Oral Presentations

Changes in antimicrobial sensitivity of fecal *E. coli* in pigs exposed to enrofloxacin by different dosing routes: evidence for the “Mutant Selection Window”

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**Introduction**

The fluoroquinolones (FQ) are synthetic, broad spectrum bactericidal antibiotics which use in Canada is restricted to companion animals and beef cattle. Since their introduction in veterinary medicine, FQ-resistant bacteria are emerging in domestic animals, but the relationship between drug use and drug resistance awaits elucidation. Recently, the “mutant selection window” (MSW) concept has been proposed to explain the enrichment of resistant bacteria during FQ exposure [1]. Because drug efflux transporters excrete FQ into the intestinal lumen, where drug-resistant zoonotic pathogens may be selected, we hypothesized that the level of selection pressure will vary depending on the FQ dosing route. The study objective was to compare the changes in fecal *E. coli* population size and antimicrobial sensitivity of pigs treated with enrofloxacin (EFX) orally, intramuscularly, or by way of local delivery implants.

**Materials and Methods**

Parts of the study have been published elsewhere [2]. Briefly, 21 healthy pigs (13.6 ± 5.9 kg) with no previous exposure to antibiotics, and instrumented with a jugular catheter were randomized across EFX-dosing groups: oral (O), intramuscular (I), or local (L: peri-femoral implants with 65 mg EFX). Pigs in groups I and O were dosed daily for 15 days with ; 5.0 mg•kg⁻¹•d⁻¹ EFX. Feces were sampled rectally for 7 days prior to and during exposure to FQ. Jugular blood was sampled during treatment, and plasma EFX and ciprofloxacin (CFX) concentrations were measured with tandem mass spectrometry. Individual daily fecal *E. coli* counts, and disk diffusion testing of 12 antibiotics (3 colonies/pig) were performed daily. The effects of dosing route and time (as divided in first-exposure, bactericidal effect, and bacterial regrowth phases) on *E. coli* inhibition diameters were estimated with a repeated-measures linear mixed model. The effect of dosing route on the duration of FQ bactericidal phase was analysed with survival analysis. The α-level was set to 0.05 for all statistical tests.

**Results**

Average plasma EFX concentrations in pigs of group L were 4.5% of those in the other two groups, and plasma CFX concentrations were 8.5% of those of EFX. Fecal *E. coli* were undetectable during the bactericidal phase in all 3 groups. The sensitivity of fecal *E. coli* to EFX (Fig. 1), CFX, nalidixic acid, ampicillin, and trimethoprim-sulfamethoxazole was significantly affected by dosing route (P<0.05) and time (P<0.05). In contrast, these factors had negligible effect on *E. coli* sensitivity to amoxicillin, ceftiofur, streptomycin, apramycin, gentamicin, florfenicol, and tetracycline.

**Discussion**

Our hypothesis was verified: the local EFX delivery minimized both the intestinal efflux and selection of drug-resistant *E. coli*. Moreover, oral EFX maximized the bactericidal effect on *E. coli*, which retarded the resistance selection process. Exposure to EFX co-selected resistance to other antibiotic classes. The i.m. dosing of EFX causes significant resistance selection pressure on potentially zoonotic intestinal bacteria such as fecal *E. coli*. Because the intestinal FQ efflux exists in other mammals, these drugs should be used with caution.

**References**