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Development and Implementation of a Ferret Venous Catheterization Model for Pharmacokinetic Studies

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PURPOSE

The ferret (Mustela putorius furo) is an indispensable experimental animal model in the fields of influenza virology, respiratory diseases, and vaccine development. However, its unique physiological and anatomical characteristics pose significant challenges for venous blood sampling. The peripheral blood vessels such as saphenous and caudal veins are extremely narrow (0.3-0.5 mm in diameter), and the subcutaneous fat layer combined with thick epidermal structures complicates visualization. Additionally, ferrets exhibit a more pronounced stress-induced vascular contraction response compared to rodents, resulting in a lower success rate of traditional blood sampling. To overcome these challenges, we have established a novel venous catheterization model for ferrets, tailored for pharmacokinetic (PK) studies requiring serial blood sampling.

METHOD

Our innovative technique, reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of WuXi AppTec, employs the Venous Access-Port (VAP) method. The procedure involves surgical placement of an indwelling jugular vein catheter: one end is introduced via the jugular vein and advanced into the vena cava, and the other end is secured to a subcutaneously implanted port. This configuration permits serial venous blood sampling from conscious ferrets. (Figure 1.)

A single bolus dose of peramivir (10 mg/kg) was administered to separate groups of ferrets via intravenous or oral routes, and a single oral gavage of aprepitant (10 mg/kg) was administered to a different group. Serial blood samples were collected from the implanted ports, and plasma was prepared for analysis. Plasma concentrations of peramivir and aprepitant were measured, and primary PK parameters for each compound were calculated and compared with values reported in the literature.

RESULT

Our venous Access-Port (VAP) method serial sampling method reduced interindividual variability—evidenced by lower standard deviations in key pharmacokinetic parameters for peramivir and aprepitant—while mean values remained comparable to those reported in the literature for conventional puncture sampling. As shown in table 1, following a 10 mg/kg intravenous bolus of peramivir, the in-house estimates versus literature values were as follows: clearance (Cl) 4.10 ± 0.245 versus 4.97 ± 3.98 mL/min/kg; terminal half-life ($t_{1/2}$) 3.09 ± 0.754 versus 3.65 ± 0.320 h; and volume of distribution at steady state (Vd_{ss}) 0.385 ± 0.0706 versus 0.355 ± 0.306 L/kg.

In table 2, following a 10 mg/kg oral gavage of peramivir, the in-house estimates versus literature values were as follows: C_{max} 643 ± 333 versus 1024 ± 1092 ng/ml; $AUC_{0\text{-}inf}$ 1648 ± 981 versus 3402 ± 3970 ng·h/mL. Although the mean values of C_{max} and $AUC_{0\text{-}inf}$ are slightly lower than those reported in the literature, the SD indicates that WuXi AppTec DMPK has better consistency.

In table 3, following a 10 mg/kg oral gavage of aprepitant, the in-house estimates versus literature values were as follows: C_{max} 409 ± 40.5 versus 327 ± 69.2 ng/ml; $AUC_{0\text{-}inf}$ 5757 ± 1388 versus 5151 ± 1660 ng·h/mL.

The catheter-port concept can be applied not only to sampling of unconventional biological fluids—such as bile and cerebrospinal fluid—in experimental animals, but also to species in which percutaneous sampling is impractical, such as ferrets.

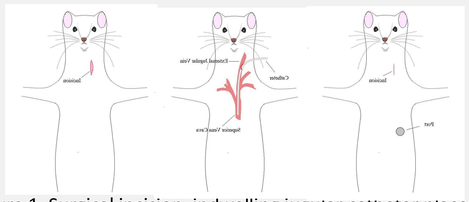

Figure 1. Surgical incision, indwelling jugular catheter placement, and subcutaneous port location for serial venous blood sampling in ferrets.

Table 1. Comparison of Key Pharmacokinetic Parameters of Peramivir Following a 10 mg/kg Intravenous Bolus in Ferrets Using Two Sampling Methods

PK Parameters	WuXi AppTec DMPK		Literature	
Route	IV		IV	
Dosage (mg/kg)	10		10	
PK Parameters	Mean	SD	Mean	SD
Cl (mL/min/kg)	4.10	0.245	4.97	3.980
Vd_{ss} (L/kg)	0.385	0.0706	0.355	0.3060
$T_{1/2}$ (h)	3.09	0.754	3.65	0.320

Table 2. Comparison of Key Pharmacokinetic Parameters of Peramivir Following a 10 mg/kg Oral Gavage in Ferrets Using Two Sampling Methods

PK Parameters	WuXi AppTec DMPK		Literature	
Route	PO		PO	
Dosage (mg/kg)	10		10	
PK Parameters	Mean	SD	Mean	SD
C_{max} (ng/mL)	643	333	1024	1092
T_{max} (h)	1.00	0.00	1.00	0.00
$AUC_{0\text{-}inf}$ (ng·h/mL)	1648	981	3402	3970

Table 3. Comparison of Key Pharmacokinetic Parameters of Aprepitant Following a 10 mg/kg Oral Gavage in Ferrets Using Two Sampling Methods

PK Parameters	WuXi AppTec DMPK		Literature	
Route	PO		PO	
Dosage (mg/kg)	10		10	
PK Parameters	Mean	SD	Mean	SD
C_{max} (ng/mL)	409	40.5	327	69.2
T_{max} (h)	3.33	1.15	3.30	1.20
$AUC_{0\text{-}inf}$ (ng·h/mL)	5757	1388	5151	1660

CONCLUSION

➢ Model Validation Success

These results indicate that the catheter port serial sampling method may offer a more precise, reliable, and cost effective approach to venous blood sampling in ferrets. It appears to improve the consistency of experimental data and may help reduce animal stress, thereby better aligning with ethical considerations.

➢ Strategic Application Advantages of Ferrets in Drug Development

- Influenza Therapeutics: Leveraging natural susceptibility to human-like influenza strains
- Respiratory Drug PK/PD: Mimicking human airway receptors (e.g., α2,6-linked sialic acid distribution)
- Vaccine Adjuvant Research: Evaluating mucosal immunity in nasopharynx-associated lymphoid tissue

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