Experiment Number: K10482B
Route: Gavage, IV
Species/Strain: Rat/Harlan Sprague Dawley

Toxicokinetics Data Summary
Compound: N-Butylbenzenesulfonamide
CAS Number: 3622-84-2

Request Date: 09/06/2019
Request Time: 16:1216
Lab: Battelle Columbus

Male

	Treatment Group (mg/kg)				
	20 IV[a]	**20 Gav[b]**	**60 Gav[b]**	**60 Gav[c]**	**200 Gav[b]**
			Plasma		
C_0min_pred (ng/mL)	10300±1200				
Cmax_pred (ng/mL)		316±46	1200±290	1360±170	3440±500
Tmax_pred (hour)		0.355±0.105	0.378±0.266	0.189±0.119	0.228±0.183
Cmax_obs (ng/mL)	14200	613	1810	1810	4510
Tmax_obs (hour)		0.167	0.333	0.333	0.0833
Alpha_Half-life (hour)	0.191±0.021				
Beta_Half-life (hour)	0.713±0.109				
k01 (hour^-1)		8.6±3.74	10±9.55	20±16.8	19±19.8
k01_Half-life (hour)		0.0809±0.0353	0.0696±0.0668	0.0349±0.0295	0.0361±0.0373
k10 (hour^-1)	3.13±0.26	0.49±0.057	0.25±0.055	0.52 ±0.045	0.26±0.020
k10_Half-life (hour)	0.221±0.018	1.42±0.17	2.72±0.58	1.34±0.12	2.70±0.21
k12 (hour^-1)	0.341±0.125				
k21 (hour^-1)	1.12±0.22				
Cl1 (mL/hr/kg)	6060±390				
Cl2 (mL/hr/kg)	659±220				
Cl1_F (mL/hr/kg)		26000±3600	11500±2400	20700±2200	14100±1800
V1 (mL/kg)	1940±220				
V2 (mL/kg)	586±122				
V1_F (mL/kg)		53300±9900	45400±12900	40000±5700	54900±8800
V2_F (mL/kg)					
MRT (hour)	0.416±0.022				
AUC_0-T (ng/mL•hr)	3610	570	3010	2760	12700
AUCinf_pred (ng/mL•hr)	3300±210	771±107	5190±1100	2900±310	14200±1800
F (percent)		23	29	29	

Female

	Treatment Group (mg/kg)			
	20 IV[b]	**20 Gav[b]**	**60 Gav[b]**	**200 Gav[b]**
	Plasma			
C_0min_pred (ng/mL)	9920±850			
Cmax_pred (ng/mL)		1540±250	3890±450	15200±1900
Tmax_pred (hour)		0.539±0.134	0.392±0.116	0.237±0.175
Cmax_obs (ng/mL)	10200	2250	4040	9430
Tmax_obs (hour)		0.167	0.167	0.0833
Alpha_Half-life (hour)	0.359±0.057			
Beta_Half-life (hour)	1.46±0.85			
k01 (hour^-1)		4.4±1.81	8.4±3.54	20±18.4
k01_Half-life (hour)		0.158±0.065	0.0824±0.0346	0.0353±0.0330
k10 (hour^-1)	1.61±0.14	0.56±0.071	0.36±0.030	0.2±0.016
k10_Half-life (hour)	0.431±0.038	1.24±0.16	1.93±0.16	3.55±0.28
k12 (hour^-1)	0.229±0.086			
k21 (hour^-1)	0.57±0.373			
Cl1 (mL/hr/kg)	3240±170			
Cl2 (mL/hr/kg)	461±151			
Cl1_F (mL/hr/kg)		5370±880	4810±500	2460±270
V1 (mL/kg)	2020±170			
V2 (mL/kg)	808±367			
V1_F (mL/kg)		9640±2250	13400±1900	12600±1800
MRT (hour)	0.871±0.151			
AUC_0-T (ng/mL•hr)	6080	2800	12200	69700
AUCinf_pred (ng/mL•hr)	6170±310	3730±610	12500±1300	81400±9100
F (percent)		60	68	

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Male

	Treatment Group (mg/kg)			
	20 IV[d]	**20 Gav[e]**	**60 Gav[e]**	**200 Gav[e]**
	Brain			
Cmax_obs (ng/g)	61200	1680	4560	13400
Tmax_obs (hour)	0.0679	0.204	0.202	0.116
Half-life (hour)	0.434	0.960	1.42	2.64
AUC_0-T (ng/g•hr)	17400	1300	7080	33600
AUCinf_pred (ng/g•hr)	17500	1370	7220	35100

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Female

	Treatment Group (mg/kg)			
	20 IV[d]	**20 Gav[e]**	**60 Gav[e]**	**200 Gav[e]**
	Brain			
Cmax_obs (ng/g)	42600	4780	11700	25800
Tmax_obs (hour)	0.0674	0.198	0.196	0.113
Half-life (hour)	0.714	1.55	2.47	6.11
AUC_0-T (ng/g•hr)	19000	7410	31000	139000
AUCinf_pred (ng/g•hr)	19200	7580	32000	187000

LEGEND

Data are displayed as mean ± SEM

MODELING METHOD & BEST FIT MODEL

[a] WinNonlin (Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA); two-compartment with bolus input, first order elimination and 1/Yhat2 weighting (Model #8)

[b] WinNonlin (Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA); one-compartment model with first order input, first order elimination, and 1/Yhat2 weighting (Model #13)

[c] WinNonlin (Versions 6.4 and 6.4, Pharsight Corporation, Mountain View, CA); one-compartment model with first order input, first order elimination, and 1/Yhat2 weighting (Model #13) with 12 hour data excluded (unexpected increase in plasma concentration at 12 hours)

[d] WinNonlin (Versions 6.4 and 6.4, Pharsight Corporation, Mountain View, CA); Noncompartmental analysis (NCA) model with bolus input, first order output and uniform weighting.

[e] WinNonlin (Versions 6.4 and 6.4, Pharsight Corporation, Mountain View, CA); NCA model with first order input, first order output, and uniform weighting.

ANALYTE

N-Butylbenzenesulfonamide

TK PARAMETERS

C_0min_pred = Fitted plasma concentration at time zero (IV Only)
Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax = Time at which Cmax predicted or observed occurs
Alpha_Half_life = Half-life for the alpha phase
Beta_Half_life = Half-life for the beta phase
k01 = Absorption rate constant, ka
k01_Half-life = Half-life of the absorption process to the central compartment
k10 = Elimination rate constant from the central compartment also ke or kelim
k10_Half-life = Half-life for the elimination process from the central compartment
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl1 = Clearance of central compartment, Clapp or apparent clearance for intravenous groups

Cl2 = Clearance of the secondary compartment
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA, Vapp apparent volume of distribution for intravenous studies
V2 = Volume of distribution for the peripheral compartment
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
MRT = Mean residence time
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
AUCinf = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

TK Parameters_1 – IV 20 mg/kg Male, IV 20 mg/kg Female

Rats were give a single intravenous dose in Cremophor:ethanol:deionized water (1:1:8) vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Time points were Pre-dose, 2, 5, 10, 15, 20, 30, 45, 60, 120, 180, and 240 min post-dose. Blood and brain tissue samples were measured using gas chromatography with mass selective detection (GC/MSD). The target limit of quantitation (LOQ) for N-Butylbenzenesulfonamide (NBBS) (IV and gavage) in plasma was 2.5 ng/mL, for NBBS in brain was 25 ng/g tissue. Samples below the LOQ were designated as below the limit of quantitation (BLOQ).

TK Parameters_2 – Gav 20 mg/kg Male, Gav 20 mg/kg Female

Rats were given a single oral gavage dose in 0.5% methylcellulose in deionized water vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Time points were Pre-dose, 2, 5, 10, 15, 20, 30, 45, 60, 120, 240, and 480 min post-dose. Blood and brain tissue samples were measured using gas chromatography with mass selective detection (GC/MSD). The target limit of quantitation (LOQ) for N-Butylbenzenesulfonamide (NBBS) (IV and gavage) in plasma was 2.5 ng/mL, for NBBS in brain was 25 ng/g tissue. Samples below the LOQ were designated as below the limit of quantitation (BLOQ).

TK Parameters_3 – Gav 60 mg/kg Male,200 mg/kg Male, Gav 60 mg/kg Female, Gav 200 mg/kg Female

Rats were given a single oral gavage dose in 0.5% methylcellulose in deionized water vehicle and allowed food and water ad libitum. Blood and brain samples were collected at 11 time points post-administration with n=3 per time point. Pre-dose, 5, 10, 20, 30, 45, 60, 120, 240, 480, 720, and 1440 min post-dose. Blood and brain tissue samples were measured using gas chromatography with mass selective detection (GC/MSD). The target limit of quantitation (LOQ) for N-Butylbenzenesulfonamide (NBBS) (IV and gavage) in plasma was 2.5 ng/mL, for NBBS in brain was 25 ng/g tissue. Samples below the LOQ were designated as below the limit of quantitation (BLOQ).