DAV131, an oral adsorbent-based product, exerts a dose-dependent protective effect of hamsters against mouse-associated Clostridium difficile lethal infection

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ABSTRACT

Objectives: Antibiotic treatments greatly impact gut microflora which can result in potentially severe, sometimes lethal Clostridium difficile infection (CDI); prevention strategies would be highly welcome. DAV131, a new adsorbent-based product, significantly reduces the level of residual antibiotics reaching the colon in several animal models. Here, we report an escalating dose study of the protective effect of DAV131 in a mouse-induced CDI model.

Methods: Male Syrian hamsters were administered 30 mg/kg moxifloxacin subcutaneously once per day for 3 days, and infected orally with CD132 1.1 strain 24 h after the last dose. Groups of 10 animals were orally administered 100, 300, 600 or 900 mg/kg DAV131 twice per day to hamsters. Mice and hamsters groups were monitored for mortality, morbidities and viable C. difficile counts were respectively determined using a bioassay and standard agar plates.

Results: Animals administered moxifloxacin alone exhibited rapid mortality upon ingestion of C. difficile spores (60% survival at the 4th, 50% at the 5th, 30% at day 6, and 0% at day 7). Whereas the lowest DAV131 dose of 100 mg/kg did not protect the animals, doses of 300, 600 and 900 mg/kg were highly protective. Regression of 600 mg/kg and 900 mg/kg DAV131 had enabled for the total protection of animals until the end of the experiment at day 22, with no signs of mortality, nor detectable counts of C. difficile in feces. At 300 mg/kg, 80% of the animals were protected from lethal outcome despite some C. difficile pathogen remaining detectable in the feces for a transitory period of 5 days.

Conclusion: Oral DAV131 exhibited a dose-dependent protection of hamsters against moxifloxacin-induced lethal CDI. The protective effect was confirmed in the limitation of C. difficile colonization in the gut, with the concurrent absence of the antibiotic by DAV131. This study clearly shows that DAV131 constitutes a protective strategy that can protect against CDI when applied concomitantly with the causative antibiotic treatment. The development of this promising strategy for the prevention of CDI in humans (code name DAV131) is under way.

RESULTS: Preventive effect of DAV131 on the induction of C. difficile lethal infection by moxifloxacin treatment

INTRODUCTION

Treatment by most antibiotics can lead to CDI by perturbing the colonic commensal flora, thereby allowing colonization of the intestine by C. difficile. Amongst antibiotics, clindamycin, cephalaxin, and fluoroquinolones are considered as the predominant risk factors (1, 2). CDI and most of all, recurrence of CDI in high risk patients are also significantly associated with antibiotic use. The prevention of CDI episodes and CDI relapses would therefore be a major medical need and could be associated with improved quality of life for patients, and a decrease of public health costs.

Da Volterra (Paris, France) has been developing a novel adsorbent-based product, which limits the metabolic output of the adsorbent-based treatments by adsorbing unwanted antibiotic residues in the lower intestine before they reach the colon. This selectivity, effective only on the moxifloxacin-induced hamster Clostridium difficile Associated Disease (CD430) model has only been demonstrated at a high dose of the product (3). Here, we report the results of a dose-dependent study of the protective effect of DAV131.

METHODS

Animals treated with 300 mg/kg bid DAV131 experienced 80% survival. Interestingly, some of the animals that survived exhibited a transient elevation of C. difficile counts (as attested for day 4 on Fig 3), as well as a concomitant pause in weight gain (Fig 4); eventually, viable C. difficile counts returned to baseline, the animals resumed weight gain and survived until the end of the experiment. These data suggest that this dose level could be close to the lower limit of efficacy for the DAV131 model in this study.

Fecal levels of moxifloxacin were also monitored for each fecal sample during the first 6 days of the study; Fig 5 shows the average moxifloxacin concentration in each group, for all of the 3 daily fecal samples. In the group receiving 100 mg/kg bid DAV131 presenting 100% mortality, fecal moxifloxacin concentrations were similar to the control group receiving moxifloxacin alone. In contrast, fecal moxifloxacin concentrations were considerably reduced in the groups that experienced total protection by DAV131. Intriguingly, in the group presenting 80% protection, fecal moxifloxacin concentrations were intermediate between these two extremes.

REFERENCES

We are grateful to colleagues for their work on this project: M. Karmali, J. de Gunzburg, A. Andremont, C. Miossec et al., 2011, 17:366-169.