

Lactational Transfer of Fentanyl Citrate in Rats

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ABSTRACT

In this study we determined plasma and milk concentrations of fentanyl citrate following exposure during pregnancy and lactation. A control and two treatment groups of 12 time-mated female CD[®] [CrI:CD[®](SD)] rats/group received fentanyl S.C. at respective dose levels of 0, 25, 50 µg/kg/day, at a dose volume of 1 mL/kg from Gestation Day 6 through Lactation Day 20. Blood samples for determination of the plasma concentrations of fentanyl were collected at 0.25, 0.5, 1, 2, 3, 8, and 24 h on LD 12 and 20. Likewise, milk was collected 3-4 hours postdose on LD 12 and 20 for analysis. Following once-daily subcutaneous administration of nominal doses of 25 or 50 µg/kg of fentanyl citrate, peak plasma concentrations of fentanyl on LD 12 were achieved at approximately 30 minutes after dosing, and systemic exposure to fentanyl increased in a dose-related manner. Composite C_{max} values were 8695 pg/mL for the 25 µg/kg/day dose group and 21,822 pg/mL for the 50 µg/kg/day dose group, and composite AUC_{0-∞} values were 16,366 and 37,899 pg-hr/mL for the same dose groups, respectively. The peak plasma concentrations of the metabolite, norfentanyl on LD12 were achieved at approximately 2 hours after dosing, and systemic exposure to norfentanyl increased in a dose-related manner. Composite C_{max} values were 1376 pg/mL for the 25 µg/kg dose group and 2348 pg/mL for the 50 µg/kg dose group, and composite AUC_{0-∞} values were 6117 and 11,936 pg-hr/mL for the same dose groups, respectively. Concentrations of fentanyl and norfentanyl in milk samples were generally several-fold higher than their respective concentrations in plasma samples collected at approximately the same time.

INTRODUCTION

Fentanyl (Figure 1) is a synthetic primary µ-opioid receptor agonist commonly used to treat chronic breakthrough pain. It is a Schedule II substance, available in parenteral, transdermal, and transbuccal preparations. More than 80% of the injected dose leaves plasma in less than 5 min, and 98.6% leaves by 1 h. Fentanyl is metabolized almost exclusively in the liver to norfentanyl, hydroxy-propionyl-fentanyl, and hydroxypropionyl-norfentanyl. The widespread use of fentanyl prompted the production of fentanyl citrate which was marketed as a general anesthetic under the trade name Sublimaze. We determined plasma and milk concentrations of fentanyl citrate following exposure during pregnancy and lactation.

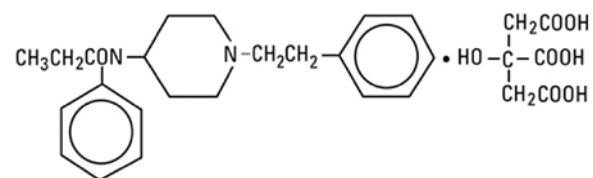


Figure 1: Chemical structure of Fentanyl Citrate

MATERIALS & METHODS

Animal Acquisition and Acclimation

A total of 62 time-mated female CD[®] [CrI:CD[®](SD)] rats (approximately 8 to 10 weeks of age) were received from Charles River Laboratories, Portage, Michigan, on May 31, 2007. An additional shipment of 17 time-mated female rats were received from Charles River Laboratories, Portage, Michigan, on June 29, 2007. All animals were acclimated from the time of arrival on GD 0 until the time of dosing on GD 6. Animals were then assigned as shown in Table 1.

Administration

The vehicle and Fentanyl Citrate were administered once a day from GD 6 through LD 20 via subcutaneous injection.

Plasma and Milk Samples Collection

Plasma Analysis Blood samples (approximately 1 mL) were collected from all surviving lactating dams via the tail vein for determination of the plasma concentrations of the test article. Samples were collected pre-dose and at 0.25, 0.5, 1, 2, 3, 8, and 24 hours post-dose on LD 12 and 20. Milk samples (0.15 to 1.5 mL) were collected according to SOP approximately 3 to 4 hours post-dose on LD 12 and 20 from the first six females/group with litters.

RESULTS

Table 1: Group Assignment

Group Number	Dose Level (µg/kg/day)	Number of Time-mated Females
1	0	12
2	25	12
3	50	12
4	100	12
4 ^a	100/50 ^b	12

^a Due to the deaths sustained at 100 µg/kg/day, additional animals were added to the high dose group.
^b Beginning on GD 12, the dose level for the additional animals was reduced to 50 µg/kg/day.

Table 2: Toxicokinetic parameters of Fentanyl Citrate in Dams on Lactation Day 12

Group	Nominal Dose (µg/kg/day)	C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-∞} (pg-hr/mL)	T _{1/2} (hr)
2	25	8,695	0.50	16,246	16,366	1.17
3	30	21,822	0.50	37,646	37,899	1.15

Table 3: Toxicokinetic parameters of Norfentanyl Citrate in Dams on Lactation Day 12

Group	Nominal Dose (µg/kg/day)	C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-∞} (pg-hr/mL)	T _{1/2} (hr)
2	25	1,376	2.0	5,623	6,117	2.04
3	50	2,348	2.0	11,245	11,936	1.82

Table 4: Milk Concentration of Fentanyl Citrate in Pups on LD 12

Group Number	Dose Level (µg/kg/day)	Interval	Concentration Average (pg/mL)	Standard Deviation
1	0	LD 12	<40	NA
2	25	LD 12	9,297.2	2,614.36
3	50	LD 12	16,819.4	9,754.963
4 ^a	100/50 ^b	LD 12	34,817	13,764.54

^a Due to the deaths sustained at 100 µg/kg/day, additional animals were added to the high dose group.
^b Beginning on GD 12, the dose level for the additional animals was reduced to 50 µg/kg/day.

*Milk samples (0.15 to 1.5 mL) were collected according to SOP approximately 3 to 4 hours postdose on LD 12 and 20 from the first six females/group with litters.

Table 5: Milk Concentration of Norfentanyl in Pups on LD 12

Group Number	Dose Level (µg/kg/day)	Interval	Concentration Average (pg/mL)	Standard Deviation
1	0	LD 12	<40	NA
2	25	LD 12	3,261.2	1,625.097
3	50	LD 12	4,560.8	3,297.638
4 ^a	100/50 ^b	LD 12	12,036	3,734.938

^a Due to the deaths sustained at 100 µg/kg/day, additional animals were added to the high dose group.
^b Beginning on GD 12, the dose level for the additional animals was reduced to 50 µg/kg/day.

Table 6: Milk Concentration of Fentanyl Citrate in Pups on LD 20

Group Number	Dose Level (µg/kg/day)	Interval	Concentration Average (pg/mL)	Standard Deviation
1	0	LD 20	<40	NA
2	25	LD 20	8,075	1,516.443
3	50	LD 20	NA	NA
4 ^a	100/50 ^b	LD 20	8,100.75	4,532.601

^a Due to the deaths sustained at 100 µg/kg/day, additional animals were added to the high dose group.
^b Beginning on GD 12, the dose level for the additional animals was reduced to 50 µg/kg/day.

Table 7: Milk Concentration of Norfentanyl in Pups on LD 20

Group Number	Dose Level (µg/kg/day)	Interval	Concentration Average (pg/mL)	Standard Deviation
1	0	LD 20	<40	NA
2	25	LD 20	2,342.33	1,042.912
3	50	LD 20	NA	NA
4 ^a	100/50 ^b	LD 20	1,212.5	255.2655

^a Due to the deaths sustained at 100 µg/kg/day, additional animals were added to the high dose group.
^b Beginning on GD 12, the dose level for the additional animals was reduced to 50 µg/kg/day.

CONCLUSION

Fentanyl concentrations were present in milk following S.C. treatment in rats during pregnancy and lactation. Concentrations of fentanyl and norfentanyl in milk samples were generally several-fold higher than their respective concentrations in maternal plasma samples collected at approximately the same time.

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