PXB-Mice with Humanized Livers Provide Better Predictions of Human Pharmacokinetics Compared to CB17-SCID Mice

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Abstract

Purpose

For drug discovery and pharmaceutical development, accurate predictions of human pharmacokinetics (PK), metabolite profiles, and drug-drug interactions (DDIs) are crucial for patient safety and drug efficacy. As the liver is the major organ participating in drug metabolism *in vivo*, several *in vitro* methods using human hepatic microsomes and hepatocytes, as well as chimeric mice with humanized livers have been employed for better preclinical predictions for drug metabolism. However, it is inconclusive as to which system provides the best predictions representing the human body using the *in vivo* platform. In this study, the aim is to investigate the translational value of PXB-mice, with humanized livers, in drug metabolism as a comparison to CB17-SCID mice by testing the PK profiles of published reference articles.

Methods

Test compounds, including amlodipine, naltrexone, and meloxicam, were administrated intravenously (IV) and orally (PO) to mice at 1 and 10 mg/kg, respectively. Blood aliquots were collected from three alternative mice at six or nine designed time points. The plasma samples were processed using acetonitrile (ACN) precipitation and analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The fundamental PK parameters of each dosing compound after IV and PO administrations were obtained from the non-compartmental analysis (NCA) using WinNonlin®. The oral bioavailability (F%) was also calculated.

Results and Discussion

In mice administered with amlodipine, the F% in CB17-SCID mice (171%) was higher than that in PXB-mice (64%). In mice treated with naltrexone, the F% in PXB-mice (18%) was three times greater than in CB17-SCID mice (5%). Moreover, the F% of meloxicam was comparable in both strains (109% in CB17-SCID mice and 98% in PXB-mice). Taken together, the data demonstrate similarity and consistency with published oral bioavailability results in mouse and human PK, with respect to PXB-mice and CB17-SCID mice, suggesting PXB-mice serve as a reliable strain for use in human PK predictions.

Conclusions

PXB-mice provide high translational values with clinical relevance for predictions of human PK during the preclinical phase.

PK Analysis of Amlodipine in PXB-Mice and CB17-SCID Mice

A

IV	$t_{1/2}$ (h)	C_0 (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{Inf} (h*ng/mL)	AUC/D (h*kg*ng/mL/mg)	AUC Extr (%)	MRT (h)	Vss (L/kg)	CL (mL/min/kg)
CB17-SCID mice	9.5	136	819	970	970	16	11	12	17
PXB-mice	9.4	73	387	455	455	15	11	24	37

PO	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{Inf} (h*ng/mL)	AUC/D (h*kg*ng/mL/mg)	AUC Extr (%)	MRT (h)	Vz/F (L/kg)	CL/F (mL/min/kg)	F (%)
CB17-SCID mice	30.3	6.0	393	13573	16549	1655	18	41	26	10	171
PXB-mice	16.5	2.0	131	2836	2931	293	3	24	81	57	64

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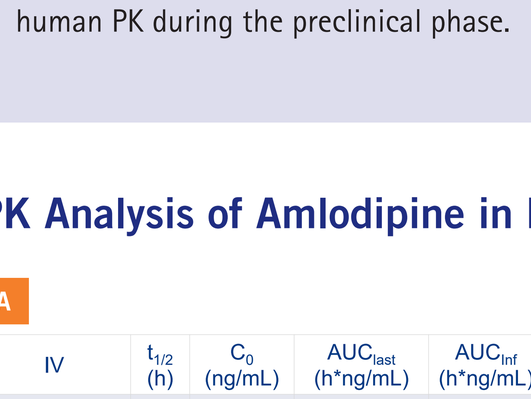

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Figure 1. The PK parameters and concentration-time profile of amlodipine after single IV (1 mg/kg) or PO (10 mg/kg) administration to PXB-mice and CB17-SCID mice. The plasma samples were obtained from these animals at 0.05, 0.5, 1, 2, 6, and 24 hours (h) after IV and 0.167, 0.5, 1, 2, 6, 24, 36, 48, and 72 h after PO administration. A. The plasma PK parameters. B. Plasma concentration-time profile in PXB-mice. C. Plasma concentration-time profile in CB17-SCID mice.

PK Analysis of Naltrexone in PXB-Mice and CB17-SCID Mice

A

IV	$t_{1/2}$ (h)	C_0 (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{Inf} (h*ng/mL)	AUC/D (h*kg*ng/mL/mg)	AUC Extr (%)	MRT (h)	Vss (L/kg)	CL (mL/min/kg)
CB17-SCID mice	0.9	216	89	90	90	1	1	7	185
PXB-mice	0.3	309	94	95	95	0	0	2	176

PO	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{Inf} (h*ng/mL)	AUC/D (h*kg*ng/mL/mg)	AUC Extr (%)	MRT (h)	Vz/F (L/kg)	CL/F (mL/min/kg)	F (%)
CB17-SCID mice	0.3	0.2	75	48	49	5	2	1	101	3397	5
PXB-mice	1.5	0.5	133	164	173	17	5	2	126	966	18

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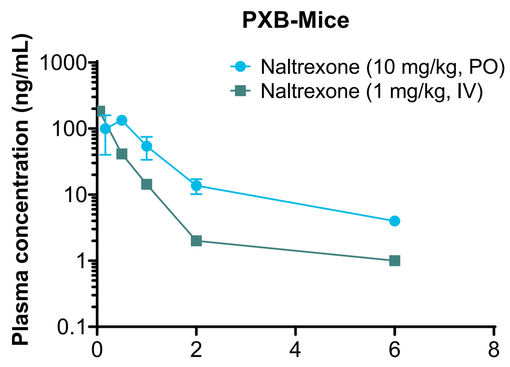

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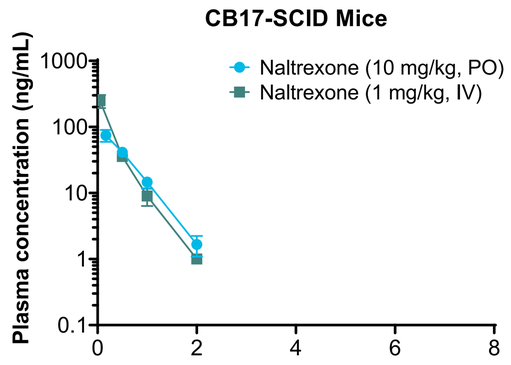

Figure 2. The PK parameters and concentration-time profile of naltrexone after single IV (1 mg/kg) or PO (10 mg/kg) administration to PXB-mice and CB17-SCID mice. The plasma samples were obtained from these animals at 0.05, 0.5, 1, 2, 6, and 24 h after IV and 0.167, 0.5, 1, 2, 6, and 24 h after PO administration. A. The plasma PK parameters. B. Plasma concentration-time profile in PXB-mice. C. Plasma concentration-time profile in CB17-SCID mice.

PK Analysis of Meloxicam in PXB-Mice and CB17-SCID Mice

A

IV	$t_{1/2}$ (h)	C_0 (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{Inf} (h*ng/mL)	AUC/D (h*kg*ng/mL/mg)	AUC Extr (%)	MRT (h)	Vss (L/kg)	CL (mL/min/kg)
CB17-SCID mice	2.4	2953	7532	9103	9103	17	3	0	2
PXB-mice	3.5	6135	33388	33680	33680	1	3	0	0

PO	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{Inf} (h*ng/mL)	AUC/D (h*kg*ng/mL/mg)	AUC Extr (%)	MRT (h)	Vz/F (L/kg)	CL/F (mL/min/kg)	F (%)
CB17-SCID mice	2.5	0.5	26050	99171	99287	9929	0	3	0	2	109
PXB-mice	5.6	1.0	42628	313454	330289	33029	5	6	0	1	98

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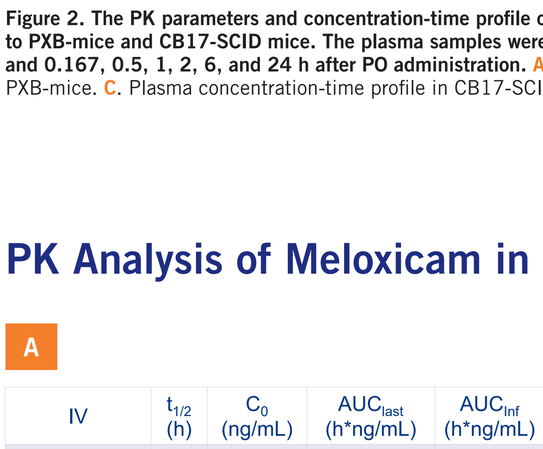

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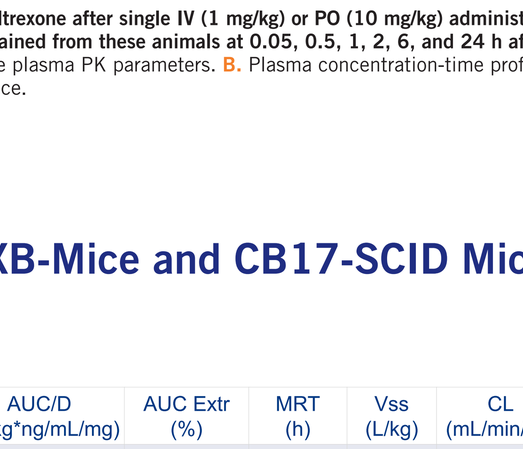

Figure 3. The PK parameters and concentration-time profile of meloxicam after single IV (1 mg/kg) or PO (10 mg/kg) administration to PXB-mice and CB17-SCID mice. The plasma samples were obtained from these animals at 0.05, 0.5, 1, 2, 6, and 24 h after IV and 0.167, 0.5, 1, 2, 6, and 24 h after PO administration. A. The plasma PK parameters. B. Plasma concentration-time profile in PXB-mice. C. Plasma concentration-time profile in CB17-SCID mice.

Summary

	PXB-Mice	CB17-SCID Mice
Amlodipine	Moderate F% as expected	High F% as expected
Naltrexone	Relatively higher F% as expected	Relatively lower F% as expected
Meloxicam	High F% as expected	High F% as expected

1. CB17-SCID mice display higher F% for amlodipine, while PXB-mice show superior values for naltrexone.
2. For meloxicam, F% remains consistent across both strains.
3. PXB-mice provide a suitable model to study human PK, as evidenced by moderate F% in naltrexone and high F% in meloxicam.

References

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