# JWH-018 Rat Pharmacokinetics

Client ID	C initial	AUC• (area)	Vc (initial central comp)	Vd (area) / kg	Vss (area)	CL (obs area)	Half-life from Vd and CL
units	ng/ml	ng-min/ml	L	L/kg	L	ml/min/kg	min
JWH-018	3304	100487	0.3	8.1	0.4	49.8	112.2

JWH-018 showed a bi-phasic distribution suggesting both distribution and elimination phases. The clearance was consistent of hepatic blood flow rates in a rat of (55 ml/min/kg). The volume of distribution for JWH-018 suggests that the drug is well distributed.
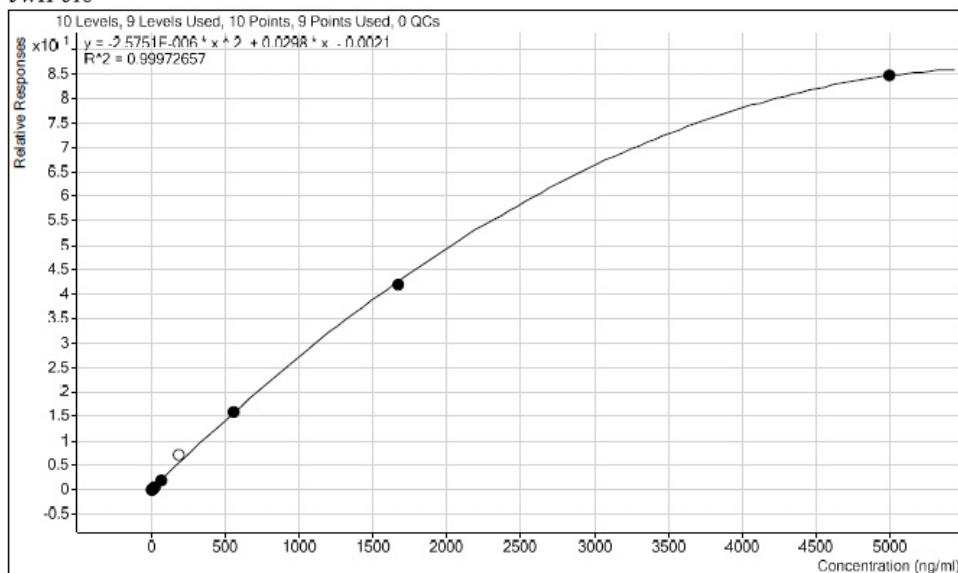

Pk of JWH-018 in Rats after IV dosing at 5mg/kg
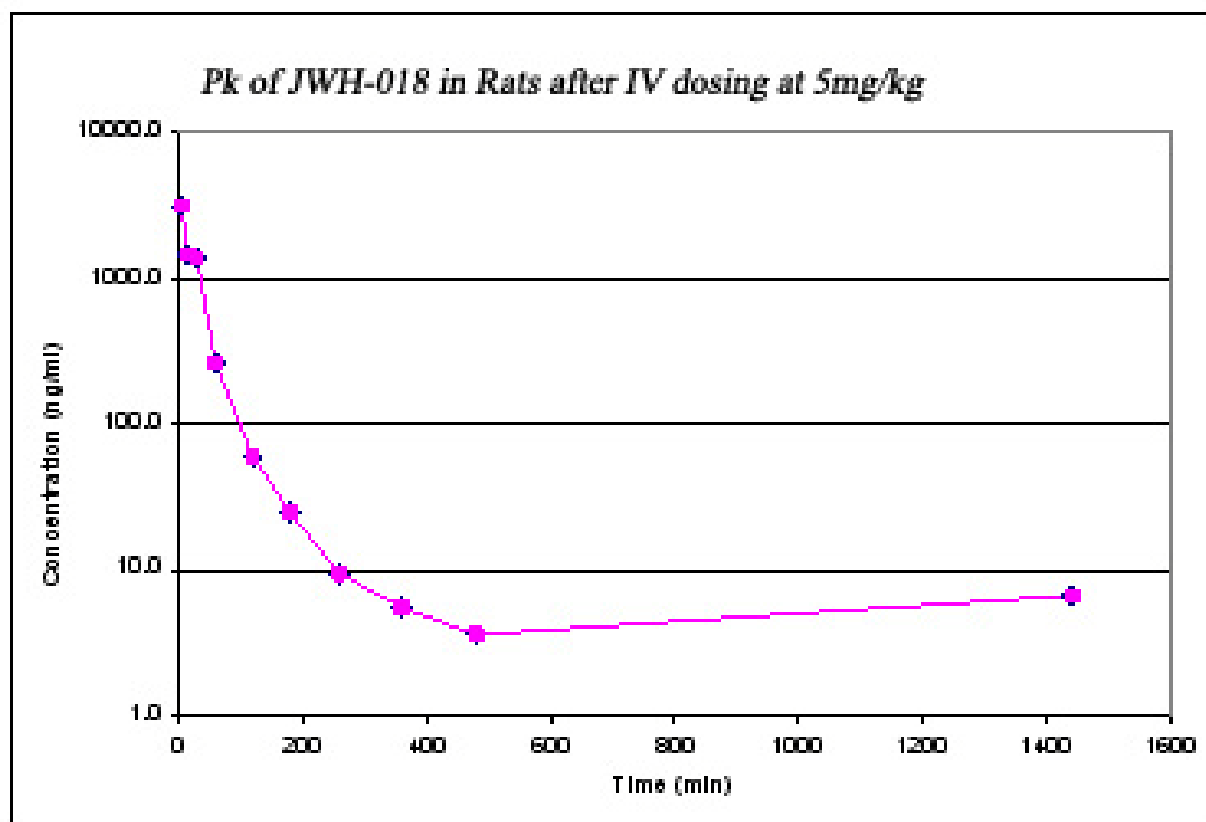
JWH-018 Plasma Concentrations:

Time (min)	Animal	Dose (mg/kg)	Plasma Conc. (ng/ml)
5	1	5	3082
5	2	5	3095
5	3	5	3281
15	1	5	1379
15	2	5	n/d*
15	3	5	1554
30	1	5	1493
30	2	5	n/d
30	3	5	1254
60	1	5	287
60	2	5	n/d
60	3	5	237
120	1	5	64
120	2	5	n/d
120	3	5	55
180	1	5	26
180	2	5	n/d
180	3	5	23
260	1	5	10
260	2	5	n/d
260	3	5	9
360	1	5	5
360	2	5	n/d
360	3	5	6
480	1	5	n/d**
480	2	5	n/d
480	3	5	4
1440	1	5	n/d
1440	2	5	n/d
144	3	5	7

*died after 15 minute of dosing, never recovered **died at 7 hours, animal was lethargic after 6 hour bleed N.B. Rats were lethargic (struggled breathing directly after dose) after dose and continued to be lethargic through the 8 hr time points (laying flat, limbs spread out not moving). All rats had ruffled fur at 24 hr but were alert and active. Analysis of the JWH-018 dosing solution showed that the actual concentration of the dosing solution was 0.79 mg/ml (0.74 mg/ml was the calculated).

Calibration Curve and Limits of Quantitation:

A typical calibration curve for JWH-018 is shown in the following figure. The lower limit of quantitation was 0.25 ng/ml for JWH-018. The upper limit of quantitation was 5000 ng/ml for JWH-018. Because of the deviation from linearity of the calibration curve at high concentrations for JWH-018, a quadratic fit was used to estimate sample concentrations at sample concentrations higher than 555 ng/ml.

JWH-018

10 Levels, 9 Levels Used, 10 Points, 9 Points Used, 0 QCs
$y = -2.5751E\text{-}006 * x^2 + 0.0298 * x - 0.0021$
$R^2 = 0.99972657$

Pharmacokinetics Bioanalysis Methods:

Bioanalytical Sample Preparation:
Plasma samples were thawed on ice. An aliquot of plasma was mixed with three volumes of methanol containing internal standard (propranolol, diclofenac, etc.). The samples were incubated ten minutes on ice, then centrifuged. The supernatant was filtered using the Captiva system (Varian). The filtrate was analyzed by LC/MS/MS.

Calibration Curves and Limit of Quantitation:
To determine the limit of quantitation of test agent, a calibration curve was prepared by at 50 times the plasma concentration by two-fold serial dilution in acetonitrile-water (1:1). The calibration samples were diluted 50-fold in control rat plasma, and processed as above.

Recovery From Plasma:
Processed samples of test agent were prepared in control plasma using the same method as was used for calibration curves. A blank was prepared by processing control plasma similarly. Reference samples were prepared in the blank plasma extract at the same final analytical concentration as the processed samples. Recovery was determined by dividing the internal standard response ratio of the processed sample by that of the corresponding reference standard.

Pharmacokinetics Standard Methods:

Three Sprague-Dawley rats were injected intravenously with test agent at 5 MPK with a solution of test agent at 0.74mg/ml in a vehicle of 10% ethanol, 10% cremophor el, 80% of 19% hydroxyl propryl-beta cyclodextrin in DIH2O. The blood was drawn at given time points and plasma was separated from blood. The plasma was then analyzed for test agent concentration.