Can DAV132, a Medical Device Releasing an Adsorbent into the Late Ileum, Decrease Significantly the Impact of Antibiotics on the Fecal Microbiota?

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ABSTRACT

Context. During antibiotic treatments a fraction of the dose administered reaches the colon and impacts the intestinal microbiota, promoting emergence and spread of resistant bacteria. Antibiotic residues can be inactivated by adsorption on various compounds, including activated charcoal (AC). DAV132 is an orally administrable medical device designed to deliver an adsorbent (AC) to the late ileum. We investigated if DAV132 could effectively reduce fecal antibiotic concentrations as well as the amount of resistant bacteria excreted.

Methods. Three types of animal models were used. First, to explore the relationship between antibiotic exposure and excretion of resistant bacteria, piglets received 15 or 1.5 mg/kg/day or placebo of oral ciprofloxacin during 5 days. We then compared between groups fecal ciprofloxacin concentrations and the concentrations of resistant enterobacteria excreted. Second, to explore colonic adsorption of antibiotics by DAV132 in the colon, beagle dogs received 10.7 mg/kg/day of i.v. levofloxacin during five days together with 0.3 or 0.6 kg/g/day or placebo of oral DAV132. We then compared between groups fecal and blood levofloxacin concentrations. Last, to explore if DAV132 could restore antibiotic-associated disruption of colonization resistance, mice received 380 mg/kg/day of subcutaneous ceftalexin or placebo for 3 days, together with 50 mg/day or placebo of oral DAV131 (DAV131 is a version of DAV132 modified for mice; in this particular case, for technical reasons, the adsorbent is available since the beginning of the small intestine), followed by intragastric challenge with 10^6 CFU of K. pneumoniae strain resistant to third generation cephalosporins (C3GR-Kp); we then compared between groups fecal ceftalexin and C3GR-Kp concentrations.

Results. In piglets, counts of resistant enterobacteria excreted were 9.2, 8.8 and 6.2 log10 CFU in animals receiving the 15, the 1.5 mg/kg/day and the placebo regimen respectively (p<0.001). In dogs, reduction of fecal levofloxacin concentration reached 71% and 82% when 0.3 and 0.6 kg/g/day of oral DAV132 was given with i.v. levofloxacin. Blood PK of levofloxacin was not modified significantly. In mice, all traces of antibiotic disappeared from the feces when oral DAV132 was given to the animals together with parental ceftalexin and a significant part of resistance to colonization by C3GR-Kp was restored.

Conclusion. Oral DAV132 could be a means to reduce exposure of the intestinal flora to antibiotics during antibiotic treatments which could be associated with a decrease in fecal excretion of antibiotic-resistant enterobacteria without affecting blood PK of the antibiotic. There appeared to be a relationship between the dose of DAV132 administered and the effect observed. The possible clinical use of DAV132 is presently under investigation.

RESULTS AND DISCUSSION

DAV132 is a medical device that has been designed to be co-administered with oral or parenteral antibiotics to reduce the impact of antibiotic residues that reach the colon during antibiotic treatments. The inactivating agent is protected by a coating (proprietary technology of Da Volterra) which allows its delivery in the last part of the ileum, in order to be fully active to adsorb colonic antibiotic residues, but not interfere with the therapeudic absorption of antibiotics through the intestinal mucosa in the upper part of the intestine.

Three sets of experiments have been performed in animals and the key results are described below:

1. First we showed in pigs that the quantity of enterobacteria resistant to ciprofloxacin excreted in the feces was a function of the quantity of antibiotic residues present in the colon.

2. Second we showed that DAV132 effectively captured antibiotic residues in the gut of dogs treated with i.v. levofloxacin (max 80% reduction) without impacting blood PK.

3. Third we showed in mice that DAV131 significantly reduced the impact of ceftoxamine on resistance to colonisation by β-lactam-resistant enterobacteria.

CONCLUSION

This set of experiments demonstrates that DAV132 is effective to reduce antibiotic concentrations in the colon without affecting the blood PK of parenteral antibiotics. The use with oral antibiotics is under investigation. This could allow to effectively reduce the impact of antibiotic treatments on the microbiota and lead to a decreased excretion of antibiotic-resistant bacteria. Clinical studies with DAV132 are on-going.