In Vivo Pharmacodynamic Activity of BC-3781

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ABSTRACT

Background: BC-3781 is an anti microbial agent of the pleuromutilin class inhibiting the prokaryotic protein synthesis. BC-3781 is undergoing clinical development for intravenous and oral treatments of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). We compared the efficacy of BC-3781 against a panel of beta-hemolytic streptococci (including methicillin-sensitive) and Streptococcus pneumoniae (including penicillin-resistant) in neutropenic murine thigh and lung infection models. Methods: Mice were treated with total doses of 5, 10, 15 and 20 mg/kg of BC-3781 at days 0 and 1 or 2. Viable cell counts in thighs and lungs were determined by a standard plate count method. Results: BC-3781 exhibited time-dependent killing with moderate neutropenic effects (PAEs) of 1-3 hours. The 24 h AUC/MIC of BC-3781 for S. pneumoniae was around 3.0 to 3.5 for all doses; re-growth at 20 mg/kg was intermediate between the other two doses. This suggests that the in vivo post-antibiotic effect (PAE) with S. pneumoniae was around 3.0 to 3.5 for BC-3781. The effect of single doses of 10, 20 and 40 mg/kg of BC-3781 on in vivo killing and re-growth of S. pneumoniae ATCC 10813 is shown in Figure 5. Each point represents the mean of three mice. The rate of killing of the strain of S. pneumoniae was not increased by higher drug concentrations. However, re-growth of S. pneumoniae began at 4 h at 10 mg/kg and at 6 h with 40 mg/kg; re-growth at 20 mg/kg was intermediate between the other two doses. This suggests that the in vivo post-antibiotic effect (PAE) with S. pneumoniae was around 3.0 to 3.5 h for BC-3781.

RESULTS

Table 1. Pharmacokinetic properties of single-dose BC-3781 and linezolid in mice

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose [mg/kg]</th>
<th>Cmax [ng/mL]</th>
<th>AUC0-24h [µg·h/mL]</th>
<th>𝜌C0 [µg/mL]</th>
<th>𝜌C24 [µg/mL]</th>
<th>T&gt;MIC [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC-3781</td>
<td>10</td>
<td>1.26</td>
<td>2.39</td>
<td>3.00</td>
<td>3.00</td>
<td>2.0</td>
</tr>
<tr>
<td>Linezolid</td>
<td>10</td>
<td>0.50</td>
<td>0.81</td>
<td>0.60</td>
<td>0.60</td>
<td>0.8</td>
</tr>
</tbody>
</table>

The effect of single doses of 10, 20 and 40 mg/kg of BC-3781 on in vivo killing and re-growth of S. pneumoniae ATCC 10813 is shown in Figure 5. Each point represents the mean of three mice. The rate of killing of the strain of S. pneumoniae was not increased by higher drug concentrations. However, re-growth of S. pneumoniae began at 4 h at 10 mg/kg and at 6 h with 40 mg/kg; re-growth at 20 mg/kg was intermediate between the other two doses. This suggests that the in vivo post-antibiotic effect (PAE) with S. pneumoniae was around 3.0 to 3.5 h for BC-3781.

Funding: This study was supported by grants from the NIH (5T32AI007166) and the W. GarfieldWellcome Trust (092337). The authors would like to thank Dr. Kelly Chom and Dr. Alice Huang for their help in preparing this manuscript.

CONCLUSIONS

BC-3781 exhibited time-dependent killing with moderate neutropenic effects (PAEs) of 1-3 hours. The 24 h AUC/MIC of BC-3781 for S. pneumoniae was around 3.0 to 3.5 for all doses; re-growth at 20 mg/kg was intermediate between the other two doses. This suggests that the in vivo post-antibiotic effect (PAE) with S. pneumoniae was around 3.0 to 3.5 h for BC-3781.

REFERENCES


In vivo Breakpoints Associated with Efficacy: The in vivo pharmacodynamic activity of BC-3781 was evaluated against S. aureus as predominant ABSSSI pathogen. The activity of 112 doses of BC-3781 was investigated in two PKPD murine thigh infection studies with similar set up. The S. aureus group included two MSSA and six MRSA strains, including hospital-associated and community-acquired strains. The pharmacodynamics of BC-3781 was similar for all S. aureus strains showing a good in vitro - in vivo correlation (MIC - static dose relationship). The total AUC/MIC values for each dose were calculated based on PK parameters of infected mice and normalized over the free fraction, as determined by in vitro experiments using equilibrium dialysis method. Accordingly, a value of 20% unbound BC-3781 was used for calculations of 24 h AUC/MIC. The individual efficacy at corresponding 24 h AUC/MIC ratios of eight S. aureus strains out of two studies and the sigmoid curve fit of mean and Cmax are depicted in Figure 5. The 24 h AUC/MIC necessarily to produce a net static effect against S. aureus was 11.5 with a 95% confidence interval band of 9.69 to 13.4. The mean 24 h AUC/MIC necessary to produce a net static effect against S. pneumoniae, depicted in Figure 6, was with 3.59 with a 95% confidence interval band of 2.45 to 4.60.

Impact of Neutrophils and Site of Infection on Activity of BC-3781: S. pneumoniae ATCC 10813 is capable of infecting the lungs and lungs of both normal and neutropenic mice. In these experiments, the lungs and the lungs were infected in the same mice. The dose-response relationship determined in the thighs and lungs of both, neutropenic and normal mice, only showed a marginal effect in enhancing activity of BC-3781 in the immuno-competent mice (Figure 7).

Figure 1. Relationship of different PK/PD indices on the antimicrobial activity of BC-3781 against S. pneumoniae ATCC 10813 in the lungs of neutropenic mice.

Figure 2. Relationship of different PK/PD indices on the antimicrobial activity of BC-3781 against S. aureus ATCC 29213 in the lungs of neutropenic mice.

Figure 3. Effect of single doses of BC-3781 on time course of antimicrobial activity with S. pneumoniae ATCC 10813 in the lungs of neutropenic mice.

Figure 4. Effect of single doses of BC-3781 on time course of antimicrobial activity with S. aureus ATCC 29213 in the lungs of neutropenic mice.

Figure 5. Inhibitory E max model and 95% CI of BC-3781 against S. pneumoniae ATCC 10813 in the lungs and lungs of normal and neutropenic mice.

Figure 6. Inhibitory E max model and 95% CI of BC-3781 against S. aureus ATCC 19618 in the lungs and lungs of normal and neutropenic mice.

Figure 7. Dose-response relationship for 10-hour dosing of BC-3781 (1x) against S. pneumoniae ATCC 10813 in the lungs and lungs of normal and neutropenic mice.

BC-3781

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Introduction

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