

Experiment Number: K10482B
Route: Gavage, IV
Species/Strain: Mouse/B6C3F1/N

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

200 Gav^c

200 Gav^c

Plasma

C ₀ min_pred (ng/mL)	62500±14600				
C _{max} _pred (ng/mL)		756±119	5530±1250	15500±2400	15500±2300
T _{max} _pred (hour)		0.131±0.030	0.130±0.057	0.136±0.051	0.134±0.050
C _{max} _obs (ng/mL)	33700	1360	7830	17800	17800
T _{max} _obs (hour)		0.0833	0.0833	0.167	0.167
Alpha_Half-life (hour)	0.0645±0.0093	0.119±0.118	0.156±0.071	0.262±0.055	0.268±0.054
Beta_Half-life (hour)	0.435±0.025	0.895±0.247	0.789±0.185	1.97±0.31	2.10±0.50
k ₀₁ (hour ⁻¹)		11.0±11.4	19±20.6	16±10.5	17±10.7
k ₀₁ _Half-life (hour)		0.0631±0.0655	0.0358±0.0381	0.0431±0.0281	0.0417±0.0268
k ₁₀ (hour ⁻¹)	8.71±1.21	3.46±2.75	3.16±1.05	2.18 ±0.40	2.14±0.38
k ₁₀ _Half-life (hour)	0.0796±0.0111	0.201±0.160	0.220±0.073	0.317±0.058	0.323±0.057
k ₁₂ (hour ⁻¹)	1.65±0.46	1.82±2.68	0.922±0.814	0.384±0.161	0.373±0.153
k ₂₁ (hour ⁻¹)	1.97±0.18	1.30±0.64	1.23±0.49	0.43±0.084	0.4±0.110
Cl ₁ (mL/hr/kg)	2790±340				
Cl ₂ (mL/hr/kg)	529±157				
Cl ₁ _F (mL/hr/kg)		46800±4900	22700±2700	19900±1900	19800±1800
Cl ₂ _F (mL/hr/kg)		24700±18400	6620±4250	3500±1170	3450±1130
V ₁ (mL/kg)	320±75				
V ₂ (mL/kg)	269±65				
V ₁ _F (mL/kg)		13600±11100	7180±2670	9120±2020	9250±1950
V ₂ _F (mL/kg)		19000±7400	5360±1900	8200±1940	8660±2150
MRT (hour)	0.211±0.022				
AUC _{0-T} (ng/mL•hr)	6440	426	2400	10500	10500
AUC _{inf} _pred (ng/mL•hr)	7180±880	427±45	2650±310	10000±900	10100±900
F (percent)			6	14	14

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Female

Treatment Group (mg/kg)

20 Gav^b

20 Gav^d

60 Gav^b

200 Gav^b

200 Gav^e

Plasma

C_0min_pred (ng/mL)					
Cmax_pred (ng/mL)	1040±190	871±175	2960±430	13700±2300	14900±2500
Tmax_pred (hour)	0.107±0.027	0.0710±0.0232	0.107±0.038	0.133±0.075	0.191±0.065
Cmax_obs (ng/mL)	779	779	2950	16100	16100
Tmax_obs (hour)	0.0333	0.0333	0.0833	0.0833	0.0833
Alpha_Half-life (hour)	0.121±0.045	0.0588±0.0836	0.177±0.042	0.354±0.119	0.310±0.173
Beta_Half-life (hour)	4.13±7.60	0.490±0.116	0.737±0.135	1.00±0.23	3.12±18.1
k01 (hour ⁻¹)	15±9.3	19.0±31.9	19±12.5	20.0±18.1	10±8.0
k01_Half-life (hour)	0.0477±0.0303	0.0364±0.0610	0.0362±0.0236	0.0347±0.0314	0.0674±0.0522
k10 (hour ⁻¹)	3.48±2.51	6.68±8.60	3.14±0.56	1.60 ±0.35	1.94±1.35
k10_Half-life (hour)	0.199±0.144	0.104±0.134	0.221±0.039	0.432±0.093	0.358±0.249
k12 (hour ⁻¹)	2.14±1.49	4.02±7.76	0.544±0.300	0.200±0.206	0.264±0.313
k21 (hour ⁻¹)	0.28±0.386	2.50±1.01	1.17±0.31	0.84±0.316	0.26±1.44
Cl1 (mL/hr/kg)					
Cl2 (mL/hr/kg)					
Cl1_F (mL/hr/kg)	36900±18900	74000±8300	43000±3500	18500±1900	17100±6100
Cl2_F (mL/hr/kg)	22800±17700	44600±32000	7460±3250	2310±2030	2340±3480
V1 (mL/kg)					
V2 (mL/kg)					
V1_F (mL/kg)	10600±4100	11100±14500	13700±2900	11500±2700	8860±3750
V2_F (mL/kg)	82400±174000	17900±8100	6360±1650	2730±1610	9130±64500
MRT (hour)					
AUC_0-T (ng/mL•hr)	259	259	1340	11300	11300
AUCinf_pred (ng/mL•hr)	541±277	270±30	1390±110	10800±1100	11700±4200
F (percent)			6	25	25

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Female

Treatment Group (mg/kg)

20 IV^a

20 IV^f

Plasma

C ₀ min_pred (ng/mL)	60800±17000	60500±59200
C _{max} _pred (ng/mL)		
T _{max} _pred (hour)		
C _{max} _obs (ng/mL)	10700	29900
T _{max} _obs (hour)		
Alpha_Half-life (hour)	0.110±0.018	0.0270±0.0159
Beta_Half-life (hour)	0.648±0.189	0.298±0.020
k ₀₁ (hour ⁻¹)		
k ₀₁ _Half-life (hour)		
k ₁₀ (hour ⁻¹)	5.94±0.88	13.1±9.3
k ₁₀ _Half-life (hour)	0.117±0.017	0.0529±0.0377
k ₁₂ (hour ⁻¹)	0.306±0.183	10.4±7.0
k ₂₁ (hour ⁻¹)	1.14±0.36	4.57±1.23
Cl ₁ (ml/hr/kg)	1960±340	4330±1280
Cl ₂ (mL/hr/kg)	101±58	3430±2230
Cl _{1_F} (mL/hr/kg)		
Cl _{2_F} (mL/hr/kg)		
V ₁ (mL/kg)	329±92	331±323
V ₂ (mL/kg)	89±37.4	750±311
V _{1_F} (mL/kg)		
V _{2_F} (mL/kg)		
MRT (hour)	0.214±0.026	0.249±0.067
AUC _{0-T} (ng/mL•hr)	3320	3320
AUC _{inf} _pred (ng/mL•hr)	10200±1800	4620±1370
F (percent)		

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Treatment Group (mg/kg)

20 IV^g

20 Gav^h

60 Gav^h

200 Gav^h

Brain

Cmax_obs (ng/g)	66800	1260	8280	23400
Tmax_obs (hour)	0.0669	0.118	0.120	0.198
Half-life (hour)	0.183	0.315	0.417	0.524
AUC_0-T (ng/g•hr)	20400	258	2390	14100
AUCinf_pred (ng/g•hr)	20500	279	2430	14200

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Female

Treatment Group (mg/kg)

20 IV^g

20 IVⁱ

20 Gav^h

60 Gav^h

200 Gav^h

Brain

Cmax_obs (ng/g)	15700	45900	733	2830	18700
Tmax_obs (hour)	0.0738	0.0738	0.199	0.198	0.362
Half-life (hour)	0.352	0.352	0.278	0.329	0.545
AUC_0-T (ng/g•hr)	4110	14600	208	1270	16600
AUCinf_pred (ng/g•hr)	4150	14600	222	1280	16600

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LEGEND

Data are displayed as mean \pm 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 $1/Y_{hat}^2$ 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 $1/Y_{hat}^2$ weighting (Model #13)
- ^c WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA; one-compartment model with first order input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #13) with 12-hour data excluded (unexpected increase in plasma concentration at 12 hours)
- ^d WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA; two-compartment model with first order input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #13). Does not include the single concentration at 4 hours.
- ^e WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA; two-compartment model with first order input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #13). Does not include the single concentration at 8 hours.
- ^f WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA; two-compartment model with bolus input, first order elimination, and $1/Y_{hat}^2$ weighting (Model #8). Does not include the single concentration at 4 hours or two concentrations at 0.0333 hours
- ^g WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA; NCA model with bolus input, first order output, and uniform weighting.
- ^h WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA; NCA model with first order input, first order output, and uniform weighting.
- ⁱ WinNonlin, Versions 6.3 and 6.4, Pharsight Corporation, Mountain View, CA; NCA model with bolus input, first order output, and uniform weighting. Does not include two concentrations at 0.0333 hours.

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ANALYTE

N-Butylbenzenesulfonamide

TK PARAMETERS

C_{0min_pred} = Fitted plasma concentration at time zero (IV Only)

C_{max} = Observed or Predicted Maximum plasma (or tissue) concentration

T_{max} = Time at which C_{max} 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, k_a

k_{01_Half-life} = Half-life of the absorption process to the central compartment

k₁₀ = Elimination rate constant from the central compartment also k_e or k_{elim}

k_{10_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, Cl_{app} or apparent clearance for intravenous groups

Cl₂ = Clearance of the secondary compartment

Cl_{1_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 V_d and V volume of distribution, V_z apparent volume of distribution NCA, V_{app} apparent volume of distribution for intravenous studies

V₂ = Volume of distribution for the peripheral compartment

V_{1_F} = Apparent volume of distribution for the central compartment includes V_{d_F}, V_F for oral groups, and V_{c_F}

MRT = Mean residence time

AUC_{0-T} = Area under the plasma concentration versus time curve, AUC, from time t_i (initial) to t_f (final), AUC_{last}

AUC_{inf} = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

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TK PARAMETERS PROTOCOL

TK Parameters_4 – IV 20 mg/kg Male Plasma, IV 20 mg/kg Female Plasma, IV 20 mg/kg Male Brain, IV 20 mg/kg Female Brain

Mice 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_5 – Gav 20 mg/kg Male Plasma, Gav 20 mg/kg Female Plasma, Gav 20 mg/kg Male Brain, Gav 20 mg/kg Female Brain

Mice 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_6 – Gav 60 mg/kg Male Plasma, Gav 200 mg/kg Male Plasma, 60 mg/kg Female Plasma, Gav 200 mg/kg Female Plasma, Gav 60 mg/kg Male Brain, Gav 200 mg/kg Male Brain, 60 mg/kg Female Brain, Gav 200 mg/kg Female Brain

Mice 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 desinated as below the limit of quantitation (BLOQ).