Differential activity of veterinary antibiotics on target pathogens versus digestive flora: development of a pharmacodynamic selectivity index for public health perspective

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Evidence based dosing regimens for antibiotics: PK/PD approaches

P-4.1. Differential activity of veterinary antibiotics on target pathogens vs. digestive flora: development of a pharmacodynamic selectivity index for public health perspective.

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Introduction: The main challenge of antimicrobial chemotherapy in animals consists in eradicating pathogenic bacteria while minimizing the transmission of resistances from animal to man. In this respect, a strategy would be to select antibiotics specifically targeting pathogenic bacteria while sparing gut flora, the critical reservoir of resistance genes in animals. We propose a pharmacodynamic index to quantify the selectivity of antibiotics on pathogenic versus commensal bacteria.For illustrating our proposal, we took the example of two beta-lactams - amoxicillin (AMOX) and cefquinome (CEFQ), a fourth-generation cephalosporin -, against Pasteurella multocida, a pathogen responsible for lung infections, and Escherichia coli, an indicator of commensal Enterobacteriaceae harboured in gut flora.

Materials and Methods: We performed in vitro time-killing experiments with different concentrations of AMOX and CEFQ on E.coli (107CFU/mL) and P.multocida (105 or 107CFU/mL). Results were modelled with an equation describing the antibacterial activity (bacterial inoculum change) versus antibiotic concentration:

$\Delta I(a)=\Delta IMAX-(((\Delta IMAX- \Delta IMIN)*(a/ ECSTATIC)\gamma)/((a/ ECSTATIC)\gamma-(\Delta IMAX -\Delta IMIN)))$

where $\Delta I(a)$ is the Mean Inoculum Change (LogCFU/mL) over 24h for an antibiotic concentration a (µg/mL), $\Delta IMAX$ and $\Delta IMIN$ (LogCFU/mL) the Mean Inoculum Changes obtained without antibiotic or when increasing antibiotic concentrations respectively, ECSTATIC (µg/mL) the antimicrobial concentration producing bacteriostatic effect ($\Delta I(ECSTATIC)=0$), and γ the sigmoid coefficient of the curve. Based on the concentration-effect relations, we defined the selectivity index (SI) as the ratio of ECSTATIC for E.coli over EC90, the concentration producing 90% of maximal antibacterial effect against P.multocida.

Results: Concentration-effect curves indicated antibacterial activities of both antibiotics correlating to their MIC for bacterial species, CEFQ being more potent than AMOX (ECSTATIC 8-to-10-fold lower). With high 107-inocula of P.multocida, SI values were 5.78 and 0.74 for AMOX and CEFQ respectively, meaning that AMOX was more potent against P.multocida than E. coli whereas CEFQ was equally potent against both bacteria. EC90 against 105-inocula of P.multocida were lower compared to 107-inocula for both AMOX (8-fold) and CEFQ (3-fold), leading to SI values of 47.69 (AMOX) and 2.36 (CEFQ) for 105-inocula. Acting against a low pathogenic inoculum increased selectivity of both antibiotics.

Conclusions: We propose a pharmacodynamic index for assessing antibiotic selectivity in the context of public health protection. Despite the fact that CEFQ is much more potent than AMOX against both P.multocida and E.coli, selectivity towards the lung pathogen was higher for AMOX, indicating that concentrations required for efficacy are less likely to impact intestinal Enterobacteriaceae. Moreover, selectivity of both antibiotics can be improved when acting against lower pathogenic inocula, corresponding to early stage of infection. Further investigations in animals will be required to determine the impact on selectivity of pharmacokinetic behaviour of the antibiotics, which controls their distribution in the anatomic locations of both the targeted pathogenic flora and the commensal intestinal flora.

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ABSTRACTS