PK/PD informed dosage regimen for antimicrobial prophylaxis in companion animal surgery: from proof of concept to pipeline.

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Introduction: The PK/PD of antimicrobial drug (AMD) for surgical prophylaxis has been very poorly studied and in human medicine, we have relied strongly on prospective clinical trials for decisions. The objective of this study is to use PK/PD principles to inform (i) the dose, (ii) the timing of administration and (iii) the interval for re-administration of AMD peri-operatively in companion animals. The example of cefazolin in dogs is presented as a proof of concept.

Materials and Methods: We used the population pharmacokinetic model of Cefazolin in 78 dogs from Cagnardi et al 2017 (1), where 25 mg/kg were administered peri-operatively.
Performing Monte Carlo simulation (Phoenix NLME 8.3, Certara), we computed the following:

(i) the time of peak concentration in the peripheral compartment, which will inform the timing between administration and first incision and
(ii) the duration for which at least 90% of the dogs of the population maintain a free plasma concentration above the Epidemiological Cut-off (ECOFF) of possible intraoperative contaminants (*S. aureus* ECOFF was 2 mg/L and *S. pseudintermedius* and *E. coli* ECOFFs were 4 mg/L). This will inform the time of re-administration.

Results: Median/slowest peak concentration was reached in the peripheral compartment after 17min and 39 mins, respectively while 30 minutes were sufficient to reach peak concentration in 95% of individuals.
For an intravenous dose of 25 mg/kg, 90% of the simulated population maintained free plasma concentration during 3.1h for *S. aureus* and 2.3h for *E. coli* and *S. pseudintermedius*. For a 20 mg/kg dose, these durations were still 2.9h and 2.1h, respectively. Administration of cefazolin 30 min prior to surgery and redosing every 2h is supported by PK/PD principles.

Conclusions: Having established a proof of concept with cephazolin, we will compute ideal dosing regimens and intervals of other perioperative AMD we secured raw PK data for (amoxicillin, ampicillin, cefalexin and cefuroxime). This satellite PK/PD study will support the ENOVAT guideline on antimicrobial prophylaxis in companion animal surgery.

(1) Cagnardi et al. Front. Pharmacol 2018; 9, 1137

Funding: The networking activities were funded by ENOVAT COST ACTION (CA18217)