Experiment Number: S0266
Route: IV, Gavage
Species/Strain: Rats/F344/N

Toxicokinetics Data Summary
Compound: Oxymetholone/ **Analyte:** Oxymetholone
CAS Number: 434-07-1

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: NIEHS CEDRA Corporation

Male

Vehicle: dimethylacetamide to water (5 to 1) mixture, Treatment Group (mg/kg)

	20 IV Plasma[a,d]	20 IV Plasma[a,e]	20 IV Plasma[a,f]	20 IV Plasma[b,g]
Half-life (hour)	0.61	2.27	1.07	1.33
Cl (L/h*kg)				2.60
V1 (L/kg)				4.98
AUCinf_pred (mg*h/L)	6.92	8.12	8.14	7.68

Male

Vehicle: 0.5 percent methylcellulose solution, Treatment Group (mg/kg)

	30 Gavage Plasma[a,h]	120 Gavage Plasma[a,i]	120 Gavage Plasma[a,j]
Cmax (mg/L)	0.820	1.13	1.61
Tmax (hour)	2.0	2.0	2.0
Half-life (hour)	5.56	3.55	3.83
AUCinf_pred (mg*h/L)	6.07	7.34	9.10

Male

Vehicle: 0.5 percent methylcellulose solution, Treatment Group (mg/kg)

	120 Gavage Plasma[a,k]	120 Gavage Plasma[a,l]	120 Gavage Plasma[c,m]
Cmax (mg/L)	1.33		
Tmax (hour)	2.0		
Half-life (hour)	3.26		3.43
Cl1_F (L/h*kg)			15.1
V1_F (L/kg)			74.7
AUCinf_pred (mg*h/L)	7.51		7.96

Female

Vehicle: 0.5 percent methylcellulose solution, Treatment Group (mg/kg)

	30 Gavage Plasma[a,n]	120 Gavage Plasma[a,o]

NO DATA RECORDED

LEGEND

MODELING SOFTWARE

Quattro Pro, Version 5.0 for Windows

MODELING METHOD & BEST FIT MODEL

[a]Quattro Pro (Version 5.0 for Windows, Borland International Inc ., Scotts Valley, CA) spreadsheet software. Non-compartmental analysis

[b]Quattro Pro (Version 5.0 for Windows, Borland International Inc ., Scotts Valley, CA) spreadsheet software. Combination B, D, and F non-compartmental analysis--combining the time points of intravenous 20 mg/kg male rat groups 1(B), 3(D), and 5(F) to get means used in the analysis. Timepoints ranged from 5-250 minutes

[c]Quattro Pro (Version 5.0 for Windows, Borland International Inc ., Scotts Valley, CA) spreadsheet software. Combination C, E, G, and H non-compartmental analysis--combining the time points of gavage 120 mg/kg male rat groups 2(C), 4(E), 6 (G) and 7(H) to get means used in the analysis. Timepoints ranged from 10-1440 minutes.

EXCEPTIONS

[d]Plasma Concentration at 2 hours equals 0.620 mg/L. Each timepoint n of 1.

[e]Plasma Concentration at 2 hours equals 0.914 mg/L. Each timepoint n of 1.

[f]Plasma Concentration at 2 hours equals 0.846 mg/L. Each timepoint n of 1.

[g]Combined average of Experiments B, D and F (all rat male IV 20 mg/kg dose mean values modeled as one curve)

[h]Plasma Concentration at 2 hours equals 0.820 mg/L. Each time point n of 3.

[i]Plasma Concentration at 2 hours equals 1.13 mg/L. Each timepoint n of 1.

[j]Plasma Concentration at 2 hours equals 1.61 mg/L. Each timepoint n of 1.

[k]Plasma Concentration at 2 hours equals 1.33 mg/L. Each timepoint 10-360 minutes n of 1, timepoints 480-1440 minutes, n of 2-3.

[l]This data set only consisted of the 8-, 12-, and 24-hour concentrations and the data was combined with experiment G

[m]Combined average of Experiments C, E, G and H (all male rat gavage 120 mg/kg mean timepoint values modeled as one curve)

[n]Plasma Concentration at 2 hours equals 0.258 mg/L. This data set only consisted of the 2-hour concentration. One timepoint, n of 3.

[o]Plasma Concentration at 2 hours equals 0.875 mg/L. This data set only consisted of the 2-hour concentration. One timepoint, n of 3.

ANALYTE

Oxymetholone

TK PARAMETERS

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax = Time at which Cmax predicted or observed occurs
Half-life = Lambda z Half-life, t 1/2, the terminal elimination half-life based on non-compartmental analysis
Cl = Clearance, includes total clearance
V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA, Vapp apparent volume of distribution for intravenous studies
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

The animal experiments with blood collection were conducted at one laboratory. Plasma samples were frozen after collection, shipped overnight on dry ice to a second, different company laboratory, and analyzed within 24 hours of arrival to minimize effects of documented instability of oxymetholone in rat plasma even at -20-degree C. Plasma samples were analyzed by a validated method using reverse-phase high performance liquid chromatography (HPLC) with UV detection (285nm) using danazol as an internal standard. Calibration standards were prepared fresh each day of sample analysis. The validated concentration range was 0.1 to 10 ug/mL. Some samples had to be diluted. The limit of detection (LOD) was 0.005 ug/mL, and the experimental limit of quantitation (ELOQ) was of 0.100 ug/mL.

TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENOUS PLASMA

20 mg/kg Male

Timepoints were combined and averaged and modeled for Group (Experiment) 1 (B), 3 (D), and 5 (F) which are all 20 mg/kg intravenously dosed male rats. Range 5.0-240 minutes with timepoints (minutes) 5.0, 10, 20, 30, 60, 120 all n of 3 and 240 with n of 2. The number of animals per treatment-timepoint in non-combined groups varied from 1-3 (See exception column). Experiments I and J were used to evaluate influence of gender in determining dose proportionality and the mice experiments L and M were used to evaluate species differences. The pharmacokinetic calculations were performed with noncompartmental methods using the Quattro Pro (Version 5.0 for Windows, Borland International Inc., Scotts Valley, CA) spreadsheet software. At each time point, the available concentrations were averaged. The elimination half-life (t1/2) was calculated as In(2) divided by the negative slope of the linear regression of the natural logarithm of the concentrations forming the terminal phase of the kinetic profiles. The area-under-the-curve (AUC) was calculated according to the linear trapezoidal rule and extrapolated by dividing the last concentration by the elimination rate constant. The clearance was calculated as the dose divided by the AUC, and the volume of distribution (Vd) was obtained by dividing the clearance by the elimination rate constant The start date given here is the in-life start date. The average age of rats and mice at first dose for the related 2-year oxymetholone studies was 7 weeks.

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The number of animals per treatment-timepoint varied from 1-3 (See exception column). Experiments I and J were used to evaluate influence of gender in determining dose proportionality and the mice experiments L and M were used to evaluate species differences. The pharmacokinetic calculations were performed with noncompartmental methods using the Quattro Pro (Version 5.0 for Windows, Borland International Inc., Scotts Valley, CA) spreadsheet software. At each time point, the available concentrations were averaged. The elimination half-life (t1/2) was calculated as in(2) divided by the negative slope of the linear regression of the natural logarithm of the concentrations forming the terminal phase of the kinetic profiles. The area-under-the-curve (AUC) was calculated according to the linear trapezoidal rule and extrapolated by dividing the last concentration by the elimination rate constant. The clearance was calculated as the dose divided by the AUC, and the volume of distribution (Vd) was obtained by dividing the clearance by the elimination rate constant The start date given here is the in-life start date. The average age of rats and mice at first dose for the related 2-year oxymetholone studies was 7 weeks.

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

30 mg/kg, 120 mg/kg Male and Female

The number of animals per treatment-timepoint varied from 1-3 (See exception column). Experiments I and J were used to evaluate influence of gender in determining dose proportionality and the mice experiments L and M were used to evaluate species differences. The pharmacokinetic calculations were performed with noncompartmental methods using the Quattro Pro (Version 5.0 for Windows, Borland International Inc., Scotts Valley, CA) spreadsheet software. At each time point, the available concentrations were averaged. The elimination half-life (t1/2) was calculated as in(2) divided by the negative slope of the linear regression of the natural logarithm of the concentrations forming the terminal phase of the kinetic profiles. The area-under-the-curve (AUC) was calculated according to the linear trapezoidal rule and extrapolated by dividing the last concentration by the elimination rate constant. The clearance was calculated as the dose divided by the AUC, and the volume of distribution (Vd) was obtained by dividing the clearance by the elimination rate constant The start date given here is the in-life start date. The average age of rats and mice at first dose for the related 2-year oxymetholone studies was 7 weeks.

TK_GAVAGE PLASMA

120 mg/kg Male

Timepoints were combined and averaged and modeled for Group (Experiment) 2 (C), 4 (E), 6 (G), and 7 (H) which are all rat male groups gavage administered 120 mg/kg oxymetholone. Range 10-1440 minutes with timepoints (minutes) 10, 40, 60, 120, 180, 480, 720 n of 3 -- 20 and 90 n of 1-- and 1140 timepoint n of 2. The number of animals per treatment-timepoint varied from 1-3 in non-combined groups (See exception column). Experiments I and J were used to evaluate influence of gender in determining dose proportionality and the mice experiments L and M were used to evaluate species differences. The pharmacokinetic calculations were performed with noncompartmental methods using the Quattro Pro (Version 5.0 for Windows, Borland International Inc., Scotts Valley, CA) spreadsheet software. At each time point, the available concentrations were averaged. The elimination half-life (t1/2) was calculated as In(2) divided by the negative slope of the linear regression of the natural logarithm of the concentrations forming the terminal phase of the kinetic profiles. The area-under-the-curve (AUC) was calculated according to the linear trapezoidal rule and extrapolated by dividing the last concentration by the elimination rate constant. The clearance was calculated as the dose divided by the AUC, and the volume of distribution (Vd) was obtained by dividing the clearance by the elimination rate constant The start date given here is the in-life start date. The average age of rats and mice at first dose for the related 2-year oxymetholone studies was 7 weeks.