Experiment Number: C96019

Route: Dosed Water, Dosed Water and Gavage Challenge, Gavage, IV

Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Test Compound: Bromochloroacetic Acid

CAS Number: 5589-96-8

Date Report Requested: 02/09/2017

Time Report Requested: 08:26:56

Lab: Battelle Columbus

Male

	Treatment Groups (mg/kg)					
	80 [b, #, 2]	**80** [c, #, 1]	**100** [a, #, 3]	**160** [b, #, 2]	**160** [c, #, 1]	**200** [a, #, 3]
	Plasma					
$C_{max(pred)}$ (ug/mL)	8.47 ± 1.78		7.26 ± 1.33	55.0 ± 5.6		23.4 ± 2.2
$T_{max(pred)}$ (min)	8.37 ± 1.08		13.1 ± 2.2	18.9 ± 1.8		21.9 ± 2.0
$C_{max(obs)}$ (ug/mL)		0.732			1.09	
$T_{max(obs)}$ (hour)		18			15	
k_{01} (min^-1)	0.120 ± 0.015		0.0764 ± 0.013	0.0530 ± 0.0051		0.0456 ± 0.0041
$t_{1/2(k01)}$ (min)	5.80 ± 0.75		9.07 ± 1.55	13.1 ± 1.2		15.2 ± 1.4
k_{10} (min^-1)	0.120 ± 0.015		0.0764 ± 0.013	0.0530 ± 0.0051		0.0456 ± 0.0041
$t_{1/2(k10)}$ (min)	5.80 ± 0.75		9.07 ± 1.55	13.1 ± 1.2		15.2 ± 1.4
Cl (mL/min/kg)						
$Cl_{1(F)}$ (mL/min/kg)	415 ± 83		387 ± 79	56.7 ± 7.1		144 ± 16
V_1 (mL/kg)						
$V_{1(F)}$ (mL/kg)	3480 ± 730		5070 ± 931	1070 ± 110		3150 ± 300
MRT (min)						
AUC_{0-t} (ug/mL*min)	90.2		248	2540		1390
AUC_{inf} (ug/mL*min)	193 ± 38		258 ± 53	2820 ± 360		1390 ± 160

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Male

	Treatment Groups (mg/kg)			
	400 [a, #, 3]	**100 IV** [d, o, 4]	**100 IV** [d, *, 4]	**100 IV** [e, #, 4]
	Plasma			
$C_{max(pred)}$ (ug/mL)	62.6 ± 5.6	190 ± 22	123 ± 8	182 ± 24
$T_{max(pred)}$ (min)	27.2 ± 2.0			
$C_{max(obs)}$ (ug/mL)				
$T_{max(obs)}$ (hour)				
k_{01} (min^-1)	0.0367 ± 0.0027			
$t_{1/2(k01)}$ (min)	18.9 ± 1.4			5.34 ± 0.68
k_{10} (min^-1)	0.0367 ± 0.0027	0.360 ± 0.031	0.142 ± 0.009	0.130 ± 0.016
$t_{1/2(k10)}$ (min)	18.9 ± 1.4	1.92 ± 0.16	4.88 ± 0.32	
Cl (mL/min/kg)		189 ± 13	115 ± 6	71.3 ± 7.1
$Cl_{1(F)}$ (mL/min/kg)	86.4 ± 9			
V_1 (mL/kg)		525 ± 61	812 ± 56	550 ± 72
$V_{1(F)}$ (mL/kg)	2350 ± 210			
MRT (min)		2.78 ± 0.24	7.04 ± 0.46	7.71 ± 0.97
AUC_{0-t} (ug/mL*min)	4100			
AUC_{inf} (ug/mL*min)	4630 ± 480	529 ± 36	867 ± 45	1400 ± 140

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Lab: Battelle Columbus

Female

	Treatment Groups (mg/kg)					
	100 [a, #, 3]	**100** [b, #, 2]	**100** [c, #, 1]	**200** [a, #, 3]	**200** [f, #, 2]	**200** [c, #, 1]
	Plasma					
$C_{max(pred)}$ (ug/mL)	3.68 ± 0.47	26.3 ± 3.1		16.3 ± 1.7	68.0 ± 6.0	
$T_{max(pred)}$ (min)	15.5 ± 1.9	19.4 ± 1.9		17.3 ± 1.7	18.4 ± 1.5	
$C_{max(obs)}$ (ug/mL)			0.99			1.37
$T_{max(obs)}$ (hour)			15			21
k_{01} (min^-1)	0.0646 ± 0.0081	0.0515 ± 0.0050		0.0579 ± 0.0056	0.0543 ± 0.0045	
$t_{1/2(k01)}$ (min)	10.7 ± 1.3	13.4 ± 1.3		12.0 ± 1.2	12.8 ± 1.0	
k_{10} (min^-1)	0.0646 ± 0.0081	0.0515 ± 0.0050		0.0579 ± 0.0056	0.0543 ± 0.0045	
$t_{1/2(k10)}$ (min)	10.7 ± 1.3	13.4 ± 1.3		12.0 ± 1.2	12.8 ± 1.0	
Cl (mL/min/kg)						
$Cl_{1(F)}$ (mL/min/kg)	646 ± 97	72.0 ± 9.6		260 ± 31	58.8 ± 6.4	
V_1 (mL/kg)						
$V_{1(F)}$ (mL/kg)	10000 ± 1000	1400 ± 170		4500 ± 460	1080 ± 100	
MRT (min)						
AUC_{0-t} (ug/ml*min)	152	1280		680	3330	
AUC_{inf} (ug/mL*min)	155 ± 23	1390 ± 190		768 ± 92	3400 ± 370	

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Female

	Treatment Groups (mg/kg)			
	400 [a, #, 3]	**100 IV** [g, #, 4]	**100 IV** [d, *, 4]	**100 IV** [d, o, 4]
	Plasma			
$C_{max(pred)}$ (ug/mL)	58.7 ± 5.6	247 ± 11	144 ± 8	219 ± 16
$T_{max(pred)}$ (min)	21.6 ± 1.8			
$C_{max(obs)}$ (ug/mL)				
$T_{max(obs)}$ (hour)				
k_{01} (min^-1)	0.0462 ± 0.0038			
$t_{1/2(k01)}$ (min)	15.0 ± 1.2	3.73 ± 0.16		
k_{10} (min^-1)	0.0462 ± 0.0038	0.186 ± 0.008	0.143 ± 0.007	0.384 ± 0.020
$t_{1/2(k10)}$ (min)	15.0 ± 1.2		4.86 ± 0.25	1.80 ± 0.09
Cl (mL/min/kg)		75.3 ± 2.2	98.9 ± 4.0	175 ± 7
$Cl_{1(F)}$ (mL/min/kg)	116 ± 13			
V_1 (mL/kg)		405 ± 18	693 ± 38	456 ± 33
$V_{1(F)}$ (mL/kg)	2510 ± 240			
MRT (min)		5.38 ± 0.23	7.01 ± 0.37	2.60 ± 0.14
AUC_{0-t} (ug/ml*min)	3090			
AUC_{inf} (ug/mL*min)	3450 ± 390	1330 ± 40	1010 ± 40	571 ± 23

LEGEND

Data are displayed as mean ± SEM

MODELING METHOD & BEST FIT MODEL

[a] WinNonlin Pharsight Corp; One-compartment equal first order absorption and elimination with 1/Yhat weighting. Model 5 with Ka equals to ke (a one-compartment model with equal first order absorption and elimination). Parameter estimates and SEM are reported to three significant figures. GXA and OXA plasma concentration time point data were not presented because most of GXA and OXA values were near or at BLOQ (4.209 ug/mL GXA and 4.192 ug/mL OXA).

[b] WinNonlin, version 4.0, 5.0, or 5.0.1, Pharsight Corporation, Mountain View, CA; One-compartment model with equal first order absorption and elimination. Parameter estimates and SEM are reported to three significant figures.

[c] WinNonlin, version 4.0, 5.0, or 5.0.1, Pharsight Corporation, Mountain View, CA; No extensive TK analysis was performed for the non-challenge group data, however, non-compartmental analysis was used to determine Cmax and AUC values for the mid and high dose BCA groups for the purpose of examining dose proportionality. No kinetic modeling was possible for the non-challenge group animals for GXA and OXA. The plasma concentrations of GXA and OXA were either BLOQ (4.349 and 4.169 µg/mL, respectively), or not detected, for all dosage groups.

[d] WinNonlin Pharsight Corp.; One-compartment model with bolus input, first order output, and 1/Y weighting. The BCA minus isomer was eliminated much faster than BCA plus isomer for rats and mice.

[e] WinNonlin Pharsight Corp; One-compartment model with bolus input, first order output, and 1/Yhat weighting. Parameter estimates are reported to three significant figures.

[f] WinNonlin, version 4.0, 5.0, or 5.0.1, Pharsight Corporation, Mountain View, CA; One-compartment model with equal first order absorption and elimination. Parameter estimates and SEM are reported to three significant figures. The BCA minus isomer was eliminated much faster than BCA plus isomer for rats and mice.

[g] WinNonlin Pharsight Corp; One-compartment model with bolus input, first order output, and 1/Y weighting. Parameter estimates are reported to three significant figures.

ANALYTE

[#] Bromochloroacetic acid

* Bromochloroacetic acid plus isomer

[o] Bromochloroacetic acid minus isomer

ROUTE & DOSING

[1] Dosed Water: Animals exposed by drinking water ad libitum

[2] Dosed Water and Gavage Challenge: Animals exposed by drinking water ad libitum and by a single gavage administration on Study day 15

[3] Gavage: Animals were administered a single gavage dose

[4] IV: Animals were given a single bolus intravenous injection

LEGEND

TK PARAMETERS

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

T_{max} = Time at which C_{max} predicted or observed occurs

k_{01} = Absorption rate constant, k_a

$t_{1/2(k01)}$ = Half-life of the absorption process to the central compartment

k_{10} = Elimination rate constant from the central compartment also k_e or k_{elim}

$t_{1/2(k10)}$ = Half-life for the elimination process from the central compartment

Cl = Clearance, includes total clearance

$Cl_{1(F)}$ = Apparent clearance of the central compartment, also $Cl_{(F)}$ for gavage groups in non-compartmental model

V_1 = 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

$V_{1(F)}$ = 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

** END OF REPORT **