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

Amelia E. Fox-King¹, Chrisabelle R. Mefferd¹, Jacqueline R. Phan², Nancy O. Nou¹, Ernesto Abel-Santos², Brian P. Hedlund¹

University of Nevada, Las Vegas, School of Life Sciences¹, Department of Chemistry and Biochemistry²

ABSTRACT

Antibiotics can leave the host gut microbiome susceptible to Clostridioides [Clostridium] difficile colonization 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 (~10^8 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.

METHODS

• 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 diarrehae, wet tail, moribundness, hunched 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).

RESULTS

• Antibiotic Treatment Survival Curve

• Group B: Relative Toxic A and B Concentration

DISCUSSION

• The vancomycin treatment in group B was able to delay clindamycin-induced fatalities until 72 hours post-C. difficile challenge with significantly higher survival rates (p=0.002, log rank test) than those in group A (Fig. 3).
• C. difficile abundance was first observed only two days post-infection in group B and the majority of presence occurring hours before fatalities transpired (Fig. 4).
• The antibiotic regimen used on group B maintained a toxin concentration value as low as the control group (0%), which was not treated with any antibiotics (Fig. 7).
• Although the vancomycin regimen was able to delay clindamycin-induced deaths, the CDI progression was still swift in group B, with the majority of physical symptoms occurring slightly before death (day 11).

CONCLUSION

C. difficile proliferation in the hamster model is rapid and lethal, therefore adequate study of CDI in this animal model poses 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 model. 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 indescribable abundance of C. difficile arising suddenly before the start of the experiment. The challenge of delaying the pathogenesis of CDI in the hamster model to facilitate study still remains and future research will be directed towards finding a viable solution.

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REFERENCES


