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Comparison of Encapsulated and Non-encapsulated Doxorubicin Pharmacokinetics Following Single Intravenous Administration of ATI-0918, an Encapsulated Liposomal Formulation, and DOXIL® in Female Rats

Ahmed Kousba[1], Richard Underbrink[2], Donald Kruppa[2];
[1]BioAgilytix, San Diego, CA, 92121. [2]Azaya Therapeutics, San Antonio, TX, 78249.

BioAgilytix

Azaya Therapeutics

ABSTRACT

Purpose:

To compare the pharmacokinetics (PK) of encapsulated and non-encapsulated doxorubicin following a 6 mg/kg IV bolus dose of ATI-0918 or DOXIL® (CAELYX®) in female rats. ATI-0918 is being developed by Azaya Therapeutics to match the physiochemical properties and release specifications of DOXIL®, a doxorubicin hydrochloride liposome injection which is marketed in the United States as DOXIL® and elsewhere as CAELYX®. ATI-0918 in being investigated in a Phase I clinical trial.

Methods:

Two groups of female rats were included in the study. Group 1 received an IV injection of 6 mg/kg ATI-0918 and Group 2 received an IV injection of 6 mg/kg CAELYX®. Blood samples were collected for up to 96 hour postdose. The plasma was analyzed for encapsulated and non-encapsulated doxorubicin by an HPLC/MS/MS assay. PK parameters of encapsulated and non-encapsulated doxorubicin were determined by non-compartmental analysis.

Results:

The encapsulated doxorubicin Cmax, AUC(0-T), AUC(0-inf) and T1/2 values following a 6 mg/kg ATI-0918 IV dosing were 197 µg/mL, 5480 µg-h/mL, 6110 µg-h/mL and 30.5 h, respectively. The corresponding values following the same dose of CAELYX® (i.e., 6 mg/kg IV) were 212 µg/mL, 6140 µg-h/mL, 7400 µg-h/mL and 39.5. The % ATI-0918/CAELYX® encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ were 92.9%, 89.3% and 82.6%, respectively.

Similarly, non-encapsulated doxorubicin PK parameters following ATI-0918 were comparable to those following CAELYX®. The % ATI-0918/CAELYX® non-encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ were 101%, 91.4% and 88.3%, respectively.

For both ATI-0918 and CAELYX®, the encapsulated doxorubicin exposure (C_{max} and AUC) was ~ 45-62x higher that that of non-encapsulated doxorubicin.

Conclusions:

The encapsulated and non-encapsulated doxorubicin PK parameters after ATI-0918 were approximately equal to the corresponding values after CAELYX® dosing. The ATI-0918/CAELYX® encapsulated and non-encapsulated doxorubicin $\%C_{max}$, $\%AUC_{(0-T)}$ and $\%AUC_{(0-inf)}$ were within 80-120%.

Purpose

To compare the pharmacokinetic exposure of encapsulated and non-encapsulated doxorubicin following a single IV bolus dose of 6 mg/kg of ATI-0918 and CAELYX® in female rats.

Introduction

Doxorubicin is an anticancer chemotherapy drug. It is an anthracycline topoisomerase inhibitor which prevents DNA replication and inhibits protein synthesis.

DOXIL® is a doxorubicin hydrochloride pegylated liposome injection which is marketed in the United States, Israel and Japan as DOXIL® and elsewhere as CAELYX®. DOXIL® is approved by the FDA for treatment of ovarian cancer, AIDS-related Kaposi's sarcoma, and in combination therapy for multiple myeloma (1).

Liposomal formulations of doxorubicin are effective in reducing doxorubicin cardiotoxicity and improving its delivery to tumor sites (2, 3).

ATI-0918 is being developed by Azaya Therapeutics to match the physiochemical properties and release specifications of DOXIL® (i.e., a generic formulation of DOXIL®). ATI-0918 has the same mechanism of action of standard doxorubicin.

Currently, the pharmacokinetic equivalence of ATI-0918 and DOXIL®/CAELYX® is being investigated by Azaya Therapeutics in patients with ovarian cancer.

This work compares the pharmacokinetics of encapsulated and non-encapsulated doxorubicin following ATI-0918 and CAELYX® dosing to female rats.

METHODS

Study Design

Two groups of female rats were included in the study. Group 1 received an IV injection of 6 mg/kg ATI-0918 and Group 2 received an IV injection of 6 mg/kg CAELYX®.
Blood samples were collected at predetermined times for up to 96 hour postdose.

Analytical Method

The plasma samples were analyzed for encapsulated and non-encapsulated doxorubicin by an HPLC/MS/MS assay.

PK Analysis

The PK parameters of encapsulated and non-encapsulated doxorubicin following ATI-0918 and CAELYX® dosing were determined by standard model independent methods (4).

The following PK parameters were calculated using Phoenix WinNonlin Professional Version 6.1 (Pharsight Corp., Saint Louis, MO).

- C_{max} is the observed maximum plasma concentration after dosing.
- T_{max} is the time to reach C_{max}.
- $AUC_{(0-T)}$ is the area under the plasma concentration-time curve from immediate post dose to the last measurable sampling time and is calculated by linear trapezoidal rule.
- $AUC_{(0-inf)}$ is the area under the plasma concentration-time curve from time zero to infinity. It is calculated as the sum of the area from time zero to the time of the last quantifiable plasma concentration (T) and the area from T to infinity, calculated as the last quantifiable plasma concentration divided by l, where λ is the terminal elimination rate constant.
- $T_{1/2}$ is apparent half-life calculated by ln(2)/λ where λ is the rate constant for the log-linear portion of the terminal phase. A minimum of three values in the post-distribution phase of the plasma concentration-time curve is required for calculation of λ.
- CL is the systemic plasma clearance calculated by dividing the dose by the $AUC_{(0-inf)}$.
- Vss is the volume of distribution after an IV dosing

Table 1

Summary Pharmacokinetic Parameters of Encapsulated and Non-encapsulated Doxorubicin in Female Rats Following a Single IV Bolus Dose of 6 mg/kg of ATI-0918 or CAELYX®

Parameter	ATI-0918			CAELYX®		
	Encapsulated	Non	Encapsulated/Non	Encapsulated	Non	Encapsulated/Non
C_{max}, µg/mL	197	3.45	57.1	212	3.40	62.4
T_{max}, h	0.500	2.00	-	0.250	4.00	-
$AUC_{(0-T)}$, µg-h/mL	5,480	117	46.8	6,140	128	48.0
$AUC_{(0-inf)}$, µg-h/mL	6,110	136	44.9	7,400	154	48.1
CL, L/h/kg	9.82E-04	-	-	8.10E-04	-	-
Vss, L/kg	0.0399	-	-	0.0423	-	-
$T_{1/2}$, h	30.5	37.9	-	39.5	39.0	-
C_{max} Ratio (ATI-0918/CAELYX®)	0.929	1.01	-	-	-	-
$AUC_{(0-T)}$ Ratio (ATI-0918/CAELYX®)	0.893	0.914	-	-	-	-
$AUC_{(0-inf)}$ Ratio (ATI-0918/CAELYX®)	0.826	0.883	-	-	-	-

Results

Doxorubicin PK after ATI-0918 Administration

The encapsulated and non-encapsulated doxorubicin concentrations in plasma displayed multi-exponential elimination with terminal $T_{1/2}$ values of 30.5 and 37.9h, respectively (Figure 1 and Table 1).

The encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$, $AUC_{(0-inf)}$, CL and Vss values were 197 µg/mL, 5480 µg-h/mL, 6110 µg-h/mL, 9.82E-04 L/h/kg and 0.0399 L/kg, respectively (Table 1). The encapsulated doxorubicin exhibited low clearance and small volume of distribution.

The non-encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ values were 3.45 µg/mL, 117 µg-h/mL and 136 µg-h/mL, respectively (Table 1).

Encapsulated doxorubicin exposure (C_{max} and AUC) was ~ 45 to 57x higher than that of non-encapsulated doxorubicin (Table 1).

Doxorubicin PK after CAELYX® Administration

The encapsulated and non-encapsulated doxorubicin concentrations in plasma displayed multi-exponential elimination with terminal $T_{1/2}$ values of 39.5 and 39.0h, respectively (Figure 2 and Table 1).

The encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$, $AUC_{(0-inf)}$, CL and Vss values were 212 µg/mL, 6140 µg-h/mL, 7400 µg-h/mL, 8.10E-04 L/h/kg and 0.0423 L/kg, respectively (Table 1). The encapsulated doxorubicin exhibited low clearance and small volume of distribution.

The non-encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ values were 3.40 µg/mL, 128 µg-h/mL and 154 µg-h/mL, respectively (Table 1).

Encapsulated doxorubicin exposure (C_{max} and AUC) was ~ 48 to 62x higher than that of non-encapsulated doxorubicin (Table 1)

Comparison of Doxorubicin PK after ATI-0918 and CAELYX®

The encapsulated and non-encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ values after ATI-0918 dosing were approximately equal to the corresponding values after CAELYX® dosing (Figures 3 and 4 and Table 1).

The ATI-0918 to CAELYX® C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ ratios of encapsulated doxorubicin were 0.929, 0.893 and 0.826, respectively (Table 1).

The ATI-0918 to CAELYX® C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ ratios of non-encapsulated doxorubicin were 1.01, 0.914 and 0.883, respectively (Table 1).

Conclusions

Encapsulated doxorubicin exposure (C_{max} and AUC) was ~ 45-62x higher than that of non-encapsulated doxorubicin after ATI-0918 and CAELYX® administration. The encapsulated and non-encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ values after ATI-0918 dosing were approximately equal to the corresponding values after CAELYX® dosing.

The % ATI-0918 / CAELYX® encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$, $AUC_{(0-inf)}$ were 92.9%, 89.3% and 82.6%, respectively. $\%C_{max}$, $\%AUC_{(0-T)}$ and $\%AUC_{(0-inf)}$ were within 80-120%.

The % ATI-0918 / CAELYX® non-encapsulated doxorubicin C_{max}, $AUC_{(0-T)}$, AUC(0-inf) were 101%, 91.4% and 88.3%. $\%C_{max}$, $\%AUC_{(0-T)}$ and $\%AUC_{(0-inf)}$ were within 80-120%.

Figure 1

Mean Plasma Concentration-Time Profiles of Encapsulated and Non-encapsulated Doxorubicin in Female Rats Following a Single IV Bolus Dose of 6 mg/kg of ATI-0918

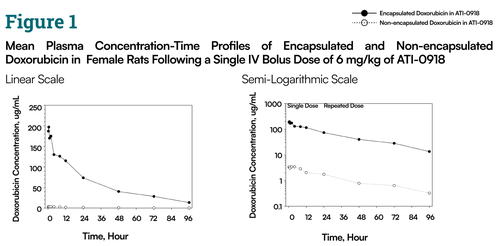


Figure 2

Mean Plasma Concentration-Time Profiles of Encapsulated and Non-encapsulated Doxorubicin in Female Rats Following a Single IV Bolus Dose of 6 mg/kg of CAELYX®

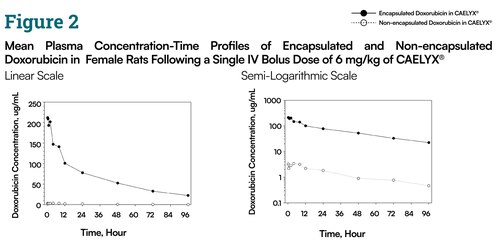


Figure 3

Comparison of Mean Plasma Concentration-Time Profiles of Encapsulated Doxorubicin in Female Rats Following a Single IV Bolus Dose of 6 mg/kg of ATI 0918 and CAELYX®

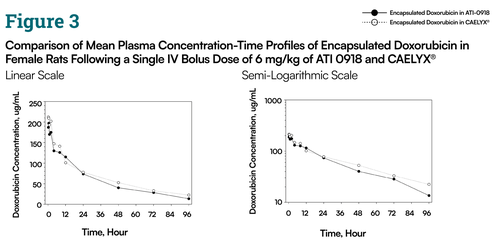
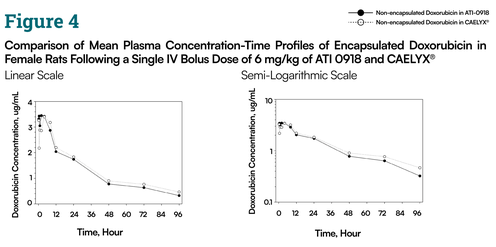


Figure 4

Comparison of Mean Plasma Concentration-Time Profiles of Encapsulated Doxorubicin in Female Rats Following a Single IV Bolus Dose of 6 mg/kg of ATI 0918 and CAELYX®



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