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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.

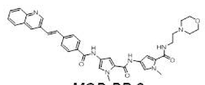
Methods: The hamsters were given 30 mg/kg oral clindamycin, followed 24 h later by *C. difficile* (strain BI1) by gavage. Twenty hours later hamsters received a single oral dose of vehicle or 100mg/kg MGB, suspended either as a freebase or colonic delivery microparticles. The concentrations of MGB were 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 263ng/ml and 15ng/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*.



MGB-BP-3

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 Eudragit 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 24h pre-infection with a single oral dose of 30mg/kg clindamycin. 24h later they were infected with 100 spores of *C. difficile*, B1/NAP1/027 (REA-type BI1).

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 predose, 0.25, 2, 4, 6, 8, 10, 12, 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

Experimental condition	Number of Hamsters	Treatment	Dosage	First dose time/hrs	Route
1	15	Vehicle	-	20	Oral
2	24	MGB-BP-3 freebase	10mg/hamster	20	Oral
3	24	MGB-BP-3 microparticles	10mg/hamster	20	Oral

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 euthanized 34h post infection due to hypothermia). At 12-14h post treatment, hamsters treated with MGB freebase or microparticles had mild symptoms of wet 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).

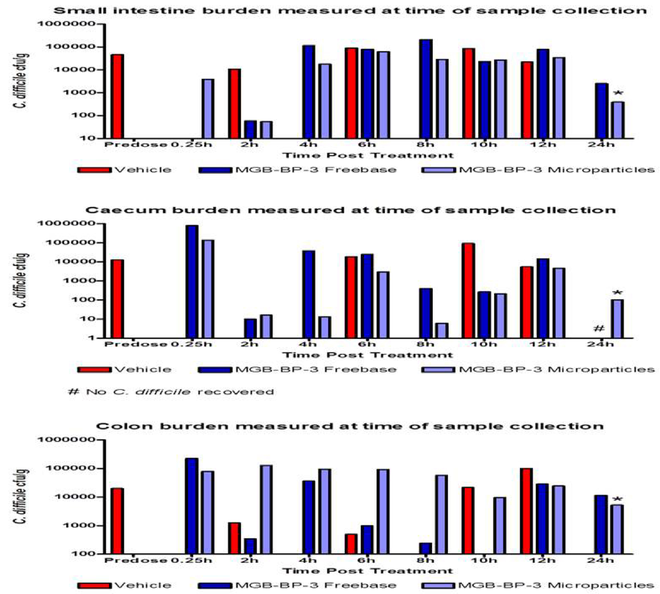


Fig. 1 - Mean *Clostridium difficile* burden in the small intestine, caecum and colon at the time of euthanasia (N=3).

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 37% 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 263 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.

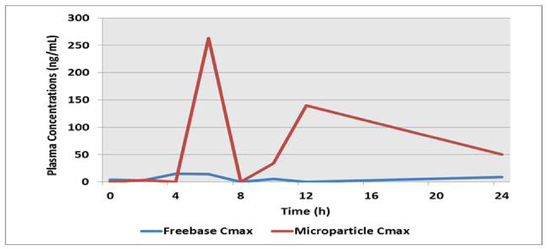


Fig. 2 – MGB concentrations in plasma after oral administration of 10mg/hamster MGB formulated as a freebase and as colonic delivery microparticles. (N=3).

RESULTS

Pharmacokinetics of MGB in the intestines

The PK of the MGB formulations in the intestines is presented in Figure 3.

MGB was rapidly detected in the small intestine following oral delivery (C_{max} within 15 minutes). However, little MGB remained in the small intestine after 12 h post administration.

The levels of freebase in the small intestine were higher than microparticles, indicating that the microparticle formulation retains the MGB before releasing into the caecum and colon.

MGB was detected in the caecum at high levels C_{max} between 2 and 6 h of administration), remaining in the caecum for 12 h post administration,

The PK of MGB in the colon was similar to the caecum with high levels following oral delivery (C_{max} between 4 and 6 h of administration). MGB remained in the colon throughout the 24 h observation period .

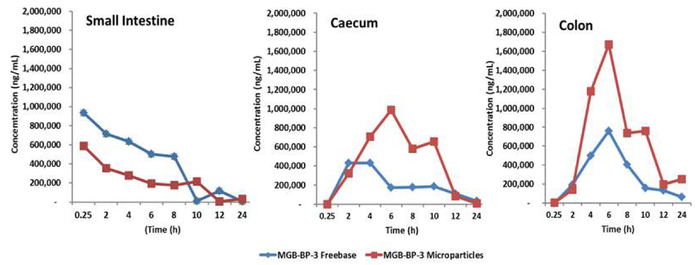


Fig. 3 – The mean MGB concentrations in the small intestine, caecum and colon after oral administration of 10mg/hamster MGB formulated as a freebase and as colonic delivery microparticles. (N=3).

The highest drug exposure was in the colon. In addition, the maximum concentration following MGB microparticles, was approximately twice MGB freebase.

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 largest 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_{max} 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

1. M. Ravic et al. MGB-BP-3, a New Class Antibacterial Agent, Effective in the Treatment of Severe Clostridium difficile Associated Diarrhoea in a Hamster CDAD Model. ICAAC 2011, Abstract B-1196b, 2011.