

Experiment Number: K02825
Route: IV, Gavage
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 2-Methylimidazole/ Analyte: 2-Methylimidazole
CAS Number: 693-98-1

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: Battelle Columbus

Male

Treatment Group (mg/kg)

10 IV Plasma^{a,c}

25 Gavage Plasma^{b,d}

50 Gavage Plasma^{b,e}

100 Gavage Plasma^{b,f}

	10 IV Plasma ^{a,c}	25 Gavage Plasma ^{b,d}	50 Gavage Plasma ^{b,e}	100 Gavage Plasma ^{b,f}
Cmax_pred (ug/mL)	5.33 ± 0.98	4.53 ± 0.87	10.0 ± 1.2	25.4 ± 2.2
Tmax_pred (hour)		0.127 ± 0.076	0.099 ± 0.038	0.166 ± 0.034
k01 (hour ⁻¹)		19.9 ± 18.7	26.0 ± 15.2	12.9 ± 4.6
k01 Half-life (hour)		0.035 ± 0.033	0.027 ± 0.016	0.0537 ± 0.0189
k10 (hour ⁻¹)	2.66 ± 0.32	2.07 ± 0.34	2.53 ± 0.15	2.18 ± 0.20
k10 Half-life (hour)	0.260 ± 0.032	0.334 ± 0.054	0.274 ± 0.016	0.318 ± 0.028
Cl (mL/hr/kg)	5000 ± 550			
Cl _{1_F} (mL/hr/kg)		8800 ± 1100	9830 ± 630	5990 ± 410
V _{ss} (mL/kg)	1880 ± 340			
MRT (hour)	0.376 ± 0.046			
AUC _{0-T} (ug/mL*hr)		2.84 ± 0.35	5.09 ± 0.32	16.7 ± 1.1
AUC _{inf_pred} (ug/ml*hr)	2.00 ± 0.22			
F (percent)		51.2	49.7	85.0

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Female

Treatment Group (mg/kg)

10 IV Plasma^{a,g}

25 Gavage Plasma^{b,h}

50 Gavage Plasma^{b,i}

100 Gavage Plasma^{b,j}

	10 IV Plasma ^{a,g}	25 Gavage Plasma ^{b,h}	50 Gavage Plasma ^{b,i}	100 Gavage Plasma ^{b,j}
Cmax_pred (ug/mL)	6.27 ± 0.57	5.89 ± 0.53	13.0 ± 0.4	27.1 ± 1.2
Tmax_pred (hour)		0.147 ± 0.027	0.165 ± 0.010	0.203 ± 0.018
k01 (hour ⁻¹)		13.7 ± 4.4	12.2 ± 1.3	9.77 ± 1.66
k01 Half-life (hour)		0.051 ± 0.016	0.057 ± 0.006	0.071 ± 0.012
k10 (hour ⁻¹)	3.01 ± 0.16	2.75 ± 0.19	2.44 ± 0.07	2.04 ± 0.12
k10 Half-life (hour)	0.231 ± 0.012	0.252 ± 0.018	0.284 ± 0.008	0.339 ± 0.020
Cl (mL/hr/kg)	4800 ± 270			
Cl _{1_F} (mL/hr/kg)		7790 ± 510	6310 ± 140	4990 ± 180
V _{ss} (mL/kg)	1600 ± 150			
MRT (hour)	0.333 ± 0.018			
AUC _{0-T} (ug/mL*hr)		3.21 ± 0.21	7.93 ± 0.17	20.0 ± 0.7
AUC _{inf_pred} (ug/ml*hr)	2.08 ± 0.12			
F (percent)		59.9	74.4	93.9

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LEGEND

MODELING SOFTWARE

WinNonlin V01.5A,

MODELING METHOD & BEST FIT MODEL

^aWinNonlin V01.5A, using Gauss-Newton (Levenberg and Hartley) method, one-compartment model with first order elimination. The concentration values were weighted $1/y^2$.

^bWinNonlin V01.5A, using Gauss-Newton (Levenberg and Hartley) method, one-compartment model with no lag phase and first order absorption and elimination. The concentration values were weighted $1/y^2$ (predicted).

EXCEPTION

^cData set fitted using concentrations up through 1 hour. The observed AUC T is 1 hour.

^dUnreliable concentrations after 1.5 hours. The observed AUC 0-T is 2.34 ug/ml*hr at 1 hour, the 4 hour value is 2.56.

^eUnreliable concentrations after 1.5 hours. The observed AUC 0-T is 4.60 ug/ml*hr at 1 hour, the 4 hour value is 4.97.

^fUnreliable concentrations after 1.5 hours, Since kinetics at 100 mg/kg is non-linear, the clearance is not constant and bioavailability is overestimated. The observed AUC 0-T is 15.0 ug/ml*hr at 1 hour, the 4 hour value is 17.0 ug/ml*hr.

^gUnreliable concentrations after 1 hour. The observed AUC T is 1 hour.

^hUnreliable concentrations after 1.5 hours. The observed AUC 0-T is 2.96 ug/ml*hr at 1 hour, the 4 hour value is 3.19.

ⁱUnreliable concentrations after 1.5 hours. The observed AUC 0-T is 6.99 ug/ml*hr at 1 hour, the 4 hour value is 7.92.

^jUnreliable concentrations after 1.5 hours, Since kinetics at 100 mg/kg is non-linear, the clearance is not constant and bioavailability is overestimated. The observed AUC 0-T is 17.2 ug/ml*hr at 1 hour, the 4 hour value is 20.0.

ANALYTE

2-Methylimidazole

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TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration

Tmax_pred = Time at which Cmax predicted or observed occurs

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

Cl = Clearance, includes total clearance

Cl_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model

Vss = Volume of distribution at steady state

MRT = Mean residence time Mean residence time

AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast

AUCinf_pred = 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

ANALYSIS METHOD

Single bolus intravenous administration into the tail vein to 27 mice. Blood was collected at 9 timepoints (5, 10, 15, 30, 45, 60, 90, 120, and 240 minutes (n=3 mice/sex/dose level bled at each timepoint.) Blood collected by cardiac puncture. Plasma samples were analyzed using a validated gas chromatography method using an internal standard and extracted with ethyl acetate. Plasma method's Limit of Quantitation (LOQ) was 0.1 ug/mL. those values below the LOQ were not used to fit the profile to a model.

TK_INTRAVENTOUS PLASMA

10 mg/kg Male

Bodyweights given are for 50 animals in the study and replacement animal IV male mouse group. Only 27 animals were used for this dose.

10 mg/kg Female

Bodyweights given are for 51 animals in the study and replacement animal IV female mouse group. Only 27 animals were used for this dose.

ANALYSIS METHOD

Single bolus oral gavage administration to 27 mice/sex. Blood was collected at 9 timepoints (5, 10, 15, 30, 45, 60, 90, 180, and 360 minutes (n=3 mice/sex/dose level bled at each timepoint.) Blood collected by cardiac puncture. Plasma samples were analyzed using a validated gas chromatography method using an internal standard and extracted with ethyl acetate. Plasma method's Limit of Quantitation (LOQ) was 0.1 ug/mL. those values below the LOQ were not used to fit the profile to a model.

TK_GAVAGE PLASMA

25 mg/kg, 50 mg/kg Male

Bodyweights given are for the 104 total number of male gavage mice-study animals, replacements, all dose levels combined. Only 27 animals from this group were used for this dose level.

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TK PARAMETERS PROTOCOL (cont'd)

25 mg/kg, 50 mg/kg Female

Bodyweights given are for the 104 total number of female gavage mice-study animals, replacements, all dose levels combined. Only 27 animals from this group were used for this dose level

ANALYSIS METHOD

Single bolus oral gavage administration to 27 mice/sex. Blood was collected at 9 timepoints (5, 10, 15, 30, 60, 90, 180, 360, and 720 minutes (n=3 mice/sex/dose level bled at each timepoint.) Blood collected by cardiac puncture. Plasma samples were analyzed using a validated gas chromatography method using an internal standard and extracted with ethyl acetate. Plasma method's Limit of Quantitation (LOQ) was 0.1 ug/mL. those values below the LOQ were not used to fit the profile to a model.

100 mg/kg Male

Bodyweights given are for the 104 total number of male gavage mice-study animals, replacements, all dose levels combined. Only 27 animals from this group were used for this dose level.

100 mg/kg Female

Bodyweights given are for the 104 total number of female gavage mice-study animals, replacements, all dose levels combined. Only 27 animals from this group were used for this dose level.