Experiment Number: K88072B
Route: Gavage, IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3'-Azido-3'-deoxythimidine
CAS Number: 30516-87-1

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

Female

	Treatment Group (mg/kg)		
	15 IV Plasma[a]	**30 IV Plasma[a]**	**60 IV Plasma[a]**
Cmax_pred (ug/mL)	15.9 ± 2.6	41.8 ± 6.0	76.0 ± 23.8
Tmax_pred (minute)	6.7 ± 2.9	8.3 ± 2.9	8.3 ± 5.8
k10 (minute^{-1})	0.0355 ± 0.0065	0.0400 ± 0.0389	0.0349 ± 0.0105
k10 Half-life (minute)	19.5	17.3	19.9
Cl1 (mL/min/kg)	34.3 ± 8.2	31.1 ± 4.0	28.9 ± 7.8
V1 (L/kg)	1.009 ± 0.378	0.778 ± 0.074	0.924 ± 0.524
Vss (L/kg)	0.941 ± 0.303	0.720 ± 0.077	0.851 ± 0.426
MRT (minute)	28.7 ± 4.7	25.2 ± 2.6	30.5 ± 9.2
AUC_0-T (ug/mL*min)	454.8 ± 110.6	975.8 ± 116.2	2163.8 ± 504.7
AUCinf_pred (ug/mL*min)	477.8 ± 92.1	1045.6 ± 73.5	2282.9 ± 414.0
F	1.000	1.000	1.000

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	Treatment Group (mg/kg)		
	15 Gavage Plasma[b]	**30 Gavage Plasma[b]**	**60 Gavage Plasma[b]**
Cmax_pred (ug/mL)	9.1 ± 1.5	18.9 ± 0.5	40.3 ± 7.2
Tmax_pred (minute)	18.3 ± 2.9	21.7 ± 7.6	15.0 ± 5.0
k01 (minute^{-1})	0.0807 ± 0.0308	0.0897 ± 0.0239	0.0892 ± 0.0490
k01 Half-life (minute)	8.6	7.7	7.8
k10 (minute^{-1})	0.0375 ± 0.0092	0.0419 ± 0.0120	0.0317 ± 0.0104
k10 Half-life (minute)	18.5	16.5	21.9
Cl1_F (mL/min/kg)	34.3 ± 8.3	31.1 ± 3.9	28.9 ± 7.8
Vss (L/kg)	1.331 ± 0.314	1.120 ± 0.052	1.281 ± 0.240
V1_F (L/kg)	0.971 ± 0.368	0.762 ± 0.106	0.964 ± 0.289
MRT (minute)	41.3 ± 1.8	36.9 ± 2.5	47.9 ± 8.5
AUC_0-T (ug/mL*min)	386.1 ± 56.6	798.1 ± 68.2	1981.2 ± 313.1
AUCinf_pred (ug/mL*min)	409.1 ± 42.0	810.6 ± 62.0	2102.3 ± 347.6
F	0.849	0.818	0.916

LEGEND

MODELING SOFTWARE

SIPHAR/Base

MODELING METHOD & BEST FIT MODEL

[a]SIPHAR/Base (SIMED, Creteil, Cedex, France), one compartment open model with first-order elimination (1/y weighting). ALL VARIANCE IS STANDARD DEVIATION (Not SE).

[b]SIPHAR/Base (SIMED, Creteil, Cedex, France), one compartment open model with first-order absorption and elimination (1/y weighting); ALL VARIANCE IS STANDARD DEVIATION (Not SE).

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
Cl1 = Clearance of central compartment, Clapp or apparent clearance for intravenous groups
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 distributionNCA, Vapp apparent volume of distribution for intravenous studies
Vss = Volume of distribution at steady state
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_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

There were three replicate plasma samples (from three different mice) for each of 11 time points per dose level with two routes. Plasma concentration versus time data for each of the three individual data sets (11 samples per set) were determined for each concentration per route using SIPHAR/Base (SIMED, Creteil, Cedex, France) software. The mean and standard deviation of the parameters (n=3) for each dose level and each route is reported here. For the purpose of determining the bioavailability of AZT in this strain of mice the mean plasma concentrations for both oral and IV administration at each dose level were evaluated simultaneously (parameters not shown here but the bioavailability (CV %) values for PO-IV simultaneous analysis weas 0.908 (6.4%), 0.827 (6.6%), and 0.927 (10.4%) for 15, 30, and 60 mg/kg n=33 per dose, respectively). Mean extent of absorption (F) calculated as follows: mean AUCt (PO)/mean AUCt (IV) for each dose.

TK_INTRAVENOUS PLASMA

15 mg/kg, 30 mg/kg, 60 mg/kg Female

B6C3F1 female mice averaging 43 days in age were given a single intravenous or oral gavage dose of 15, 30, or 60 mg/kg of 3'-Azido-3'-deoxythimidine (AZT). There were no vehicle controls in this study. The vehicle for mice dosed intravenously (17.2-22.1 g bodyweight range) was deionized water and for mice dosed by oral gavage (17.2-22.4 g bodyweight range) was 0.5% methylcellulose in deionized water with dose volumes for both routes 10 mL AZT/kg body weight. Female mice were weighed on the day before dosing to calculate dose amounts. Mice were given pelleted feed and tap water ad libitum. Blood samples were collected at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, and 120 minutes postdose from the retro-orbital sinus with n=3 animals/dose group/timepoint. After blood samples were taken, the animals were humanely sacrificed by CO2 asphyxiation. These two studies had separate reports (report date 7/30/1990 for intravenous, 12/17/1990 for gavage) but were performed in tandem to determine the bioavailability of AZT in this strain of mice with the animals provided by the NTP from the same source. Plasma was harvested and analyzed for AZT by HPLC with UV detection (267 nm). Lowest standard was 0.100 ug/mL.

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

15 mg/kg, 30 mg/kg, 60 mg/kg Female

B6C3F1 female mice averaging 43 days in age were given a single intravenous or oral gavage dose of 15, 30, or 60 mg/kg of 3'-Azido-3'-deoxythimidine (AZT). There were no vehicle controls in this study. The vehicle for mice dosed intravenously (17.2-22.1 g bodyweight range) was deionized water and for mice dosed by oral gavage (17.2-22.4 g bodyweight range) was 0.5% methylcellulose in deionized water with dose volumes for both routes 10 mL AZT/kg body weight. Female mice were weighed on the day before dosing to calculate dose amounts. Mice were given pelleted feed and tap water ad libitum. Blood samples were collected at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, and 120 minutes postdose from the retro-orbital sinus with n=3 animals/dose group/timepoint. After blood samples were taken, the animals were humanely sacrificed by CO2 asphyxiation. These two studies had separate reports (report date 7/30/1990 for intravenous, 12/17/1990 for gavage) but were performed in tandem to determine the bioavailability of AZT in this strain of mice with the animals provided by the NTP from the same source. Plasma was harvested and analyzed for AZT by HPLC with UV detection (267 nm). Lowest standard was 0.100 ug/mL.