ELDERLY PATIENTS

Increased systemic exposure to delafloxacin is observed in the elderly, but this could be explained in part by age-related reductions in creatinine clearance; further information is needed (see section 5b, Drug distribution) (Hoover *et al.*, 2016a).

5. PHARMACOKINETICS AND PHARMACODYNAMICS

5a. Bioavailability

Delafloxacin is rapidly absorbed after oral administration, with peak concentrations occurring within 1 hour (Hoover *et al.*, 2016a). The mean absolute bioavailability of delafloxacin is 58.8% (Hoover *et al.*, 2016b). Protein binding is estimated to be 16% (Rubino *et al.*, 2010).

After an oral dose, the delafloxacin C_{max} and AUC increase linearly over the dose range of 50–1600 mg, with the $AUC_{0-\infty}$ dose-proportional at doses ≥ 200 mg and steady state reached by day 3, with minimal accumulation (Hoover *et al.*, 2016a). There are no gender-based differences in delafloxacin absorption, but the co-administration of food slightly decreases the delafloxacin C_{max} (Hoover *et al.*, 2016a).

After a single 300-mg i.v. delafloxacin dose in healthy males, the C_{max}, $AUC_{0-\infty}$, T_{max}, and $t_{1/2}$ values were 8.98 μg/ml, 21.31 μg h/ml, 1 hour, and 2.35 hours, respectively (McEwen *et al.*, 2015).

Delafloxacin was assessed in a randomized, double-blind placebo-controlled, single- and ascending-dose study of i.v. delafloxacin (300, 450, 600, 750, 900, 1200 mg) in 62 healthy adults. Delafloxacin C_{max} values increased proportionally with increasing single i.v. dose, but the AUC values increased more than proportionally to dose for the same dose range (Hoover *et al.*, 2016b). The mean terminal half-life was approximately 12 hours (range: 8–17 hours). The volume of distribution at steady state was approximately 35 liters (i.e. similar to total body water). Delafloxacin 300 mg i.v. twice daily resulted in minimal accumulation (Hoover *et al.*, 2016b). Overall, 300 mg i.v. and 450 mg oral delafloxacin resulted in similar total systemic exposure, suggesting that these doses would be equivalent if considering an i.v./oral switch (Hoover *et al.*, 2016b).

5b. Drug distribution

Pharmacokinetic studies demonstrate peak serum concentrations after single i.v. doses of 300 mg and 450 mg, of 10.4 μg/ml, and 16.1 μg/ml, respectively. After an oral 400-mg dose, the peak concentration is 7.22 μg/ml. Serum half-life is 6.2–12.5 hours, although it is prolonged in more severe forms of renal impairment. The half-life of delafloxacin increases with multiple doses (Hoover *et al.*, 2016a).

In the elderly, both the C_{max} and $AUC_{0-\infty}$ are 35% higher than in young adults, but this may be due to differences in renal function (Hoover *et al.*, 2016a).

So *et al.* (2015) assessed the effects of urine matrix and its varying pH on the potency of various fluoroquinolones, including delafloxacin and ciprofloxacin, against 16 urogenic Enterobacteriaceae in the urine of patients with suspected urinary tract infection (most of which had a pH of 6.5 or less). Delafloxacin MICs were two- to fivefold doubling dilutions lower than those of ciprofloxacin. Furthermore, in contrast to ciprofloxacin, the potency of delafloxacin appeared to be enhanced in the acidic environment commonly observed in the setting of urinary tract infection. Whether this characteristic translates into improved clinical efficacy in patients with urinary tract infections is currently uncertain.

Detailed tissue penetration studies regarding delafloxacin are yet to be reported. However, *in vitro* studies assessing biofilms associated with various ATCC strains of MRSA and methicillin-susceptible *S. aureus* isolates, including biofilm mass and bacterial viability, suggest that delafloxacin (and daptomycin) were most potent among the drugs tested in reducing viability by > 50% at clinically achievable concentrations, although no drugs tested destroyed mature biofilm matrix (Siala *et al.*, 2013; Bauer *et al.*, 2013).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Similar to other fluoroquinolones the key pharmacokinetic parameter associated with clinical efficacy for delafloxacin is thought to be the AUC/MIC (see Chapter 101, Ciprofloxacin). In addition, the selection of resistance to delafloxacin is considered to be infrequent (10^{-9} to 10^{-11}) (Remy *et al.*, 2012) and the concentrations preventing the selection of mutations (mutant prevention concentrations [MPC]) are also thought to be low, with values ranging from one to four times the initial MIC. Such values are about 8- to 32-fold lower than for many other fluoroquinolones (Hermsen *et al.*, 2005; Drlica and Zhao, 2007; Van Bambeke, 2015).

Early studies using *in vitro* pharmacodynamic simulation models to assess delafloxacin appear to have not considered the possible role of protein binding. These simulations included assessments of delafloxacin activity against *S. aureus*, *S. pneumoniae*, *E. coli*, and *P. aeruginosa*, with comparisons to ciprofloxacin and levofloxacin (Firsov *et al.*, 2004; Firsov *et al.*, 2005; Zinner *et al.* 2004; Van Bambeke, 2015). In a recent study utilizing a murine neutropenic lung infection model assessing delafloxacin activity against *S. aureus*, *S. pneumoniae*, and *K. pneumoniae*, median free drug AUC/MIC targets associated with net stasis were very low for all pathogen groups (0.04, 0.4, 9.68, respectively), while 1-log kill targets were two- to fivefold higher (Lepak and Andes, 2016).

5d. Excretion

After intravenous administration of delafloxacin, approximately 66% is excreted in urine, most of which (30–40%) is unchanged. The predominant clearance pathway for excretion