Systemic Exposure Profile and Tissue Penetration (Lung, Kidney, Bone Marrow, and Gallbladder) in Rabbits After KPI-10 Intravenous Administration

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Abstract

Background: KPI-10 is a next-generation fluoroquinolone (FQ) with potent activity against FQ-resistant pathogens. The aim of the study was to assess the pharmacokinetics of KPI-10 in a rabbit model by measuring plasmatic and tissue concentrations after intravenous (IV) administration.

Methods: Blood and tissue samples were collected after KPI-10 infusion (20 mg/kg, 1hr-infusion) at the following time points: 0 (end of the infusion), 30 min, 90 min, 4 hr, 8 hr, 12hr, and 24 hr after the end of IV infusion. Concentrations of KPI-10 in plasma and tissues were determined in a microbiological assay with *Bacillus subtilis* as the test organism and antibiotic medium No. 2 as the diffusion medium (lower detection limit, 0.25 mg/ml; intraday and interday variations, <10%).

Results: After IV administration of a 20 mg/kg dose, the peak concentration and area under the curve (AUC) of KPI-10 in plasma were 7.4 mg/ml and 7.0 mg.h/ml, respectively. These values are consistent with the results previously published for other FQs. Corresponding C_{max},AUC were 109.6;596.7, 23.3;30.9, 40.7;38.3, and 5.2 mg/g;4.1 mg.h/g in the gallbladder, lung, kidney, and bone marrow, respectively. High KPI-10 concentrations were measured in the gallbladder and in the kidney, which suggest KPI-10 elimination by both hepatic and renal pathways (as for ciprofloxacin). The 1-hr infusion of KPI-10 in rabbits was well tolerated; the drug produced no obvious signs of tissue injury.

Conclusion: According to the present data, KPI-10 is very well distributed to the tissues, with tissue concentrations at least 4-fold higher than those in plasma for all tissues tested except for bone marrow. Given that KPI-10 displays low MIC values against both FQ-susceptible and FQ-resistant pathogens, these data strongly suggest that KPI-10 should achieve tissue concentrations above MICs of most target pathogens.

Background

Fluoroquinolones are a family of broad-spectrum antibiotics typically known for their excellent activity against Gram-negative pathogens. These antibiotics demonstrate good activity against many pathogens involved in pneumonia and urinary tract infections, but rising resistance has left currently available fluoroquinolones less useful against infections caused by such resistant bacteria. Resistance to fluoroquinolones has been linked to mutations in the *gyrA* gene, with alterations in the fluoroquinolone resistance-determining region (QRDR) of *gyrA*, as well as in the topoisomerase IV *parC* gene. Owing to the increasing number of multidrug-resistant isolates and the lack of available treatments, development of new therapeutic alternatives is mandatory. KPI-10 is a next-generation fluoroquinolone with potent activity against Gram-negative and Gram-positive multidrug-resistant pathogens, including fluoroquinolone-resistant strains.

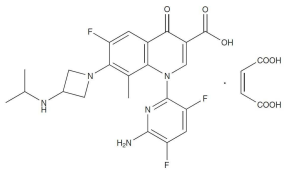

Figure 1. **Structure of KPI-10**

Materials & Methods

Animals. 18 female New-Zealand rabbits (weight, 2.2 to 2.5 kg) were used in this study. The Committee of Animal Ethics of the University of Nantes approved all animal experimentation in this study.

Spontaneous pharmacokinetics of KPI-10 after IV administration. The spontaneous pharmacokinetic (PK) profile of KPI-10 was evaluated in a healthy rabbit model after a 1hr IV infusion of 20 mg/kg. Blood samples were collected after KPI-10 infusion at the following time points: 0 (end of the infusion), 30 min, 90 min, 4 hr, 8 hr, 12hr, and 24 hr after the end of IV infusion. Blood samples (1.5 mL per time point) were obtained through a catheter positioned in the median artery of the ear, which was placed contralateral to the antibiotic infusion.

Microbiological assay of KPI-10. Plasma was separated from whole blood after refrigerated centrifugation (5000g, 10 min, 4°C), and all plasma samples obtained were frozen at –80°C until the time of the microbiological assay. Antibiotic Medium no. 5 (Difco laboratories, Detroit, MI, USA) was used as the diffusion medium for the determination of KPI-10 concentrations. *Bacillus subtilis* was chosen as the test organism in reason of its ability to produce a clear crisp zone on AM2 and to provide results within 18 hours. The limit of detection for KPI-10 with *B. subtilis* is about 0.25 mg/L. The preparation of antibiotic standards was performed at the following concentrations for KPI-10: 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64 and 128 mg/L (according to the expected concentrations). The precision and the exactness of the regression curve are shown by the coefficient of correlation (R2>0.9) and the coefficient of variation (CV<10%). The KPI-10 concentrations were determined by extrapolation from the regression line.

Assessment of the concentration of KPI-10 in rabbit lung tissue, bone marrow, and gallbladder after IV administration. We assessed the penetration of KPI-10 into lung tissue, bone marrow, and gallbladder after IV administration of the drug. KPI-10 was administered to the animals via the marginal ear vein as an infusion of 1 hr. Blood samples were collected after KPI-10 infusion at the following time points: 0 (end of the infusion), 90 min, 4 hr, 8 hr, and 12 hr after the end of infusion with 3 rabbits per time point. Animals were euthanized by administration of a 100-mg intravenous bolus of thiopental. Blood samples were also collected by intracardiac puncture. The right and left lungs were excised, immediately placed on ice, gently pressed in sterile gauze, weighed, and homogenized in 500 µL to 1000 µL of saline buffer. Bile and bone marrow were removed and immediately placed on ice. The measured concentration of KPI-10 was expressed per weight of tissue (micrograms per gram) or in micrograms per milliliter.

Results

- All rabbits were clinically healthy throughout the experiment. There were no identifiable reactions following administration of KPI-10 by IV route.
- KPI-10 concentrations obtained after administration of a 20 mg/kg dose are shown in Figure 2, Figure 3, Figure 4, and Figure 5, for plasma, lung tissue, gallbladder, kidney, and bone marrow, respectively.
- Cmax and AUC values determined after IV administration of KPI-10 in rabbits are summarized in Table 1 and Table 2, respectively.

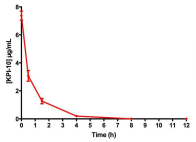

Figure 2. PK of KPI-10 in plasma after IV administration (1 hour-infusion) of a 20 mg/kg dose. Error bars represent standard deviation.

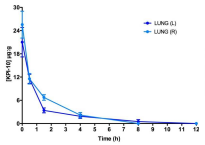

Figure 3. PK of KPI-10 in lung tissues after IV administration (1 hour-infusion) of a 20 mg/kg dose. Error bars represent standard deviation.

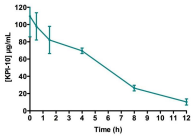

Figure 4. PK of KPI-10 in the gallbladder after IV administration (1 hour-infusion) of a 20 mg/kg dose. Error bars represent standard deviation.

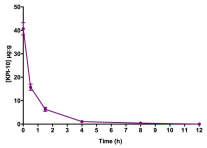

Figure 5. PK of KPI-10 in the kidney after IV administration (1 hour-infusion) of a 20 mg/kg dose.

Tissue	Cmax (µg/ml or µg/g)
Plasma	7.4 ± 0.6
gallbladder	109.6 ± 41.3
Left lung	21.0 ± 6.6
Right lung	25.5 ± 6.0
Kidney	40.7 ± 4.5
Bone marrow	5.2 ± 1.4

Table 1. Cmax obtained in plasma and tissues after IV administration of KPI-10 (1 hour-infusion, 20 mg/kg dose).

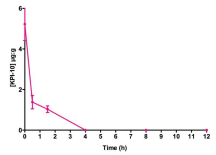

Figure 6. PK of KPI-10 in (bone) marrow after IV administration (1 hour-infusion) of a 20 mg/kg dose.

Tissue	AUC (µg.h/ml or µg.h/g)
Plasma	7.0
gallbladder	596.7
Left lung	28.0
Right lung	33.9
Kidney	38.3
Bone marrow	4.1

Table 2. AUC values obtained in plasma and tissues after IV administration of KPI-10 (1 hour-infusion, 20 mg/kg dose).

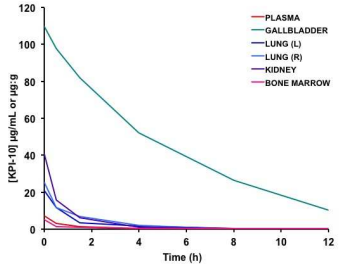

Figure 7. Comparative PK of KPI-10 in plasma, gallbladder, lung (left/right), kidney, and (bone) marrow after IV administration (1 hour-infusion) of a 20 mg/kg dose. Error bars represent standard deviation.

Discussion / Conclusion

After IV administration of a 20 mg/kg dose, the peak level of KPI-10 in plasma was approximately 7 µg/ml. This C_{max} value is consistent with the results previously published for other fluoroquinolones, such as ciprofloxacin (0.4 to 3.6 µg/ml) (1), norfloxacin (0.8 to 3.9 µg/ml) (2), and ofloxacin (1.3 to 10.7 µg/ml) (3).

- High KPI-10 concentrations were measured in the gallbladder and in the kidney, which suggest KPI-10 elimination by both hepatic and renal pathway (as for ciprofloxacin).
- The concentrations of KPI-10 are at least 4-fold higher in the lung and kidney tissues compared to plasma. These data are consistent with clinical studies assessing the tissue penetration of ciprofloxacin and ofloxacin, which revealed 2 to 4-fold higher drug concentrations in lung, kidney, and prostate tissues compared with those in plasma.
- Finally, very high concentrations of KPI-10 were observed in the gallbladder with a C_{max} of 109.6 ± 41.3 µg/g and a low elimination rate, with an apparent half-life of 8 hours. These data suggest an important hepatic clearance, which would be superior to renal elimination of the drug.
- According to the present data, KPI-10 is very well distributed to the tissues, with tissue concentrations at least 4-fold higher than those in plasma for all tissues tested except bone marrow.
- Given that KPI-10 displayed good activity against both fluoroquinolone-susceptible and -resistant pathogens, these data strongly suggest that this novel fluoroquinolone will achieve tissue concentrations above MICs of most target pathogens.

References

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