Vancomycin Delays Clindamycin-Induced Fatality in the Hamster Model of Clostridioides [Clostridium] difficile Infection

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ABSTRACT

Antibiotics can leave the host gut microbiome susceptible to Clostridioides [Clostridium] difficile colitogenic and lethal toxin production. For instance, clindamycin-induced susceptibility to C. difficile infection (CDI) results in rapid fatality in hamster models, yet vancomycin has been shown to offer increased survival in hamsters challenged with C. difficile. We aim to develop an antibiotic treatment that will facilitate CDI susceptibility without prompt fatality in hamster models. An antibiotic regimen starting with a continuous vancomycin treatment along with a single clindamycin dosage is thought to reduce the major disruption in the indigenous gut microbiome and prevent clindamycin-induced death. Quantitative polymerase chain reaction (qPCR) of the rpoC gene was used to determine the abundance of C. difficile in the hamster gut flora over the course of an antibiotic treatment, while toxin A and B production was quantified using a toxin immunoassay (ELISA). The vancomycin-centered antibiotic regimen significantly increased survival rates during administration, whereas clindamycin-induced fatalities occurred after a single dosage. qPCR determined that C. difficile proliferation was rapid. C. difficile was detected in feces two days post-C. difficile challenge in vancomycin and clindamycin-treated animals, with C. difficile remaining in high abundance (>10⁸ gene copies/g feces), until death the following day. Vancomycin administered continuously for five days with one clindamycin treatment postponed C. difficile toxin production, while still leaving hosts susceptible to infection. These results suggest that incorporating vancomycin into an antibiotic regimen will delay clindamycin-induced death whilst permitting C. difficile susceptibility, but it cannot delay the rapid pathogenesis of CDI and subsequent fatalities in the hamster model.

OBJECTIVES

- Quantify C. difficile abundance through qPCR assay of rpoC gene
- Determine relative toxin A and B concentration during antibiotic treatment by ELISA
- Determine effectiveness of a vancomycin-centered antibiotic regimen on CDI hamster model

INTRODUCTION

- C. difficile is an anaerobic, rod-shaped, spore-forming, opportunistic pathogen that is associated with nosocomial diarrhea following antibiotic treatment.
- In the United States, approximately 15,000-20,000 people die annually from C. difficile infections (CDI) and result in prolonged hospital stays, which cost the United States health care system over $4.8 billion each year (1, 2, 3, 6).
- Pathogenesis of CDI is directly related to the production of toxin A and toxin B, which bind to receptors on the epithelial cells of the intestinal wall, initiating fluid secretion and loosening of tight epithelial cell junctions (2, 4).
- Clindamycin is an antibiotic that works well against Gram-negative bacteria, but overuse of this antibiotic has led to a rise of clindamycin-resistant bacterial strains and CDI outbreaks.
- Vancomycin is a bactericidal antibiotic that is commonly used to treat CDI in humans and has proven to increase survival rates in hamster models after clindamycin challenge (10).
- Hamsters can experience lethal clindamycin toxicity after a single dose, rendering them harder to infect and study, which has resulted in the search to find a better antibiotic regimen that will allow hamsters to become susceptible to C. difficile infections without rapid fatality (5, 10, 11).
- This research proposes that an antibiotic regimen that initiates vancomycin treatment with a single dose of clindamycin will postpone clindamycin-induced death whilst permitting inducible susceptibility to CDI with delayed pathogenesis.

RESULTS

- Three groups of five male hamsters were used to study the effect of a vancomycin-centered antibiotic regimen.
- Hamsters were examined each day for signs of CDI including but not limited to diarrea, wet tail, anorectal lesions, hunch back, and lethargy.
- The rpoC gene was quantified by real time PCR using the SYBR method.
- Relative toxin concentration was assessed from fecal samples utilizing a sandwich toxin immunoassay (ELISA).

METHODS

- Antibiotic Treatment Survival Curve

CONCLUSION

CDI progression in the hamster model is rapid and lethal, therefore adequate study of CDI in this animal model proposes many challenges. This experiment proposed that an antibiotic regimen that utilized vancomycin before and after a single dosage of clindamycin would prevent clindamycin-induced death, while simultaneously permitting CDI susceptibility with gradual disease progression in the hamster models. In conjunction with Fekety et al., we found that vancomycin was effective at reducing clindamycin-induced fatalities and additionally maintained toxin A and B concentrations at 0% during the antibiotic treatment (10). In spite of this, vancomycin was not effective at postponing the rapid onset of CDI in the hamster model due to the inextinguishable abundance of C. difficile arising suddenly before challenge. The challenge of delaying the pathogenesis of CDI in the hamster model to facilitate study will remain and future research will be directed towards finding a viable solution.

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REFERENCES

- C. difficile Severity: Symptoms of CDI, such as diarrhea, occurred 24 hours prior to fatalities in group A and group B.
- Survival Rates: The vancomycin treatment in group B had survival rates significantly higher (p=0.002, rank test) than that of the clindamycin-only treatment in Group A.
- C. difficile Quantification: All hamsters in group B had presence of C. difficile between 8.97-18.0 log copies/g feces upon death.
- Relative Toxin A and B Concentration: All hamsters in group B died three days post C. difficile challenge (day 11) and had toxins A and B present in their system varying from 72-147%.