Abstract

HUMAN PHARMACOKINETICS AND MONTE CARLO SIMULATION

1] The magnitude of the %T>MIC required for a static effect with Doripenem was similar to that previously observed with other carbapenems. Potential utility of DORI against ESBL-producing isolates.

METHODS: Physicians and house staff practicing in a 24-bed medical-surgical-trauma ICU are now required to

AUC 1.65 mg*h/L

3] These data suggest that Dosing

PK-PD targets were defined as the target exposure associated with a static and/or 1-log kill. CONCLUSIONS: ESBL production in the strains had no impact on the T>MIC needed for in vivo efficacy nor the DOR activity against ESBL-producing and non-ESBL isolates. We defined the PK/PD parameter target necessary for efficacy in an animal infection of cephalosporin resistance was also determined and is listed in Table 1. MICs were determined in MHB by standard techniques. All MICs were performed at least in duplicate. The gram-negative strains included ESBL producing isolates.

Concentration (mg/L)

Time  (hrs)

% T>MIC

02

03

04

05

06

07

08

09

10

MAGNITUDE OF TIME ABOVE MIC NECESSARY FOR EFFICACY

The half-life of Doripenem in individual mice was determined by linear least-squares regression. AUC was calculated by the trapezoidal rule from mean concentrations and extrapolated to infinity. DOSING STRATEGIES

To determine if the %T>MIC required for efficacy was similar for both ESBL and non-ESBL producing gram-negative bacilli, we evaluated the activity of a hourly dosing regimen of Doripenem against 10 strains of gram-negative bacilli with MICs ranging from 0.015 to 0.05 mg/L. For the gram-negative bacilli both cephalosporin-resistant and -susceptible strains (due to ESBL production) were used.

Doripenem was administered subcutaneously. Dose levels ranged from 0.01 to 0.56 mg/kg. Each dose level was provided every 6 h (4 times) over the 24 h treatment period.

DATA ANALYSIS

The in vivo response curves was mathematically characterized using a maximum effect model. This methodology uses the Hill equation to estimate by non-linear regression the maximum effect (Emax), the dose (%Emax) required to obtain 50% of the Emax, and the slope of the dose-response relationship. From these parameters we use then calculate the dose required to produce a net bactericidal effect over 24 h. These parameters were also used to calculate the dose required to produce a 1-log kill organism.

In vivo Doripenem Activity Against 10 Gram-Negative Bacteria in a Neutropenic Murine Infection Model

Figure 2

% T>MIC

Table 3 demonstrates the impact of varying dose, interval, and infusion durations on PK-PD target attainment (% of MICs of 0.12 and 0.25 mg/L. Simulations based on a range of median MIC dilutions from 0.25-10 mg/L were considered.

Table 1: Doripenem In-vitro Activity Against Cephalosporin-Susceptible and -Resistant Gram-Negative Bacilli

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (mg/L)</th>
<th>0.015</th>
<th>0.03</th>
<th>0.06</th>
<th>0.12</th>
<th>0.25</th>
<th>0.5</th>
<th>1.0</th>
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<tbody>
<tr>
<td>E. coli 25922</td>
<td>0.015</td>
<td>22.1</td>
<td>38</td>
<td>113</td>
<td>47</td>
<td>na</td>
<td>na</td>
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<td>K. pneumoniae 51504</td>
<td>0.06</td>
<td>55.6</td>
<td>34</td>
<td>216</td>
<td>49</td>
<td>na</td>
<td>na</td>
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<td>P. aeruginosa 27853</td>
<td>0.50</td>
<td>46</td>
<td>23</td>
<td>100</td>
<td>28</td>
<td>245</td>
<td>35</td>
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<td>E. cloacae 31-54a</td>
<td>0.50</td>
<td>23.7</td>
<td>20</td>
<td>78.4</td>
<td>27</td>
<td>276</td>
<td>36</td>
<td>36</td>
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</tr>
<tr>
<td>E. coli 154</td>
<td>0.06</td>
<td>8.0</td>
<td>32.0</td>
<td>TEM27</td>
<td></td>
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<td></td>
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<tr>
<td>K. pneumoniae 149</td>
<td></td>
<td>32.0</td>
<td>4.0</td>
<td>SHV1, CTX M10</td>
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<tr>
<td>E. cloacae 31-54a</td>
<td></td>
<td>0.12</td>
<td>1.0</td>
<td>Amp C</td>
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Conclusions

1] The magnitude of the %T>MIC required for a static effect with Doripenem was similar to that previously observed with other carbapenems. 2] Drug resistance due to ESBL production did not impact the %T>MIC required for efficacy. 3] These data suggest that Doripenem may be useful for the treatment of infections caused by ESBL-producing bacilli.