

Fidaxomicin and Vancomycin Postantibiotic Effect against *C. difficile*
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Background:

Fidaxomicin (FDX) (formerly OPT-80 and PAR-101) is the first in a new class of narrow spectrum macrocyclic antibiotic drugs that is being developed for the treatment of *Clostridium difficile* infections (CDI). In a recent Phase 3 clinical trial, FDX demonstrated significantly lower recurrence ($p = 0.004$) and better global cure rate ($p = 0.006$) compared to vancomycin. The clinical success may be attributed to targeted bactericidal activity against *C. difficile* and minimal disruption of the gut flora. Another positive attribute is the reported long postantibiotic effect. In this study, we reevaluated the FDX PAE to further demonstrate that the long recovery rate is not an artifact of residual drug that may have nonspecifically adsorbed to the plastic surfaces during the experiment.

Methods:

The PAE of FDX and vancomycin was measured by recovery kinetic curves after one hour of exposure of ATCC *C. difficile* strains (9689 and 43255) to drugs at 4xMIC. To eliminate any potential artifact due to nonspecific binding of drug, following drug removal, the cells were transferred to a new tube and their recovery rate was compared to the cells that remained in the original tube. The PAE was determined as the time required for the titer to increase one log (i.e. 10-fold) over the post-washing titer.

Results:

FDX was found to have a prolonged PAE, an average 10 hrs with the 2 ATCC strains. This result was reproduced in duplicate experiments and the results did not vary more than 2.5 hrs; PAE for strain 9689 was at 9.5 and 10 hrs and for strain 43255 at 9 and 11.5 hrs. The long recovery rates reported earlier most probably represented the postantibiotic sub-MIC effect (PAE-SME); contributed by potential non-specific binding of drug to plastic surfaces. Vancomycin at 4xMIC, used as a control, with the same method, performed as previously reported with a PAE of 0 - 1.5 hrs.

Conclusions:

The findings of this study confirm that FDX PAE is prolonged. Notably it is much longer than that of comparator drug vancomycin (an average of 10 hrs vs. 0 – 1.5 hrs, respectively). Prolonged PAE and prolonged PA-SME could be advantageous in a severe diarrhea condition like CDI in which drugs are administered 2 or 4 times per day but the rapid transit time in the bowel could eliminate the drug in the bowel before the next dose. The residual PAE would provide antimicrobial activity against *C. difficile* even in the absence of drug levels. In addition, a prolonged PAE may allow for reduced dosing of FDX without impairing efficacy.

Keywords:

Fidaxomicin, FDX, OPT-80, *C. difficile*, *C. difficile* infections, Postantibiotic effect