An Application of a Physiologically Based Pharmacokinetic Approach to Predict Ceftazidime Pharmacokinetics in Pregnant Population

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Supplementary document

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Table S1 Ceftazidime PBPK model input parameters

	Parameter	**value**	**Reference**
Physicochemical properties and binding	Mol Weight (g/mol)	546.580	Zhou et al., 2019 (1)
	log P	-3.750	
	Compound Type	Diprotic Acid	
	pKa 1	2.430	
	pKa 2	2.890	
	B/P	0.550	Default
	fup (Binding Protein)	0.9 (Human Serum Albumin)	Predicted and used as input
Absorption	Absorption (For intramuscular dosing only)		
	fa : Mean (%CV)	1 (0%CV)	assumed
	Ka (1/h): Mean (%CV)	2 (30%CV)	Adjusted to recover (2, 3)
	Tlag (h): Mean(%CV)	1.5 (30%CV)	
Distribution	Distribution Model	Full PBPK Model	
	Vss (L/kg)	0.20 (Predicted using Method 2 after (4))	
	Maternal Kp Scalar	1.0	
	Fetal Kp Scalar	1.0	
Elimination	Elimination option	Enzyme Kinetics	
	CL_R (L/h)	6.000	Zhou et al., 2019 (1)
	Biliary CLint (µL/min/million hepatocyte)	0.085 (30% CV)	Adjusted to recover Harding et al., 1983 (2)
Pregnancy Model			
Feo- placental model	CL_{PDM} (L/h/mL of placenta volume)	0.00137	Predicted (see text)
	CL_{PDF} (L/h/mL of placenta volume)	0.00137	Predicted (see text)
	fetal $CL_{Swallowing}$ (L/h/kg fetal weight): Mean (%CV)	0.00476 (30%)	see text
	fetal CL_R (L/h/kg fetal weight)	Predicted	GW-dependent (see text)
	$CL_{\text{fetus <--> amniotic fluid}}$ (L/h/kg fetal weight)	Predicted	GW-dependent (see text)

Mol Weight= molecular weight; logP=neutral species octanol: buffer partition coefficient; pKa= dissociation constant at logarithmic scale; BP=blood-to-plasma partition ratio; fup=fraction unbound in plasma; CL_R= renal clearance; CL_{PDM}=Passive diffusion clearance for Maternal-placental barrier; CL_{PDF}=Passive diffusion clearance for Placental-Fetal barrier

Table S2. Collected clinical data on fraction of the dose excreted in the urine from healthy adult non-pregnant subjects (Predicted mean (SD) 87(4) %) .

Study design			**Observed**		
Ref	**Dose**	**Sample Size (age range (years)**	**mean**	**SD**	**Ratio**
Harding et al 1983 (5)	0.5 g i.v.	4 M: 20-49 years	100		0.86
	1 g i.v.	4 M: 20-49 years	91.6		0.95
	1g i.m.	8 M: 20-49 years	82		1.06
Tjandramaga et al 1982 (6)	1g i.v.bolus (3min)	8 (0F): 22-24 years	96.2	5.5	0.90
	1g i.m.	8 (0F): 22-24 years	92.6	6.3	0.94
Harding et al 1983 (2)	0.5g i.v.	8 M: 20-49 years	85.6	8.2	1.01
	1 g i.v.	8 M: 20-49 years	85.1	4.8	1.02
	1 g 20 min i.v. inf	8 M: 20-49 years	83.7	7.65	1.04
	2 g 20-min i.v. inf	8 M: 20-49 years	87.1	4.2	1.00
	0.5g im	8 M: 20-49 years	85	6.5	1.02
	1g i.m.	8 M: 20-49 years	78.9	12	1.10
Kemmerich et al 1983 (7)	2g i.v. inf 20min	8 (50% F): 20-30yrs	72	12	1.22
Sommers et al 1983 (8)	1g i.v. bolus	16 (8F): 20-45 years	76	3	0.87
	1g i.m.	16 (8F): 20-45 years	74.7	3	0.86
Drusano et al., 1984 (9)	2g inf over 30min	6 (0F): 18 -35 years	80	10	1.10
Koyama et al. 1983 (3)	0.5g i.v. bolus	3 M: 31 years	91.2		1.04
	1g i.v. bolus	3 M: 31 years	89.3		0.97
	1g i.v. inf for 1 h	3 M: 27-29 years	89.6		0.96
	1g i.v. bolus	3 M: 23-27 years	95		1.09
	2g i.v. inf for 1 h	3 M: 27-29 years	90.2		0.96
	2g i.v. inf for 2 h	3 M : 23-38 years	93.3		0.93
	0.5g im	3 M: 23-35 years	91.3		0.94
Saito et al., 1994(10)	1g i.v. inf for 1 h	6 M: 20-23 years	91	5.1	0.95

i.v.=intravenous; i.m. =intramuscular; inf=infusion ; M= male; F=female.

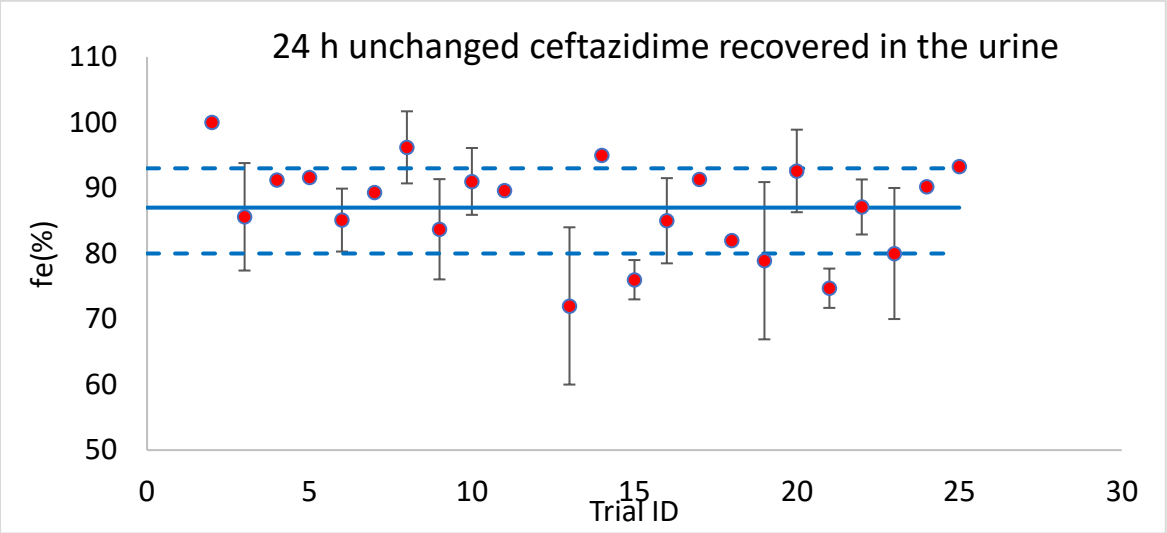

Figure S1. Fraction of ceftazidime excreted as unchanged ceftazidime in urine. Horizontal lines represent the PBPK model results (solid= mean; dashed= 5th and 95th percentiles) circles represent reported mean values in different clinical trials with error bars represent standard deviation.

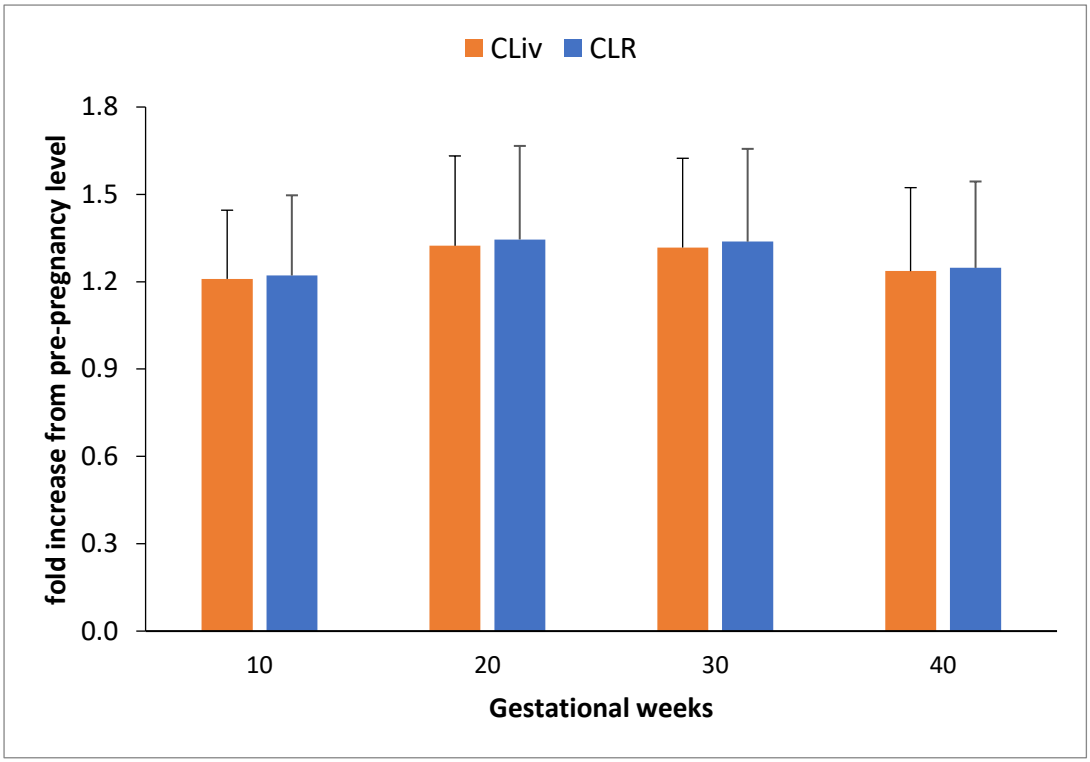

Figure S2. Fold change in systemic and renal clearance of ceftazidime at 10, 20, 30, and 40 GWs. Error bars represent standard error.

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