

Experiment Number: K06898
Route: Gavage, IV
Species/Strain: Rats/Fischer 344

Toxicokinetics Data Summary
Compound: alpha/beta-Thujone mixture/ Analyte: alpha-Thujone
CAS Number: 76231-76-0

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

Male

Treatment Group (mg/kg)

3.0 IV Plasma^c

25 Gavage Plasma^{b,d}

50 Gavage Plasma^{b,d}

	3.0 IV Plasma ^c	25 Gavage Plasma ^{b,d}	50 Gavage Plasma ^{b,d}
C ₀ min_pred (ng/mL)	1110 ± 200		
C _{max} _pred (ng/mL)		255 ± 29	462 ± 55
T _{max} _pred (minute)		15.1 ± 3.7	12.9 ± 3.7
C _{max} _obs (ng/mL)		286 ± 125	666 ± 100
T _{max} _obs (minute)		9.75 ± 0.50	10.0 ± 0.0
Alpha Half-life (minute)	6.48 ± 1.10		
Beta Half-life (minute)	165 ± 9		
k ₀₁ (minute ⁻¹)		0.281 ± 0.093	0.344 ± 0.129
k ₀₁ Half-life (minute)		2.47 ± 0.81	2.01 ± 0.75
k ₁₀ (minute ⁻¹)	0.0349 ± 0.0057	0.00435 ± 0.00042	0.00427 ± 0.00039
k ₁₀ Half-life (minute)	19.8 ± 3.2	160 ± 16	162 ± 15
k ₁₂ (minute ⁻¹)	0.0633 ± 0.0127		
k ₂₁ (minute ⁻¹)	0.0129 ± 0.0014		
Cl ₁ (mL/min/kg)	94.2 ± 4.2		
Cl ₂ (mL/min/kg)	171 ± 21		
Cl _{1_F} (mL/min/kg)		400 ± 37	437 ± 41
V ₁ (mL/kg)	2700 ± 490		
V ₂ (mL/kg)	13200 ± 1000		
V _{1_F} (mL/kg)		92000 ± 12000	102000 ± 13000
MRT (minute)	169 ± 9		
AUC _{0-T} (ng mL ⁻¹ min)		57500	96400
AUC _{inf} _pred (ng*mL ⁻¹ *min)	31800 ± 1400	62600 ± 5800	114000 ± 11000

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Female

Treatment Group (mg/kg)

3.0 IV Plasma^c

25 Gavage Plasma^{b,d}

50 Gavage Plasma^{b,d}

	3.0 IV Plasma ^c	25 Gavage Plasma ^{b,d}	50 Gavage Plasma ^{b,d}
C_0min_pred (ng/mL)	885 ± 185		
Cmax_pred (ng/mL)		383 ± 88	483 ± 87
Tmax_pred (minute)		16.0 ± 7.0	16.0 ± 6.5
Cmax_obs (ng/mL)		731 ± 127	752 ± 112
Tmax_obs (minute)		10.0 ± 0.0	10.0 ± 0.0
Alpha Half-life (minute)	6.79 ± 1.17		
Beta Half-life (minute)	53.2 ± 10.8		
k01 (minute ⁻¹)		0.213 ± 0.135	0.259 ± 0.142
k01 Half-life (minute)		3.25 ± 2.07	2.68 ± 1.46
k10 (minute ⁻¹)	0.0746 ± 0.0113	0.00807 ± 0.00142	0.00446 ± 0.00067
k10 Half-life (minute)	9.29 ± 1.41	85.9 ± 15.1	156 ± 23
k12 (minute ⁻¹)	0.0227 ± 0.0061		
k21 (minute ⁻¹)	0.0178 ± 0.0042		
Cl1 (mL/min/kg)	253 ± 22		
Cl2 (mL/min/kg)	76.8 ± 17.2		
Cl1_F (mL/min/kg)		464 ± 85	430 ± 63
V1 (mL/kg)	3390 ± 710		
V2 (mL/kg)	4310 ± 970		
V1_F (mL/kg)		57400 ± 16200	96400 ± 19600
MRT (minute)	30.5 ± 4.2		
AUC_0-T (ng mL ⁻¹ min)		44300	106000
AUCinf_pred (ng*mL ⁻¹ *min)	11900 ± 1000	53900 ± 9800	116000 ± 17000

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Male

Treatment Group (mg/kg)

3.0 IV Brain^a

25 Gavage Brain^a

50 Gavage Brain^a

Cmax_obs (ng/g)	2560 ± 590	508 ± 75	1400 ± 210
Tmax_obs (minute)	9.00	42.0	17.0
Half-life (minute)	54.9	80.7	106
AUC_0-T (ng*g ⁻¹ * min)	82700		
AUC_0-T (ng/g*min)		101000	192000
AUCinf_pred (ng/g*min)		107000	218000
AUCinf_pred (ng*g ⁻¹ min)	83500		

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Female

Treatment Group (mg/kg)

3.0 IV Brain^a

25 Gavage Brain^a

50 Gavage Brain^a

Cmax_obs (ng/g)	3090 ± 200	2180 ± 260	2900 ± 500
Tmax_obs (minute)	10.7	16.3	16.0
Half-life (minute)	61.5	121	141
AUC_0-T (ng*g ⁻¹ *min)	95600		
AUC_0-T (ng/g* min)		188000	396000
AUCinf_pred (ng*g*min)		191000	407000
AUCinf_pred (ng*g ⁻¹ * min)	96600		

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LEGEND

MODELING SOFTWARE

WinNonlin Version 5.0.1

MODELING METHOD & BEST FIT MODEL

^aWinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Noncompartmental Analysis (NCA)

^bWinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, one-compartment with first order absorption and elimination with $1/Y_{hat}^2$ weighting (Model No. 3)

^cWinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Two compartment model with bolus input and first order elimination with $1/Y_{hat}^2$ weighting (Model No. 8)

EXCEPTION

^dAUC 0-T standard error of the mean, SE, was ND, not detected.

ANALYTE

Alpha-Thujone

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TK PARAMETERS

C_0min_pred = Fitted plasma concentration at time zero (IV only)

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

Tmax_pred = Time at which Cmax predicted or observed occurs

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

Tmax_obs = Time at which Cmax predicted or observed occurs

Half-life = λ_z Half life, $t_{1/2}$, the terminal elimination half-life based on non-compartmental analysis

Alpha Half-Life = Half-life for the alpha phase

Beta Half-Life = Half-life for the beta phase

k01 = Absorption rate constant, k_a

k01 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}

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, Cl_{app} 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 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

V1_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_pred} = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

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TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Target times for blood and brain collection for the intravenous phase of the study were - male rats at 5, 10, 20, and 45 minutes, and 1, 2, 4, 6, 8, and 12 hours; female rats at 5, 10, 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, and 3 hours; and male and female mice at 2, 5, 7, 10, 15, 20, 30, and 45 minutes, and 1 and 1.5 hours. Target times for blood and brain collection for the gavage phase of the study were: male and female rats at 2, 5, 10, and 30 minutes, and 1.5, 3, 6, and 12 hours; and male and female mice at 2, 5, 10, 20, and 40 minutes, and 1.5 hours, 2 hours (40 mg/kg female mice only), 3 hours, 4 hours (80 mg/kg female mice only), 5 hours (40 mg/kg male mice only), and 6 hours (80 mg/kg male mice only).

TK_INTRAVENTOUS PLASMA

3.0 mg/kg Male and Female

The test article had a purity of 70 percent alpha-Thujone and 11 percent beta-Thujone. Thirty animals/species/sex/compound/dosage group (excluding replacements) were given a single IV injection of a,b-thujone in Cremophor-ethanol-water (1,1,8) using a catheter surgically implanted by the animal supplier into the jugular vein. Dosages were administered at a volume of 2 mL/kg (rats) and 4 mL/kg (mice). Animals were weighed the morning of dosing for calculation of the dosing volume. The dosing volume was administered as a bolus push. Dosed 7/1-3/02.

TK_GAVAGE PLASMA

25 mg/kg, 50 mg/kg Male and Female

Twenty-four animals/species/sex/compound/dosage group (excluding replacements) were given a single oral gavage administration of a,b-thujone in 0.5 percent aqueous methylcellulose. Doses were administered at a volume of 5 mL/kg (rats) and 10 mL/kg (mice). Non-fasted animals were given a single gavage administration. Dosed 12/17-20/02.

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TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENOUS BRAIN

3.0 mg/kg Male and Female

The test article had a purity of 70 percent alpha-Thujone and 11 percent beta-Thujone. Thirty animals/species/sex/compound/dosage group (excluding replacements) were given a single IV injection of a,b-thujone in Cremophor-ethanol-water (1,1,8) using a catheter surgically implanted by the animal supplier into the jugular vein. Dosages were administered at a volume of 2 mL/kg (rats) and 4 mL/kg (mice). Animals were weighed the morning of dosing for calculation of the dosing volume. The dosing volume was administered as a bolus push. Dosed 7/1-3/02.

TK_GAVAGE BRAIN

25 mg/kg, 50 mg/kg Male and Female

Twenty-four animals/species/sex/compound/dosage group (excluding replacements) were given a single oral gavage administration of a,b-thujone in 0.5 percent aqueous methylcellulose. Doses were administered at a volume of 5 mL/kg (rats) and 10 mL/kg (mice). Non-fasted animals were given a single gavage administration. Dosed 12/17-20/02.