Disposition of MGB-BP-3, a New Class of Antibacterial Agent, After Oral Administration in a Hamster Model of Severe Clostridium difficile Associated Diarrhoea (CDAD)

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ABSTRACT

Background: MGB-BP-3 (MGB) is a new class of antibacterial agent that binds selectively to the Minor Groove of DNA and possesses strong activity against Gm +ve bacteria, including MRSA, VRE and C. difficile. A recent study showed MGB to be very effective in the eradication of C. difficile in a severe CDAD hamster model. This study assessed the disposition of two MGB formulations in plasma and intestines after oral administration.

Methods: The hamsters were given 30 mg/kg oral clindamycin, followed 24 h later by C. difficile strain (B1) by gavage. Twenty hours later hamsters received a single oral dose of vehicle or 100 mg/kg MGB, suspended either as a freebase or colonic delivery microparticles. The concentrations of MGB were assessed in plasma and intestines over a 24 hour period. In addition, the contents from the small intestine, caecum and colon were collected for C. difficile burden assessment.

Results: A severe infection caused by C. difficile was established in all hamsters. Following the single dose of MGB, transient reductions in burden were observed in all regions of the GI tract sampled. The PK profiles indicate that, following oral administration, only a few animals had a detectable presence of MGB in plasma. The maximum plasma concentrations of the microparticle and freebase formulations were 253mg/ml and 15mg/ml respectively. The freebase suspension of MGB achieved higher concentration in the small intestines and the microparticles in the caecum and colon. MGB remained in the colon for the 24 hour observation period. The largest drug exposure was measured in the colon. The maximum MGB concentration with microparticles was 1.673μg/ml, and with freebase 937μg/ml. The microparticle concentrations exceeded MGB’s MIC for C. difficile by more than 1000 fold.

Conclusion: Our results indicate that MGB has a favourable pharmacokinetic profile for the treatment of C. difficile infections.

INTRODUCTION

MGB is a new class of antibacterial agent that binds selectively to the Minor Groove of DNA and possesses strong activity against Gm +ve bacteria, including MRSA, VRE, Streptococci and C. difficile.

Recent study (1) showed MGB to be very effective in the eradication of C. difficile in a severe CDAD hamster model. The aim of this study was to assess the disposition of two MGB formulations in plasma and intestines after oral administration.

METHODS

Material

MGB as a freebase suspension or a formulation for localised delivery of drugs to the ileo-colonic regions of the GI tract. Kuecept’s ProRelease™ technology was used to load MGB into delayed release microparticles using the cationic polymer Eubright L100 with a target drug loading of 20 % w/w. The release of MGB was achieved at a pH of 6.8.

Hamster model of severe C. difficile induced diarrhoea

Hamsters were preconditioned 24 h pre-infection with a single oral dose of 30mg/kg clindamycin. 24 h later they were infected with 100 spores of C. difficile B1/NAP1/027 (RE- type B1). 20h post infection hamsters received a single oral dose of the vehicle or 10mg/hamster (approximately 100 mg/kg) of MGB, freebase suspension or colonic delivery microparticles (Table 1). Concentrations of MGB were assessed in plasma and intestines at timepoints: 0.25, 2, 4, 6, 8, 10, and 24 h post dose. In addition, C. difficile burden was assessed in the small intestine, caecum and colon. 3 hamsters were used in each treatment group at each time point (Table 1).

Table 1 – Treatment groups

<table>
<thead>
<tr>
<th>Experimental condition</th>
<th>Number of Hamsters</th>
<th>Treatment</th>
<th>Dosage</th>
<th>First dose time/hrs</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>Vehicle</td>
<td>-</td>
<td>20</td>
<td>Oral</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>MGB-BP-3 freebase</td>
<td>10mg/hamster</td>
<td>20</td>
<td>Oral</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>MGB-BP-3 microparticles</td>
<td>10mg/hamster</td>
<td>20</td>
<td>Oral</td>
</tr>
</tbody>
</table>

RESULTS

Severe CDAD was established 30 h post infection in vehicle treated animals (all succumbed to infection within 12 h post treatment). In contrast, the clinical condition of the MGB freebase and microparticle treated hamsters stabilised (except one hamster dosed with MGB microparticles which was euthanised 36 h post infection due to hypothermia). At 12-14h post treatment, hamsters treated with MGB freebase or microparticles had mild symptoms of weight tail and moderate hypothermia (34-36°C). In 5 of 6 treated hamsters, symptoms had resolved by the time of collection at the 24 h post-treatment sample. Both MGB formulations were well tolerated and there were no signs of poor tolerability.

C. difficile intestinal burden assessment.

At the time of treatment high C. difficile burdens were observed in the small intestine (~46,000 CFU/g), colon (~20,000 CFU/g) and caecum (~12,600 CFU/g). Following a single dose of MGB, transient reductions in burden were observed in all sections of the GI tract sampled (Figure 1).

Pharmacokinetics of MGB in plasma

The PK following oral administration show very little MGB in plasma (Figure 2). MGB freebase suspension was detected in only 27% of hamsters with a maximum individual concentration of 15 ng/ml. In contrast the microparticle formulation was observed in only 25% of hamsters, with the maximum individual peak being 203 ng/ml. The freebase peaked 4 h, and the microparticles 6 h after oral administration. In two animals (one for each formulation) MGB was detected 24 h after oral administration.

CONCLUSIONS

• MGB was highly effective at improving survival in a hamster CDAD model after a single administration.
• MGB freebase and microparticle formulation administered as a single dose of 10mg/hamster caused transient reduction in the C. difficile burden in all sections of the GI tract.
• The highest suppression of burden in the small intestine was observed 2 h post treatment, and in the caecum and colon 2 – 10 h post treatment.
• Plasma concentrations of MGB after oral administration were very low, suggesting negligible systemic absorption.
• The freebase suspension of MGB achieved higher concentrations in the small intestines and the microparticles in the caecum and colon. The longest drug exposure was measured in the colon where it remained for the 24 h observation period.
• The maximum intestinal MGB concentration with microparticles was 1.673μg/ml, and freebase 937μg/ml. T_{1/2} for freebase was 15 min, and for microparticles 6 h. The microparticle concentrations exceeded MGB’s MIC for C. difficile by more than 1000 fold.
• The results indicate that MGB has a favourable PK profile for the treatment of C. difficile infections.

REFERENCES