

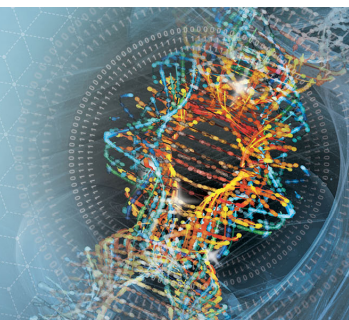
Vaginal Tamoxifen for Treatment of Vulvovaginal Atrophy: Pharmacokinetics and Safety in a Rabbit Model

D. R. Friend^a, J. A. Chollet^b, F. Mermelstein^c

^aDaré Bioscience, Inc., ^bBeth Deaconess Medical Center, ^cHarvard Medical School



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CONTACT INFORMATION: David R. Friend, Ph.D., Daré Bioscience, San Diego, CA 92122;
dfriend@darbioscience.com

PURPOSE

To evaluate the pharmacokinetics and local tolerability of vaginal tamoxifen in female rabbits. This work is part of an effort to develop a vaginal tamoxifen product capable of treating symptoms of vulvovaginal atrophy (VVA) in hormone-receptor positive breast cancer patients. Standard treatment with oral or vaginal estrogen is contraindicated in this patient population. Tamoxifen has been found to be an estrogen agonist in vaginal tissue and should have pharmacologic effects similar to vaginally applied estrogen (orally, tamoxifen is an estrogen antagonist in breast tissue).

OBJECTIVES

- 1) To determine the pharmacokinetics of vaginally administered tamoxifen, including metabolism
- 2) Determine the vaginal tolerability and reproductive organ effects of vaginally administered tamoxifen

METHODS

A granulation of tablet excipients (lactose, Starch 1500, microcrystalline cellulose, Crospovidone XL, Methocel EP5, and magnesium stearate) was prepared with a final concentration of tamoxifen citrate of 1.5 mg (equivalent to 1.0 mg tamoxifen in 80 mg blend) or 30.4 mg (equivalent to 20 mg tamoxifen in 80 mg of blend) in 1.0 mL vehicle (0.9% sodium chloride). Female New Zealand White Hra (NZW)SPF albino rabbits ($n = 6$ per group approximately 7.5 months of age) were administered 1.0 mL of 1) vehicle, 2) placebo blend, 3) 1.0 mg tamoxifen blend, or 4) 20 mg tamoxifen blend vaginally once-daily for 28 days. Four of six animals were sacrificed on Day 29 while the remaining two animals were

sacrificed on Day 42 (recovery animals). Blood (1.0 mL) was withdrawn pre-dose, 0.5, 1, 3, 8, and 24 h post-dose on Days 1 and 28 for pharmacokinetic (PK) analysis. Plasma samples were analyzed for tamoxifen, 4-hydroxytamoxifen, and *N*-desmethyltamoxifen using a validated LC-MS/MS method. Vaginal tissues were graded histologically using the grading system of Eckstein.

RESULTS

Fig 1 shows the mean plasma concentration of tamoxifen over 24 h on Day (A) and Day 28 (B) following vaginal administration of 1 or 20 mg tamoxifen. Concentrations of tamoxifen were substantially higher than the two metabolites measured.

PK parameters evaluated (T_{max} , C_{max} , and AUC_{0-t}) are shown in Table 1 for tamoxifen, 4-hydroxytamoxifen, and *N*-desmethyltamoxifen at Day 1 and Day 28. Ratios of mean 4-hydroxytamoxifen to tamoxifen AUC_{0-t} values ranged from 0.0702 to 0.148 on Day 28. Ratios of mean *N*-desmethyltamoxifen to tamoxifen AUC_{0-t} values could only be determined in the 20 mg tamoxifen dose group on Day 28 (0.0214). These findings indicated that tamoxifen accounted for

Table 1. Mean (standard deviation) PK parameters for tamoxifen, 4-Hydroxytamoxifen, and *N*-desmethyltamoxifen^a

Analyte	Tamoxifen Dose (mg)	T_{max} (h) ^b	C_{max} (ng/mL)	AUC_{0-t} (ng*h/mL)
Day 1				
Tamoxifen	1	1	1.44 (0.786)	13.2 (8.24)
	20	0.5	3.65 (2.96)	23.0 (23.7)
4-Hydroxy-tamoxifen	1	-	0 (0)	0 (0)
	20	13.5	0.0708 (0.110)	0.963 (1.69)
<i>N</i> -Desmethyl-tamoxifen	1	-	0 (0)	0 (0)
	20	-	0 (0)	0 (0)
Day 28				
Tamoxifen	1	1.0	0.824 (0.819)	8.85 (11.6)
	20	0.5	2.33 (0.667)	26.5 (16.4)
4-Hydroxy-tamoxifen	1	8	0.0463 (0.0739)	0.621 (0.985)
	20	1	0.219 (0.140)	3.93 (2.89)
<i>N</i> -Desmethyl-tamoxifen	1	-	0 (0)	0 (0)
	20	1	0.118 (0.289)	0.556 (1.39)

^a $n = 6$ for Day 1 and $n = 5$ for Day 28
^bMedian values reported

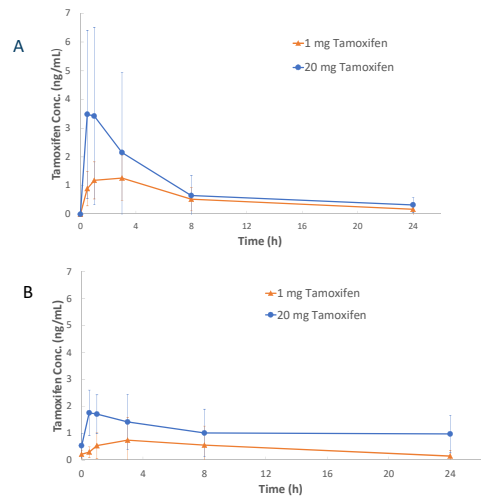


Fig 1. Tamoxifen plasma concentrations following 1 mg or 20 mg tamoxifen vaginally to rabbits. A: plasma concentrations over Day 1; B: plasma concentrations following 28 days once-daily administration. Values are mean \pm SD ($n = 6$) except the 1 mg tamoxifen group on Day 28 ($n = 5$).

Approximately 85% or more of the total systemic exposure to tamoxifen, 4-hydroxytamoxifen, and *N*-desmethyltamoxifen following once-daily intravaginal administration of 1 to 20 mg tamoxifen for 28 days to female rabbits. These results suggest that tamoxifen administered vaginally is metabolized less extensively than observed following oral administration in mice, rats, and humans.¹⁻³

The Eckstein scores of the proximal, mid, and distal vagina of Vehicle Control females at the terminal necropsy were all considered to be of minimal magnitude (individual scores ranging from 1 to 2 in the proximal vagina, 1 to 3 in the mid vagina, and 2 to 3 in the distal vagina). The Eckstein scores of these three regions of the vagina in placebo control females

were typically of minimal magnitude, with the exception of scores of the proximal and mid vagina of one female in this group which were of mild severity due to increased leukocytic infiltration (individual scores ranging from 2 to 5 in the proximal vagina, 2 to 7 in the mid vagina, and 2 to 3 in the distal vagina). These data are shown in Fig. 2.

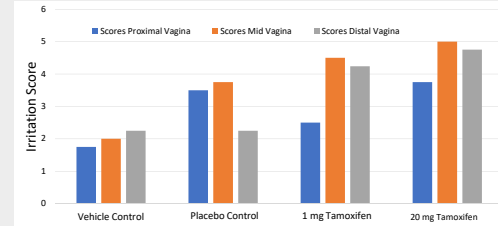


Fig. 2. Summary of histopathologic grading for the rabbit proximal, mid, and distal vagina following 28 days of once daily dosing of the vehicle control, placebo control, 1 mg tamoxifen, or 20 mg tamoxifen ($n = 4$).

CONCLUSIONS

Overall, tamoxifen was absorbed and metabolized following vaginal administration and local irritation was minimal to none at both doses. These data along with a recently published study on vaginal administration of tamoxifen suggest that vaginally delivered tamoxifen may represent a safe and effective treatment for women suffering from VVA who are at risk, suffering from or are breast cancer survivors, where estrogens are contraindicated.

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