

Lack of Placental Transfer of Enfuvirtide in an ex vivo Human Placental cotyledon Perfusion Model

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Abstract [Updated]

Background: Enfuvirtide (T20) is classified as FDA pregnancy category B based on results of studies performed in animals, but up to date, there are very few data on its use in HIV positive pregnant women.

T20, is a synthetic 36 aminoacids peptide that binds to HIV-1 glycoprotein 41, blocking the fusion of viral and cellular membranes. T20 exhibits a small volume of distribution (5.48L), low systemic clearance (1.4 L/h) and high plasma protein binding (92%). When administered at the recommended dose of 90mg twice daily in adults, subcutaneous absorption is slow and bioavailability is high (84.3%).

Methods: Placentas obtained from uncomplicated full-term pregnancies were collected immediately after delivery. Three isolated cotyledons were perfused according to the modified method described by Schneider et al, with human serum albumin (2g/l) in the Earles perfusate. Maternal perfusion comprised antipyrine 20 mg/L as internal control and enfuvirtide (90 mg/1250ml). Antipyrine and T20 concentrations were determined by HPLC coupled with spectrofluorimetry or UV detection with a limit of quantification (LOQ) of 50 ng/mL and 50g/L, respectively. Fetal rate transfer (FRT: ratio of fetal to maternal concentrations) and clearance index (CI: ratio of T20 FRT to antipyrine FRT) were calculated.

Results: In all three validated experiments, T20 was below LOQ in the fetal compartment. Concentrations measured in the maternal compartment were significantly above C_{max} (5.0 1,7 mg/mL) with a mean of 12,4 mg/mL [range: 6,5-16,2 mg/mL]. Mean antipyrine FTR was 36% [range: 22-45%]

Conclusion: Even at maternal concentrations twice above therapeutic levels, no transplacental passage of T20 was observed in the ex vivo human placental perfusion model. The high molecular weight and high protein binding of T20 (4492 kDa) may account for the lack of placental transfer. This result suggests that T-20 could be used in HIV infected pregnant women without causing fetal exposure

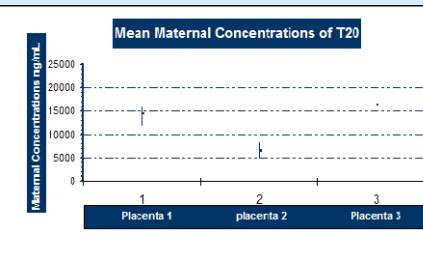
Study Aim

The purpose of this study was to determine the maternal-fetal placental transfer of T20 using an ex vivo Human Placental cotyledon

Perfusion Model.

RESULTS

- Three placentas were validated for perfusion.
- Mean fetal transfer for antipyrine was 36% [22-45%].
- In the maternal compartment, mean concentration of enfuvirtide, at steady- state conditions, was 12400 ng/mL [6500 – 16200 ng/ml]
- Enfuvirtide was not detected in any fetal venous samples (50ng/mL).



Results

Time (min)	Placenta 1		Placenta 2		Placenta 3	
	FC (ng/ml)	MC (ng/ml)	FC (ng/ml)	MC (ng/ml)	FC (ng/ml)	MC (ng/ml)
0-5	< 50	15366	< 50	7033	< 50	17110
5-10	< 50	15627	< 50	4660	< 50	19540
10-15	< 50	14408	< 50	5875	< 50	18711
15-20	< 50	11636	< 50	6414	< 50	17528
20-25	< 50	14168	< 50	6150	< 50	15989
25-30	< 50	14459	< 50	5920	< 50	16985
30-35	< 50	14951	< 50	7011	< 50	17314
35-40	< 50	14726	< 50	6410	< 50	14757
40-45	< 50	13875	< 50	6956	< 50	17191
45-50	< 50	15985	< 50	6969	< 50	15537
50-55	< 50	15635	< 50	8258	< 50	15478
55-60	< 50	14442	< 50	7176	< 50	15002
60-65	< 50	15542	< 50	6997	< 50	15312
65-70	< 50	13636	< 50	6144	< 50	15816
70-75	< 50	13840	< 50	6146	< 50	14808
75-80	< 50	11811	< 50	6112	< 50	15110
80-85	< 50	15376	< 50	6850	< 50	15129
85-90	< 50	13072	< 50	6432	< 50	14268
Median MC		14382		6514		16387

Study Design and Methods

Type of Study:

- ex vivo study of placentas obtained from uncomplicated full-term pregnancies.

Population:

- HIV-seronegative women pregnant women greater or equal to 37 weeks gestation, receiving no drug treatment, except oxytocin or epidural anesthesia during labor.
- Vaginal delivery.

Drug Perfusion:

- Antipyrine 20 mg/L as internal control.
- Enfuvirtide (90 mg/1250ml).
- Perfusion length time was 90 minutes.

Pharmacokinetic Design:

- Antipyrine and T20 concentrations were determined by HPLC coupled with spectrofluorimetry or UV detection with LOQ of 50 ng/mL and 50g/L, respectively.
- Ratio of fetal to maternal concentrations and clearance index ratio of T20 and antipyrine were calculated.
- A fetal transfer rate of antipyrine above 20% was required to validate and to compare each experience.
- The fetal circulation was established at a flow rate of 6 mL/min.
- The maternal flow rate was 12 mL/min.

Note:

- pH was adjusted to 7.4 ± 0.1 for the maternal and 7.3 ± 0.1 for the fetal solutions respectively by the addition of a solution of sodium bicarbonate and hydrochloric acid.

Summary

- At maternal concentrations twice above therapeutic levels, no transplacental passage of T20 was observed.
- High molecular weight and ionized state may account for the lack of placental transfer.
- It is unlikely that enfuvirtide lead to any toxicity to the fetus.
- Our study suggests that enfuvirtide could be used in HIV infected pregnant women without causing fetal exposure.