). The results were analyzed by geographic region (continents) due to initially recognized differences in resistance rates. Also, variations occurring in the resistance rates for imipenem and meropenem in specific North American sites were assessed as to their impact on doripenem’s spectrum of activity and potency versus P. aeruginosa.

RESULTS

• The rank order of the 3 carbapenems tested against P. aeruginosa strains at the breakpoint MIC was consistent: doripenem (≤8 mg/L) susceptibility > meropenem (73-88% susceptibility) > imipenem (70-86% susceptibility) (Table 1).

• In all 3 regions, the inhibition of P. aeruginosa at 8 mg/L, was equal for imipenem and meropenem (Figures 2-4).

• Important differences were noted in the susceptibility rates for the 3 carbapenems between regions, with greatest susceptibility for P. aeruginosa isolated in North America (64-75%) > Europe (76-84%) > Latin America (73-80%) (Table 1 and Figure 1).

• In Latin America, imipenem had 3% greater coverage at 2 mg/L, than meropenem. Whereas meropenem had 3% greater coverage at 4 mg/L, than imipenem (Table 1 and Figure 3).

• In some North American medical centers (17%), imipenem had a greater susceptibility rate than meropenem (data not shown). However, susceptibility to doripenem remained 4-1.5% greater than imipenem in these institutions. The cause of these variations appears to be strain and resistance mechanisms (efflux, OMP alterations, chromosomal AmpC expression).

CONCLUSIONS

• High volume, reference method surveillance studies of doripenem confirmed the uniformly broader coverage of P. aeruginosa strains compared with imipenem and meropenem.

• The enhanced doripenem activity was not altered by site or geographic variations in resistance mechanisms.

SELECTED REFERENCES


