

CHAPTER IV

RESULTS

During the entire 100-143 days of treatment all monkeys did not show significant weight loss and/or anorexia. Pulse and respiratory rates were maintained in normal range of 98-121 and 32-44 /minute, respectively. Some monkeys (no.41, no.64, no.71 and 92) showed excessive hair loss around head, back and front leg regions (figure 27). The incidence of hair loss was not related to dose of morphine. However, tremble could be detected occasionally in some monkeys (no.81, no.93, no.95 and no.98) treated with 1.6-3.2 mg/kg/day morphine.

Morphine withdrawal showed typical symptoms of loss of appetite, nervous and tended to be more aggressive. Most of these symptoms were found in 1.6-3.2 mg/kg/day treated group but returned to be normal within 7 days after the drug withdrawal.

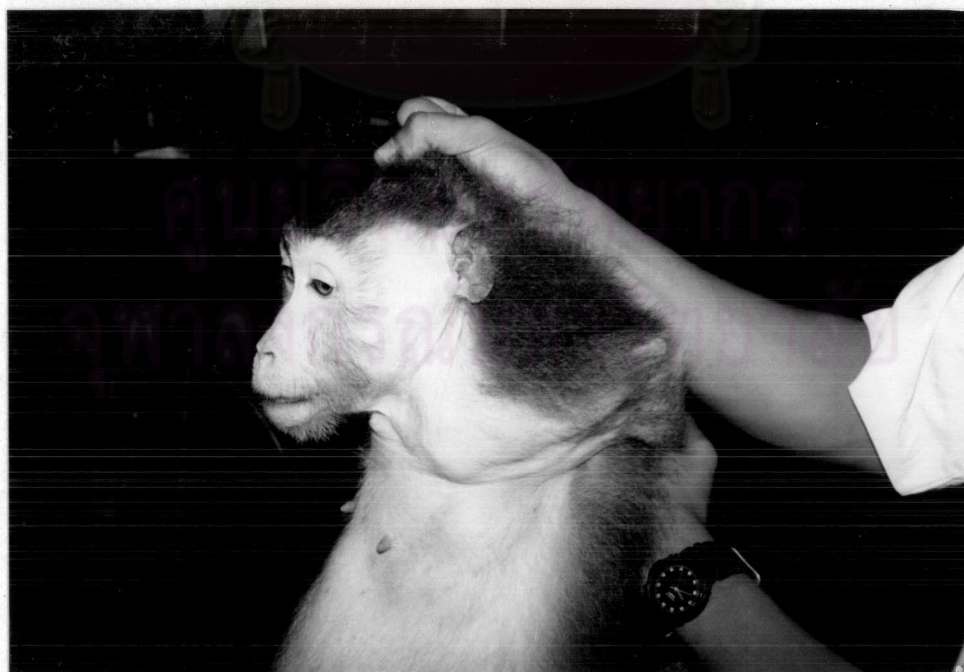


Figure 27. Hair loss around head and front leg regions.

Metabolic Turnover of Morphine

1. Pre-treatment

Table 3 turnover rate and half-life of morphine were not significantly difference during menstrual cycle. Mean values of turnover rate measured during D8 - D10 and D22 - D25 were 0.0038 and 0.0032 % min⁻¹, with half-lives of 183 and 216 min., respectively.

2. Treatment and Post-treatment

- Low and Moderate Doses (0.1-0.8 mg/kg/day)

There were no significant alteration of metabolic turnover of morphine in 0.1-0.8 mg/kg/day morphine treated groups measured on D30 and D60 excepted only one monkey of 0.8 mg/kg/day morphine treatment group (no.611, figure 67), whom exhibited unusually high value of turnover rate measured on D30 of treatment.

- High Doses (1.6 and 3.2 mg/kg/day)

Turnover rate of monkeys treated with 1.6 mg/kg/day morphine fluctuated greatly during the first few weeks of treatment. The value declined gradually after 30 days of treatment and reach steady state around day 80 of treatment (figure 28). Monkeys treated with 3.2 mg/kg/day morphine showed lesser degree of fluctuation. Definite decline in turnover rate could be detected as early as 2 weeks of treatment and reached the steady state on day 45 in all monkeys (figure 29). Withdrawal of morphine induced prompt rebound of the plasma turnover rate and readjustment to the pre-treatment values within approximately 30 days in both groups.

Table 3 Metabolic turnover and half-life of morphine in adult female cynomolgus monkeys treated with morphine, \bar{x} (SD).

Doses mg/kg/day (n)	Pre - treatment				Treatment						Post-treatment					
	D10-D12		D22-D25		day 30		day 60		day 120		day 30		day 60		day 90	
	\bar{x}	$t_{1/2\beta}$	\bar{x}	$t_{1/2\beta}$	\bar{x}	$t_{1/2\beta}$	\bar{x}	$t_{1/2\beta}$	\bar{x}	$t_{1/2\beta}$	\bar{x}	$t_{1/2\beta}$	\bar{x}	$t_{1/2\beta}$	\bar{x}	$t_{1/2\beta}$
0.1 (2)	.38 (.05)	168.0 (35.5)	.35 (.03)	198.3 (26.9)	.36 (.04)	182.2 (19.7)	.33 (.03)	196.0 (16.3)	-	-	.34 (.04)	188.0 (22.3)	-	-	-	-
0.2 (3)	.29 (.04)	221.8 (43.8)	.31 (.05)	215.8 (24.5)	.27 (.07)	240.3 (57.4)	.28 (.04)	228.2 (27.4)	-	-	.36 (.05)	162.5 (18.7)	-	-	-	-
0.4 (3)	.36 (.02)	189.0 (19.0)	.32 (.05)	209.9 (39.6)	.30 (.06)	192.6 (43.0)	.32 (.04)	199.6 (23.4)	-	-	.28 (.03)	235.6 (14.2)	-	-	-	-
0.8 (3)	.28 (.06)	236.5 (58.9)	.34 (.05)	201.7 (41.9)	.48 (.03)	133.1 (12.6)	.34 (.03)	186.9 (19.0)	-	-	.31 (.04)	172.5 (18.0)	-	-	-	-
1.6 (3)	.27 (.06)	241.8 (21.2)	.30 (.04)	228.7 (36.4)	.28 (.05)	247.5 (68.6)	.25 (.02)	277.2 (29.0)	.16* (.03)	412.3* (65.5)	.28 (.05)	251.6 (45.2)	.34 (.03)	202.1 (32.2)	.26 (.05)	242.4 (53.3)
3.2 (3)	.36 (.04)	178.2 (27.6)	.31 (.03)	209.9 (46.3)	.20* (.07)	346.1* (91.1)	.13* (.03)	463.0* (68.3)	.15* (.04)	447.3* (93.6)	.30 (.06)	223.6 (71.2)	.31 (.07)	221.3 (71.3)	.31 (.04)	212.3 (45.0)
overall	.38 (.04)	183.8 (21.5)	.32 (.10)	216.6 (51.6)												

* significantly difference from overall pre-treatment values, $p < 0.05$ ** significantly difference from overall pre-treatment values, $p < 0.01$

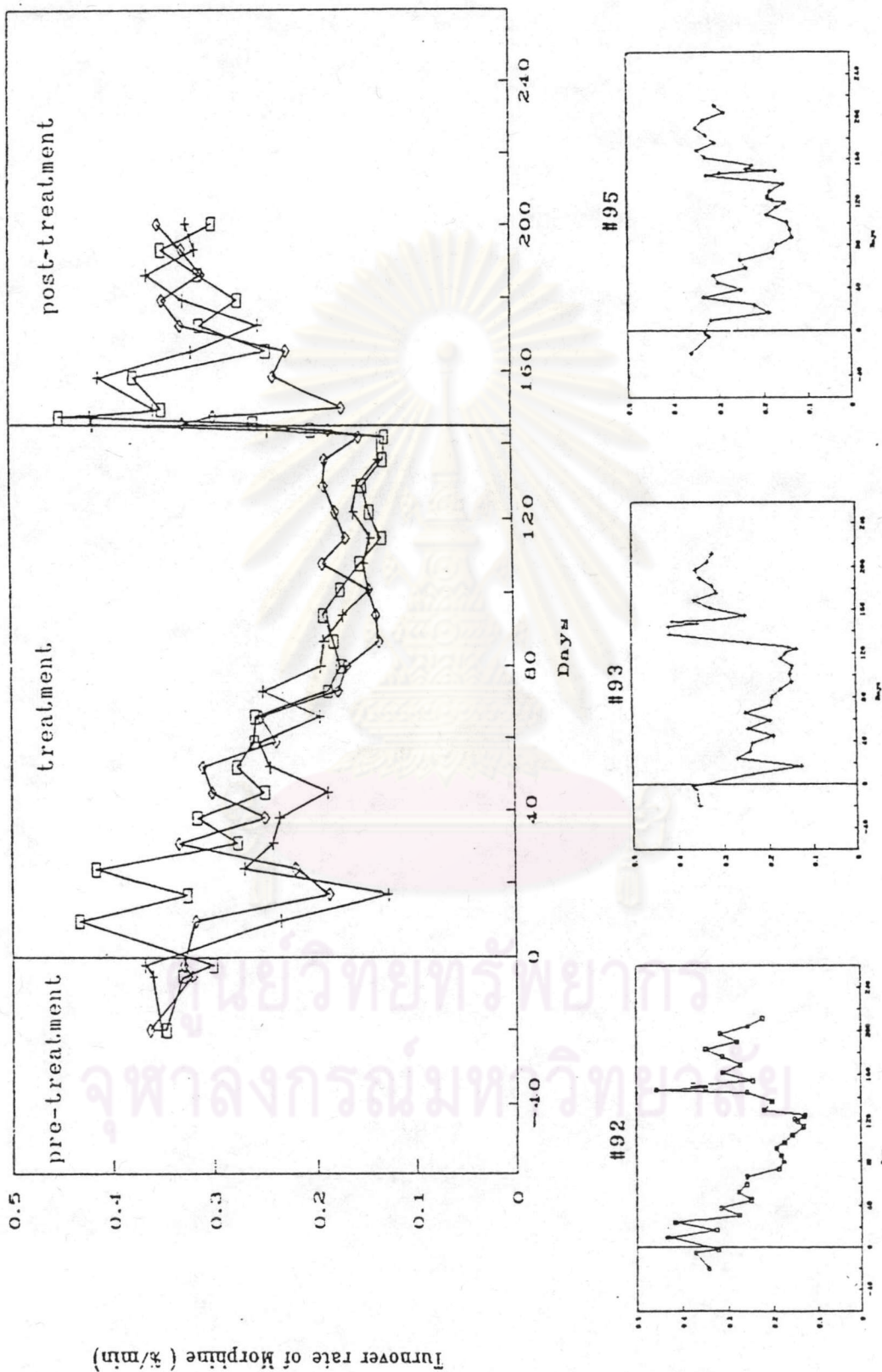


Figure 28 Metabolic turnover profiles of morphine during morphine hydrochloride treatment and withdrawal periods in the dose of 1.6 mg/kg/day.

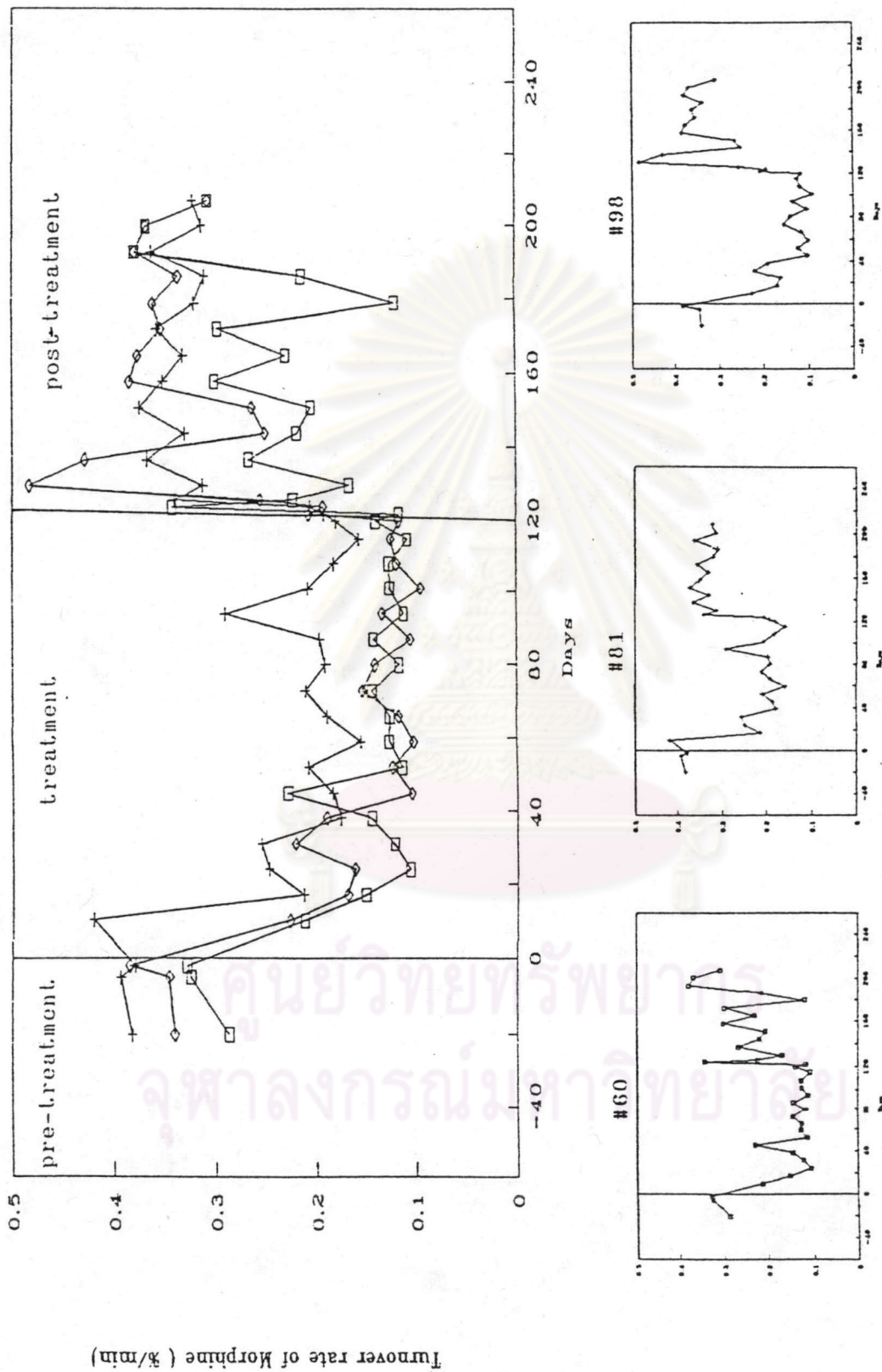


Figure 29 Metabolic turnover profiles of morphine during morphine hydrochloride treatment and withdrawal periods in the dose of 3.2 mg/kg/day.

Serum Levels of Sex Steroids, PRL and Cortisol

1. Pre-treatment

a) E_2 and P

Results presented in table 4 and figure 30 were grouped according to relative similarities of the length of the menstrual cycle. They were divided into 3 subgroups as follows:

i) 28-31 days cycle.

Levels of E_2 in this group were increased during D12 and D16 of the cycle. Maximal values detected are as high as 362.1 pg/ml on D15. The levels decreased sharply from D19 and progressively declined to as low as 57.3 and 44.9 pg/ml during the last 1-2 days prior to the onset of next menstrual bleeding.

Levels of P were lowest during the first 5 days of the cycle but increased approximately twice as much when measured on D10 and further increased to as much as 3690-7840 pg/ml on D12 and D16 respectively. After this period P levels declined gradually and then showed sudden decrease 1-2 days prior to the onset of next menstrual bleeding. None of monkey in this group showed abnormal patterns of E_2 and P secretion during the entire range of the cycle.

ii) 32-35 days cycles

Serum levels of E_2 and P were very similar to monkeys in group i) except maximal rise E_2 and P peak in this group were detected approximately 3-4 days later. Sudden drop of E_2 and P were also found 1-2 days prior to onset of menstrual bleeding of the next cycle.

iii) 36-39 days cycle

Patterns of serum E_2 and P levels were very similar to the 33-35 days cycle with the exception delayed rising of P levels and no sharp decline of this hormone at least until D33 of the cycle.

b) PRL and Cortisol

Results were presented in table 5 and figure 31. Serum levels of PRL and cortisol were not altered significantly during various phases of the cycle irrespective of the length of the cycle. The values measured were 112 - 636 mIU/L and 906 - 1742 ng/ml for PRL and cortisol respectively.



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Table 4 Serum levels of E_2 and P in adult female cynomolgus monkeys during pre-treatment cycles.

Length of menstrual cycle day (n)	Hormones	Day of the menstrual cycle, \bar{x} (S.D.)									
		5	10	12	15-16	19-21	23	25-26	30	33	
28 - 31 (5-22)	E_2	43.7	49.2	148.9	352.5	102.6	76.2	57.3	44.9		
	pg/ml	(23.2)	(41.1)	(72.1)	(65.7)	(55.6)	(12.3)	(35.3)	(21.4)		
	P	0.64	1.84	3.69	7.84	8.27	4.32	5.32	2.18		
	ng/ml	(0.31)	(0.54)	(2.24)	(3.42)	(2.67)	(3.94)	(1.24)	(2.32)		
32 - 35 (7)	E_2	61.2	72.2	92.1	182.2	431.0	216.7	81.3	61.2	59.5	
	pg/ml	(31.4)	(34.2)	(42.8)	(82.3)	(157.2)	(72.6)	(38.5)	(25.6)	(31.1)	
	P	0.58	1.62	1.69	4.98	6.87	5.75	2.64	3.31	1.85	
	ng/ml	(0.40)	(0.82)	(1.02)	(3.76)	(3.19)	(2.89)	(1.61)	(1.12)	(0.76)	
36 - 39 (10)	E_2	56.2	59.2	92.4	123.4	315.9	172.3	74.1	83.2	58.5	
	pg/ml	(25.7)	(18.3)	(41.8)	(61.0)	(132.7)	(113.5)	(24.1)	(34.2)	(26.3)	
	P	0.71	0.97	0.86	2.14	9.27	7.03	4.84	2.73	2.85	
	ng/ml	(0.42)	(0.36)	(0.44)	(1.10)	(3.06)	(4.13)	(2.31)	(1.91)	(1.36)	



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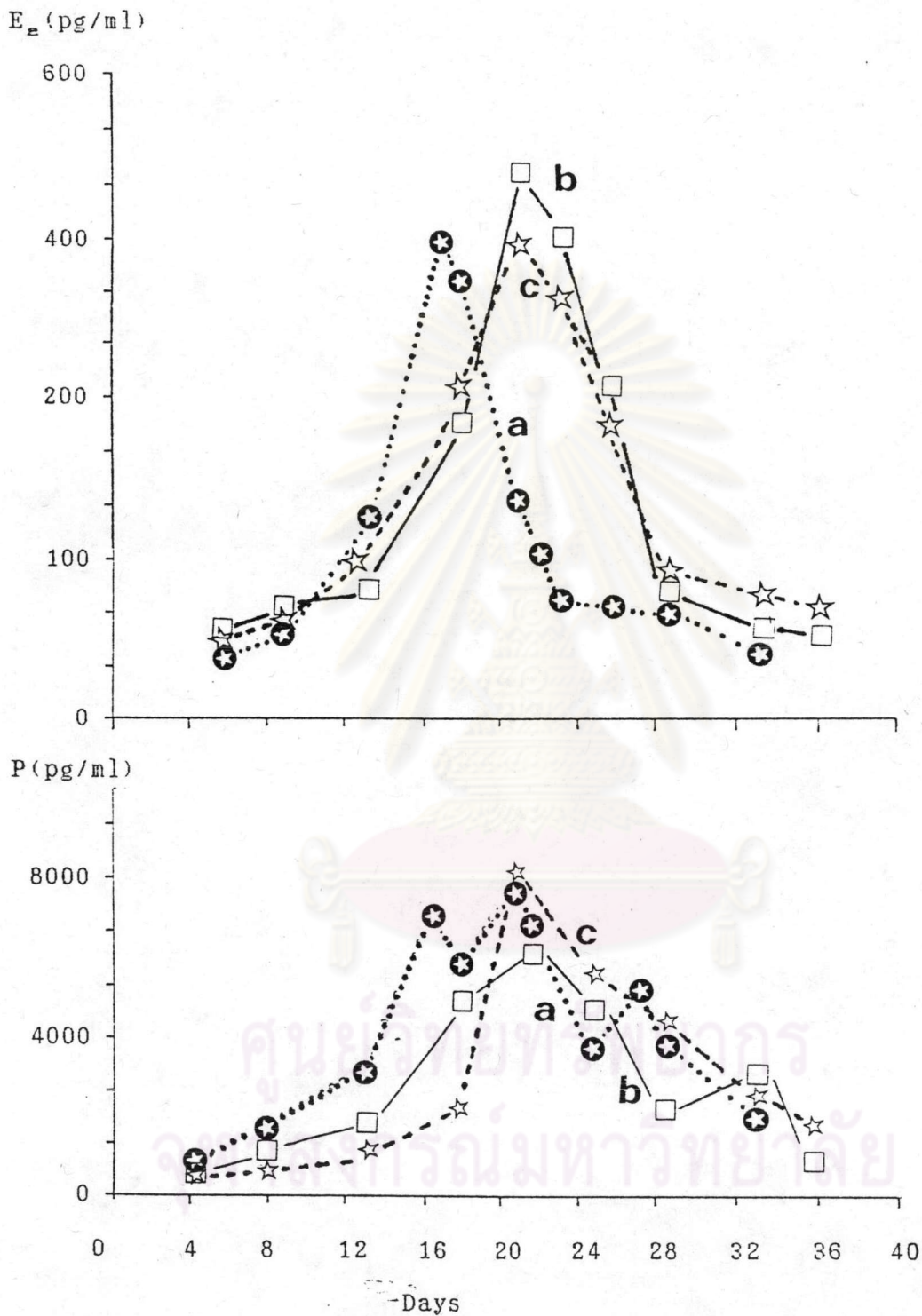


Figure 30. Serum levels of E_2 and P in 3 types of normal menstrual cycle in female monkeys with menstruation
 a) 28-31 days cycle, b) 32-35 days cycle
 c) 36-39 days cycle.

Table 5 Serum levels of PRL and cortisol in adult female cynomolgus monkeys during pre-treatment cycles.

Length of menstrual cycle day (n)	Hormone	Day of the menstrual cycle, \bar{x} (S.D.)								
		5	10	12	19-20	25-26	30	33		
28 - 31 (5-22)	PRL	322.6	241.5	282.9	266.8	195.5	218.4			
	mIU/L	(101.4)	(94.2)	(138.2)	(42.6)	(72.4)	(59.7)			
	cortisol ng/ml	1368 (84.5)	1273 (132.4)	1243 (97.7)	1407 (133.4)	1184 (118.5)	1341 (63.3)			
32 - 35 (7)	PRL	248.5	325.5	198.6	271.4	178.2	232.3	203.6		
	mIU/L	(78.6)	(131.1)	(89.7)	(39.6)	(84.2)	(24.9)	(58.3)		
	cortisol ng/ml	1418 (141.2)	1534 (206.6)	1148 (206.4)	1240 (84.5)	1405 (188.5)	1273 (99.9)	1243 (132.9)		
36 - 39 (10)	E_2	56.2	59.2	92.4	123.4	315.9	172.3	74.1	83.2	58.5
	pg/ml	(25.7)	(18.3)	(41.8)	(61.0)	(132.7)	(113.5)	(24.1)	(34.2)	(26.3)
	P	0.71	0.97	0.86	2.14	9.27	7.03	4.84	2.73	2.85
	ng/ml	(0.42)	(0.36)	(0.44)	(1.10)	(3.06)	(4.13)	(2.31)	(1.91)	(1.36)

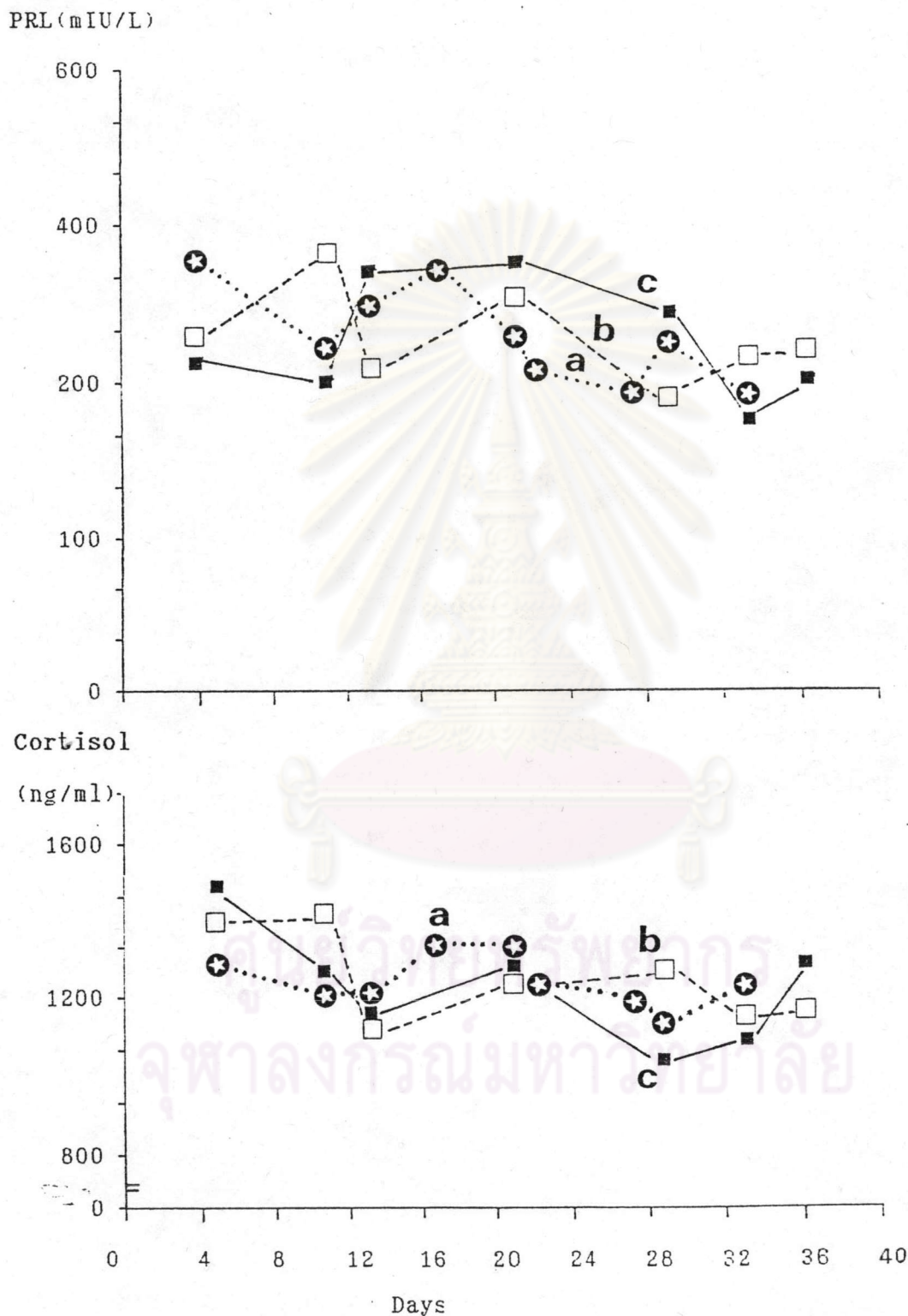


Figure 31. Serum levels of PRL and cortisol in 3 types of normal menstrual cycle in female monkeys with menstruation a) 28-31 days cycle, b) 32-35 days cycle c) 36-39 days cycle.

Table 6 Patterns of menstrual bleeding in 17 monkeys treated daily with morphine hydrochloride.

Doses of morphine mg/kg/day	Monkey number	Treatment duration days	Menstrual cycle length (duration of bleeding) days		
			pre-treatment	treatment	post-treatment
0.1	601	100	31, 30	33, 28, 32	33 ^M , 30, 29, 28
			(3) (3)	(2) (3) (2)	(3) (3) (3) (3)
			32, 32	48, 30	29 ^M , 32, 30, 30 p
			(3) (3)	(2) (2)	(2) (3) (2) (2)
0.2	41	100	32, 33	30, 28, 29	28 ^M , 28, 30, 28
			(3) (3)	(3) (2) (3)	(2) (2) (3) (4)
			29, 28	30, 28, 28	37 ^M , 29
			(4) (5)	(5) (4) (4)	(5) (5) p
0.4	99	100	30, 32	26, 34, 32	31 ^M , 29, 30, 27
			(3) (4)	(4) (3) (3)	(3) (3) (4) (4)
			36, 38	41, 27, 30	29 ^M p
			(2) (3)	(2) (3) (3)	(3)
0.4	616	100	36, 36	34, 32, 31	37 ^M , 40, 38, 36
			(3) (3)	(3) (4) (4)	(4) (3) (3) (3)
			35, 34	57	46 ^M , 34, 31 p
			(4) (5)	(5)	(4) (5) (4)

Doses of morphine mg/kg/day	Monkey number	Treatment duration days	Menstrual cycle length (duration of bleeding) days		
			pre-treatment	treatment	post-treatment
0.8	71	100	36, 37	72	48 ^m , 45, 40, 36
			(5) (4)	(5)	(4) (4) (5) (4)
			37, 39	89	47 ^m , 42, 37, 40
	102	100	(3) (4)	(3)	(4) (3) (4) (3)
			38, 37	47, 33	33 ^m , 28, 35, 30
			(4) (4)	(4) (3)	(4) (4) (3) (4)
	92	143	29, 28	27, 32, 29, 32	34 ^m , 31, 28, 33
			(4) (4)	(4) (3) (5) (8)	(9) (8) (6) (4)
			31, 31	72, 51	29 ^m , 40, 46, 29
	93	145	(3) (3)	(3) (3)	(3) (4) (3) (3)
28, 31			113	68 ^m , 27, 27, 29	
(3) (3)			(3)	(5) (4) (4) (5)	
95	147	28, 30	-	154 ^m , 30, 27, 25	
		(3) (3)	(3)	(2) (2) (3) (3)	
		28, 27	-	101 ^m , 61, 33, 30	
60	120	(2) (3)	(2) (3)	(2) (3) (3) (3)	
		28, 29	-	177 ^m , 33, 31, 28	
		(3) (3)	(3)	(3) (3) (3) (2)	
81	120	28, 29	-	177 ^m , 33, 31, 28	
		(3) (3)	(3)	(3) (3) (3) (2)	
		28, 29	-	177 ^m , 33, 31, 28	
98	120	(3) (3)	(3)	(3) (3) (3) (2)	
		28, 29	-	177 ^m , 33, 31, 28	
		(3) (3)	(3)	(3) (3) (3) (2)	

^m = transitional cycle

p = pregnancy

2. Treatment and Post-treatment

a) E_2 and P

- Low and Moderate Doses

Monkeys treated with daily doses of 0.1-0.2 mg/kg morphine still have normal fluctuations of serum E_2 and P levels with regularity of the cycle during entire period of morphine treatment except one monkey treated with 0.1 mg/kg/day (no.615) showed deviation of the first treatment cycle to 48 days.

Cycles lengthened with the large morphine doses (0.4 and 0.8 mg/kg/day). Only one monkey (no.616) of 0.4 mg/kg/day morphine treated group retained regular menstrual cycles throughout treatment period. Other 2 monkeys of the same group however prolonged first cycle and only one of these could be readjusted subsequently to normal cycle length with normal E_2 and P levels. Two out of 3 monkeys in 0.8 mg/kg/day morphine treated group, on the other hand, showed extremely prolongation of their first menstrual cycle associated with. One monkey had her first treatment cycle extended to 47 days with sporadic rise of E_2 and P, subsequent cycle, however, could adjust to have become normal cycle with normal fluctuation of E_2 and P levels observed during pre-treatment cycle, despite continuation of morphine administration.

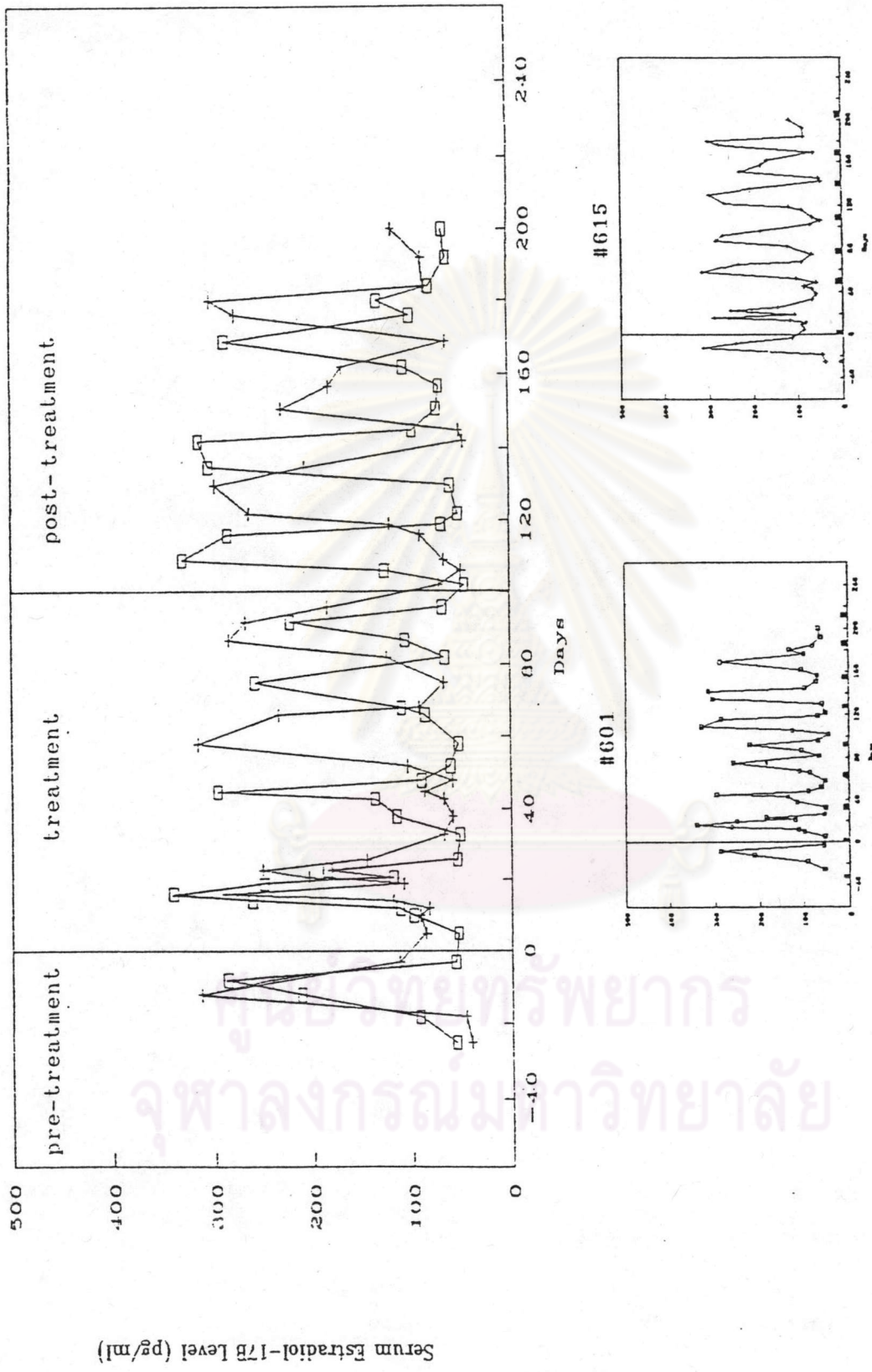


Figure 32 The serum estradiol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.1 mg/kg/day, ■ = menstruation.

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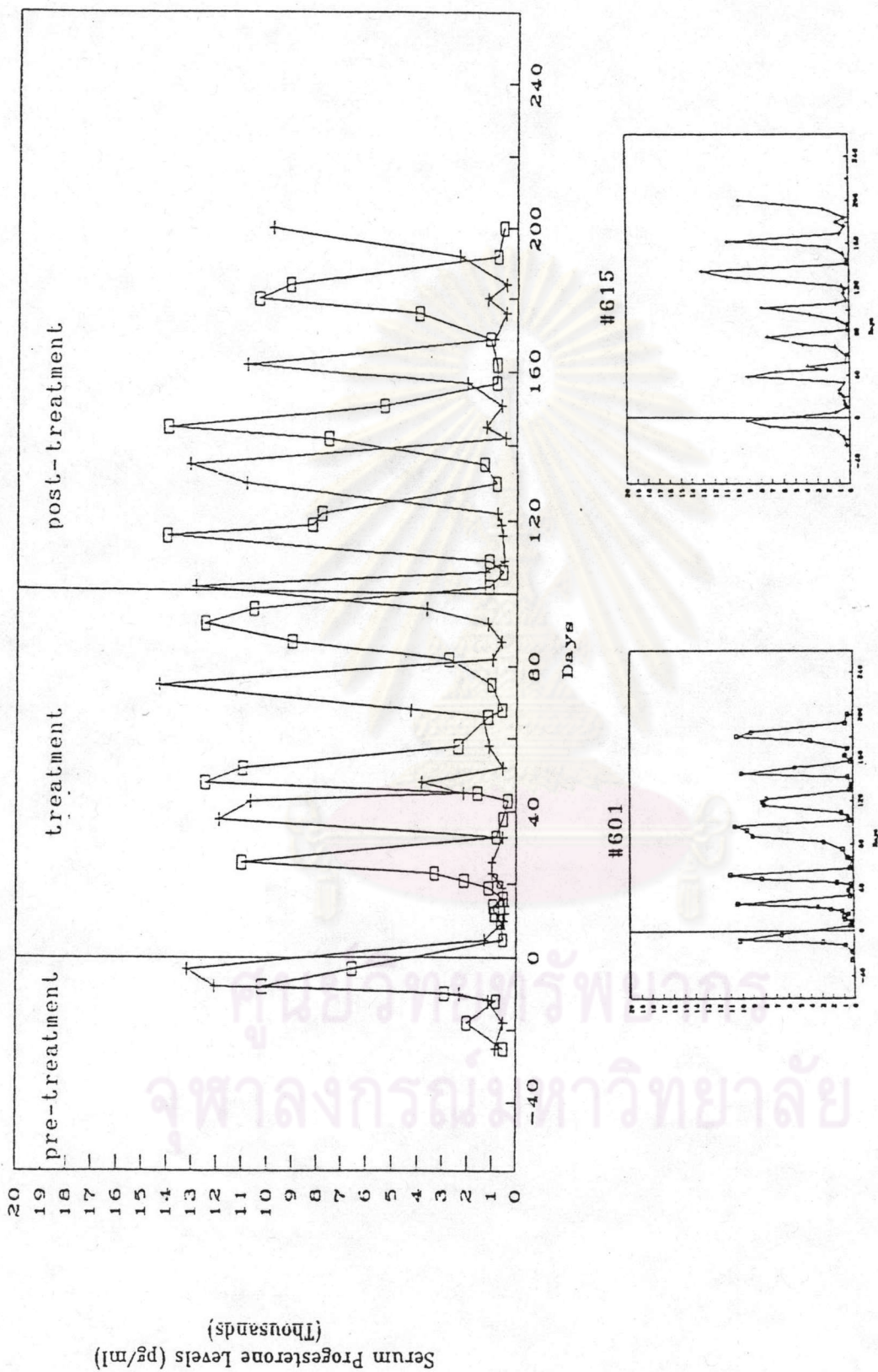


Figure 33 The serum progesterone profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.1 mg/kg/day.

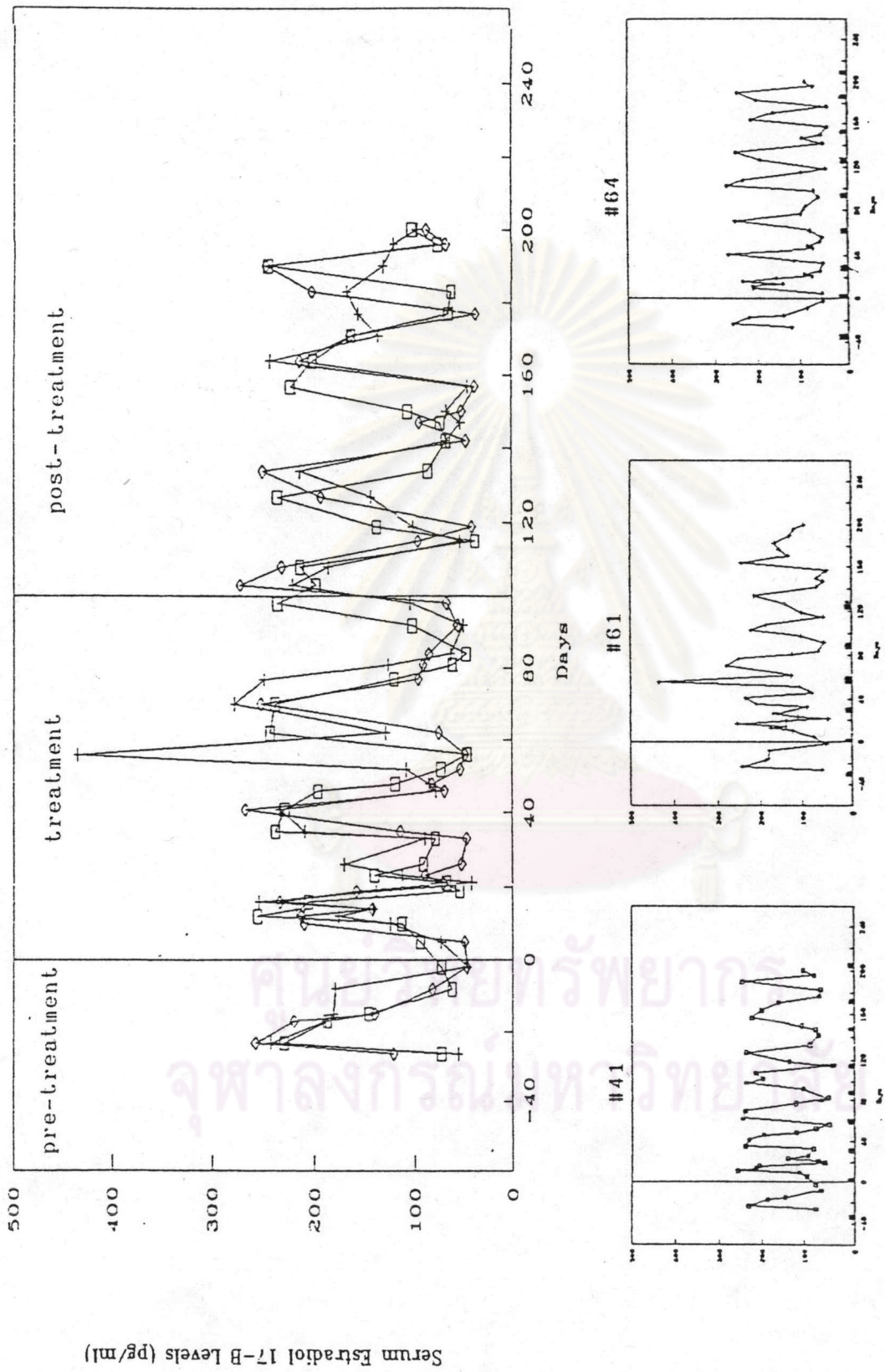


Figure 34 The serum estradiol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.2 mg/kg/day, ■ = menstruation, ○ = withdrawal.

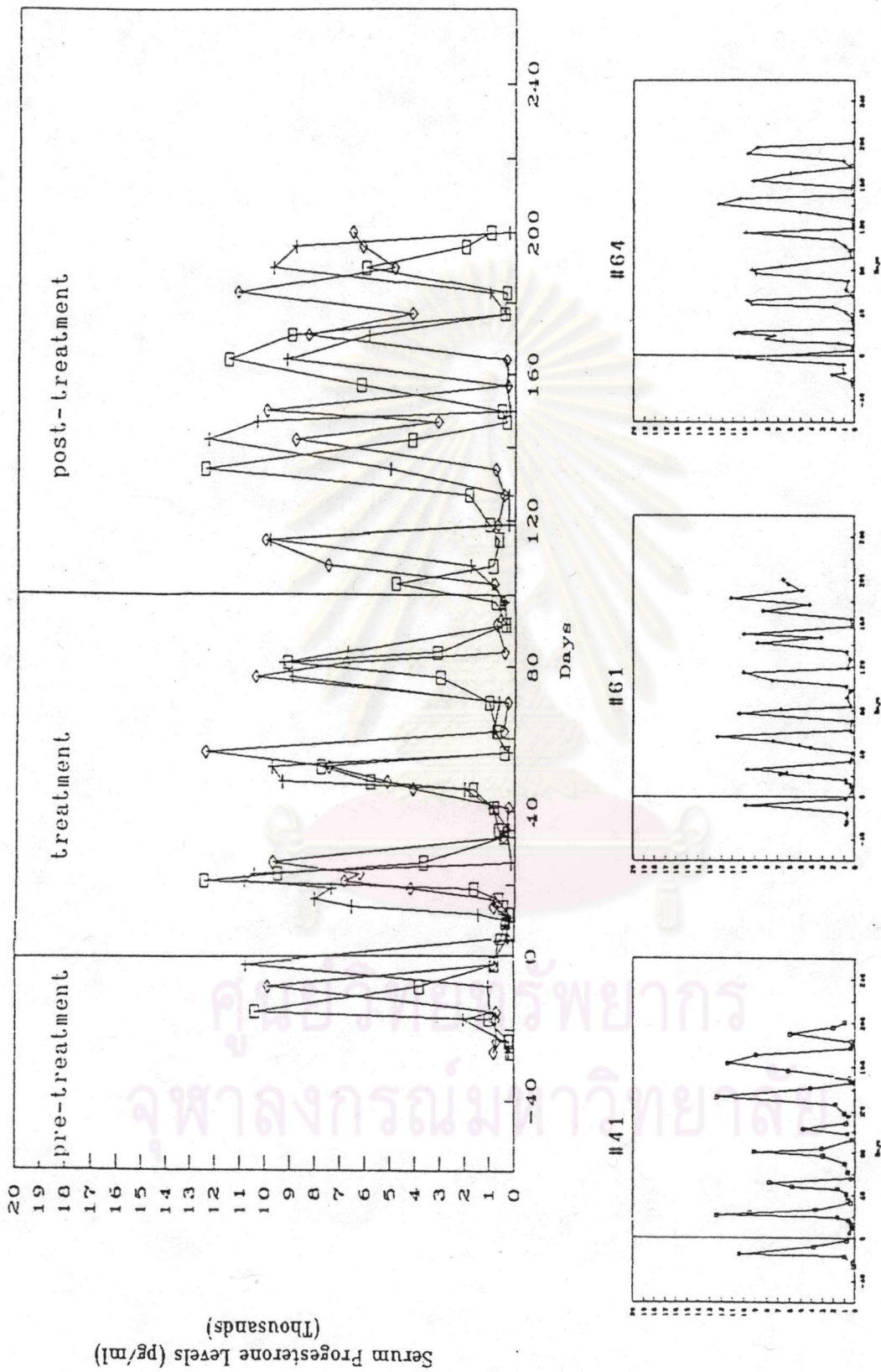


Figure 35 The serum progesterone profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.2 mg/kg/day.

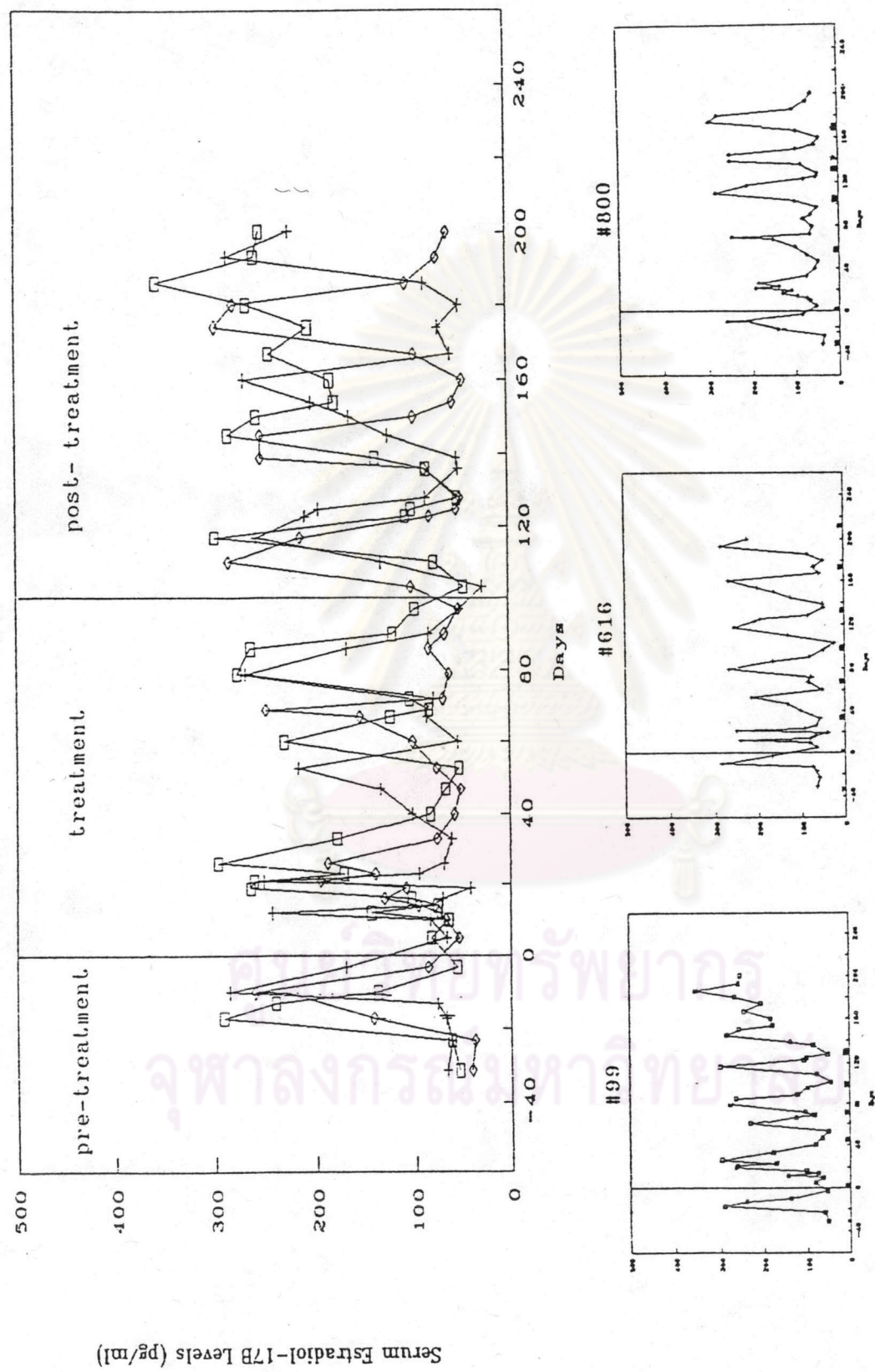


Figure 36 The serum estradiol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.4 mg/kg/day, ■ = menstruation.

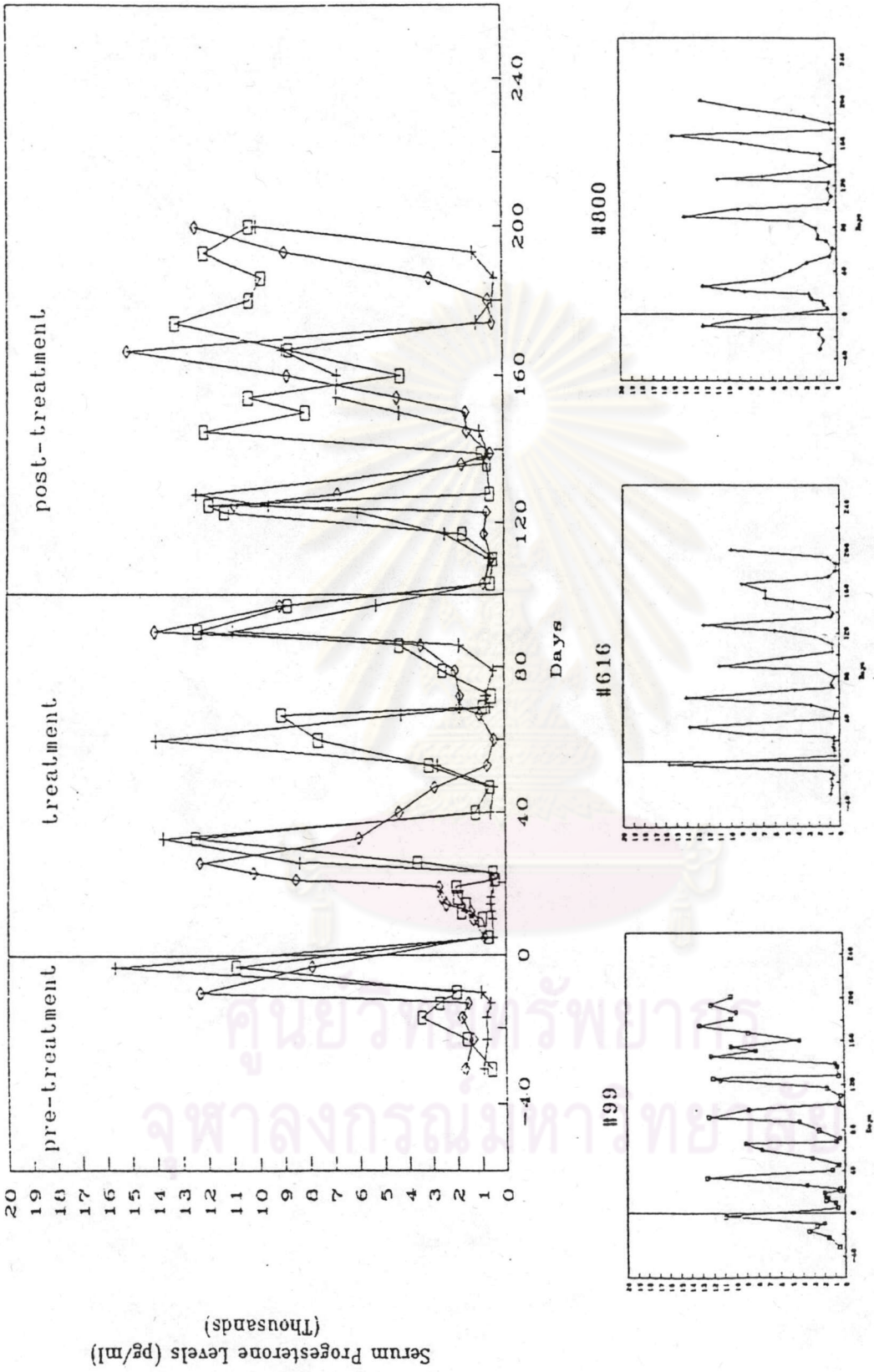


Figure 37 The serum progesterone profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.4 mg/kg/day.

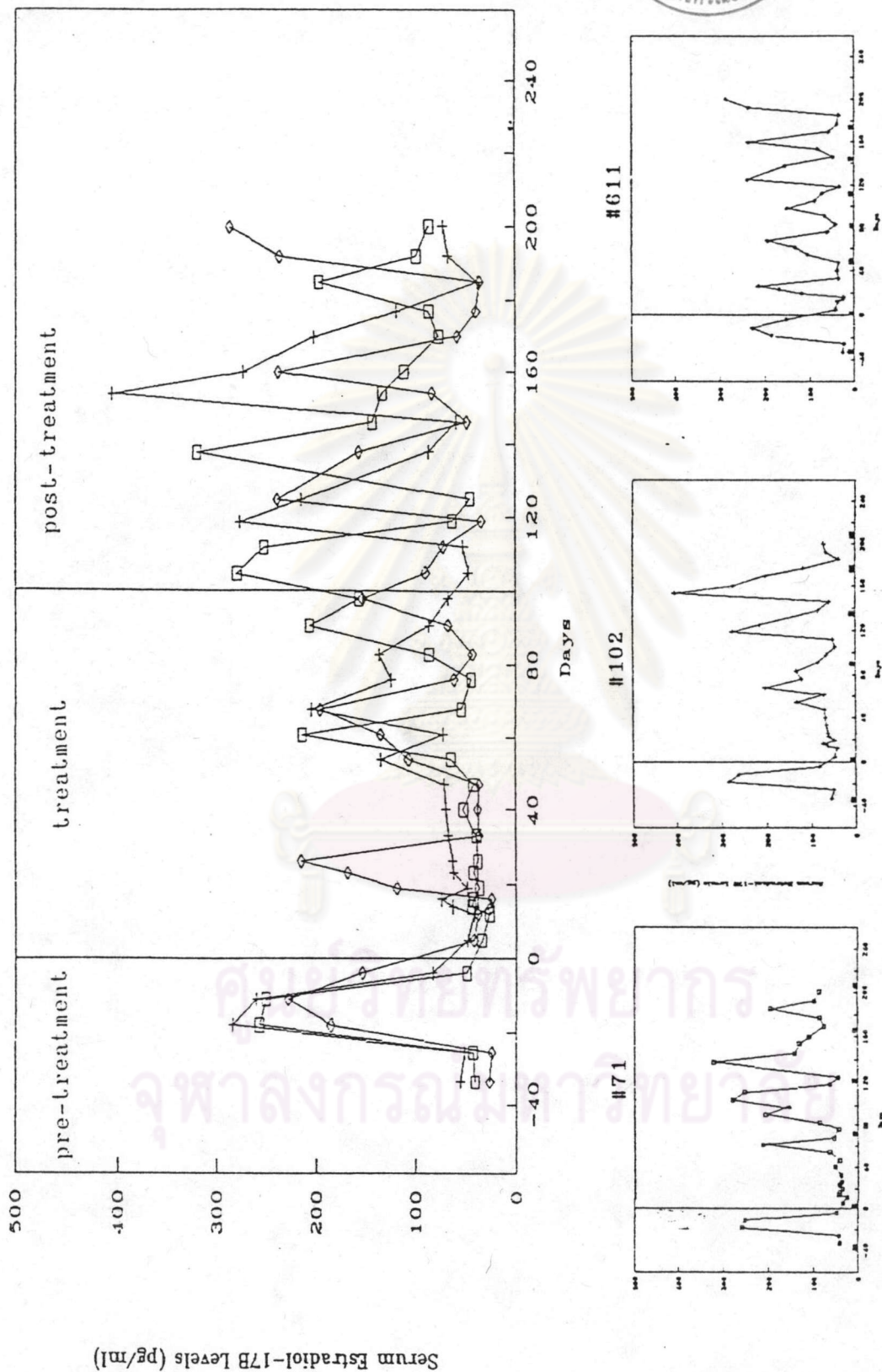


Figure 38 The serum estradiol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.8 mg/kg/day, ■ = menstruation.

Serum Estradiol-17B Levels (pg/ml)

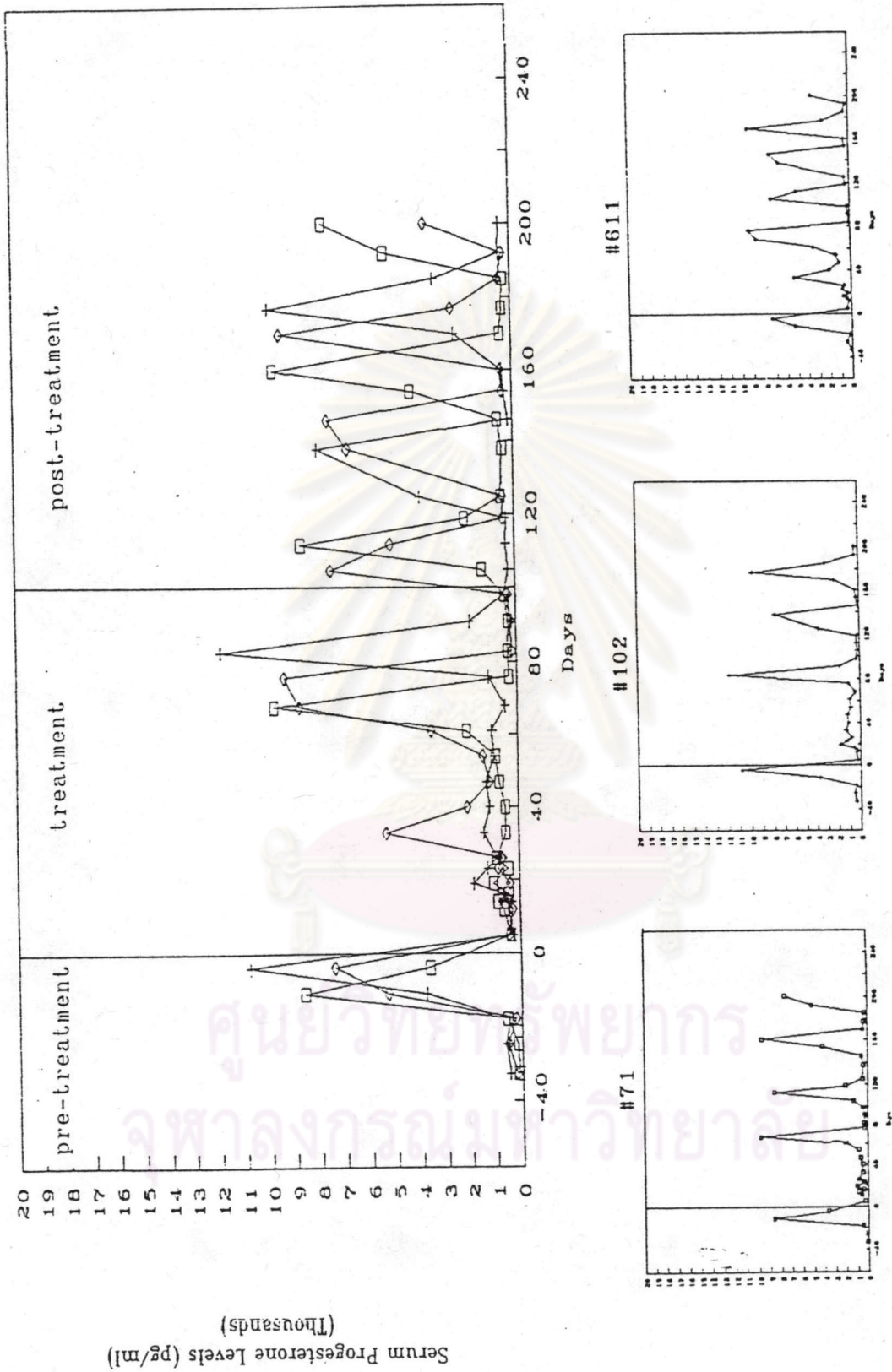


Figure 39 The serum progesterone profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.8 mg/kg/day.

- High Doses

Two monkeys treated with 1.6 mg/kg/day morphine postponed cycle length, suppression of endogenous E_2 and P secretion, comparable with those of 0.8 mg/kg/day treated group. However, monkey no. 92 could readjust her cycle length as well as endogenous E_2 and P secretion similar to the pattern found during pre-treatment cycles but the bleeding duration was prolonged to 8-9 days during the last few cycles of late treatment and early post-treatment cycle (menorrhagia). On the otherhand, all monkeys treated with 3.2 mg/kg/day morphine were amenorrhic during the whole of 120 days treatment period. Serum E_2 levels always below 100 pg/ml during entire treatment period except a few sporadic low rises of E_2 levels could be detected in some monkeys, but the values were still lower than 200 pg/ml. Serum P levels were completely suppressed during the entire period of treatment.

Withdrawal of morphine on day 100 had showed apparent influence upon the usual duration of the cycle length and normal patterns of E_2 and P secretion among monkeys treated with daily dose of 0.1-0.4 mg/kg morphine. Cycle length of these monkeys was readjusted promptly to the normal range of 27-40 days and remained within this range throughout their first 100 days of drug withdrawal. Reproductive potential among 0.2 and 0.4 mg/kg/day morphine treated groups were high since successful mating with subsequent normal pregnancy lactation were evidenced in four monkeys placed with normal fertile males during the first few cycle of drug withdrawal. All of 0.8 mg/kg/day morphine treated monkeys showed prolongation of the menstrual

cycle during treatment period but they promptly responded to morphine withdrawal by reexhibiting normal menstrual cycle again within 13-34 days with normal post-treatment cycles of 28-45 days in all. Serum levels of E_2 and P also rose as expected during late follicular and luteal phase of the cycle, respectively. Similarly, monkeys treated with 1.6 mg/kg/day started to menstrual cycle again within 7-36 days after the drug withdrawal and followed by relatively regular cycle length of 27-34 days. They also showed similar E_2 and P profiles to other groups of monkeys previously treated with lower doses of morphine. Monkeys treated with 3.2 mg/kg/day took slightly longer, 34-61 days, to achieve their normal cycles. Only one monkey (no.81) exhibited prolong menstrual cycle of 61 days during the first post-treatment cycle. All other cycles recorded were with in the range of 25-33 days with normal serum E_2 and P profile.



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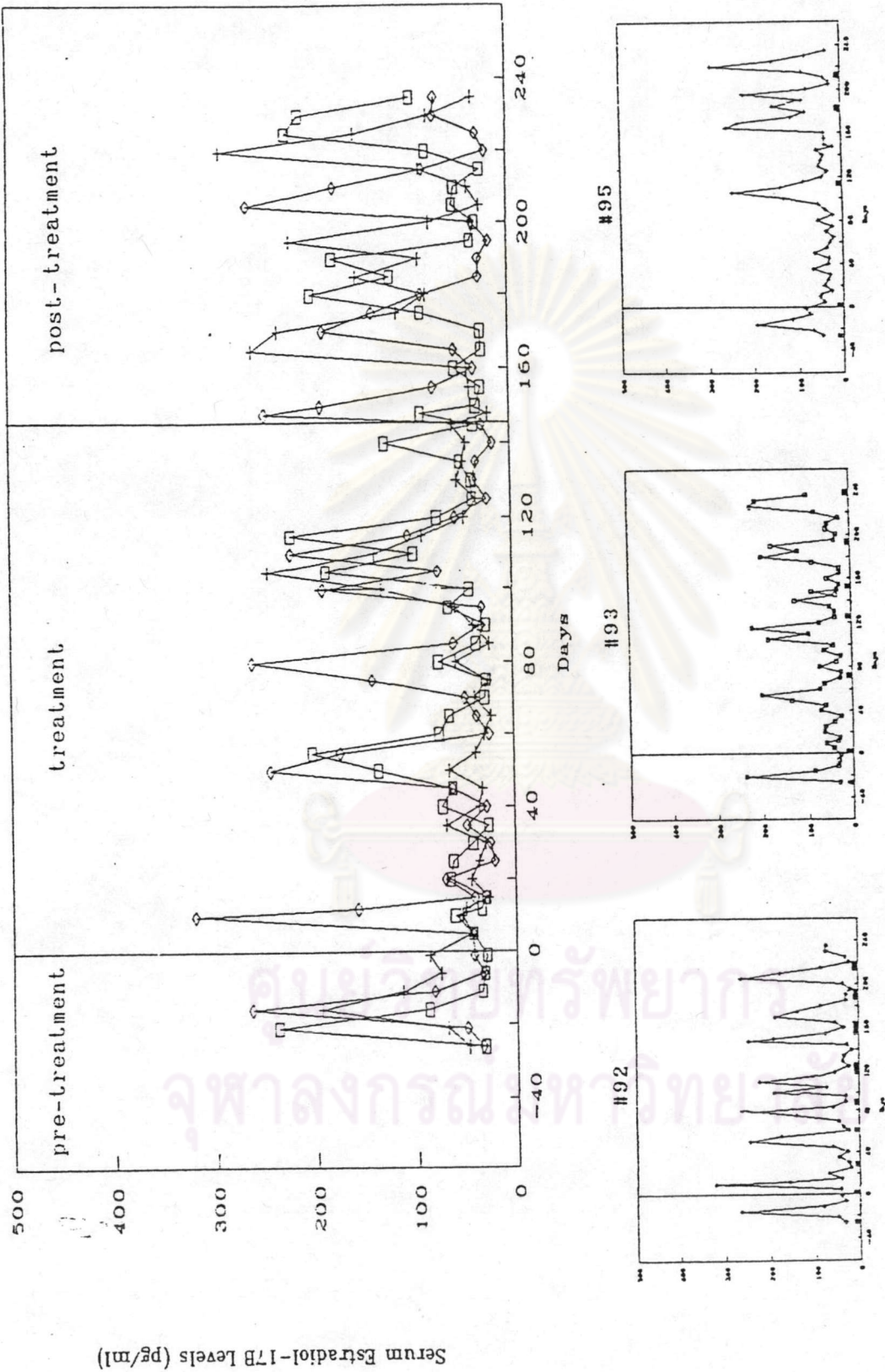


Figure 40 The serum estradiol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 1.6 mg/kg/day, ■ = menstruation.

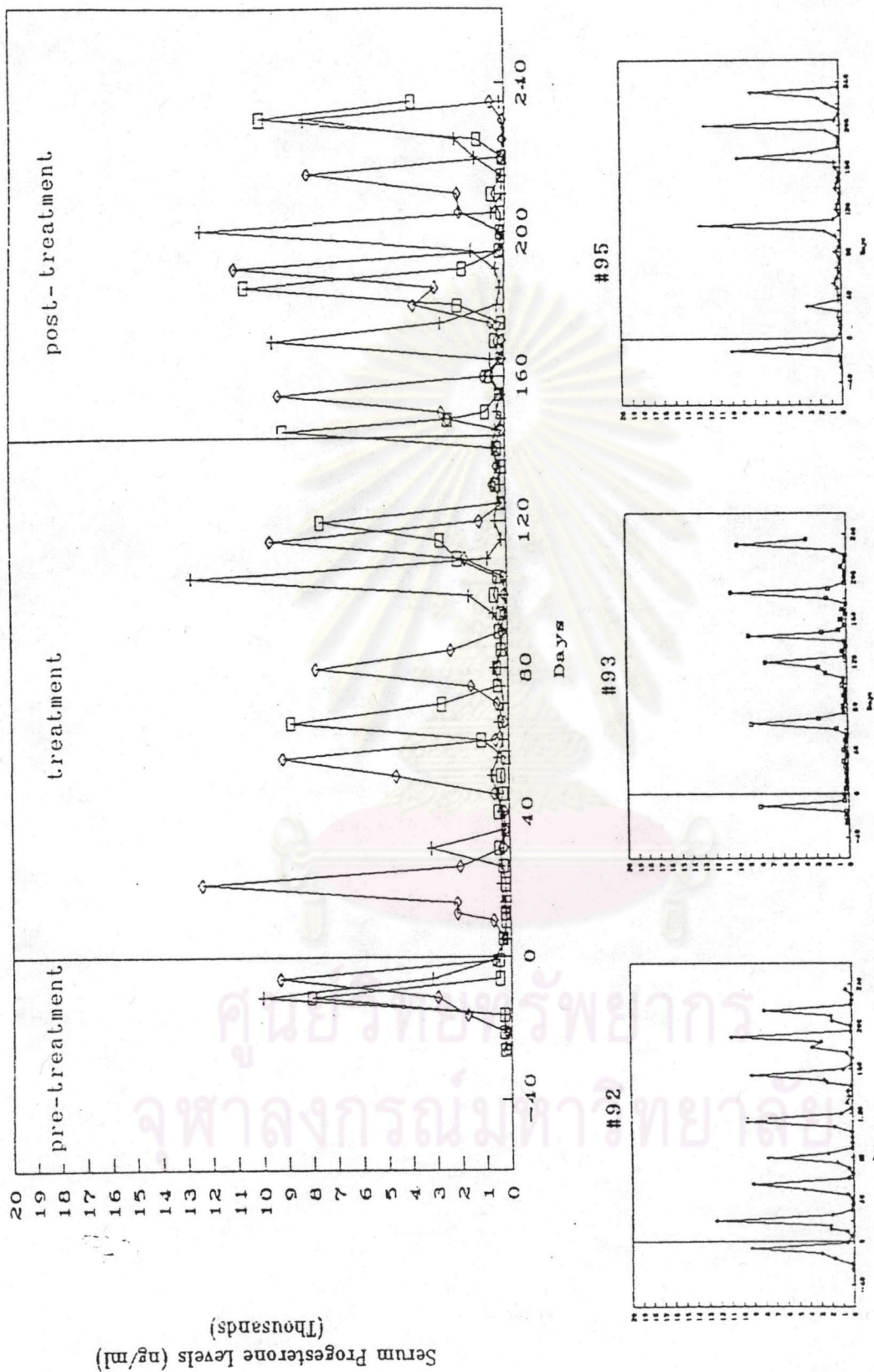


Figure 41 The serum progesterone profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 1.6 mg/kg/day.

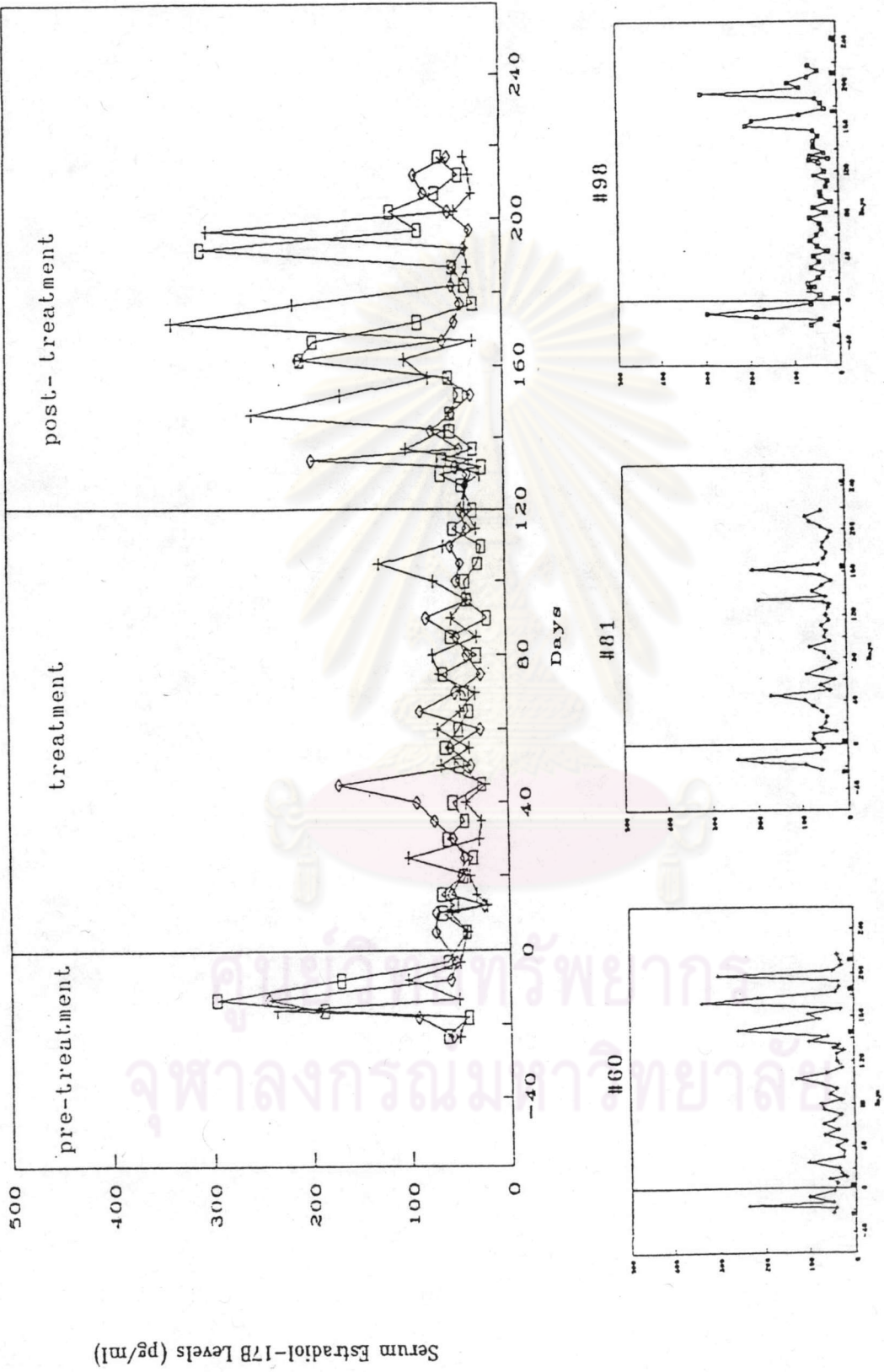


Figure 42 The serum estradiol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 3.2 mg/kg/day, ■ = menstruation.

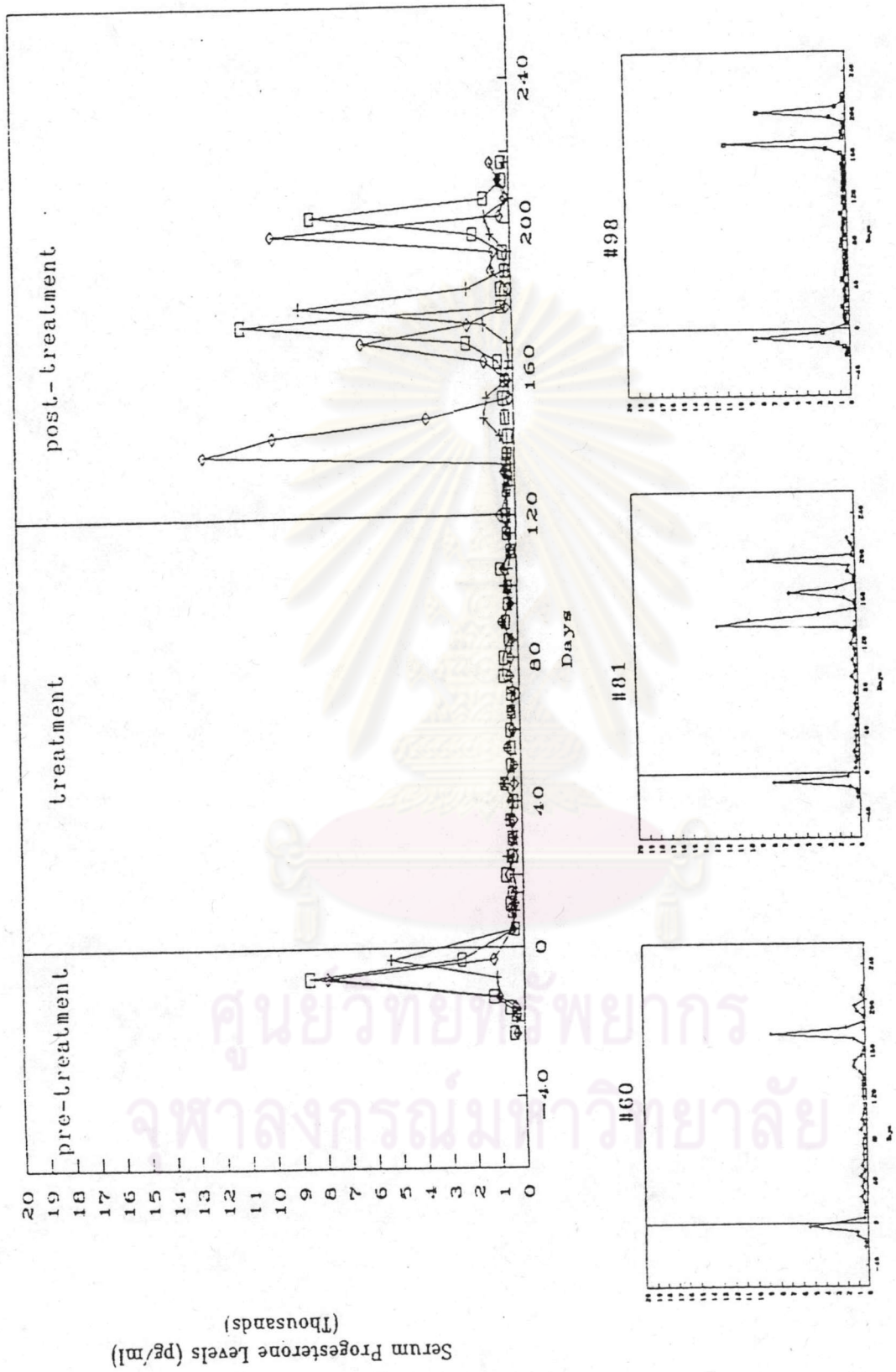


Figure 43 The serum progesterone profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 3.2 mg/kg/day.

b) PRL and Cortisol

Morning serum PRL levels showed dose dependent response to daily morphine hydrochloride injection. Slight increment of PRL were found in 0.1-0.2 mg/kg/day morphine treated groups. Significant increment of serum PRL levels were found in monkeys treated with 0.4 mg/kg/day morphine and over. The response could be detected as early as 5 days of treatment. Consistent increment were found in monkey groups treated with 0.8 mg/kg/day morphine and over. Maximal serum PRL levels were detected 3,754 (days 12), 2,868 (day 10) and 3,617 (day 10) mIU/L in monkey group treated with 0.8, 1.6 and 3.2 mg/kg/day of morphine, respectively. More oscillation of morning PRL levels during morphine treatment were greatly in 3.2 mg/kg/day morphine treated group.

Hyperprolactinemia was associated with spontaneous galactorrhea in 5 out of 6 monkeys treated with 1.6-3.2 mg/kg/day morphine. The onset of spontaneous galactorrhea was not as prompt as hyperprolactinemia. Minimal duration was found on day 92-110 and 26-51 in monkeys treated with 1.6 and 3.2 mg/kg/day morphine respectively. On the other hand, one monkey treated with 1.6 mg/kg/day morphine whom able to adapt to exhibit regularity of menstrual cycle associated with menorrhagia failed to show spontaneous galactorrhea. Maximal serum PRL levels measured during treatment period were lowest in this group and never exceeded 2,000 mIU/L during entire period of morphine treatment. However, the oscillation of PRL levels were least comparing with other monkeys in 1.6-3.2 mg/kg/day morphine treated groups.

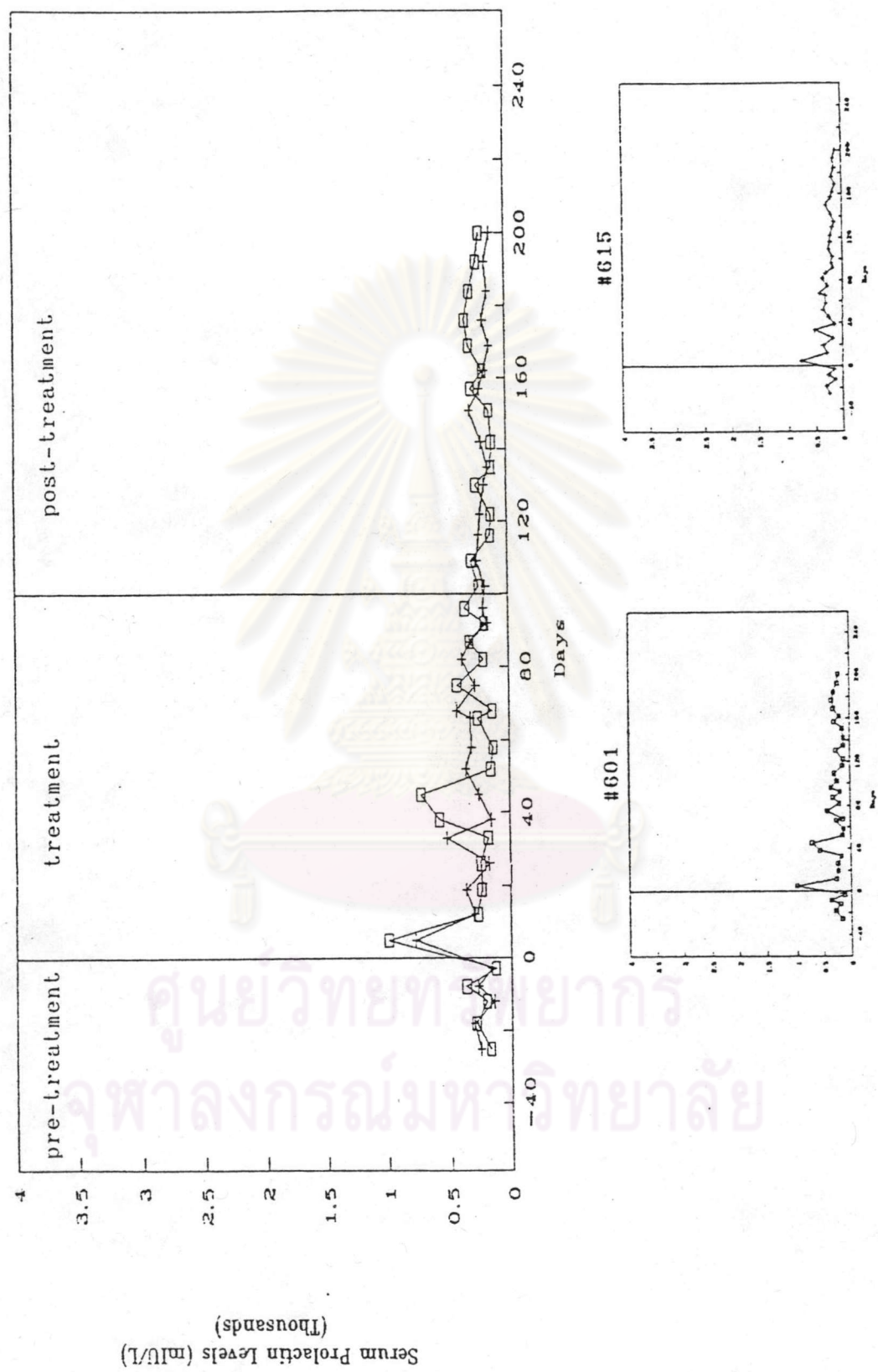


Figure 44 The serum prolactin profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.1 mg/kg/day.

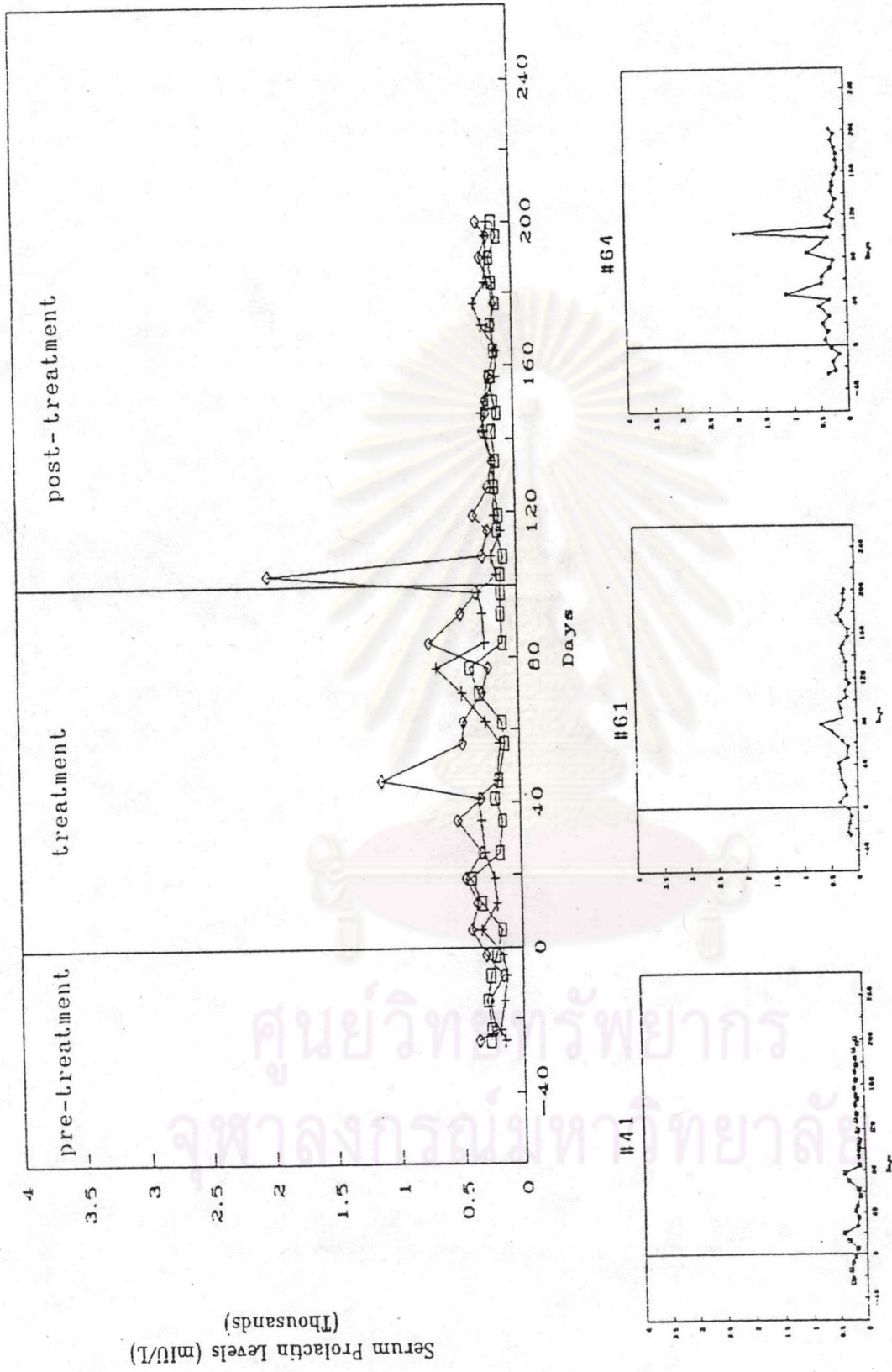


Figure 45 The serum PRL profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.2 mg/kg/day.

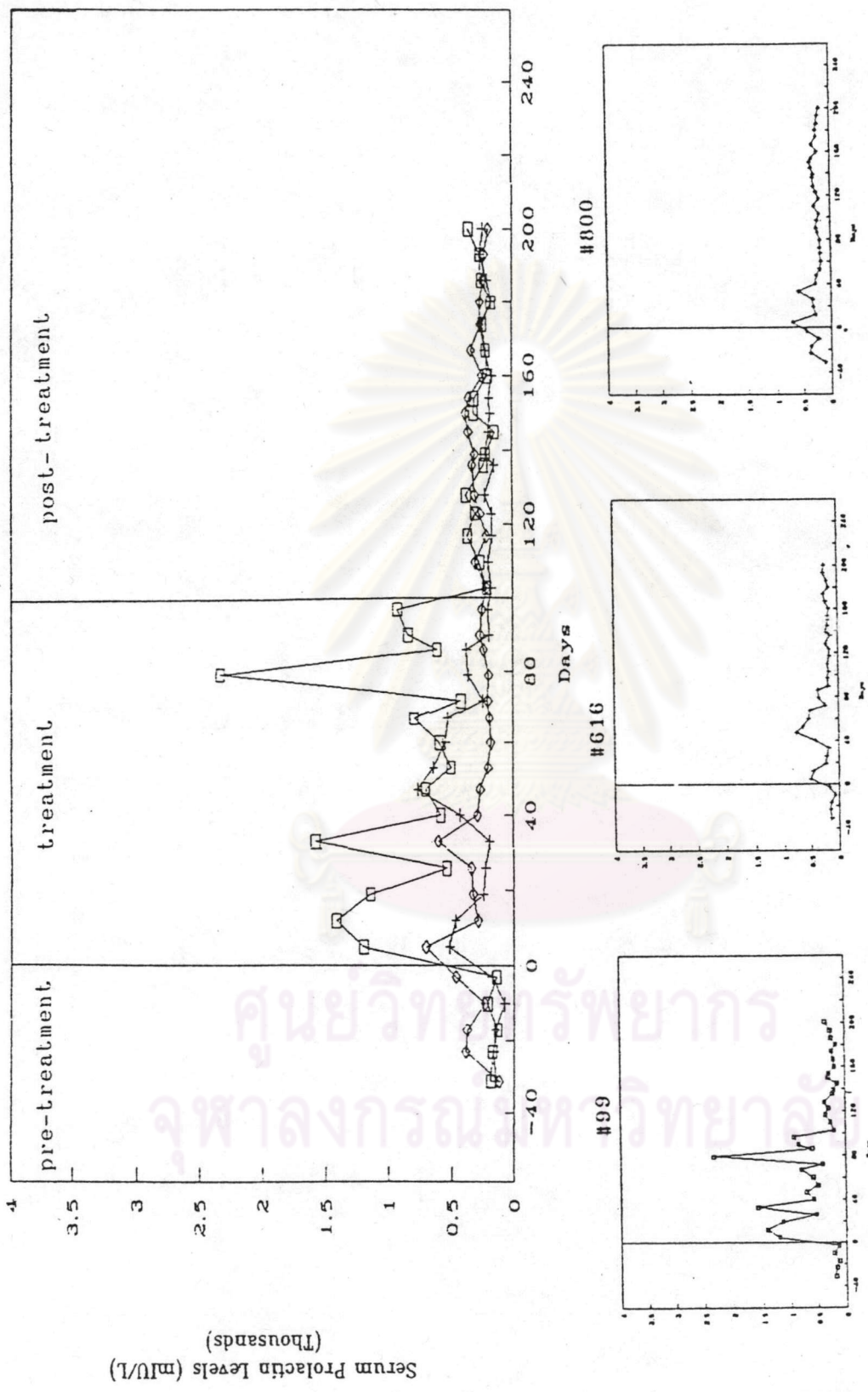


Figure 46 The serum PRL profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.4 mg/kg/day.

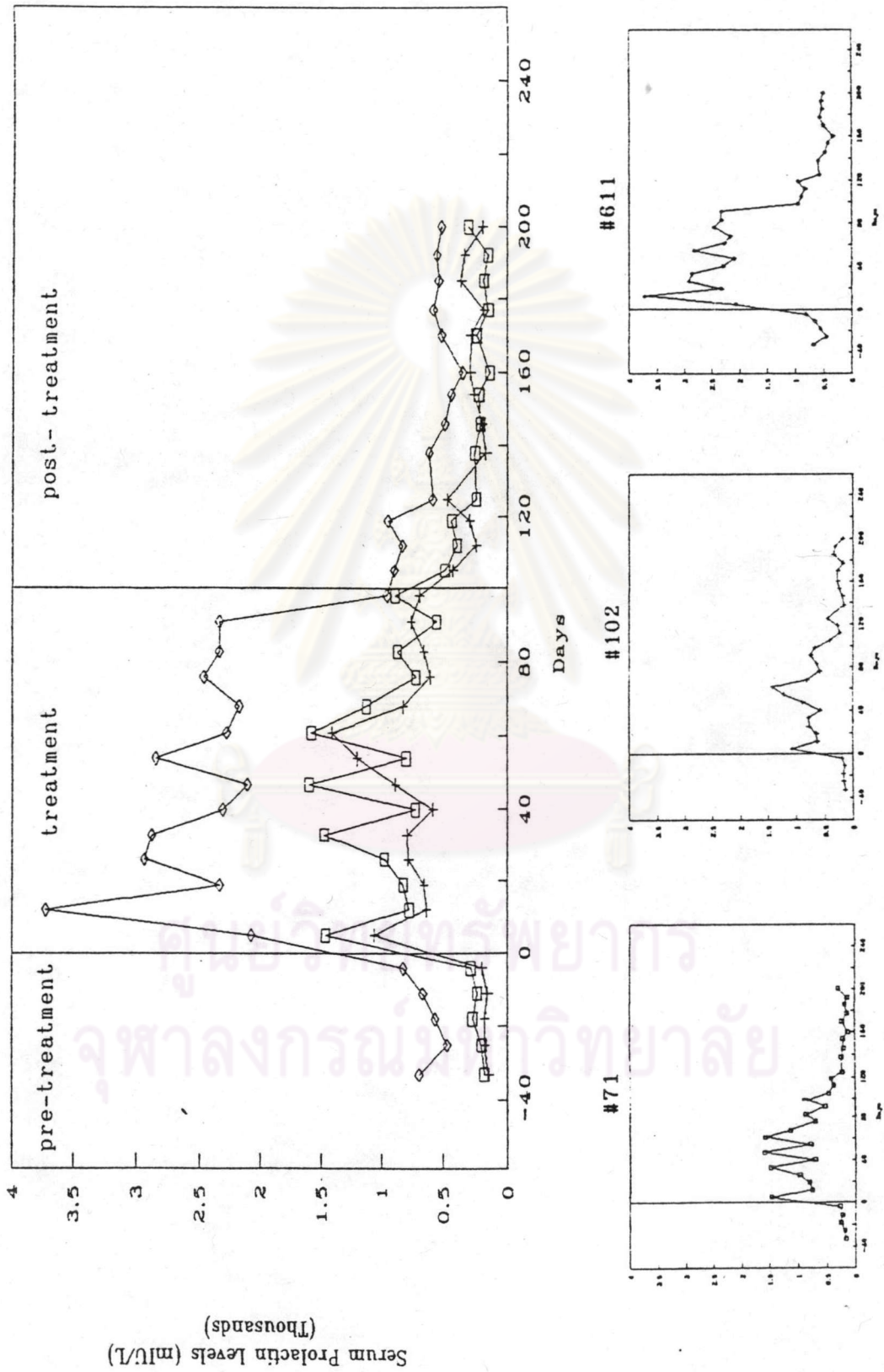


Figure 47 The serum PRL profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.8 mg/kg/day.

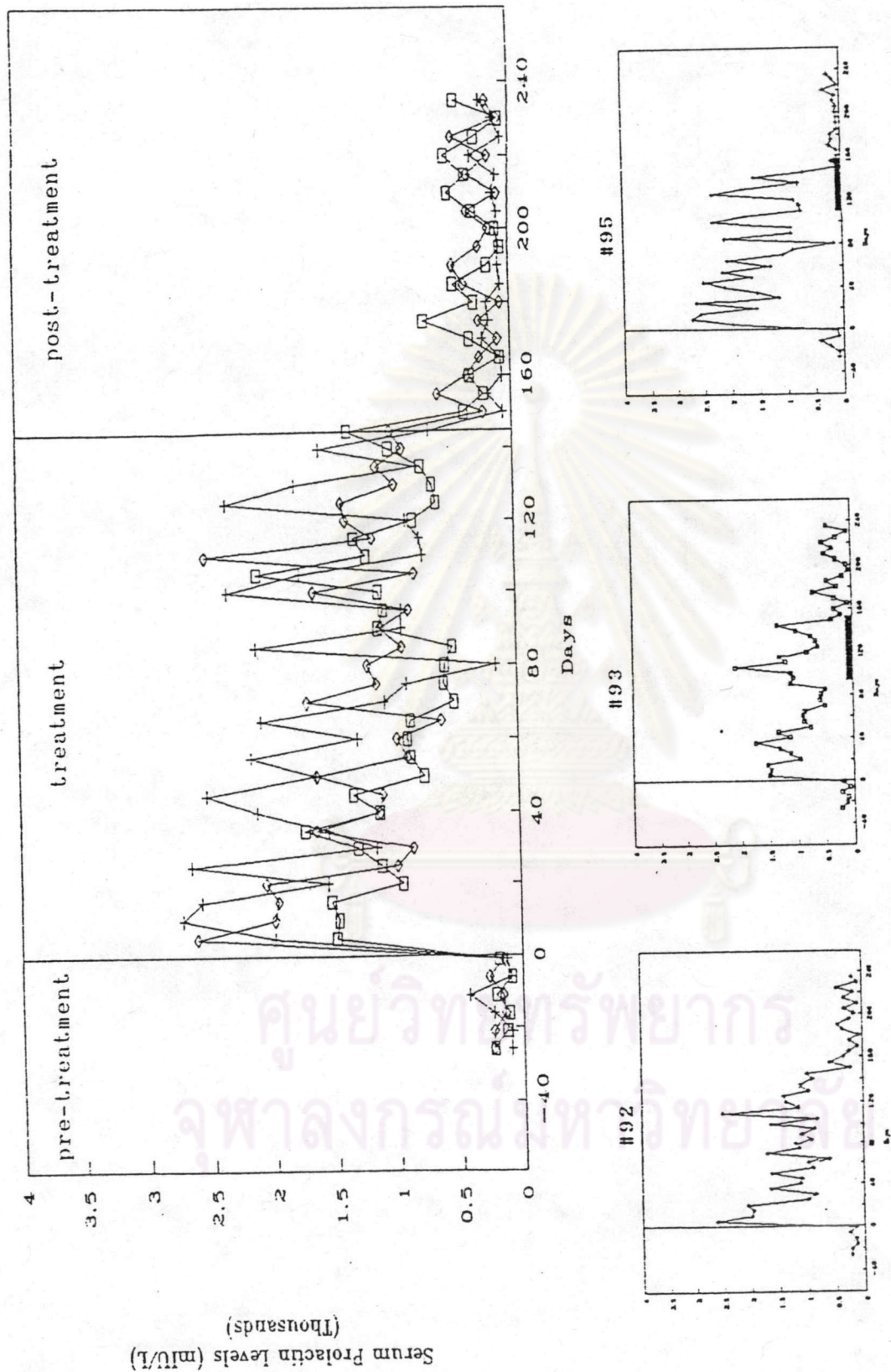


Figure 48 The serum PRL profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 1.6 mg/kg/day., ■ = galactorrhea.

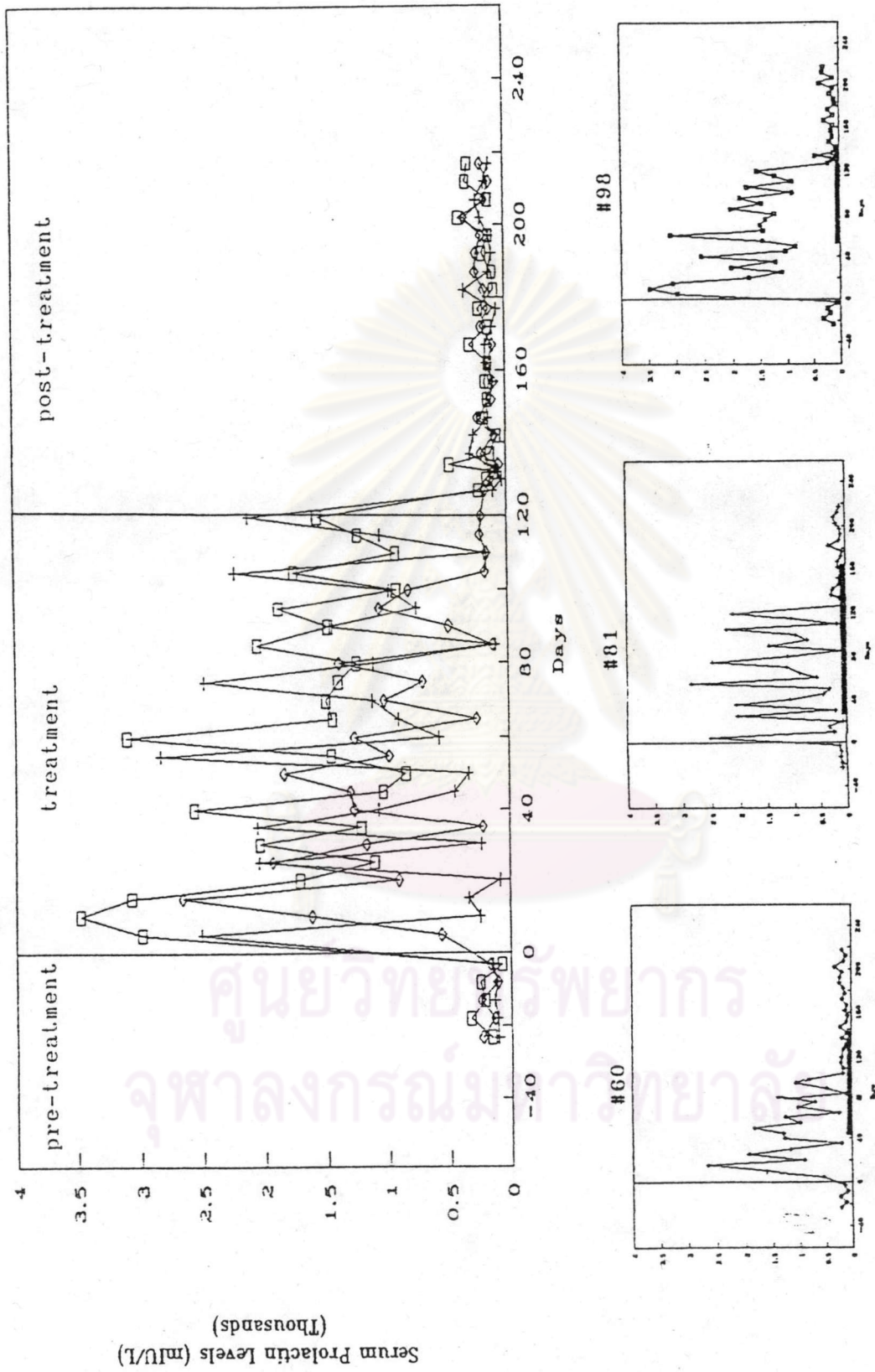


Figure 49 The serum PRL profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 3.2 mg/kg/day, ■ = galactorrhea.

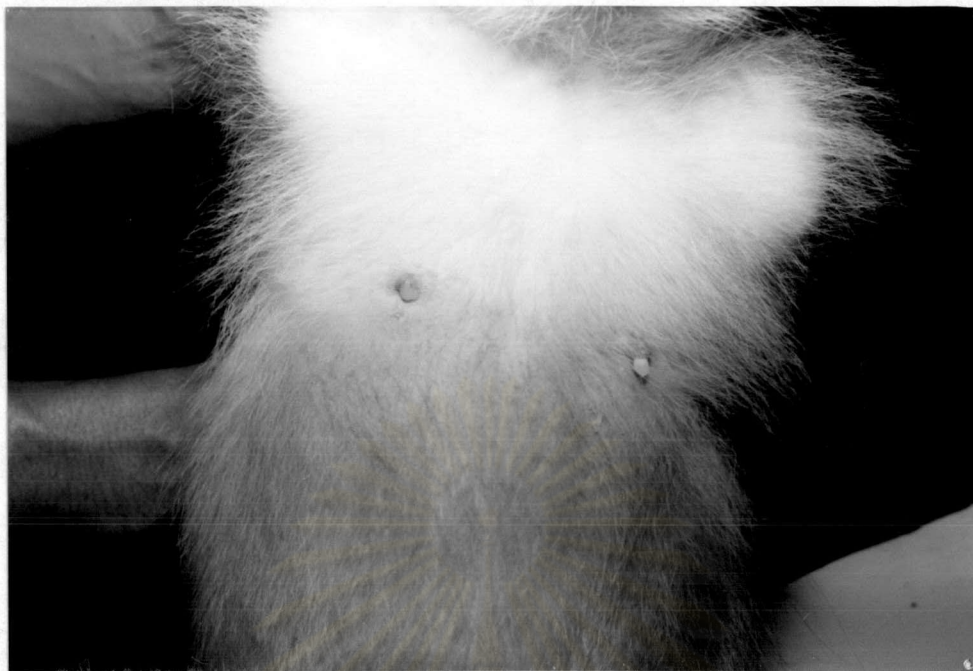


Figure 50. Spontaneous galactorrhea in monkey no.81 during daily treated with 3.2 mg/kg morphine hydrochloride.

Withdrawal of morphine led to prompt decline of serum PRL to their pre-treatment values in all groups.

Daily 0.1-0.2 mg/kg/day morphine treatments had no discernable effect on serum cortisol levels, when these were increased, the level of serum cortisol tended to decline and became clearly below normal control in 1.6 and 3.2 treated groups.

Patterns of serum cortisol levels after morphine withdrawal showed great deal of individual variations among high dosage of morphine treated groups (0.8-3.2 mg/kg/day). Monkeys which have serum cortisol levels decline below pre-treatment values will took several weeks (later than 90 days) to recover, whereas monkeys with minimal changes were unaffected.

The patterns of metabolic turnover of morphine, serum levels of E_2 , P, PRL and cortisol are summarized in figure 57-73.

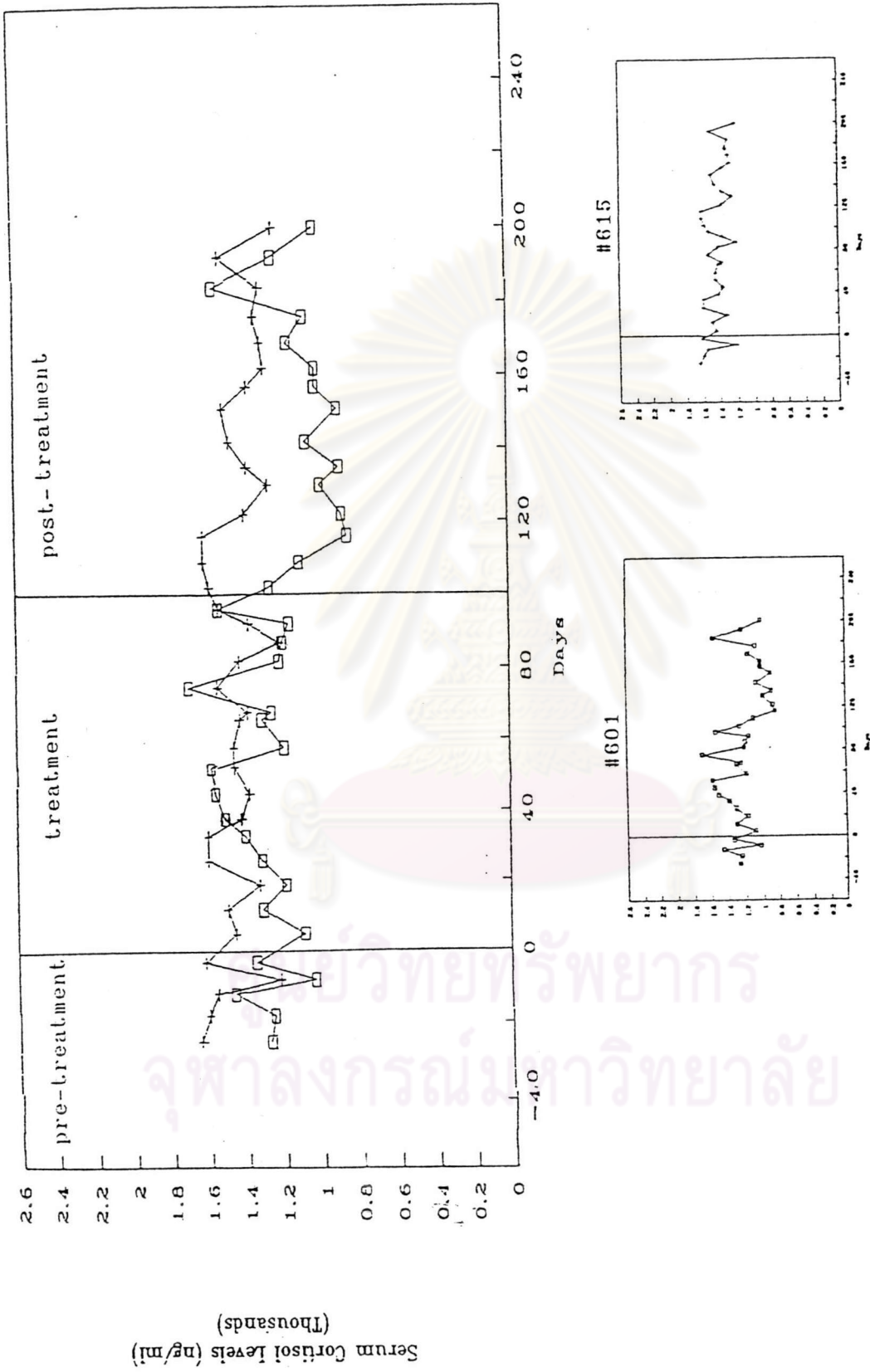


Figure 51 The serum cortisol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.1 mg/kg/day.

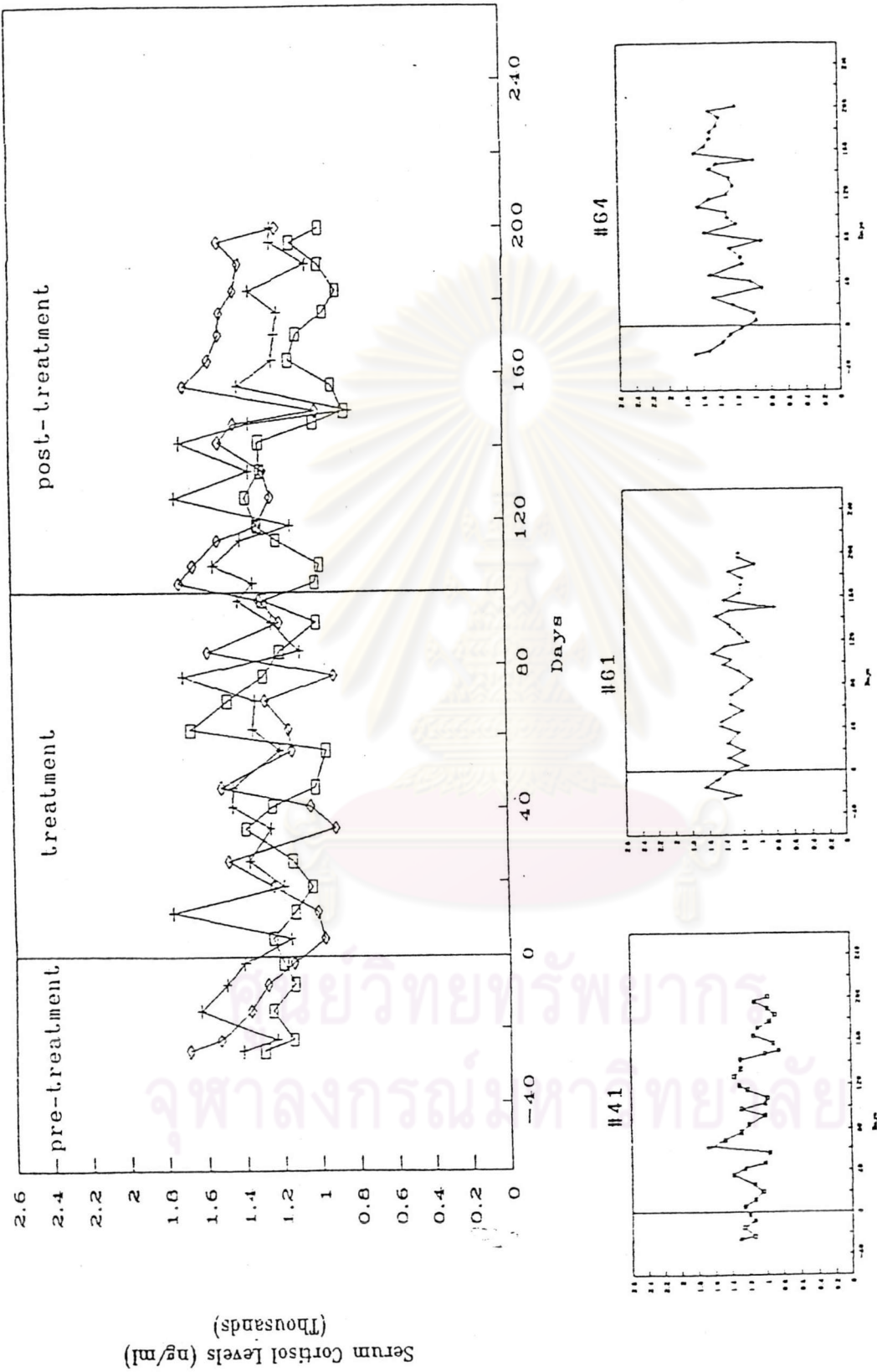


Figure 52 The serum cortisol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.2 mg/kg/day.

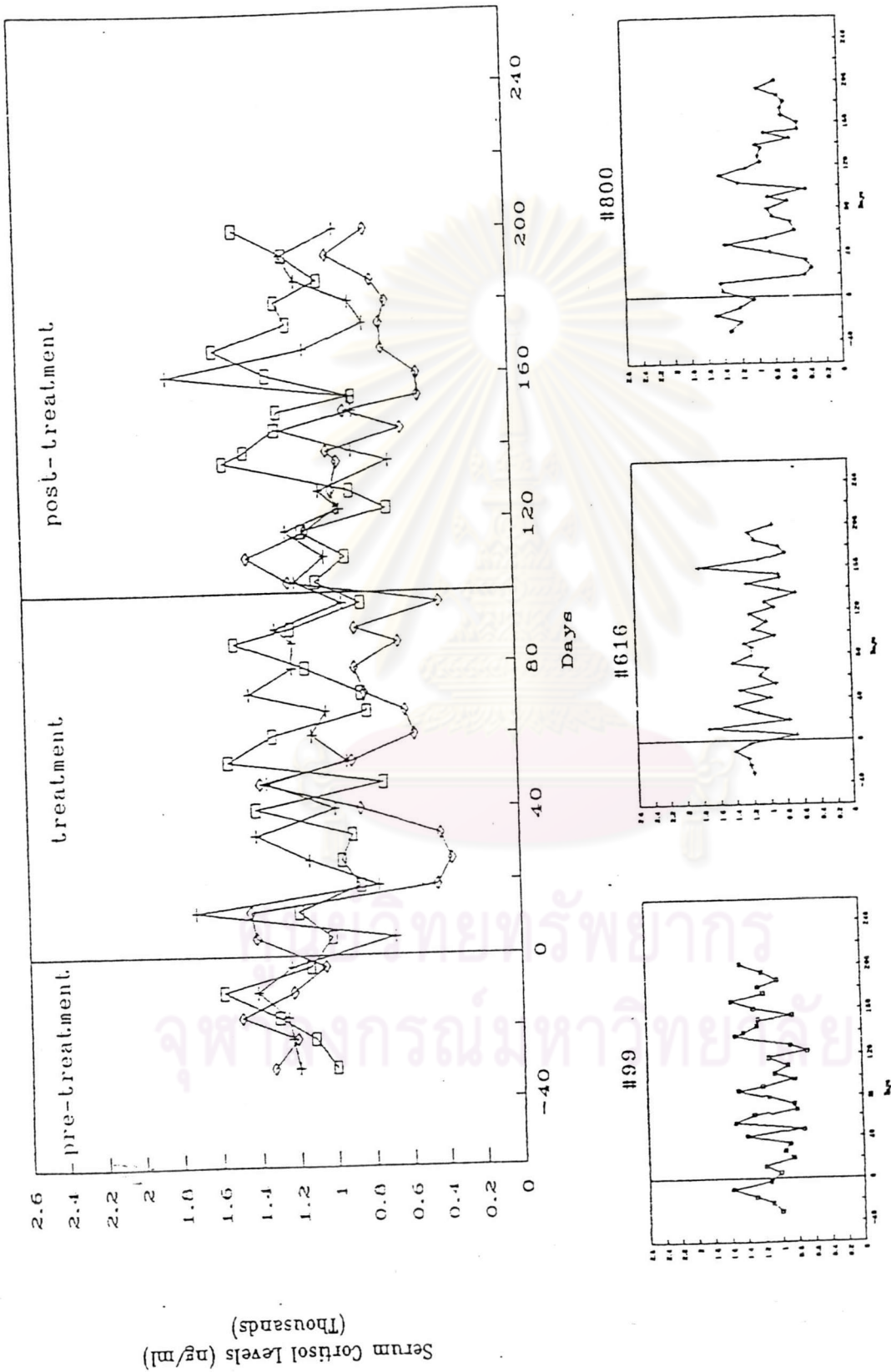


Figure 53 The serum cortisol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.4 mg/kg/day.

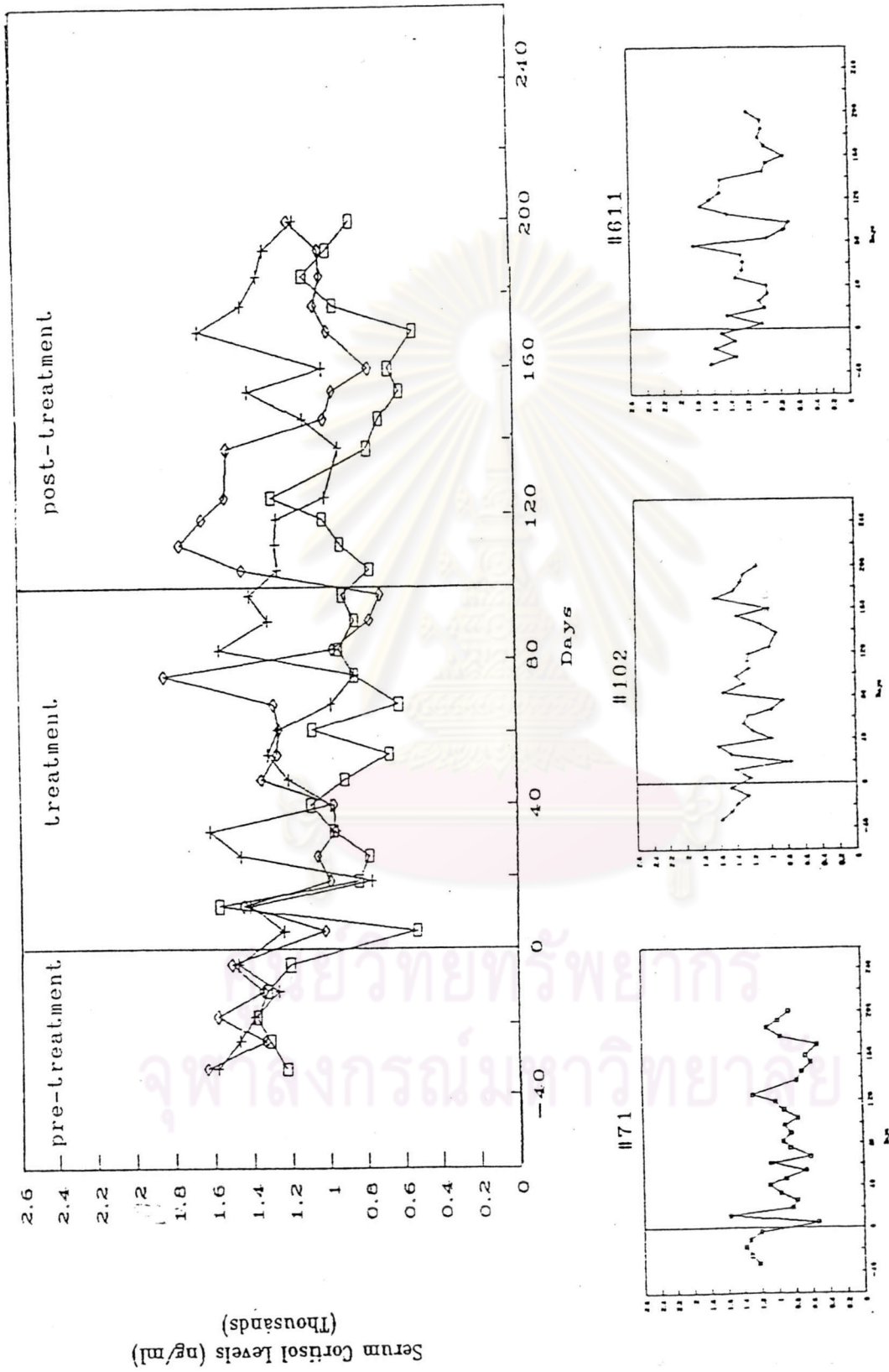


Figure 54 The serum cortisol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 0.8 mg/kg/day.

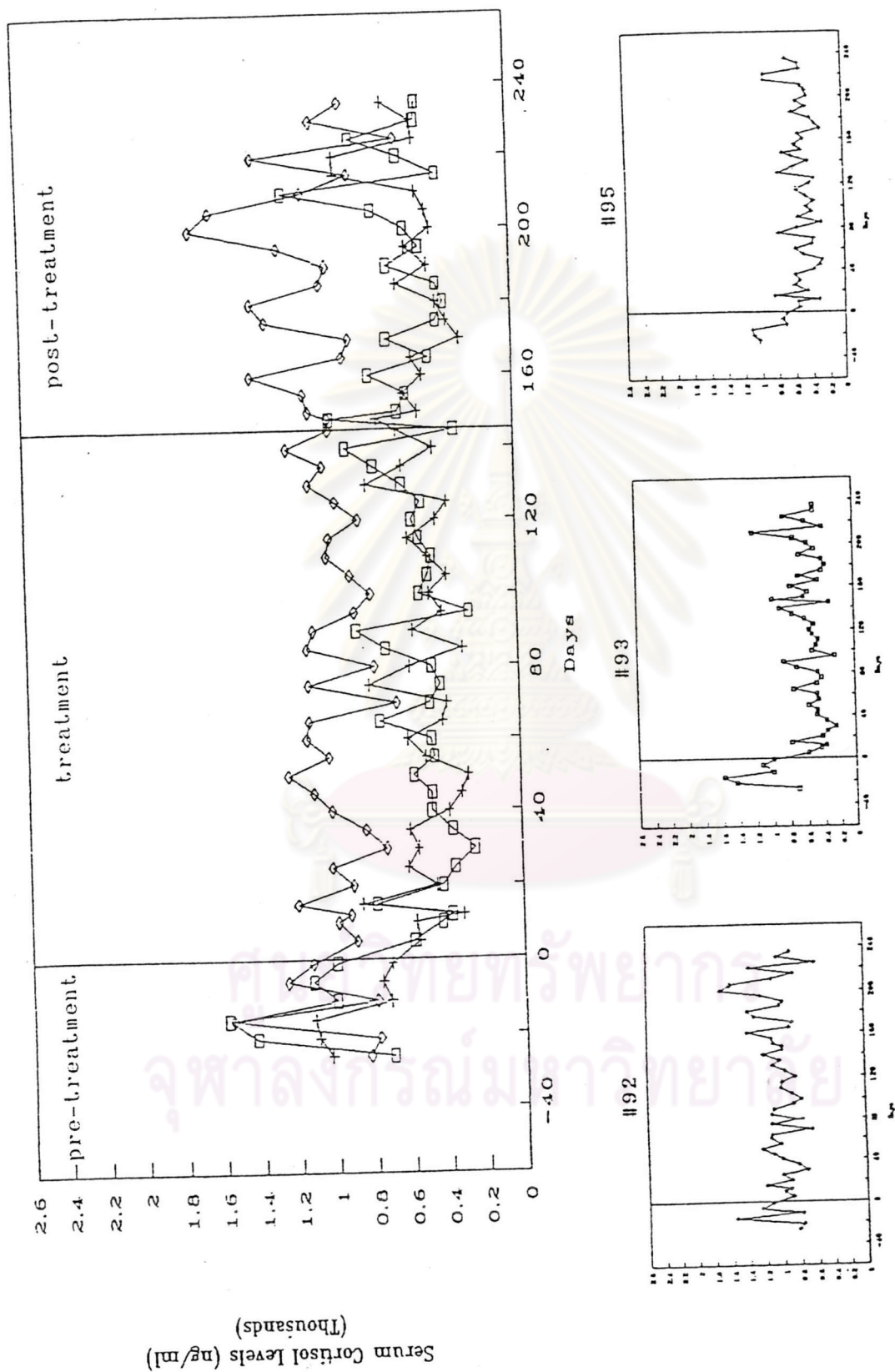


Figure 55 The serum cortisol profiles during morphine hydrochloride treatment and withdrawal periods in the dose of 1.6 mg/kg/day.

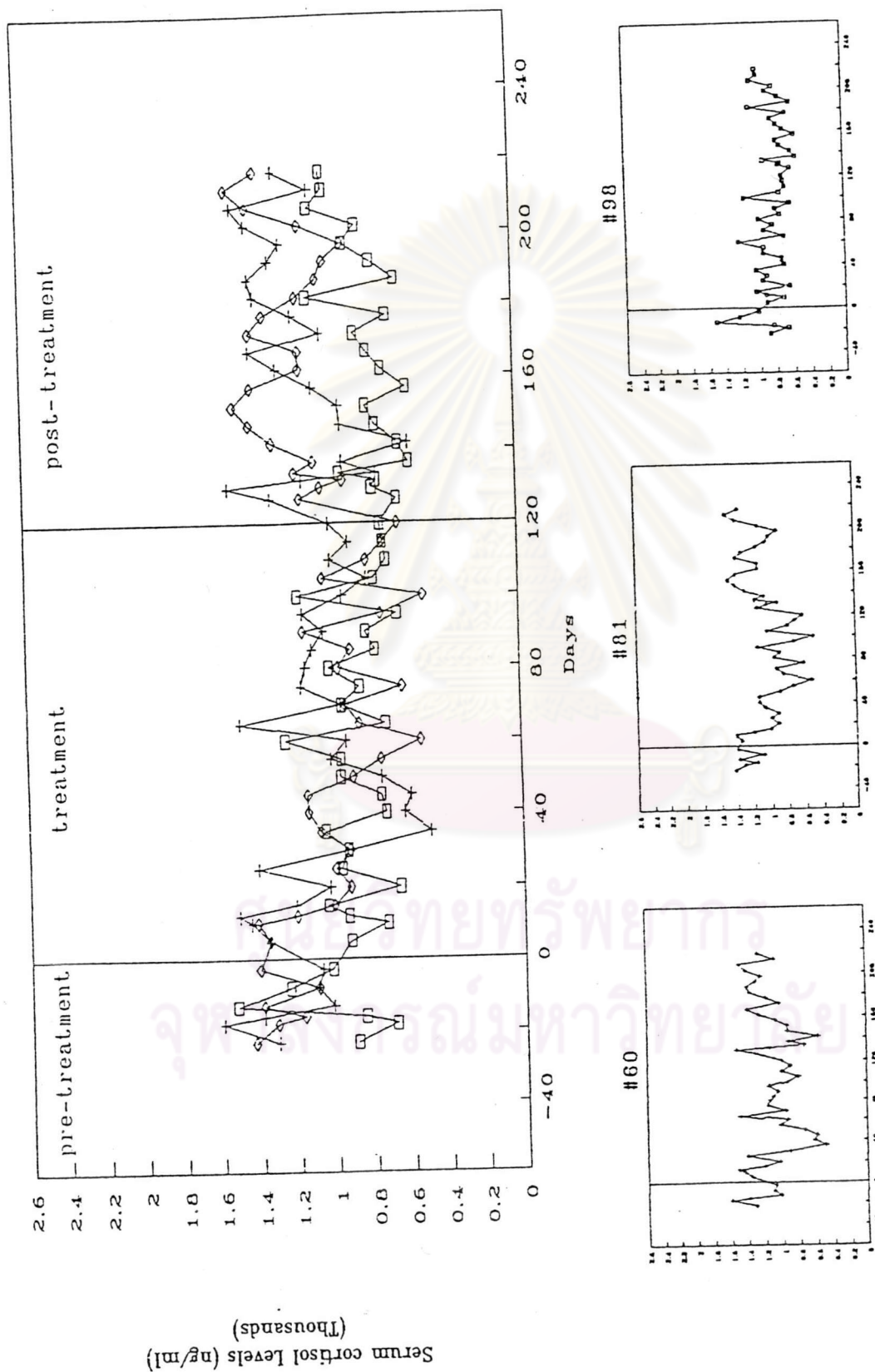


Figure 56 The serum cortisol profiles during morphine hydrochloride treatment, and withdrawal periods in the dose of 3.2 mg/kg/day.

Sexual Behaviours

- Low and Moderate Doses (0.1-0.8 mg/kg/day)

There were no apparent behavioural changes observed in female monkeys treated with 0.1 mg/kg/day morphine hydrochloride ($p > 0.05$). Behaviours are present as following.

a). Approach

One each out of monkeys treated with 0.2, 0.4 and 0.8 mg/kg/day morphine showed significant decline in frequency of the approach to the male ($p < 0.05$) the first treatment cycle.

None of female 0.2 mg/kg/day treated monkeys showed significant alteration in frequency when compare between pre-treatment cycle and immediate treatment cycle. However one out of three monkeys treated with 0.4-0.8 mg/kg/day morphine treated group showed significant decline ($p < 0.05$).

b). Presentation

Only two out of three monkeys treated with 0.4 mg/kg/day morphine showed significant decline in frequency of presentation to the male ($p < 0.05$). The other monkey in the group failed to show presentation during the period of study. Similar situation were also found in all monkeys treated with 0.8 mg/kg/day morphine .

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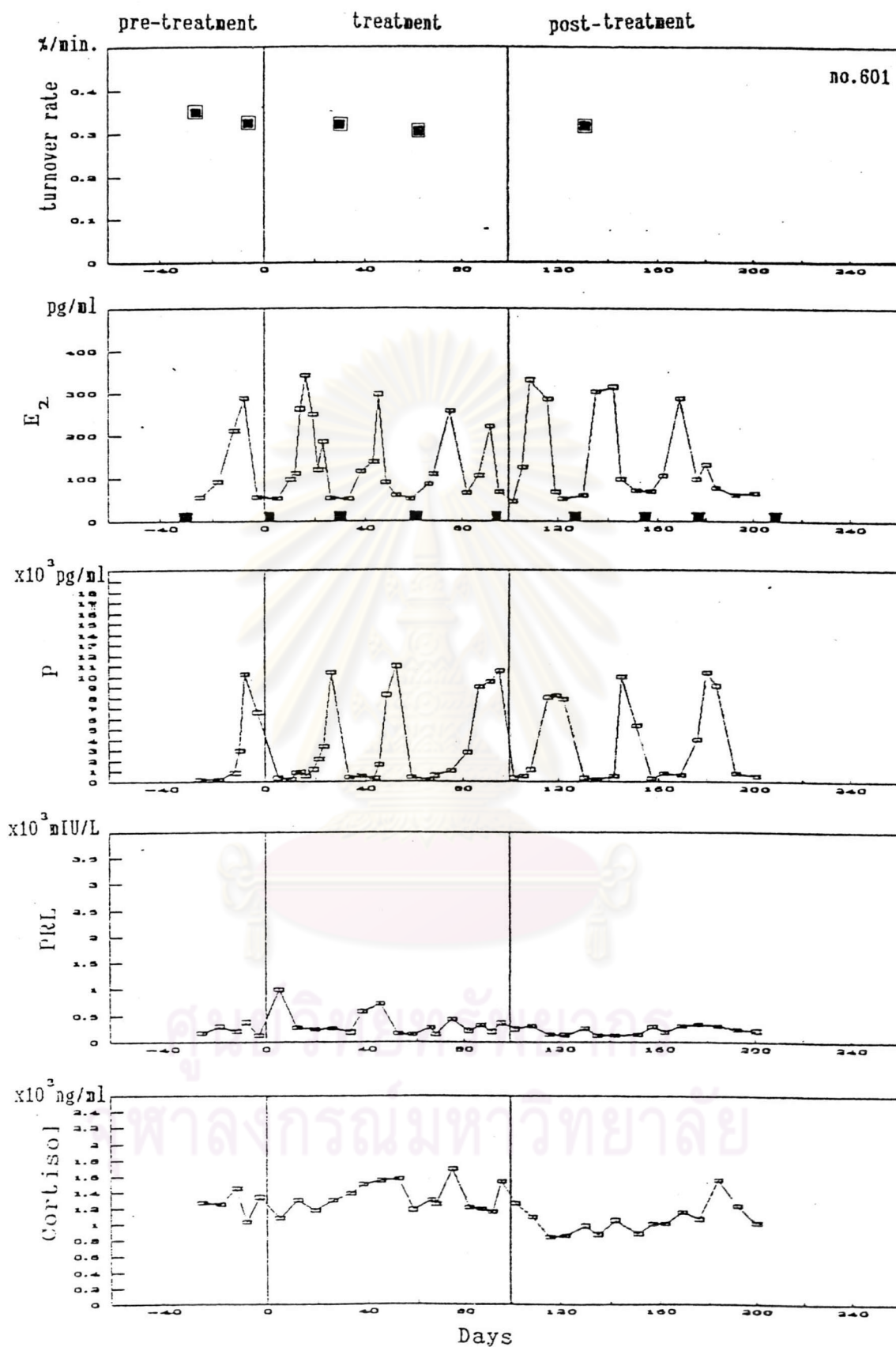


Figure 57 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol and menstrual bleeding (-) in monkey no.601 of 0.1 mg/kg/day morphine treatment group.

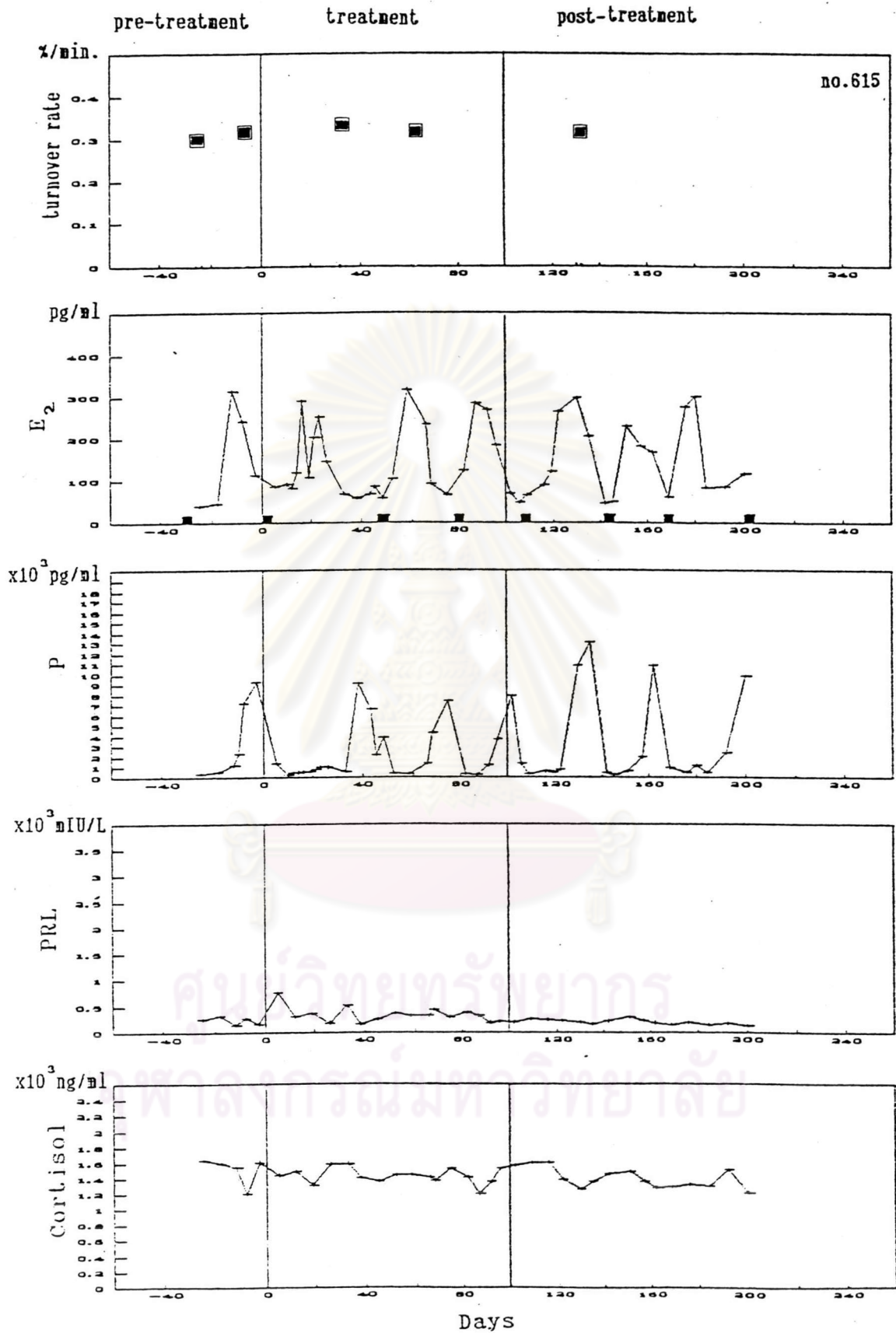


Figure 58 Turnover rate of morphine, serum levels of E_2 , P, PRL, cortisol and menstrual bleeding (-) in monkey no.615 of 0.1 mg/kg/day morphine treatment group.

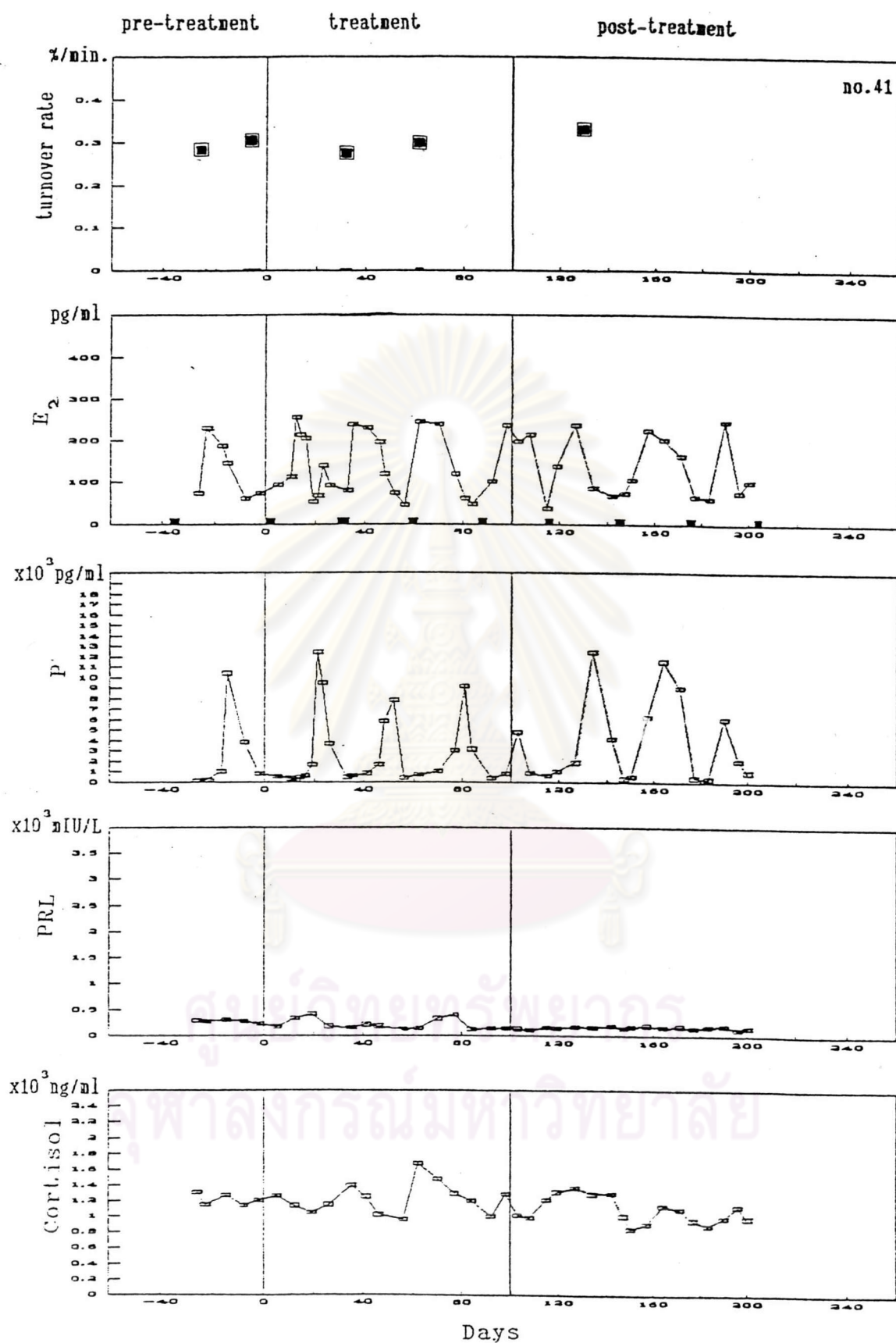


Figure 59 Turnover rate of morphine, serum levels of E_2 , P, PRL, cortisol and menstrual bleeding (=) in monkey no.41 of 0.2 mg/kg/day morphine treatment group.

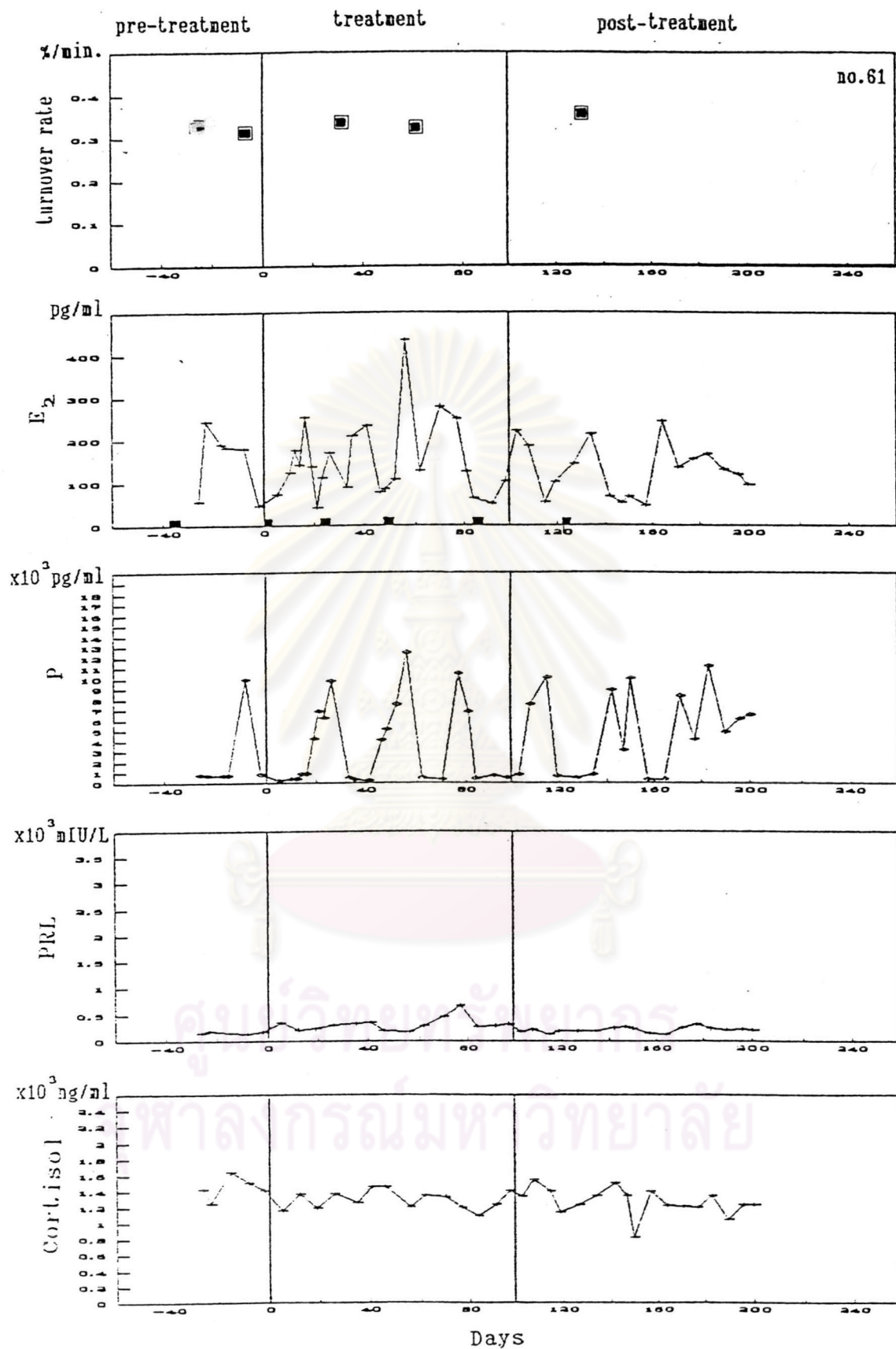


Figure 60 Turnover rate of morphine, serum levels of E_2 , P, PRL, cortisol and menstrual bleeding (-) in monkey no.61 of 0.2 mg/kg/day morphine treatment group.

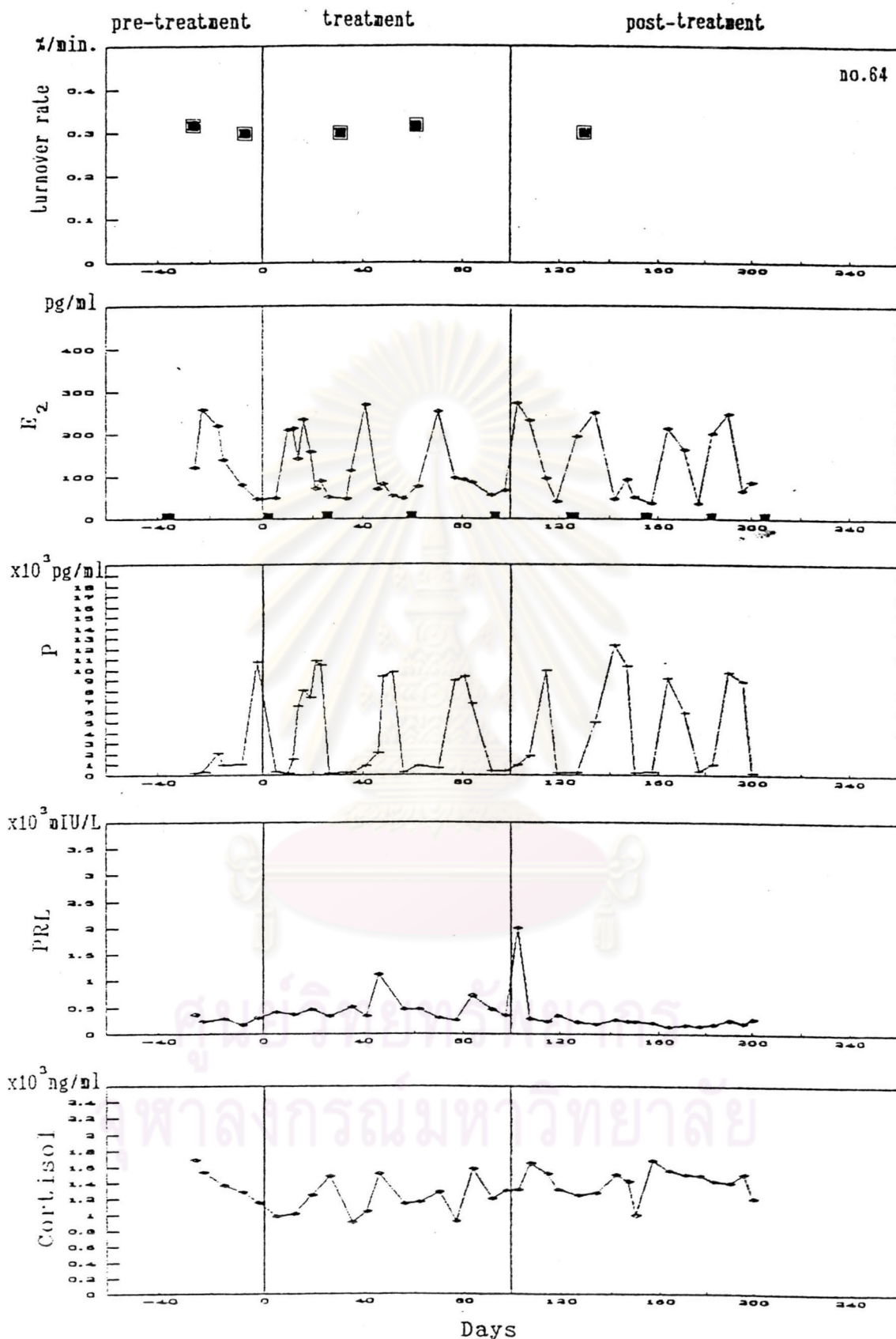


Figure 61 Turnover rate of morphine, serum levels of E_2 , P, PRL, cortisol and menstrual bleeding (=) in monkey no.64 of 0.2 mg/kg/day morphine treatment group.

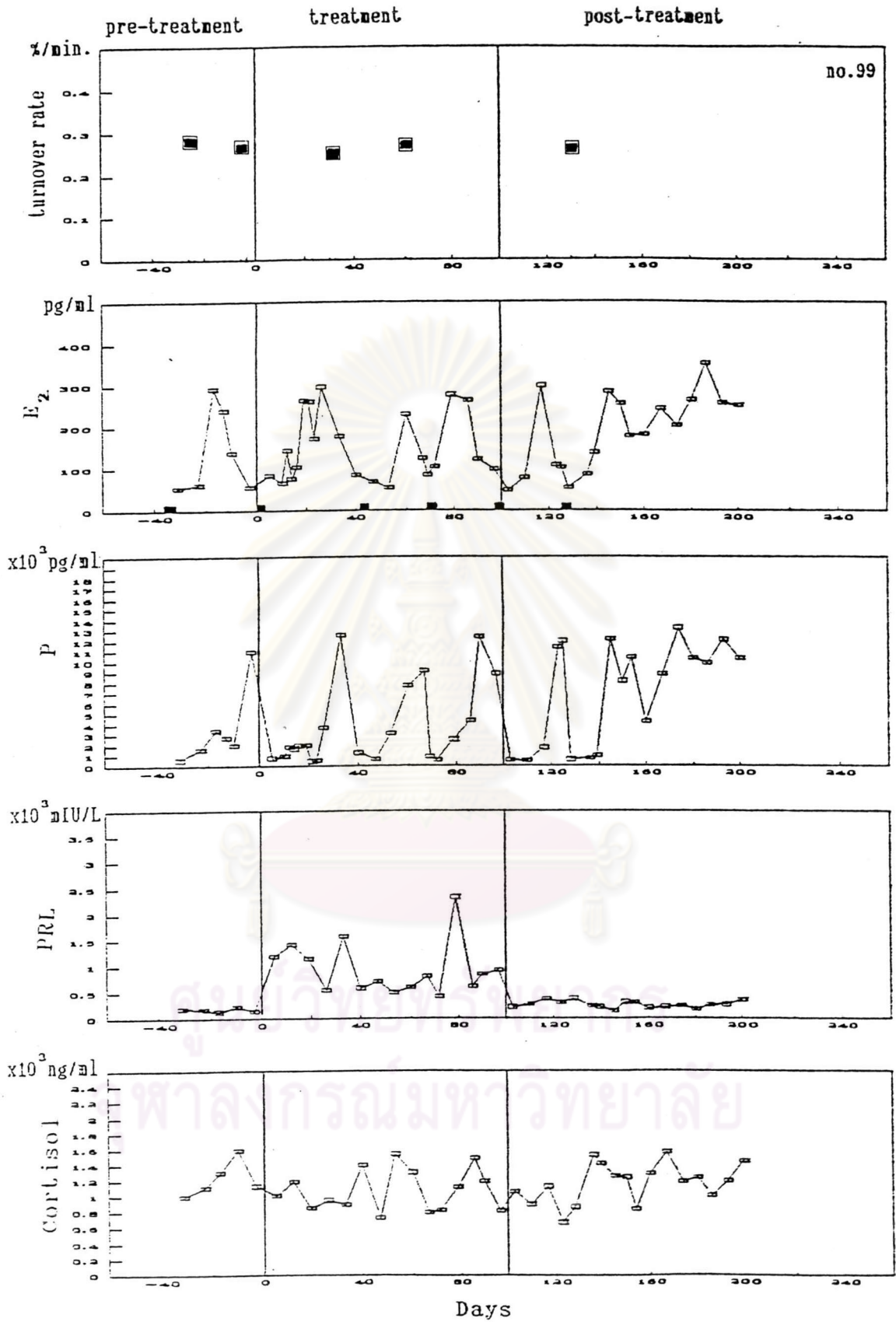


Figure 62 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol and menstrual bleeding (=) in monkey no.99 of 0.4 mg/kg/day morphine treatment group.

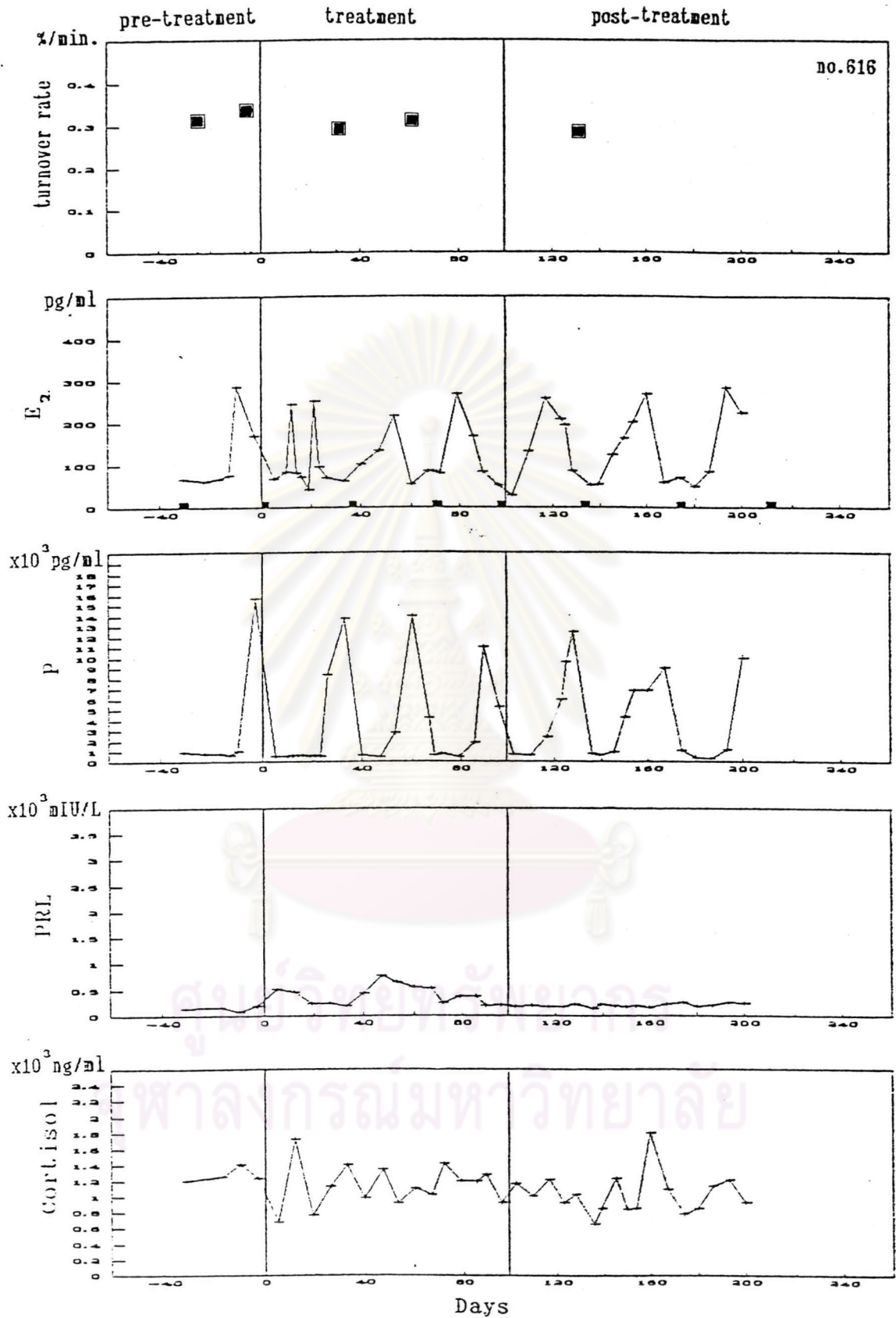


Figure 63 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol and menstrual bleeding (-) in monkey no.616 of 0.4 mg/kg/day morphine treatment group.

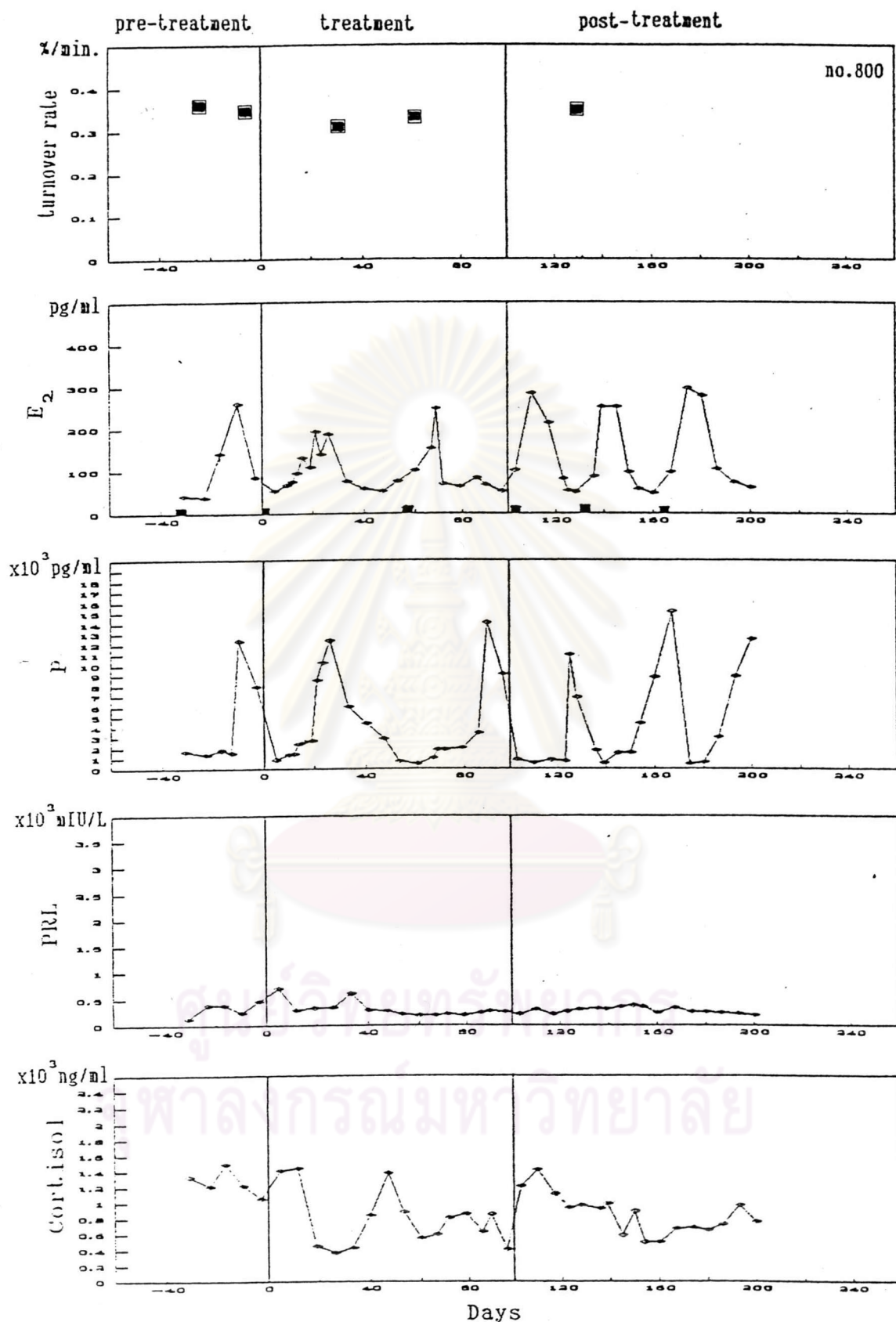


Figure 64 Turnover rate of morphine, serum levels of E_2 , P, PRL, cortisol and menstrual bleeding (-) in monkey no.800 of 0.4 mg/kg/day morphine treatment group.

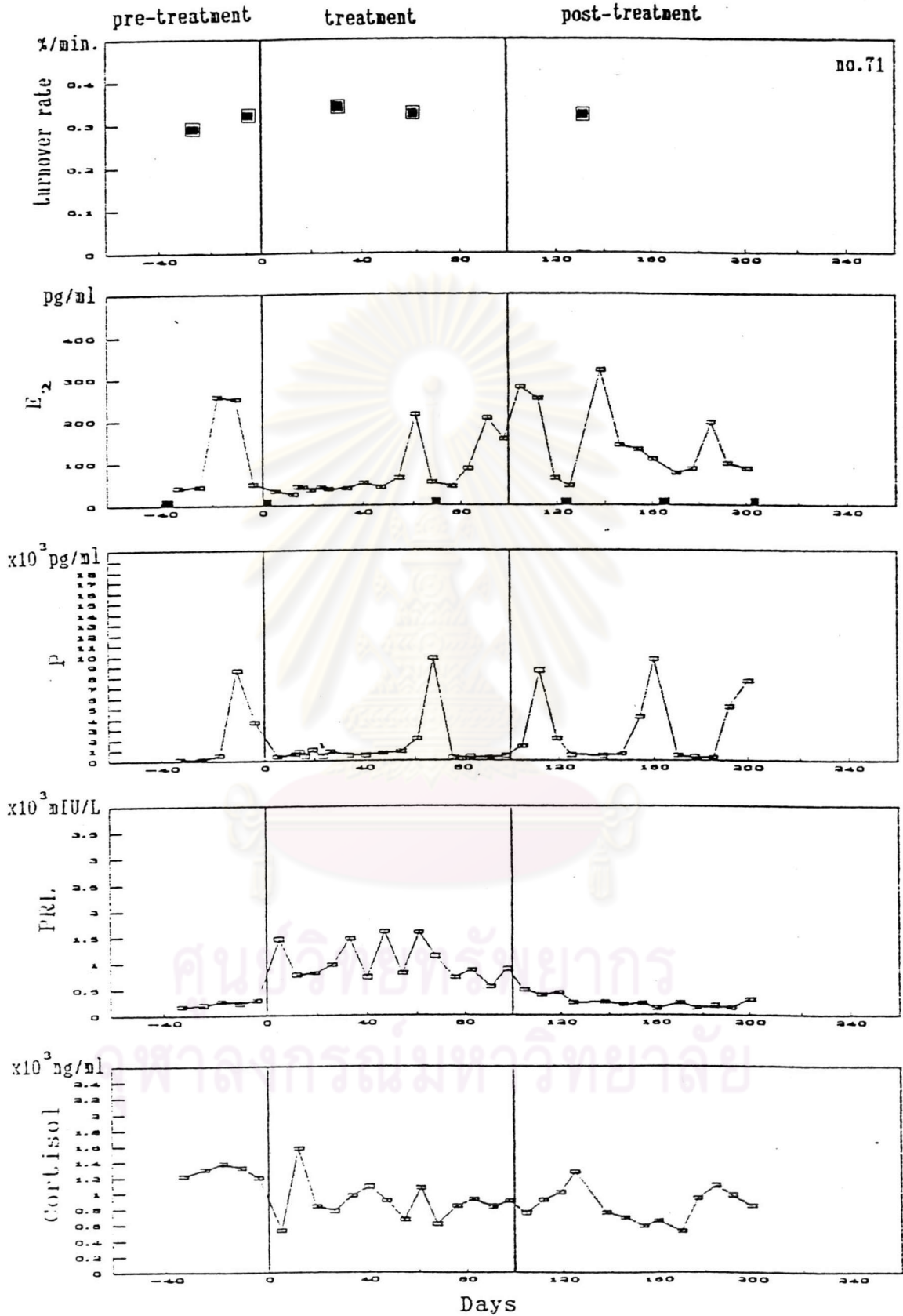


Figure 65 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol and menstrual bleeding (■) in monkey no.71 of 0.8 mg/kg/day morphine treatment group.

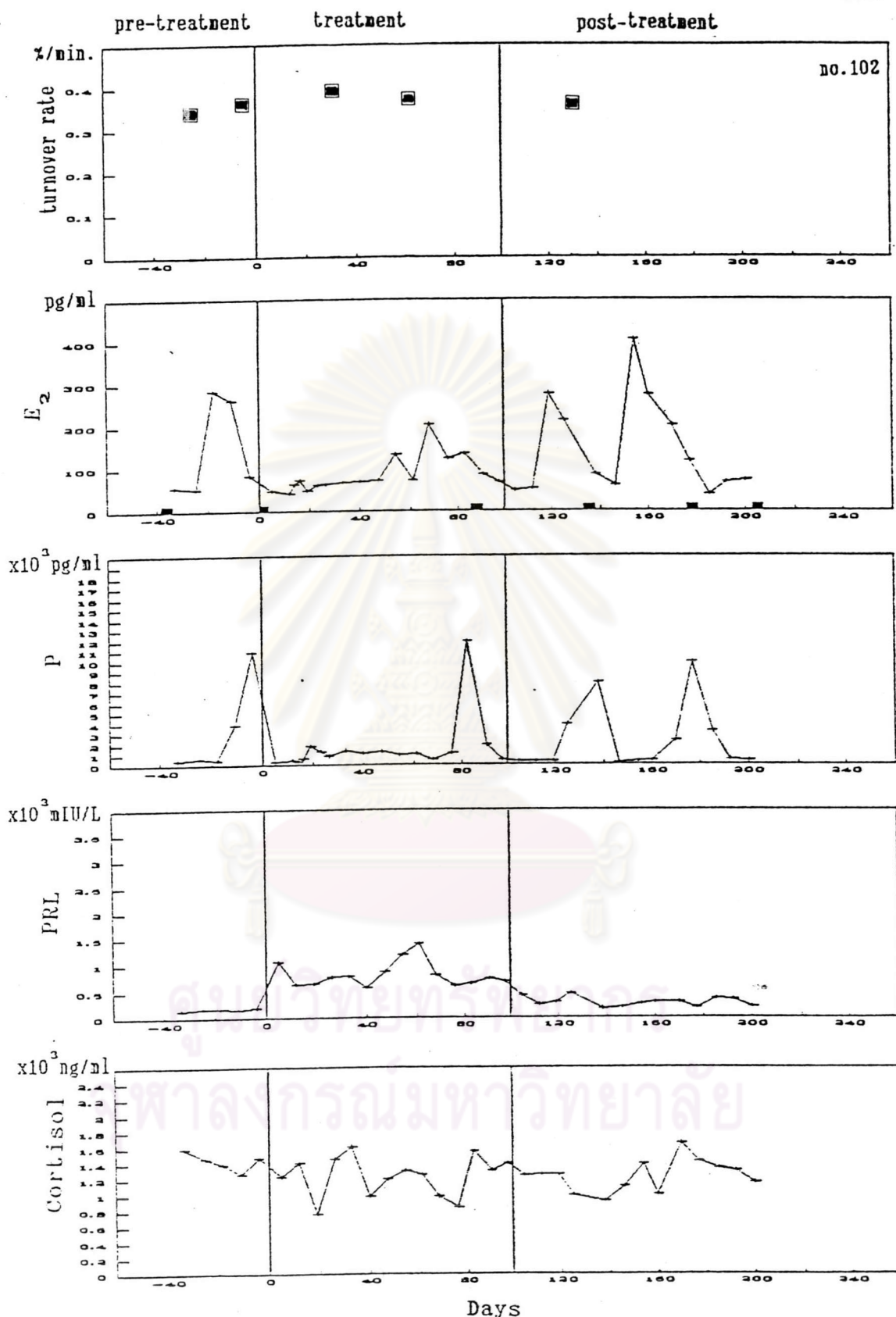


Figure 66 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol and menstrual bleeding (-) in monkey no.102 of 0.8 mg/kg/day morphine treatment group.

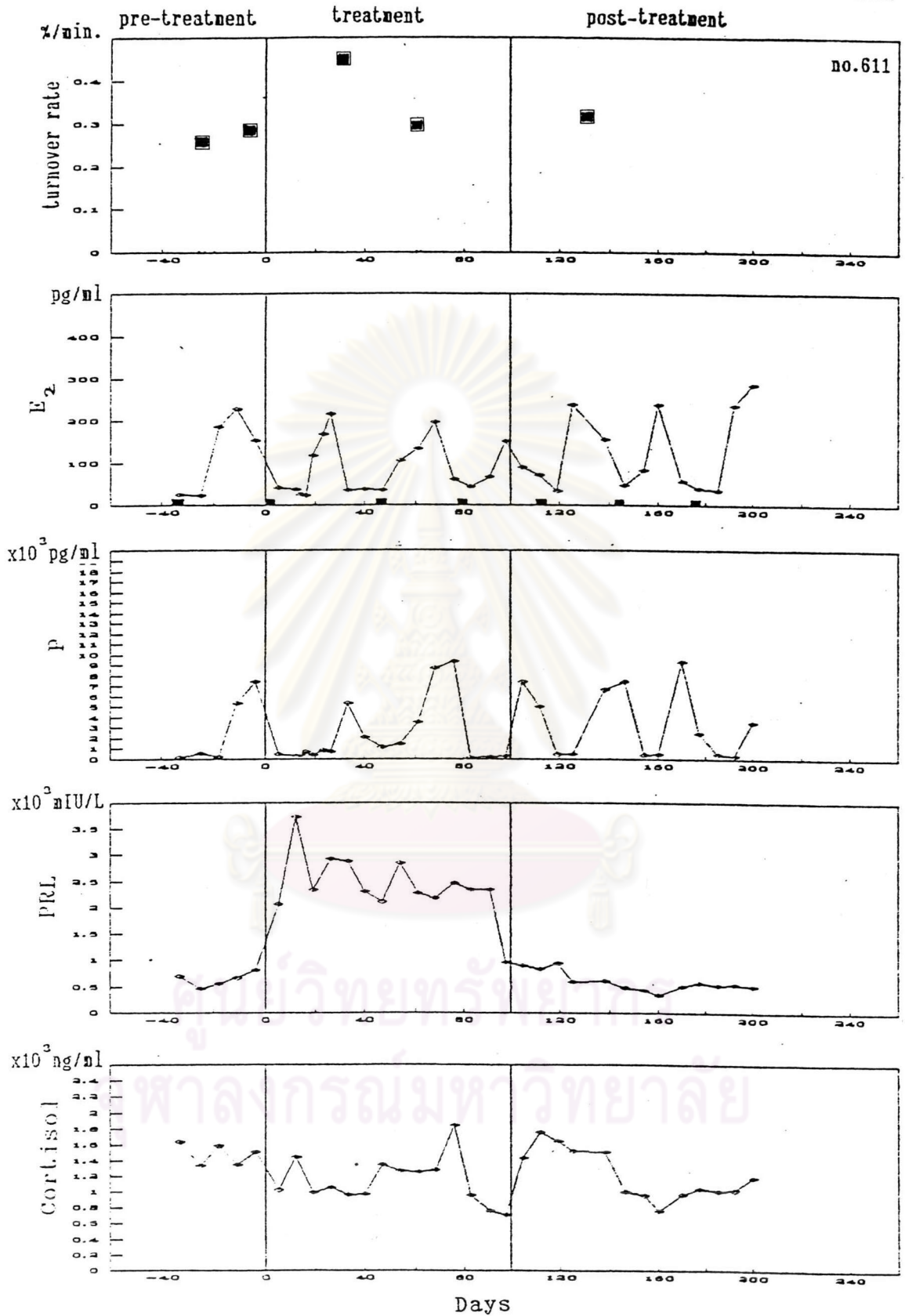


Figure 67 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol and menstrual bleeding (-) in monkey no.611 of 0.8 mg/kg/day morphine treatment group.

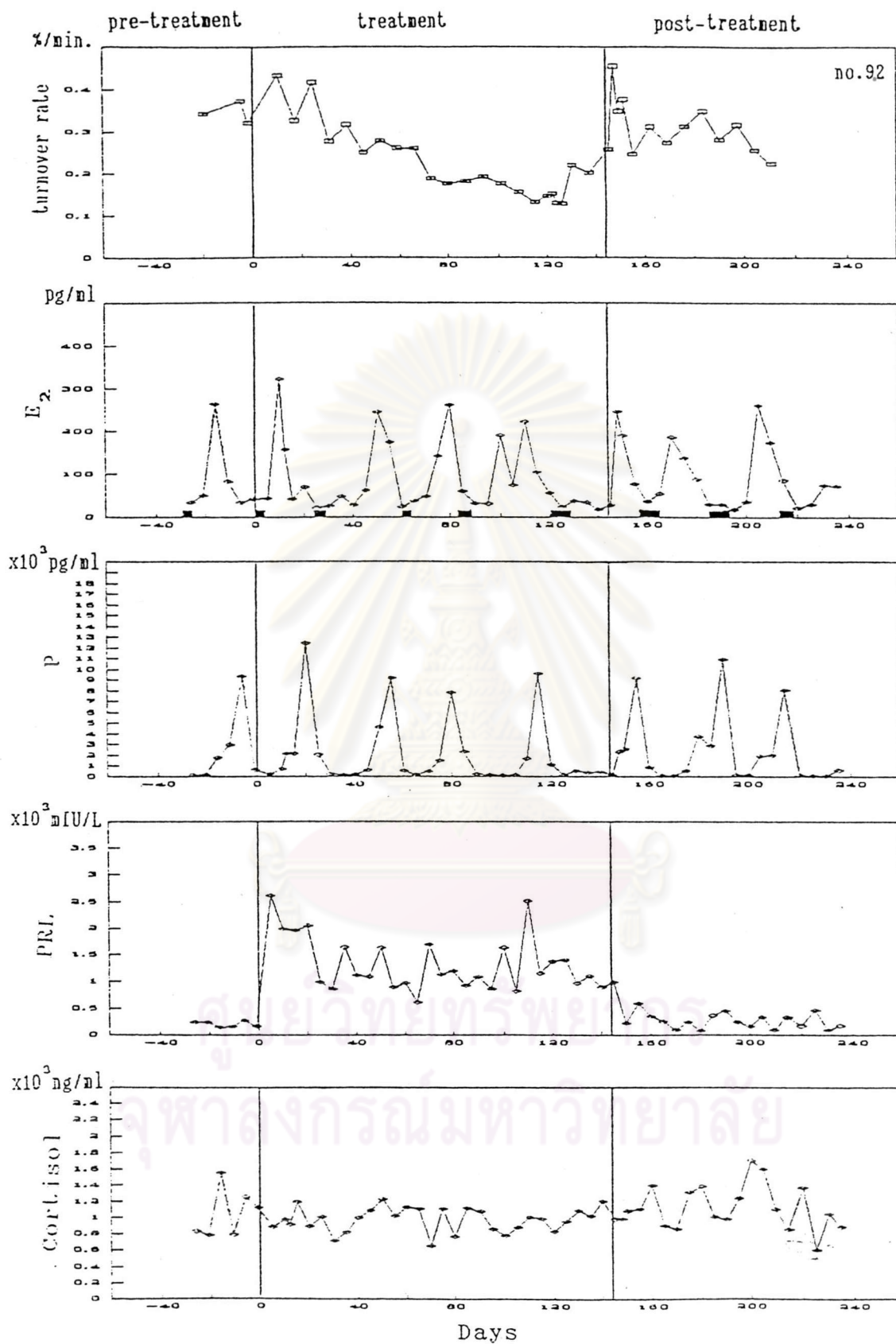


Figure 68 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol and menstrual bleeding (-) in monkey no.92 of 1.6 mg/kg/day morphine treatment group.

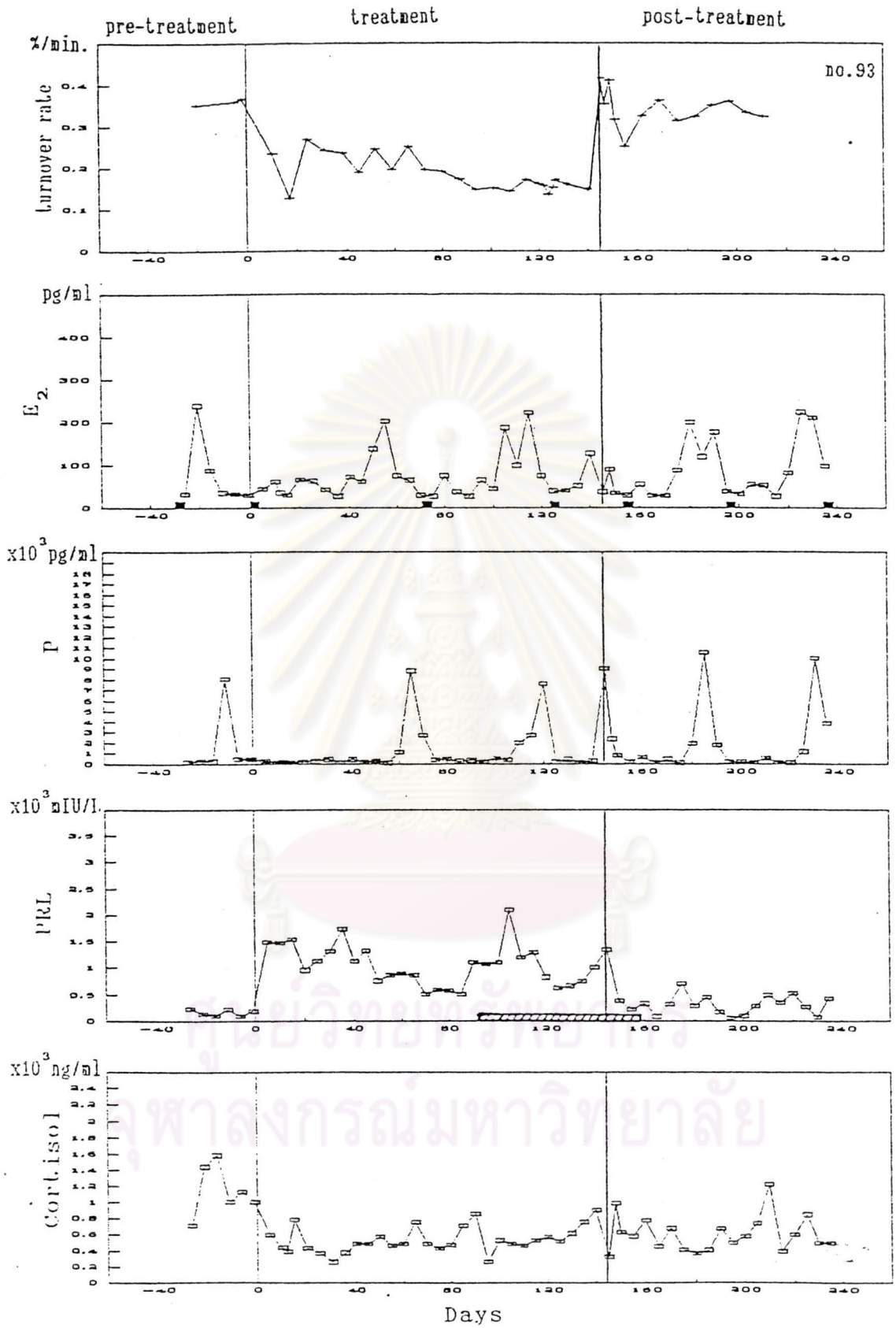


Figure 69 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol, galactorrhea(▨) and menstrual bleeding (-) in monkey no.93 of 1.6 mg/kg/day morphine treatment group.

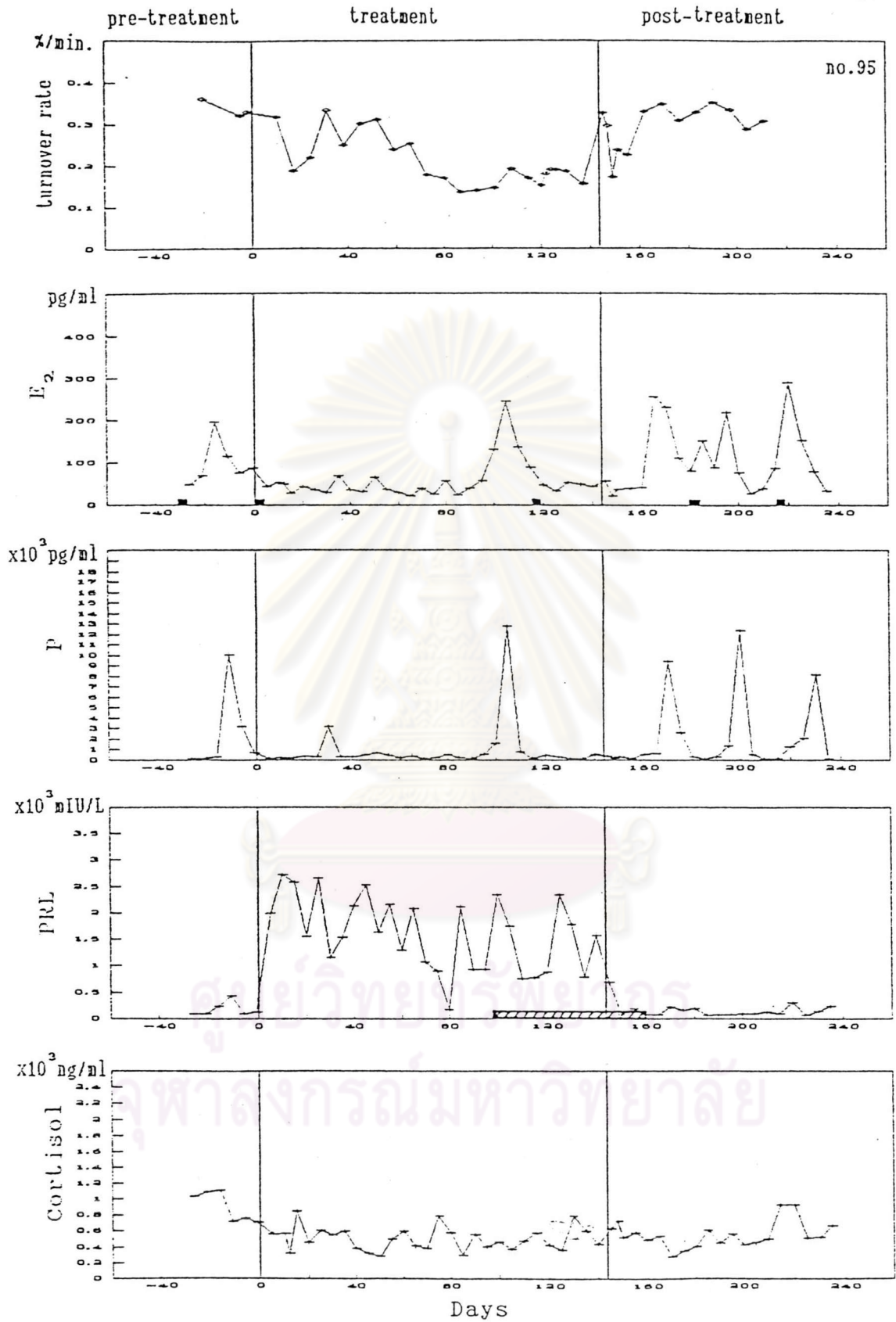


Figure 70 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol, galactorrhea(▨) and menstrual bleeding (▬) in monkey no.95 of 1.6 mg/kg/day morphine treatment group.

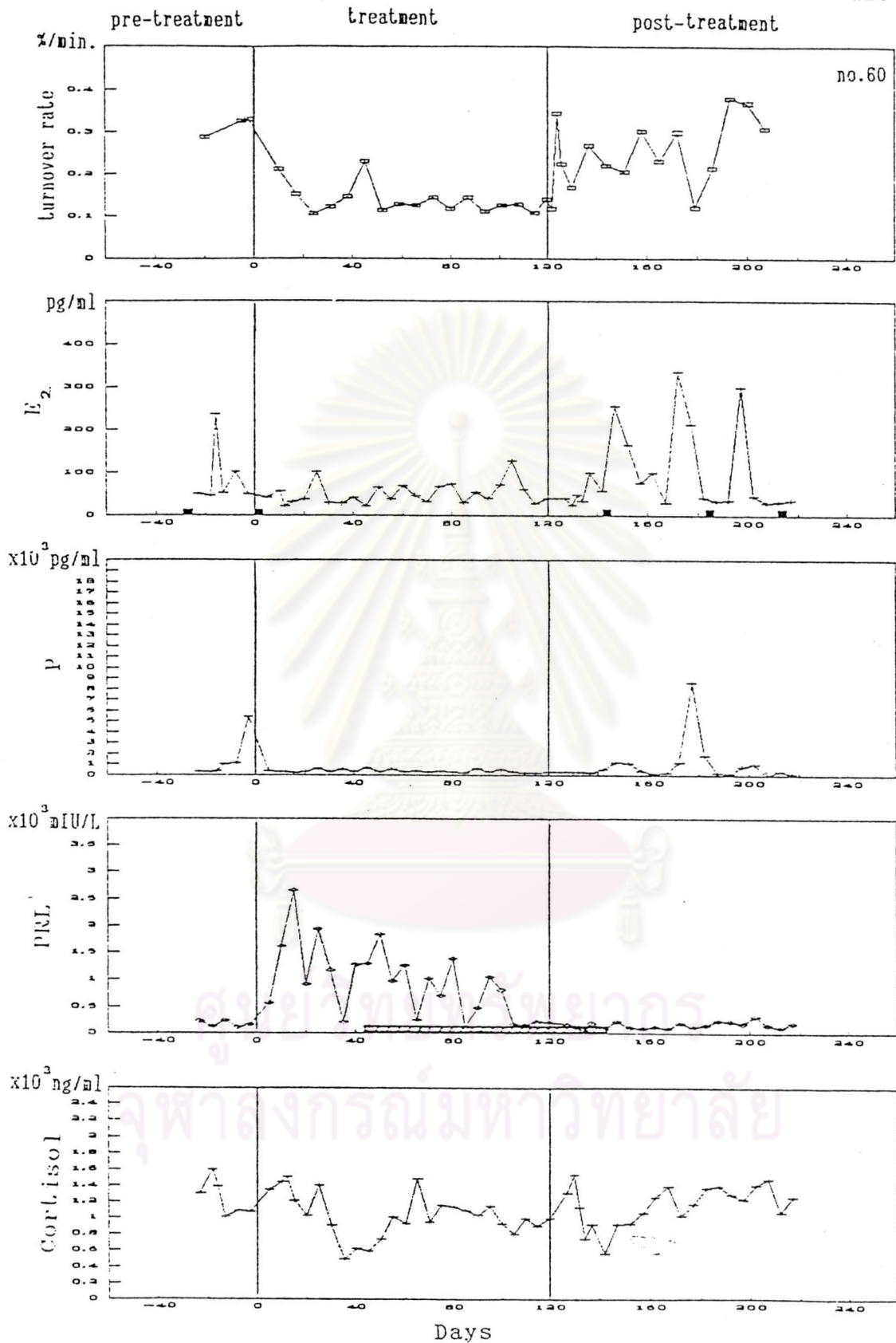


Figure 71 Turnover rate of morphine, serum levels of E_2 , P, PRL, cortisol, galactorrhea(\square) and menstrual bleeding (-) in monkey no.60 of 3.2 mg/kg/day morphine treatment group.

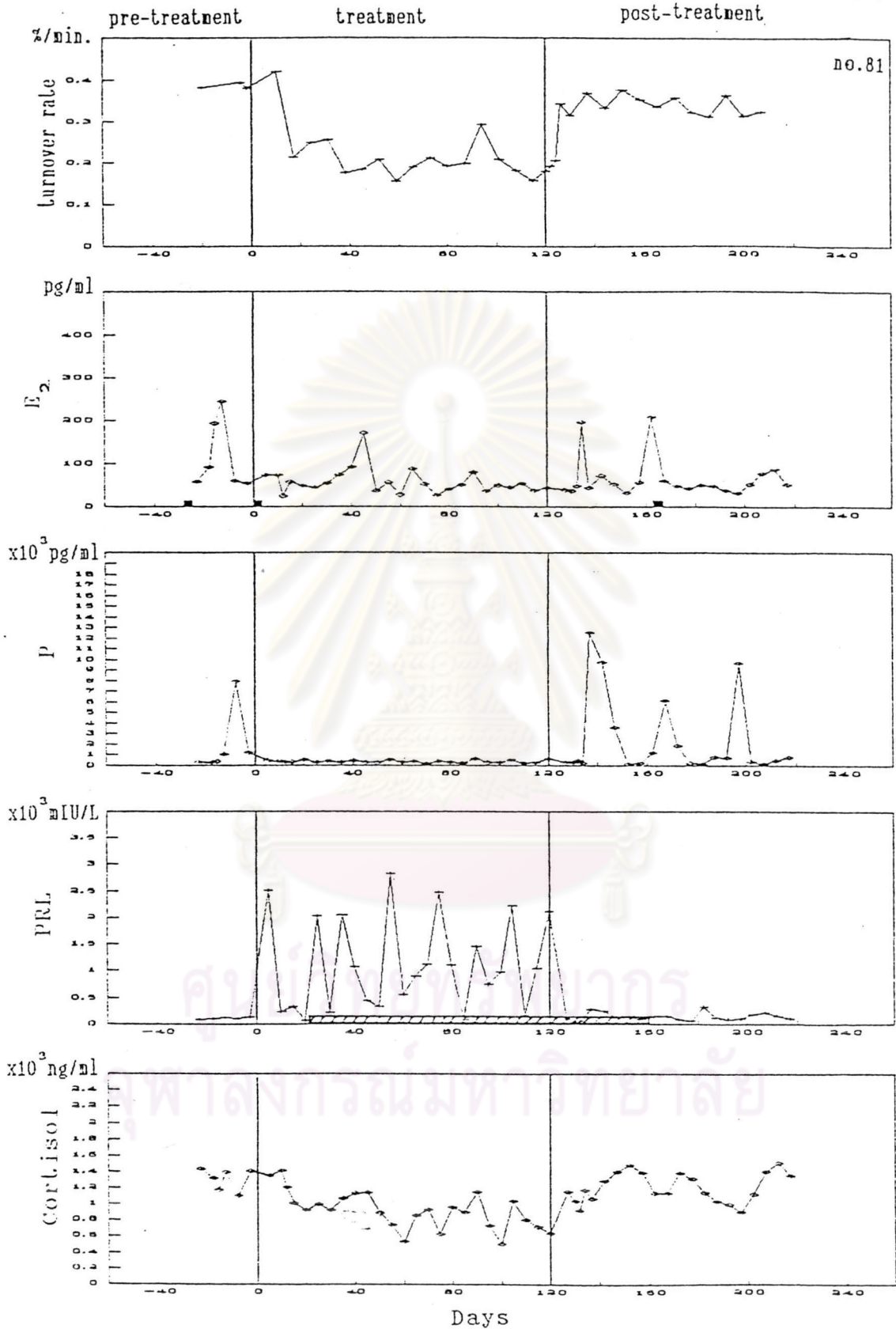


Figure 72 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol, galactorrhea(▨) and menstrual bleeding (-) in monkey no.81 of 3.2 mg/kg/day morphine treatment group.

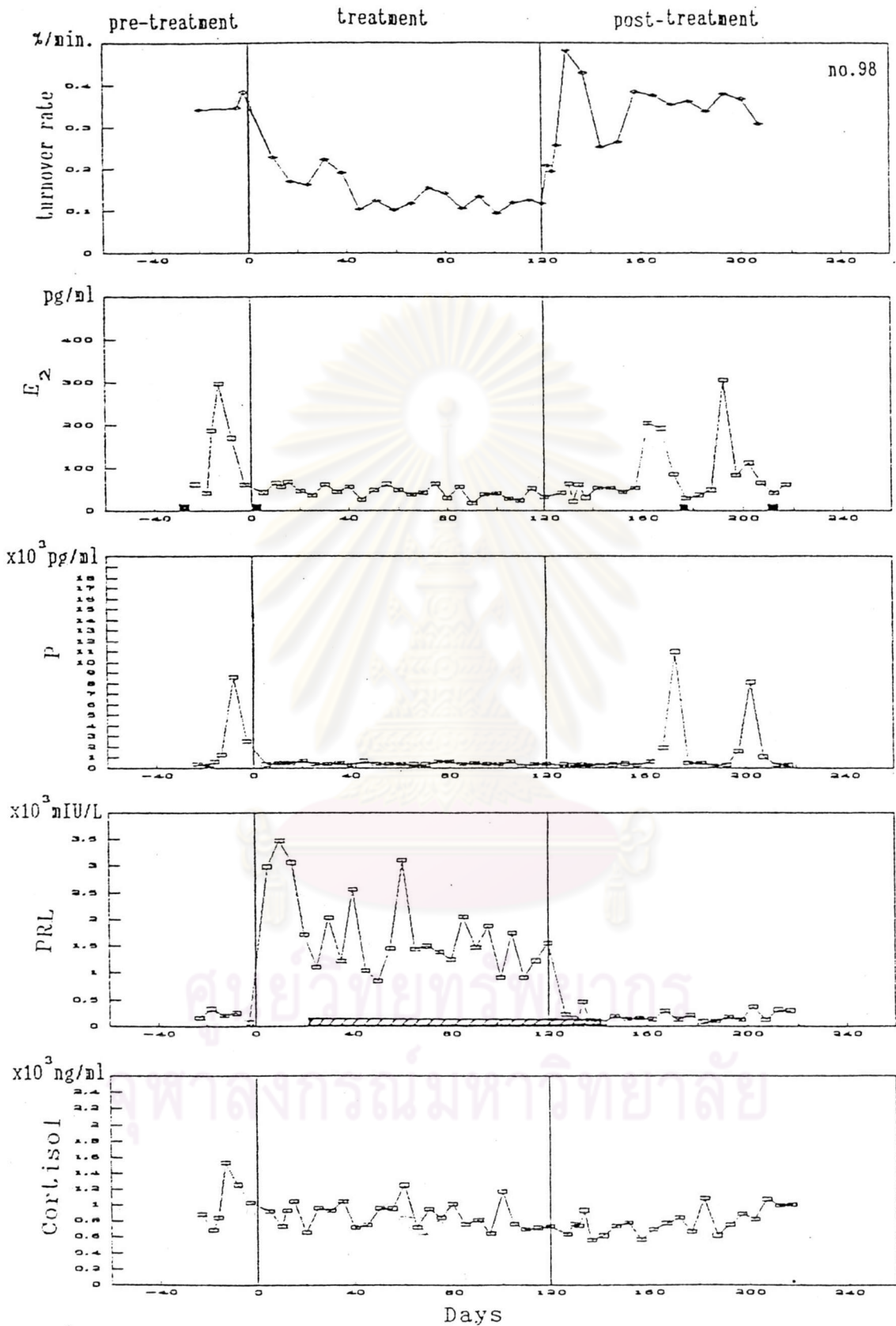


Figure 73 Turnover rate of morphine, serum levels of E₂, P, PRL, cortisol, galactorrhea (▭) and menstrual bleeding (■) in monkey no.98 of 3.2 mg/kg/day morphine treatment group.

Table 7 Approached behaviour of female monkeys treated with 0.1-0.8 mg/kg/day morphine hydrochloride during pairing with a vasectomized male.

Behaviour of females

Dose of morphine mg/kg/day	Monkey Number	Frequency/test ($\bar{x} \pm SD$)	
		Pre-treatment	Treatment
0.1	601	3.48±1.27	2.04±1.41
	615	8.33±4.17	4.00±2.37
0.2	61	6.00±2.76	4.47±1.75
	64	10.5±2.88	2.83±1.83 **
0.4	99	5.15±2.07	2.83±0.74 *
	616	4.50±2.74	1.50±1.38
	800	10.17±3.47	8.26±1.17
0.8	71	1.17±1.17	0.00±0.00
	102	10.33±1.75	0.17±0.41 **
	611	7.50±4.09	3.60±3.91

Behaviour of male

Dose of morphine mg/kg/day	Monkey Number	Frequency/test ($\bar{x} \pm SD$)	
		Pre-treatment	Treatment
0.1	601	2.57±1.38	1.50±1.05
	615	2.83±1.72	1.50±1.76
0.2	61	1.33±0.82	1.50±1.05
	64	1.83±1.17	3.83±1.17 *
0.4	99	1.13±1.60	0.50±0.84
	616	0.00±0.00	0.00±0.00
	800	2.00±1.90	0.17±0.41 *
0.8	71	2.5±1.38	0.67±0.82 *
	102	1.50±1.64	1.17±0.75
	611	0.00±0.00	0.00±0.00

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

Table 8 Presentation behaviour of female monkeys treated with 0.1-0.8 mg/kg/day morphine hydrochloride during pairing with a vasectomized male.

Behaviour of females

Dose of morphine		Monkey	Frequency/test ($\bar{x} \pm SD$)	
mg/kg/day	Number	Pre-treatment	Treatment	
0.1	601	3.17±1.17	3.12±1.18	
	615	0.33±0.52	0.00±0.00	
0.2	61	1.67±1.37	0.17±0.41	
	64	2.00±1.26	0.00±0.00	
0.4	99	3.17±1.47	0.17±0.14	**
	616	1.67±1.21	0.17±0.41	*
	800	0.50±1.2	0.00±0.00	
0.8	71	1.00±1.55	0.00±0.00	
	102	0.67±0.82	0.00±0.00	
	611	0.00±0.00	0.00±0.00	

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

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c). Inspection

Paradoxical results were found among monkeys treated with 0.1-0.8 mg/kg/day morphine. Monkeys received 0.1-0.4 mg/kg/day showed reduction in frequency of inspection from the male. Significant reduction were found in all monkeys treated with 0.4 mg/kg/day morphine. On the other hand, monkey treated with 0.8 mg/kg/day morphine showed no difference in statistics but trend to be increased than studied during pre-treatment cycle.

d). Mount

Morphine suppressed mounting behaviour in all but one monkey (no.61) treated with 0.2 mg/kg/day morphine whom showed significantly higher frequency of mounting behaviour than the recorded during pre-treatment cycle ($p < 0.05$).

e). Invitation to groom

The invitation to groom of the male to morphine treated females was not different in all groups. However, the female from 0.2 (no.64) and 0.8 (no.102) mg/kg/day morphine treated group showed significantly reduction in frequency lesser than being recorded during pre-treatment period ($p < 0.05$).

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Table 9 Inspected behaviour of vasectomized male during pairing with morphine treated female monkeys, 0.1-0.8 mg/kg/day morphine hydrochloride

Dose of morphine mg/kg/day	Monkey Number	Frequency/test ($\bar{x} \pm SD$)	
		Pre-treatment	Treatment
0.1	601	0.50±0.55	0.33±0.52
	615	0.67±0.52	0.00±0.00
0.2	61	4.50±2.26	2.00±1.90
	64	1.83±1.73	0.83±0.75
0.4	99	2.17±1.33	0.17±0.41 *
	616	2.33±2.06	0.33±0.52 *
	800	4.33±1.37	1.17±1.17 **
0.8	71	0.33±0.52	0.83±0.75
	102	1.67±0.82	3.33±2.16
	611	0.33±0.82	0.20±0.45

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

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Table 10 Mouting behaviour of vasectomized male during pairing with morphine treated female monkeys, 0.1-0.8 mg/kg/day morphine hydrochloride

Dose of morphine		Monkey	Frequency/test ($\bar{x} \pm SD$)	
mg/kg/day	Number	Pre-treatment	Treatment	
0.1	601	0.50±0.55	0.33±0.52	
	615	0.67±0.52	0.00±0.00	
0.2	61	0.50±0.84	2.00±0.03	*
	64	0.33±0.52	0.00±0.00	
0.4	99	0.00±0.00	0.00±0.00	
	616	0.00±0.00	0.00±0.00	
	800	1.33±1.21	0.00±0.00	
0.8	71	3.33±1.21	0.50±0.55	**
	102	0.50±0.48	0.00±0.00	
	611	0.33±0.52	0.00±0.00	

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

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Table 11 Invited to groom behaviour of female monkeys treated with 0.1-0.8 mg/kg/day morphine hydrochloride during pairing with a vasectomized male.

Behaviour of females

Dose of morphine		Monkey	Frequency/test ($\bar{x} \pm SD$)	
mg/kg/day	Number	Pre-treatment	Treatment	
0.1	601	1.05±0.69	1.34±1.06	
	615	1.83±1.60	3.00±2.10	
0.2	61	2.00±1.67	2.50±1.52	
	64	5.33±1.86	1.50±1.52 *	
0.4	99	2.50±1.52	2.17±0.75	
	616	3.17±1.60	3.67±1.37	
	800	1.83±1.03	1.83±1.17	
0.8	71	2.33±1.97	2.33±1.97	
	102	6.17±1.94	3.50±2.07 *	
	611	5.50±3.08	4.60±1.82	

Behaviour of male

Dose of morphine		Monkey	Frequency/test ($\bar{x} \pm SD$)	
mg/kg/day	Number	Pre-treatment	Treatment	
0.1	601	3.01±0.89	2.33±1.21	
	615	1.83±1.47	3.17±1.17	
0.2	61	3.17±0.94	2.17±0.98	
	64	1.33±0.52	1.33±1.21	
0.4	99	4.17±1.60	3.17±0.89	
	616	3.00±1.26	2.67±1.75	
	800	2.83±2.23	1.17±1.17	
0.8	71	2.17±1.94	3.33±1.21	
	102	2.67±1.37	2.17±1.17	
	611	2.83±1.17	1.80±1.10	

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

f). Groom

Daily injection of low dose of morphine (0.1-0.8 mg/kg) increased grooming frequency in most monkeys (excepted monkey no.64, no.616, no.102 and no.611).

On the other hand, variable grooming frequencies of the male partner were recorded. Significant increase both of grooming and the time for the behaviour were found in one out of three female monkeys treated with 0.2, 0.4 and 0.8 mg/kg/day morphine ($p < 0.05$), but only of 0.04 mg/kg/day morphine treated group showed significant decline in grooming frequency.

g). Locomotor Activity

Variation of locomotor activities were noted during pre-treatment and treatment period but distances of movement were not altered significantly from the pre-treatment record in both sexes ($p > 0.05$).

h). Yawn

Yawning behaviour were rarely observed in the female during entire experimental period. The difference between pre-treatment and treatment period of the males as well the females were not significance ($p > 0.05$).



Table 12 Grooming behaviour of female monkeys treated with 0.1-0.8 mg/kg/day morphine hydrochloride during pairing with a vasectomized male.

Behaviour of females

Dose of morphine		Monkey	Frequency/test ($\bar{x} \pm SD$)	
mg/kg/day	Number	Pre-treatment	Treatment	
0.1	601	1.38±1.47	3.21±2.18	
	615	1.00±2.00	3.50±1.67	
0.2	61	0.50±0.84	2.67±2.16	*
	64	1.83±4.49	0.00±0.00	
0.4	99	4.50±2.26	5.33±1.03	
	616	8.17±2.32	2.50±1.38	**
	800	2.83±0.75	2.00±0.89	
0.8	71	6.50±2.74	4.83±0.78	
	102	6.17±5.00	0.33±0.82	**
	611	4.00±2.37	0.33±0.52	**

Behaviour of male

Dose of morphine		Monkey	Frequency/test ($\bar{x} \pm SD$)	
mg/kg/day	Number	Pre-treatment	Treatment	
0.1	601	4.13±1.64	5.67±1.63	
	615	4.00±3.10	7.00±2.45	
0.2	61	1.67±2.25	8.17±2.22	**
	64	8.33±5.92	8.83±2.56	
0.4	99	11.5±3.39	8.50±2.59	
	616	9.00±1.90	5.67±2.07	*
	800	1.17±1.33	6.05±2.74	**
0.8	71	3.67±1.21	6.33±0.20	*
	102	4.83±0.41	4.67±1.21	
	611	8.00±3.35	6.60±1.14	

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

Table 13 Grooming time behaviour of female monkeys treated with 0.1-0.8 mg/kg/day morphine hydrochloride during pairing with a vasectomized male.

Behaviour of females

Dose of morphine mg/kg/day	Monkey Number	Minutes/test ($\bar{x} \pm SD$)	
		Pre-treatment	Treatment
0.1	601	18.62±8.06	21.39±7.29
	615	1.86±3.70	8.49±6.28
0.2	61	0.73±1.80	1.45±3.34
	64	4.73±11.59	0.00±0.00
0.4	99	3.41±2.60	8.71±1.26 *
	616	9.50±4.78	8.88±4.94
	800	7.70±4.58	13.8±4.26 *
0.8	71	16.62±8.42	20.38±5.36
	102	3.39±2.89	1.27±3.10
	611	4.40±3.57	0.07±0.10 *

Behaviour of male

Dose of morphine mg/kg/day	Monkey Number	Minutes/test ($\bar{x} \pm SD$)	
		Pre-treatment	Treatment
0.1	601	10.35±3.78	9.85±2.45
	615	3.94±5.90	12.12±4.01
0.2	61	2.70±5.51	14.87±7.32 *
	64	14.31±10.74	11.23±4.41
0.4	99	20.29±5.02	14.40±5.54
	616	25.57±3.26	17.00±7.09
	800	0.86±1.17	8.34±3.70 **
0.8	71	5.79±3.65	17.47±2.91 **
	102	8.42±1.98	9.88±2.90
	611	27.42±3.29	27.71±7.71

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

Table 14 Locomotoractivity of female monkeys treated with 0.1-0.8 mg/kg/day morphine hydrochloride during pairing with a vasectomized male.

Behaviour of females

Dose of morphine		Monkey		Feet/test ($\bar{x} \pm SD$)	
mg/kg/day	Number	Pre-treatment	Treatment		
0.1	601	320.67±144.62	270.00±141.20		
	615	114.67±87.58	396.50±267.85		
0.2	61	619.67±95.39	507.83±333.81		
	64	552.50±285.46	394.17±165.88		
0.4	99	418.67±213.76	308.83±120.26		
	616	107.88±104.94	151.67±93.91		
	800	1583.83±534.59	938.50 ±97.17		
0.8	71	231.17±168.14	51.50±28.51		
	102	203.61±121.45	161.00±82.15		
	611	143.00±68.60	207.40±146.21		

Behaviour of male

Dose of morphine		Monkey		Feet/test ($\bar{x} \pm SD$)	
mg/kg/day	Number	Pre-treatment	Treatment		
0.1	601	143.17±83.91	113.83±30.78		
	615	345.83±132.42	396.50±278.85		
0.2	61	457.00±133.78	263.00±208.69		
	64	296.00±86.43	622.83±272.81		
0.4	99	185.33±125.80	126.00±71.09		
	616	51.67±23.40	103.83±67.30		
	800	329.17±80.75	151.50±76.90		
0.8	71	215.17±162.50	79.17±34.70		
	102	156.67±74.12	403.00±265.50		
	611	113.83±49.65	178.80±121.17		

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

Table 15 Yawning behaviour of female monkeys treated with 0.1-0.8 mg/kg/day morphine hydrochloride during pairing with a vasectomized male.

Behaviour of females

Dose of morphine mg/kg/day	Monkey Number	Frequency/test ($\bar{x} \pm SD$)	
		Pre-treatment	Treatment
0.1	601	0.33±0.52	0.50±0.55
	615	0.00±0.00	0.17±0.41
0.2	61	0.00±0.00	0.00±0.00
	64	0.00±0.00	0.00±0.00
0.4	99	0.17±0.41	0.17±0.41
	616	0.00±0.00	0.50±1.50
	800	0.17±0.41	0.67±0.82
0.8	71	0.64±0.28	0.17±0.41
	102	0.00±0.00	0.00±0.00
	611	0.33±0.52	0.20±0.45

Behaviour of male

Dose of morphine mg/kg/day	Monkey Number	Frequency/test ($\bar{x} \pm SD$)	
		Pre-treatment	Treatment
0.1	601	4.78±2.37	3.12±1.64
	615	3.67±2.25	4.83±1.72
0.2	61	4.33±2.50	2.50±3.27
	64	6.17±4.45	5.33±2.07
0.4	99	2.33±1.63	2.67±1.75
	616	1.17±0.98	3.00±1.55
	800	4.17±1.83	3.33±1.63
0.8	71	3.67±4.34	3.00±2.19
	102	4.83±3.19	3.33±2.80
	611	3.17±2.48	2.20±1.92

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

- High Doses (1.6 and 3.2 mg/kg/day)

a). Approach

The frequency of approach in female treated with 1.6 mg/kg/day morphine showed a gradual decline, particularly in those with regular menstruation (no.92). Abrupt declined in frequency were found in 3.2 mg/kg/day treated group.

Inconsistent results were found in the male partner in all treatment group. Withdrawal of morphine tended to increase in approached frequency almost instantly in all females and male.

b). Presentation

Significant decline of presentational behaviour was found in almost of monkeys treated with 1.6-3.2 mg/kg/day morphine soon as the start of treatment. Withdrawal of morphine was unable to restore normal frequency even in the record post-treatment cycle.

c). Inspection

Inspection behaviour decreased in most monkeys treated with 1.6-3.2 mg/kg/day morphine. And this appeared to have extended into post-treatment period in the high dose groups.

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Table 16 Approached behaviour of female monkeys treated with 1.6-3.2 mg/kg/day morphine hydrochloride during pairing with a vasectomized male

Behaviour of females		Frequency/test ($\bar{x} \pm SD$)							
Dose of morphine Monkey		Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2	
ng/kg/day	Number								
1.6	92	11.67 \pm 2.25	12.83 \pm 3.43	10.83 \pm 4.71	8.67 \pm 5.16	3.50 \pm 5.75 *	3.00 \pm 2.97 *	6.00 \pm 2.12	
	93	13.17 \pm 4.71	9.83 \pm 3.87	9.50 \pm 3.27	9.83 \pm 5.12		11.00 \pm 5.01	11.00 \pm 5.12	
	95	13.33 \pm 8.41	10.33 \pm 2.25	11.67 \pm 6.95			13.67 \pm 5.89	15.00 \pm 5.89	
3.2	60	2.83 \pm 1.47	1.50 \pm 1.22				3.67 \pm 2.58	6.00 \pm 2.45 *	
	81	2.50 \pm 1.05	1.33 \pm 2.42				3.50 \pm 1.87	1.33 \pm 1.51	
	98	2.00 \pm 1.26	1.83 \pm 1.47				2.17 \pm 0.89	1.33 \pm 1.21	
Behaviour of male									
Dose of morphine Monkey		Frequency/test ($\bar{x} \pm SD$)							
ng/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2	
1.6	92	0.33 \pm 0.82	0.50 \pm 0.84	0.83 \pm 0.98	1.00 \pm 1.26	1.33 \pm 0.82	2.50 \pm 1.97 *	0.80 \pm 0.84	
	93	0.33 \pm 0.52	0.00 \pm 0.00	0.17 \pm 0.41	0.83 \pm 0.75		0.20 \pm 0.45	0.60 \pm 0.89	
	95	0.00 \pm 0.00	0.33 \pm 0.82	0.17 \pm 0.41			0.00 \pm 0.00	1.67 \pm 2.42	
3.2	60	0.00 \pm 0.00	0.33 \pm 0.08				0.50 \pm 1.22	0.83 \pm 1.17	
	81	1.17 \pm 1.17	1.17 \pm 1.33				2.33 \pm 1.75	1.33 \pm 0.82	
	98	0.17 \pm 0.41	0.33 \pm 0.82				1.00 \pm 0.89	0.33 \pm 1.52	

* Significantly different, $P < 0.05$ ** Significantly different, $P < 0.01$

Table 17 Presentation behaviour of female monkeys treated with 1.6 and 3.2 mg/kg/day morphine hydrochloride during pairing with a vasectomized male.

Behaviour of females		Frequency/test ($\bar{x} \pm SD$)						
Dose of morphine	Monkey	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
mg/kg/day	Number							
1.6	92	1.17 \pm 0.98	0.00 \pm 0.00	0.00 \pm 0.00	0.17 \pm 0.41	0.33 \pm 0.52	0.33 \pm 0.52	0.00 \pm 0.00
	93	3.67 \pm 1.86	0.33 \pm 0.52 **	1.00 \pm 0.89 *	0.00 \pm 0.00	0.40 \pm 0.55 **	2.00 \pm 1.41	
	95	6.50 \pm 5.09	3.00 \pm 2.00	1.00 \pm 0.63 *		2.17 \pm 1.60	5.17 \pm 4.97	
3.2	60	1.17 \pm 0.41	0.33 \pm 0.82 *			0.33 \pm 1.03	0.16 \pm 0.41 **	
	81	0.00 \pm 0.00	0.00 \pm 0.00			0.00 \pm 0.00	0.00 \pm 0.00	
	98	2.67 \pm 1.37	0.33 \pm 0.52 **			0.33 \pm 0.85 **	0.33 \pm 0.82 **	

* Significantly different, $p < 0.05$

** Significantly different, $p < 0.01$

Table 4B Inspected behaviour of vasectomized male during pairing with morphine treated female monkeys, 1.6 and 3.2 mg/kg/day morphine hydrochloride

Dose of morphine Monkey		Frequency/test (x ± SD)						
mg/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
1.6	92	1.67 ± 1.03	0.83 ± 0.75	0.50 ± 0.55 *	1.17 ± 1.17	0.17 ± 0.41 *	0.67 ± 0.52	1.20 ± 0.45
	93	5.67 ± 3.20	4.17 ± 3.54	2.67 ± 1.21	2.84 ± 1.72		3.00 ± 1.87	3.20 ± 2.59
	95	4.33 ± 1.37	2.04 ± 0.30 *	2.33 ± 0.82 *			2.33 ± 1.51	6.67 ± 4.08
3.2	60	2.83 ± 0.75	1.67 ± 2.66				1.83 ± 1.17	0.83 ± 1.17 *
	81	1.67 ± 1.97	0.00 ± 0.00				2.00 ± 1.26	1.50 ± 0.55
	98	3.83 ± 1.94	1.67 ± 1.21 *				1.33 ± 1.03 *	0.50 ± 0.55 **

* Significantly different, P < 0.05

** Significantly different, P < 0.01

d). Mount

All female monkeys treated with 1.6 and 3.2 mg/kg/day of morphine showed lesser degree of acceptance to male partner during treatment cycles, especially in monkey no.93 in the second 1.6 mg/kg/day treatment cycle and monkeys no.60 and no.98 in 3.2 mg/kg/day morphine treated group. However, withdrawal of morphine promptly restore mounting behaviour in most monkeys.

e). Invitation to groom

Inconsistent results were found in both male partner and female treated partners. Withdrawal of morphine showed prompt restoration in frequency of invitation to groom in all cases.



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Table 19 Mounting behaviour of vasectomized male during pairing with morphine treated female monkeys, 1.6 and 3.2 mg/kg/day morphine hydrochloride

Dose of morphine Monkey ng/kg/day	Monkey Number	Frequency/test (x ± SD)						
		Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1 Post-treatment-2	
1.6	92	1.83 ± 0.98	1.67 ± 0.52	0.50 ± 0.55	1.33 ± 0.82	0.67 ± 0.82	1.67 ± 0.82	0.80 ± 0.45
	93	2.17 ± 0.41	1.67 ± 0.52	1.00 ± 0.63 **	0.00 ± 0.00		1.40 ± 0.55 *	1.20 ± 0.84 *
	95	0.67 ± 0.15	0.17 ± 0.41	0.00 ± 0.00			0.17 ± 0.41	0.83 ± 1.17
3.2	60	2.00 ± 0.20	0.67 ± 0.82 **				1.67 ± 0.52	2.00 ± 0.30
	81	1.33 ± 0.52	0.67 ± 0.82				0.33 ± 0.52 *	0.00 ± 0.00
	98	1.61 ± 0.41	0.17 ± 0.41 **				2.00 ± 0.54	2.00 ± 0.10

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

Table 20 Invited to groom behaviour of female monkeys treated with morphine treated female monkey, 1.6-3.2 mg/kg/day morphine hydrochloride.

Behaviour of females		Frequency/test ($\bar{x} \pm SD$)							
Dose of morphine Monkey									
mg/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2	
1.6	92	0.33 ± 0.52	0.33 ± 0.52	0.50 ± 0.84	0.50 ± 0.84	0.17 ± 0.41	0.17 ± 0.41	0.40 ± 0.55	
	93	0.33 ± 0.52	0.83 ± 0.75	2.00 ± 1.10 **	1.00 ± 0.89		2.60 ± 0.4	3.20 ± 2.77 *	
	95	1.67 ± 1.03	1.17 ± 0.75	2.33 ± 1.51			2.83 ± 1.17	1.33 ± 1.51	
3.2	60	2.83 ± 1.72	1.00 ± 1.26				1.67 ± 0.52	2.33 ± 1.37	
	81	5.33 ± 2.73	0.67 ± 0.82 **				2.83 ± 1.72	2.33 ± 0.82	
	98	0.00 ± 0.00	0.00 ± 0.00				0.00 ± 0.00	0.00 ± 0.00	

Behaviour of male		Frequency/test ($\bar{x} \pm SD$)							
Dose of morphine Monkey									
mg/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2	
1.6	92	0.67 ± 0.82	0.83 ± 0.75	0.33 ± 0.52	2.00 ± 1.67	2.00 ± 1.90	2.67 ± 1.37 *	2.40 ± 0.89 *	
	93	0.67 ± 1.21	0.50 ± 0.55	0.33 ± 0.52	0.83 ± 0.75		0.40 ± 0.89	4.00 ± 2.45 **	
	95	0.17 ± 0.41	0.67 ± 1.63	0.83 ± 0.75			4.17 ± 2.14 **	0.67 ± 1.21	
3.2	60	1.17 ± 0.98	1.00 ± 0.63				1.50 ± 0.84	1.33 ± 0.82	
	81	1.33 ± 0.82	0.00 ± 0.00				0.00 ± 0.00	0.33 ± 0.52 *	
	98	2.33 ± 2.07	1.00 ± 0.89				1.67 ± 1.63	1.33 ± 0.82	

* Significantly different, $P < 0.05$

** Significantly different, $P < 0.01$

f). Groom

Individual variation of grooming frequency in female monkeys treated with 1.6 mg/kg/day morphine group. The monkey that maintained regular cycle (no.92) showed a great deal of changes in frequency of grooming during the first few treatment cycles but increased significantly during the late treatment cycles. Withdrawal of morphine did not change the frequency of this behaviour. Other two monkeys (no.93 and no.95) whom unable to exhibit regular cycle throughout treatment period showed relative unchange grooming frequency, but withdrawal of morphine showed sudden and significant increase in frequency of this behaviour.

The 3.2 mg/kg/day morphine treated group showed similar decline in frequency of grooming during the first treatment cycle. However, morphine withdrawal showed sudden recovery of grooming frequency in monkey no.98, gradually recovered in monkey no.81 and showed further decline in frequency of grooming in monkey no.60.

Grooming behaviour of the male in 1.6 mg/kg/day morphine treated group showed relatively unchange in one female exhibited regularity of the cycle throughout treatment period. Withdrawal of the drug also showed unchanges in this behaviour. More fluctuation were found in the other two monkeys that were unable to exhibit regularity of the menstrual cycle during morphine treatment.

Table 21 Grooming behaviour of female monkeys treated with morphine treated female monkey, 1.6-3.2 mg/kg/day morphine hydrochloride.

Behaviour of females		Frequency/test (x ± SD)						
Dose of morphine Monkey		Frequency/test (x ± SD)						
ng/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
1.6	92	0.67 ± 0.52	0.00 ± 0.00	0.50 ± 1.22	8.68 ± 5.68 *	8.50 ± 5.82 **	5.17 ± 2.64 **	4.40 ± 2.97 *
	93	2.83 ± 2.48	1.00 ± 2.89	3.44 ± 2.16	1.00 ± 1.10		8.60 ± 5.13	15.20 ± 3.83 **
	95	1.50 ± 1.87	0.50 ± 1.22	1.00 ± 1.55			5.00 ± 2.37 *	1.17 ± 1.17
3.2	60	4.17 ± 0.75	1.50 ± 1.52 *				1.50 ± 1.97 *	0.83 ± 0.41 **
	81	2.83 ± 2.93	0.00 ± 0.00				0.33 ± 0.82 *	1.33 ± 1.51
	98	7.33 ± 3.67	1.67 ± 1.51 *				8.83 ± 2.23	6.00 ± 1.41
Behaviour of male		Frequency/test (x ± SD)						
Dose of morphine Monkey		Frequency/test (x ± SD)						
ng/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
1.6	92	1.00 ± 1.26	1.67 ± 1.63	1.00 ± 1.55	2.33 ± 1.21	1.83 ± 1.33	0.33 ± 0.52	0.40 ± 0.55
	93	1.71 ± 0.75	1.00 ± 1.89	3.33 ± 2.25 *	2.00 ± 1.26		1.40 ± 0.55	3.80 ± 1.79 *
	95	4.67 ± 1.03	5.17 ± 1.72	4.00 ± 1.10			2.67 ± 1.86	1.83 ± 1.72 **
3.2	60	4.33 ± 1.37	1.67 ± 1.03 *				0.83 ± 0.98 **	1.33 ± 0.82 **
	81	4.83 ± 2.23	2.33 ± 1.97				1.00 ± 0.63 **	2.67 ± 0.82
	98	0.33 ± 0.83	0.83 ± 0.98				0.17 ± 0.41	0.67 ± 1.21

* Significantly different, P < 0.05

** Significantly different, P < 0.01

Table 22 Grooming time behaviour of female monkeys treated with morphine treated female monkey, 1.6-3.2 mg/kg/day morphine hydrochloride.

Behaviour of females		Minutes/test (x ± SD)						
Dose of morphine Monkey		Minutes/test (x ± SD)						
mg/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
1.6	92	0.40 ± 0.44	0.00 ± 0.00	1.61 ± 3.95	16.71 ± 10.06 *	17.42 ± 6.41 **	16.15 ± 4.56 **	12.19 ± 5.16 **
	93	3.21 ± 5.00	2.42 ± 2.35	5.66 ± 4.20	1.86 ± 0.58		12.94 ± 7.25 *	21.46 ± 5.92 **
	95	3.45 ± 4.31	1.25 ± 3.06	1.74 ± 2.90			8.85 ± 4.06	2.32 ± 4.61
3.2	60	14.43 ± 7.13	6.04 ± 5.36				5.98 ± 9.05	0.78 ± 1.34 **
	81	4.58 ± 5.25	0.00 ± 0.00				0.25 ± 0.61 *	2.32 ± 3.21
	98	17.86 ± 7.65	4.81 ± 5.92 *				28.49 ± 4.79 *	23.25 ± 4.09
Behaviour of male		Minutes/test (x ± SD)						
Dose of morphine Monkey		Minutes/test (x ± SD)						
mg/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
1.6	92	2.31 ± 3.44	3.13 ± 4.11	3.12 ± 4.09	5.89 ± 2.76	6.55 ± 5.04	0.57 ± 0.94	1.05 ± 1.44
	93	0.82 ± 0.62	4.99 ± 5.37	7.82 ± 5.74 *	4.37 ± 3.68		3.34 ± 2.35 *	6.65 ± 4.72 *
	95	12.57 ± 7.32	15.34 ± 4.18	14.42 ± 6.51			7.35 ± 4.13	1.60 ± 1.72 **
3.2	60	13.37 ± 3.24	3.33 ± 3.76 **				4.91 ± 6.67 *	4.26 ± 2.01 **
	81	15.18 ± 4.23	6.90 ± 6.74 *				5.64 ± 5.03 *	6.49 ± 4.85 *
	98	0.25 ± 0.39	1.57 ± 1.74				0.00 ± 0.00	0.35 ± 0.21

* Significantly different, P < 0.05

** Significantly different, P < 0.01

In 3.2 mg/kg/day morphine treated group, the male showed similar grooming patterns with the female partners with significant decline of grooming frequency when pairing with monkey no.60 during the first treatment cycle. Similar patterns were found when pairing with monkey no.81 but relatively unchanged when pairing with female partner no.98.

g). Locomotor Activity

Distances of movement decline in all monkeys treated 1.6 mg/kg/day morphine. Decline throughout treatment and post-treatment period were evidenced in monkey no.92 and no.93. However monkey no.95 showed rebound effect after morphine withdrawal. The locomotor activity of this monkey also persisted in the second post-treatment cycle.

Similar to 1.6 mg/kg/day morphine treated group, locomotor activity of monkeys treated with 3.2 mg/kg/day morphine declined promptly in all cases. However, varied results were obtained after morphine withdrawal: two monkeys (no.60 and no.81) increased the activity 2-7.5 times greater than the first treatment cycle but one monkey (no.98) was unable to recover the activity to the original pre-treatment value during two post-treatment cycles.

The male showed consistent decline in locomotor activity during pairing with female monkeys treated with 1.6 mg/kg/day morphine. Relatively unchanged were found in the male pairing with monkeys treated with 3.2 mg/kg/day morphine. Inconsistent results were found after morphine withdrawal in both groups.

Table 23 Locomotor activity of female monkeys treated with morphine treated female monkey, 1.6-3.2 mg/kg/day morphine hydrochloride.

Behaviour of females		Feet/test (x ± SD)						
Dose of morphine Monkey		Feet/test (x ± SD)						
ng/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
1.6	92	460.83 ± 79.62	435.00 ± 71.15	386.33 ± 131.86	216.67 ± 181.54 *	89.50 ± 63.30 **	235.67 ± 41.48 **	208.00 ± 48.53 **
	93	1250.30 ± 294.27	815.50 ± 217.51 *	744.00 ± 300.30 *	820.50 ± 208.90 *		485.60 ± 178.80 **	331.80 ± 257.90 **
	95	888.67 ± 545.93	527.00 ± 142.00	416.67 ± 223.60			903.17 ± 441.08	1352.17 ± 380.45
3.2	60	211.67 ± 81.37	98.50 ± 34.67 *				754.67 ± 519.60 *	1161.67 ± 245.34 **
	81	219.83 ± 51.23	164.50 ± 28.34				248.33 ± 78.09	310.50 ± 68.55
	98	212.67 ± 107.42	117.67 ± 47.32				46.33 ± 27.88 **	104.00 ± 45.87 *
Behaviour of male		Feet/test (x ± SD)						
Dose of morphine Monkey		Feet/test (x ± SD)						
ng/kg/day	Number	Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
1.6	92	403.00 ± 108.97	362.17 ± 62.47	339.17 ± 55.56	265.50 ± 179.38	140.67 ± 94.74 **	179.33 ± 30.35 **	156.80 ± 25.69 **
	93	379.67 ± 117.78	278.67 ± 72.09	174.17 ± 73.64 *	281.67 ± 43.87		173.40 ± 38.36 *	61.80 ± 29.52 **
	95	408.67 ± 131.86	313.67 ± 102.50	245.17 ± 110.09			292.83 ± 152.09	327.33 ± 90.60
3.2	60	134.83 ± 46.26	189.67 ± 73.24				177.67 ± 69.41	188.33 ± 42.40
	81	205.00 ± 71.74	370.67 ± 80.38				354.17 ± 57.01	233.00 ± 70.78
	98	200.50 ± 93.78	179.50 ± 55.71				65.50 ± 18.65 **	114.67 ± 76.00 *

* Significantly different, P < 0.05

** Significantly different, P < 0.01

h). Yawn

Female monkeys treated with 1.6 and 3.2 mg/kg/day morphine rarely exhibited yawning behaviour during the period of study.

Significant reduction in yawning frequency of the male were recorded during pairing with treated female with 1.6 mg/kg/day (no.92 and no.93), but the frequency was relatively unaffected when pairing with monkey no.95. However, when pairing with the female no.60 of 3.2 mg/kg/day morphine treated group the yawning behaviour increased greatly and remained high even during post-treatment cycle. The frequency was unable to alter when pairing with monkeys no.81 and no.98. Pairing with other female members of both groups showed greatly variable in yawning frequency during post-treatment cycle.

Major results during long term morphine treatment in these female monkeys and after the drug withdrawal are summarized in table 25.

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Table 24 Yawning behaviour of female monkeys treated with morphine treated female monkey, 1.6-3.2 mg/kg/day morphine hydrochloride.

Behaviour of females		Frequency/test (x ± SD)						
Dose of morphine Monkey		Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
mg/kg/day	Number							
1.6	92	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	93	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	95	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
3.2	60	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.33 ± 1.52	0.17 ± 1.41
	81	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	98	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Behaviour of male		Frequency/test (x ± SD)						
Dose of morphine Monkey		Pre-treatment	Treatment-1	Treatment-2	Treatment-3	Treatment-4	Post-treatment-1	Post-treatment-2
mg/kg/day	Number							
1.6	92	9.67 ± 4.46	8.33 ± 1.63	3.67 ± 1.97 *	5.17 ± 2.79	2.67 ± 1.97 **	2.17 ± 2.48 *	4.80 ± 3.35
	93	9.00 ± 3.10	4.33 ± 1.97 *	2.50 ± 3.33 **	5.00 ± 2.10 *		5.20 ± 0.45	1.00 ± 1.71 **
	95	3.83 ± 1.94	2.17 ± 2.04	4.50 ± 3.67			6.17 ± 4.36	5.00 ± 4.24
3.2	60	1.00 ± 0.63	8.50 ± 6.98 *				5.00 ± 1.41 **	9.67 ± 3.01 **
	81	5.33 ± 2.66	2.83 ± 3.82				4.17 ± 3.82	7.17 ± 4.79
	98	3.00 ± 1.41	4.83 ± 3.87				2.17 ± 3.43	2.50 ± 2.35

* Significantly different, P < 0.05

** Significantly different, P < 0.01

Table 25. Major results during chronic morphine treatment and after the drug withdrawal in adult female cynomolgus monkeys

Dose of morphine (mg/kg/day)	Period of study	Metabolic turnover	Cycle length (days)	Serum PRL levels	Galactorrhea	Serum cortisol levels (ng/ml)	Reproductive behaviours (D13-D18)
0.1	Treatment (100 days)	normal	normal (29-40)	normal	-	normal (1305_1300)	fluctuate & normal
	Post-Treatment (100 days)	normal	normal (29-33)	normal	-	normal (1212_1531)	-
0.2	Treatment (100 days)	normal	normal (29-33)	normal	-	normal (1201_1409)	fluctuate & normal
	Post-Treatment (100 days)	normal	normal (29-30)	normal	-	normal (1190_1513)	-
0.4	Treatment (100 days)	normal	slightly postponed (27-57)	consistently increased	-	slightly decreased (1011_1642)	fluctuate & decreased
	Post-Treatment (100 days)	normal	normal (31-40)	promptly declined to normal	-	normal (1290_1497)	-

Dose of morphine (mg/kg/day)	Period of study	Metabolic turnover	Cycle length (days)	Serum PRL levels	Gonadotrophin	Serum cortisol levels (ng/ml)	Reproductive behaviours
0.0	Treatment (100 days)	fluctuate & readjusted	postponed (33-40)	consistently increased	-	fluctuated & decreased (1022_1576)	fluctuate & decreased
	Post-Treatment (100 days)	normal	normal (28-45)	promptly decreased to normal	-	fluctuated & decreased (1031_1629)	-
1.0	Treatment (143 days)	gradually decreased	postponed 2 in 3 (51-113)	consistently increased	2 in 3	fluctuated & decreased (745_1679)	decreased
	Post-Treatment (90 days)	normal	returned within 23-30 days	promptly decreased to normal	disappeared on D 7-10	fluctuated & decreased (1031_1512)	decreased
3.2	Treatment (120 days)	suddenly decreased	amenorrhoea	consistently increased	all monkeys	fluctuated & decreased (911_1457)	decreased
	Post-Treatment (90 days)	normal	returned within 34-61 days	promptly decreased to normal	disappeared on D 22-45	fluctuated & decreased (1102_1712)	decreased