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Letter to the Editors regarding the Scientific Paper by González, Moreno, Fumuso, *et al.*

It has come to our attention that the discussion of pharmacokinetic/pharmacodynamic (PK/PD) relationships associated with fluoroquinolones (FQs) that was previously published by Martinez *et al.*, (2006) has been misinterpreted by González *et al.* in their 2010 manuscript published in this journal. Specifically, on page 298, column 1 or their manuscript, Gonzalez *et al.*, state the following: *Interestingly, fluroquinolones appear to exhibit a* '*concentration-dependent*' *activity against Gram-negative bacteria, but a* '*time-dependent*' *activity against Gram-positives* (Martinez *et al.*, 2006).

The manuscript by Martinez *et al.* describes the PK/PD of FQs as exhibiting concentration-dependent killing, and that the PK/PD parameters of interest are either the area under the concentration/time curve (AUC) divided by the minimum inhibitory concentration (MIC) of the targeted pathogen, or the peak drug concentration (C_{max}) divided by the MIC (C_{max}/MIC). Martinez, *et al.* further state that concentration-dependent killing indicates that for any given MIC, as active drug concentrations increase, the rate and extent of microbial killing likewise increases (up to some maximum response). This is in contrast to compounds that are typically considered to be time-dependent where killing activity shows little improvement as drug concentrations increase above the MIC of the targeted pathogen. Rather, the extent of killing is a function of the duration of the time when drug concentrations are maintained above the MIC (T > MIC). The differences in these two types of killing behavior are described elsewhere (Toutain *et al.*, 2002; Czock & Keller, 2007).

In general, we can consider all cidal compounds to reflect some degree of both time –dependent and concentration-dependent killing effects. For this reason, time and exposure (AUC/MIC) is considered one of the pivotal PK/PD metrics for the fluoroquinolones. When there is little post-antibiotic effect (PAE), the AUC/MIC will need to be higher (i.e., less time is spent in the absence of adequate drug concentrations). A minimal PAE is generally associated with Gram negative bacteria and therefore these pathogens tend to require a higher AUC/MIC value to achieve adequate kill effect. In contrast, if the PAE is long, as is the case with many Gram positive organisms, the necessary AUC/MIC can be reduced because the impact of the killing activity remains even when the drug concentrations have dropped below the MIC (Nightingale *et al.*, 2000). This point should not be interpreted as indicating that Gram positive organisms are associated with time-dependent killing.

In summary, differences in the magnitude of the PK/PD metric associated with the rate and extent of bacterial kill reflect specific pathogen-drug interactions. In most situations, the PK/PD metric correlated with cidal activity of the fluoroquinlones is AUC/MIC. The magnitude of the associated targeted value for that metric, along with the corresponding desired antimicrobial effect, is largely influenced by the duration of the PAE. Nevertheless, regardless of the corresponding duration of the PAE, all FQs, both Gram negative and Gram positive organisms, exhibit concentration-dependent killing.

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REFERENCES

Czock, D. & Keller, F. (2007) Mechanism-based pharmacokinetic-pharmacodynamic modeling of antimicrobial drug effects. *Journal of Pharmacokinetics and Pharmacodynamics*, **34**, 727–751.

González, C., Moreno, L., Fumuso, E., García, J., Rivulgo, M., Confalonier, A., Sparo, M. & Sánchez Bruni, S. (2010) Enrofloxacin-based therapeutic strategy for the prevention of endometritis in susceptible mares. *Journal of Veterinary Pharmacology and Therapeutics*, **33**, 287–294.

Martinez, M., McDermott, P. & Walker, R. (2006) Pharmacology of the fluoroquinolones: a perspective for the use in domestic animals. *The Veterinary Journal*, **172**, 10–28.

Nightingale, C.H., Grant, E.M. & Quintiliani, R. (2000) Pharmacodynamics and pharmacokinetics of levofloxacin. *Chemotherapy*, **46** (Suppl. 1), 6–14.

Toutain, P.L., del Castillo, J.R. & Bousquet-Mélou, A. (2002) The pharmacokinetic-pharmacodynamic approach to a rational dosage regimen for antibiotics. *Research in Veterinary Science*, **73**, 105–114.

Reply to the Editor

Regarding the Letter to the Editor signed by Marilyn Martinez and Ted Whittem, in which they expressed concern about a paragraph in the discussion of a recently published paper by González *et al.*, 2010. Their contention is that this paragraph misinterprets the previous report by Martínez *et al.*, 2006.

The authors wish to clarify that our discussion was, in fact, written in the context of comments made in a later article (Martínez *et al.*, 2006; page 20, 4th paragraph) and not the one cited (i.e. Martinez *et al.*, 2004). We believe that, whilst the interpretation regarding the global PK/PD relationship for fluoroquinolones (FQ) is correct, the wording of the mentioned paragraph could have been better. However, we also believe that our discussion does not affect either the quality or relevance of the reported data.

In the article published by Martínez *et al.*, 2006; the authors clearly stated that: '….*FQ are highly effective in the presence of high Cmax/*MIC values, exceptions to this rule have been observed. For example in the case of *Bacillus anthracis*…..'. Later, they also referenced other authors who had demonstrated *in vitro*, (for gemifloxacin in a *S. pnumoniae* model), that '… *time to kill 99% of inoculums depends on Cmax/*AUC, but the ability of to maintain this decrease is related to AUC/MIC (based on area under bacterial killing curve) (MacGowan *et al.*, 2000, 2001). Those authors concluded that '*If the duration of time between doses is extended beyond 24 h (as was tested by gemifloxacin), effectiveness may also depend upon the duration of time that drug concentrations exceed the MIC (T > MIC) (*MacGowan *et al.*, 2001)'. Although, other more recent examples are also available, we wish to make it absolutely clear that our statement (i.e. '*FQ appear to exhibit*…') was not intended as a dogmatic assertion concerning the global concept of PK/PD relationships for FQ. Rather, it was intended to point out that under certain situations, the duration of exposure to the fluoroquinolone can also have an important role in determining the characteristics of its antimicrobial activity.

In conclusion, we can confirm that we entirely agree with the interpretation of Martinez, M and Whittem, T. as stated in their letter. Moreover, we acknowledge and appreciate their keen and detailed interest in our paper.

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REFERENCES

González, C., Moreno, L., Fumuso, E., García, J., Rivulgo, M., Confalonieri, A., Sparo, M. & Sánchez Bruni, S. (2010) Enrofloxacin-based therapeutic strategy for the prevention of endometritis in susceptible mares. *Journal of Veterinary Pharmacology and Therapeutics*, **33,** 287–294.

MacGowan, A., Rogers, C., Holt, H., Wootom, M. & Bowker, K. (2000) Assessment of different antibacterial effect measures used in in vitro models of infection and subsequent use in pharmacodynamic correlations for moxifloxacin. *Journal of Antimicrobial Chemotherapy*, **46,** 73–78.

MacGowan, A., Rogers, C., Holt, H., Wootom, M. & Bowker, K. (2001) Pharmacodynamics of gemifloxacin against Streptococcus pneumonia in an in vitro pharmacokinetics model of infection. *Antimicrobial Agents and Chemotherapy*, **45,** 2916–2921.

Martínez, M., McDermott, P. & Walker, R. (2006) Pharmacology of the fluoroquinolones: a perspective for the use in domestic animals. *The Veterinary Journal*, **172,** 10–28.