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EFFECT OF BROMOCRYPTINE ON SERUM LEVELS OF LH, E_2, P AND PRL IN SPONTANEOUS GALACTORRHEA FEMALE CYNOMOLGUS MONKEYS

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Abstract

Five spontaneous female galactorrhea cynomolgus monkeys (Macaca fascicularis) *in the Primate Research Unit of Chulalongkorn University were studied. All animals were older than 10 years and found to have had galactorrhea for at least three months prior to the study and were suspected of being infertile. They all showed hyperprolactinemia (154-1154 mU/L compared to 109-244 mU/L in normal female) with low levels or absence of the preovulatory E_2 and LH surges.*

Bromocryptine was force-fed twice daily at the dose of 2.5 mg/day for 30 days. Serum PRL levels of all galactorrhea monkeys returned to normal levels during bromocryptine treatment and galactorrhea disappeared within 15 days of the drug treatment, resulting in increases in serum levels of LH, E_2 and P which reflect the increases in pituitary LH and ovarian E_2 and P secretions. Recurrence of hyperprolactinemia and galactorrhea was observed within 1-2 days after bromocryptine withdrawal. Continuous treatment of bromocryptine for a period of three months improved sexual receptivity in all these monkeys but no pregnancy was detected.

Introduction

Bromocryptine, a specific dopamine receptor agonist, has been used as an effective drug for treatment of hyperprolactinemia, galactorrhea, menstrual disorder and infertility in women[1-3]. It is known that in humans, galactorrhea is always accompanied by the outcome of infertility[4-5]. This infertility condition found in galactorrhea patients results from high serum prolactin levels or hyperprolactinemia[6], which is known to inhibit ovarian function[1,7,8].

In monkeys, the report of the natural occurrence of galactorrhea seems to be less, except for one case of galactorrhea cynomolgus monkey in a colony at the Primate Research Unit of Chulalongkorn University, Bangkok[9]. Another case is a report on hyperprolactinemia in monkeys by Aso *et al.*[10], who used sulpiride to induce hyperprolactinemia in baboon *(Papio cynocephalus),* thus enabling the use of this monkey as a model comparative to humans for determination of hormonal changes during the condition.

In our cynomolgus monkey colony, the occurence of galactorrhea which happens in their own accord in five female monkeys is certainly an extraordinary and interesting

phenomenon. The incidence of such spontaneous galactorrhea has stimulated our interest to pursue the events in detail. Therefore the aim of our study was composed of three parts. First, the clinical history and observations of the galactorrhea monkeys were followed. Second, hormonal investigations and therapeutic measures were performed in cases of hyperprolactinemia using bromocryptine as the drug of choice since it is normally used for treatment of galactorrhea patients[1,11,12]. Finally, the effect of bromocryptine on fertility improvement in these galactorrhea monkeys was investigated.

Materials and Methods

Animals

Nine sexually mature female *Macaca fascicularis* with body weights ranging from 3.5-4.5 kg were used. The five monkeys that showed evidence of galactorrhea were over 10 years old. The other four females (7-10 years old), which have regular menstrual cycles of 28-32 days, were used as the control group. These monkeys were housed at the Primate Research Unit of Chulalongkorn University. They were kept in individual squeeze cages with good ventilation and natural light. Additional fluorescent light was provided from 06.00-18.00 hr. Monkeys were fed daily in the morning with monkey chow (Pokphand Animal Feed Co. Ltd., Thailand) and in the afternoon with fresh pineapples, bananas, cucumbers and sweet potatoes as supplements. The animals were housed under this condition and kept on this ration for more than two years before this study was implemented.

The clinical observations of five galactorrhea monkeys were as follows:

24, 74, 58 were about 10-12 years old, while # 11 and # 29 were over 15 years old. All monkeys except # 24 had records of normal pregnancies and deliveries in the last two years. # 24 displayed normal menstrual cycles and mating behavior but had never been pregnant. These monkeys all exhibited symptoms of galactorrhea at least three months before the study, with a special note on monkey # 74 which secreted immense amount of milk. They also failed to conceive for a long period of time, even though they had many times been subjected to mating with fertile males before and during the experimental periods.

Protocol

Blood samples were collected consecutively from the first day of menstrual cycle until the end of the cycle in the control monkeys and the galactorrhea monkeys with regular cycles, and until the 100^{th} day in the galactorrhea monkeys with irregular menstrual cycles. The serum hormone levels were determined to obtain baseline data for the control and galactorrhea groups. All galactorrhea monkeys were force-fed with bromocryptine (Parlodel 2.5 mg : Sandoz Ltd. Basle Switzerland) in two daily divided doses (1.25 $\times$ 2 mg/day) at 8.00 hr and 17.00 hr for 30 days (Figures 1-5). Blood samples

were collected one day before bromocryptine treatment as a pretreatment sample and every other day throughout the 30 days of treatment and also during the 12 day post-therapeutic period. The first sample during treatment was taken 2 hours after the administration of the first dose. The serum hormone levels were determined to observe the inclination or fluctuation in relationship to the therapeutic program. Then bromocryptine was further given to all galactorrhea monkeys except # 24 at the same dose (2.5 mg in two daily divided doses) for a period of 3 months. Since monkey # 24 had never been pregnant and bromocryptine did not seem to improve her LH, E_2 and P secretions, therefore three-month treatment with bromocryptine was not administered to this monkey. During every mid-cycle, these monkeys were subjected to mating with healthy males as shown in Figures 1-5. The pregnancy detection was performed by urinary hemaglutination inhibition test during day 17-27 of post-mating[13].

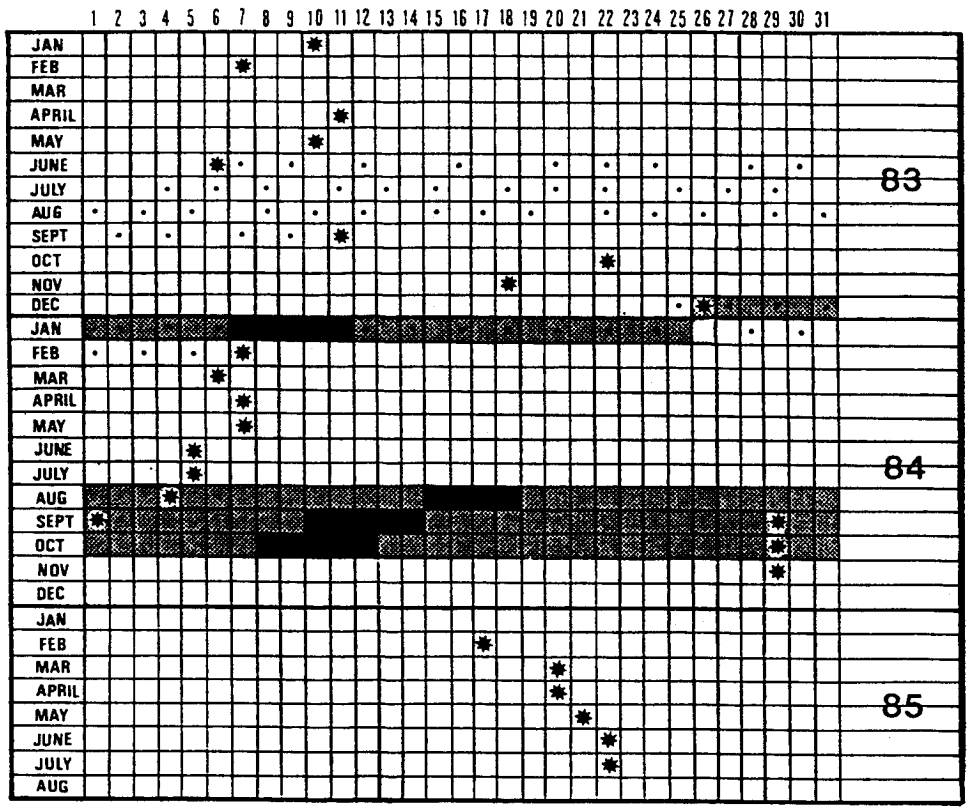


Fig. 1. Menstrual records of monkey # 11 and study protocol.

★ first day of menstrual cycle; ● day of blood collections; ▨ day of bromocryptine treatment; ■ day of mating during bromocryptine treatment.

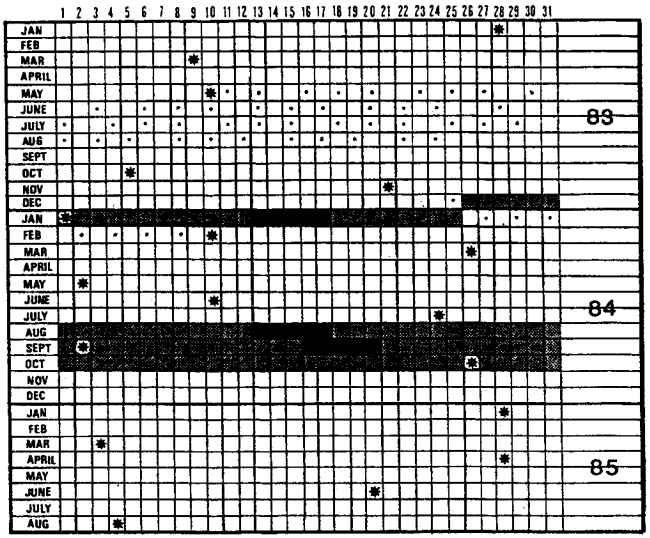


Fig. 2. Menstrual records of monkey # 58 and study protocol.

★ first day of menstrual cycle; ● day of blood collections; ⁝⁝ day of bromocryptine treatment; ■ day of mating during bromocryptine treatment.

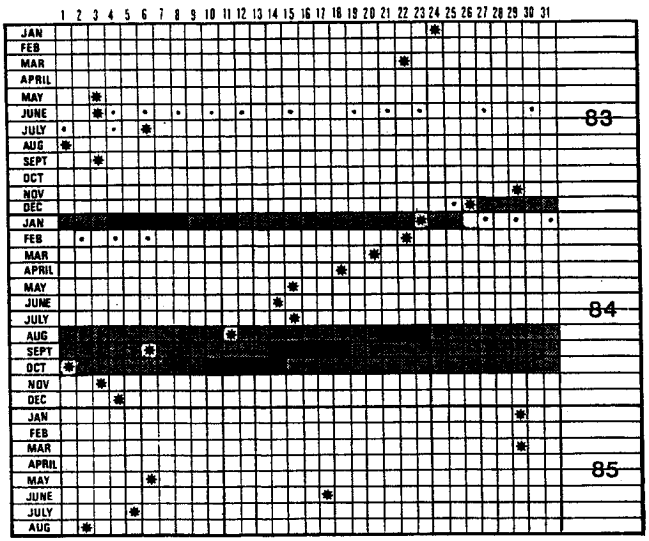


Fig. 3. Menstrual records of monkey # 74 and study protocol.

★ first day of menstrual cycle; ● day of blood collections; ⁝⁝ day of bromocryptine treatment; ■ day of mating during bromocryptine treatment.

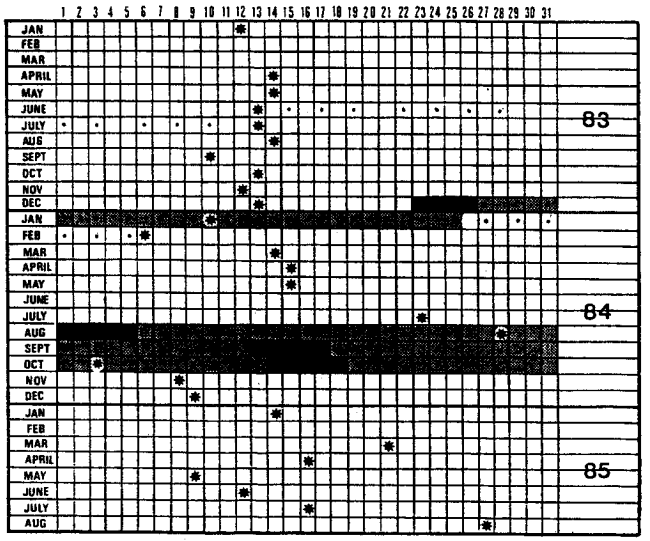


Fig. 4. Menstrual records of monkey # 29 and study protocol.

★ first day of menstrual cycle; ● day of blood collections; ⁝⁝ day of bromocryptine treatment; ■ day of mating during bromocryptine treatment.

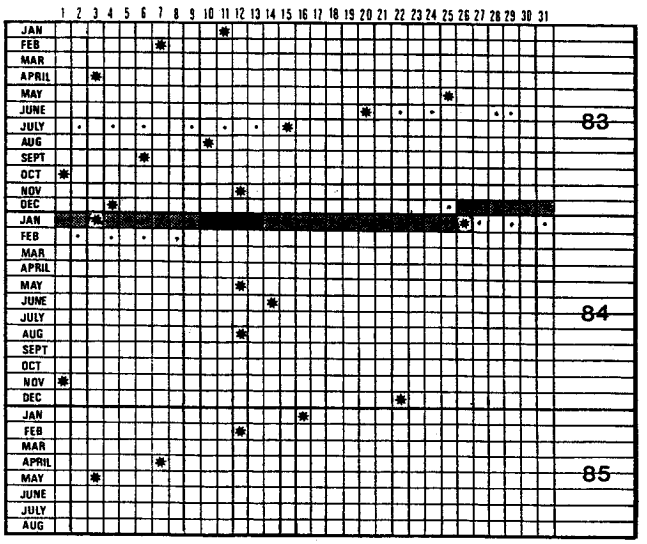


Fig. 5. Menstrual records of monkey # 24 and study protocol.

★ first day of menstrual cycle; ● day of blood collections; ⁝⁝ day of bromocryptine treatment; ■ day of mating during bromocryptine treatment.

Blood samples of 3-5 ml obtained at 09.30-11.00 hr through femoral venepuncture in non-anesthetised monkeys. To prevent anemic states, oral hematinic's (NUTROPLEX LIQUID^R : United American Pharmaceutical Inc. U.S.A.), was given to monkeys after every blood collection.

Hormone assays

Progesterone (P) and estradiol 17 ß (E_2) were measured by the radioimmunoassay (RIA) technique using the methods and reagents provided by WHO Special Programme of Research, Development and Research Training in Reproduction[14]. [^{3}H] – P and [^{3}H] – E_2 were purchased from Amersham (England). The sensitivities of the assay were 20 fmol/tube for P and 17 fmol/tube for E_2. The interassay precision, expressed in % coefficient of variation (C.V.) was 12.3 for P and 13.1 for E_2. The intrassay precision in % C.V. was 5.4 for P and 7.5 for E_2. The average percentage recovery of known amount of hormones added to the assay buffer was found to be 85-90% for P and 90-95% for E_2.

Prolactin (PRL) was measured by RIA methods in accordance with WHO Match Reagent Programme 1981[14], using heterologous assay of human kits which separates bound (Bi) hormone from the free (Bo) form by the second antibody method. The sensitivity of the assay was 105 mU/L. The % C.V. of interassay and intraassay were 4.77 and 0.64 respectively. The accuracy of the assay was over 95%.

LH was measured by the double antibody technique using heterologous RIA system developed by WHO Collaborating Center for Research and Training in Reproduction as described in the WHO Method Manual 1984 for RIA of Rhesus Luteinizing Hormone (rh LH)[15]. This system utilized a highly purified cynomolgus LH preparation (WP-XV-63) as iodinated LH, an anti-hCG serum (R/3) and a highly purified rh LH (WP-XB-20) as standard. The sensitivity of the assay calculated from the amount of hormone giving 90% Bi/Bo was 1-2 ng/tube.

Statistical analysis

Differences between pretreatment, during treatment and post-treatment of bromocryptine and comparisons between groups were carried out using analysis of variance at level of significance of $P < 0.05$.

Results

Hormone profiles in galactorrhea monkeys

Control group. Figure 6 shows the hormone profile of the normal female monkeys. Extremely high serum levels of LH (250 ng/mL), indicative of a typical preovulatory surges of LH and E_2 (2.4 ± 0.2 nmol/L) were observed in the control monkeys. They had a mean cycle

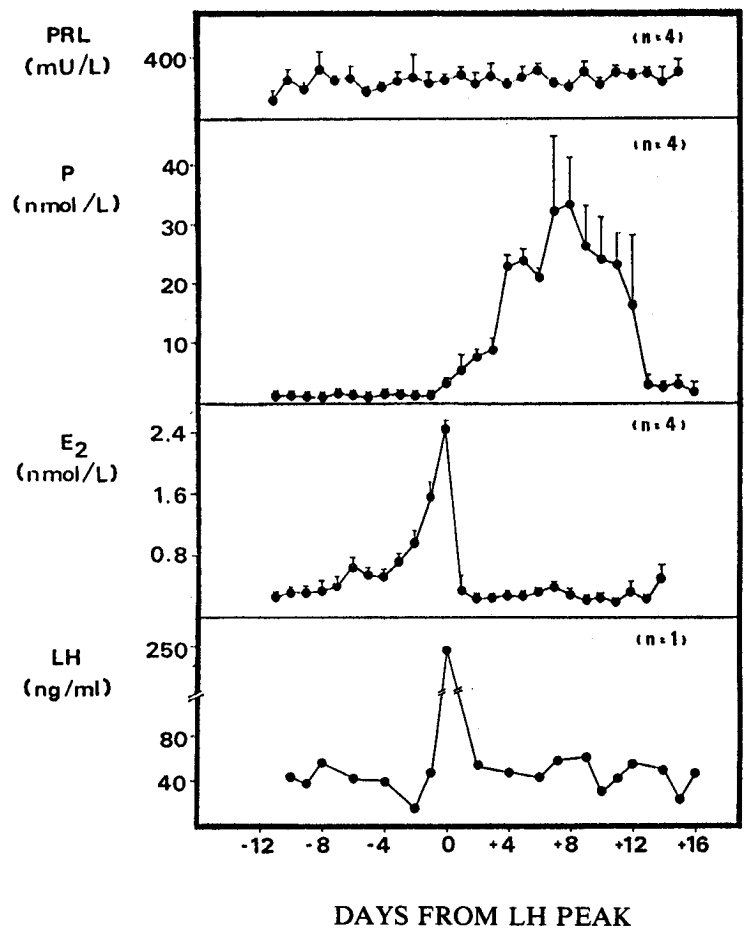


Figure 6. Serum levels of LH, E_2, P and PRL in control female monkeys. Each point is the mean ± S.E.M. (n = 4) except for the LH value, where data from only one monkey is presented.

length of 31 ± 2.1 days with P luteal peak (range 10-14 nmol/L) lasting 12-15 days. There was no cyclic change of serum PRL levels which fluctuated between 109-224 mU/L throughout the entire period of the cycle.

Irregular cycle galactorrhea monkeys. This group consisted of two monkeys (# 11 and 58). They showed varied periods of menstrual absence and recurrence as well as prolonged cycles. Prior to bromocryptine treatment, they both had periods of menstrual disappearance of over 100 days. There was neither an E_2 nor an LH peak and levels of P in the serum were found to be less than 1.0 nmol/L throughout the period of 100 days. However, the serum PRL levels were high, ranging from 197-1154 mU/L and from 154-521 mU/L in monkey # 11 and # 58 respectively (Figures 7 A, 7 B).

Regular cycle galactorrhea monkeys. These were monkeys # 74, 29 and 24. The cycle length averages were 31, 30 and 24 days for monkeys # 74, 29 and 24 respectively (Figures 7 C, 7 D, 7 E). Monkey # 74 (Figure 7 C) showed the E_2 peak at mid-cycle of 1.4 nmol/L and the LH surge of 84 ng/ml. The elevation of P during the luteal phase of this monkey (# 74) lasted for 12-15 days with a range of 12-35 nmol/L. Similar hormonal patterns were found in monkey # 29 (Figure 7 D) which showed an E_2 peak of 1.1 nmol/L accompanied by an LH surge of 66 ng/ml. The luteal phase elevation of P lasted for 15 days and reached the luteal peak range of 12-28 nmol/L.

Monkey # 24 (Figure 7 E), inspite of having a regular menstrual cycle, exhibited an LH surge of 91 ng/ml on day 15 of the cycle but showed no E_2 surge. Luteal phase of P reached the highest peak of only 14.8 nmol/L and lasted for 9 days. However, the menstrual cycle of this monkey lasted only 24 days.

Serum, levels of PRL in all three regular cycle galactorrhea monkeys were about three times higher than in the control group ranging from 290-748 mU/L in # 74 from 315-693 mU/L in # 29 from 357-780 mU/L in # 24.

Effect of bromocryptine on serum hormone levels in galactorrhea monkeys

Irregular cycle galactorrhea monkeys. Monkey # 11 (Figure 7 A) showed a dramatic decrease in serum PRL level throughout a 30 day period of bromocryptine treatment. The PRL levels dropped significantly (from 526 to 208 mU/L) within two hours after the first dose of drug administration. After bromocryptine withdrawal, serum PRL levels increased to the level just prior to the drug treatment (413 mU/L). However P levels were unchanged during the therapeutic period but increased significantly during 10 days of the post-treatment period. The serum levels of E_2 and LH increased after 20 days of treatment (Figure 7 A). In monkey # 58 (Figure 7 B), changes in serum levels of P, PRL, E_2 and LH were similar to that found in monkey # 11 (Figure 7 A) but with a slight delayed rise (on the 25th day) in E_2 and LH levels.

Regular cycle galactorrhea monkeys. Like the previous group, serum PRL levels dropped dramatically in all three monkeys (# 74, 29 and 24) within two hours after the first dose of drug administration and increased right after the drug withdrawal (Figures 7 C-E). There were no changes in the pattern of LH, E_2 and P during the 30 day period of bromocryptine treatment as compared to pretreatment cycles in monkeys # 74 (Figure 7 C) and # 29 (Figure 7 D). It is of interest that in monkey # 24, bromocryptine suppressed not only serum PRL but also suppressed P and E_2 levels during the 30 days of therapeutic period, while no marked effect on serum LH levels was observed (Figure 7 E).

It was noted that effects of bromocryptine on serum PRL levels were similar in all treated monkeys even though the initiation of bromocryptine treatment was different, at day 2 in monkey # 11 (Figure 7 A), day 37 in monkey # 58 (Figure 7 B), day 2 in monkey # 74 (Figure 7C), day 14 in monkey # 29 (Figure 7 D) and day 23 in monkey # 24 (Figure 7 E).

Effect of bromocryptine administration and withdrawal on galactorrhea monkeys

Galactorrhea was reduced and disappeared not later than the 15^{th} day of bromocryptine treatment in all treated monkeys and recurred within the first day of bromocryptine withdrawal.

Effect of bromocryptine on fertility improvement in galactorrhea monkeys

During three months of bromocryptine treatment, 3 out of 4 treated monkeys showed absolute disappearance of galactorrhea within the second week of the therapeutic period. Only one monkey (# 74) failed to stop galactorrhea. All monkeys were exposed to healthy fertile males during every mid-cycle period to resume mating and pregnancy (Figures 1, 2, 3 and 4 for monkeys # 11, 58, 74 and 29 respectively). They all showed higher receptive mating behavior throughout the three months of treatment. But none of the monkeys became pregnant.

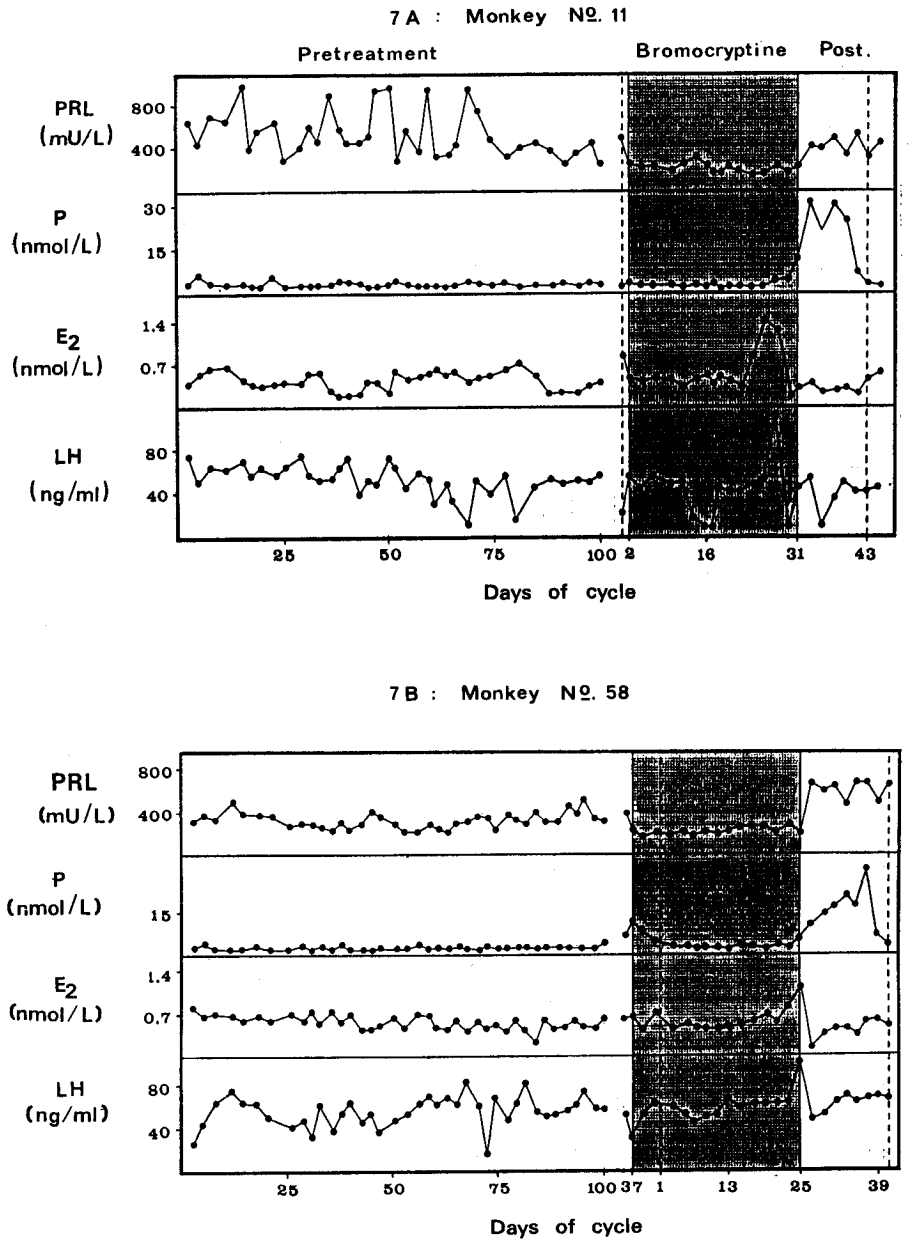
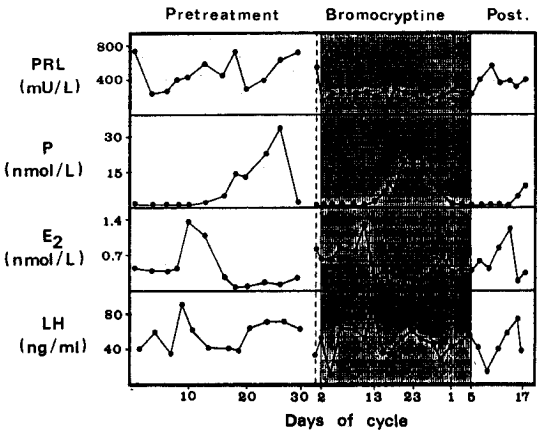
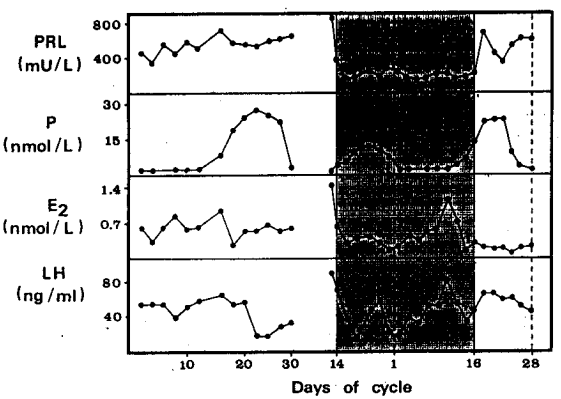


Figure 7. Serum levels of LH, E_2, P and PRL in five galactorrhea monkeys during pretreatment, treatment and post-treatment with bromocryptine. Bromocryptine was administered daily in two divided doses (1.25 × 2 mg/day) at 08.00 hr and 17.00 hr for 30 days (shaded area). 7A: monkey # 11; 7B: monkey # 58; 7C: monkey # 74; 7D: monkey # 29; 7E: monkey # 24.

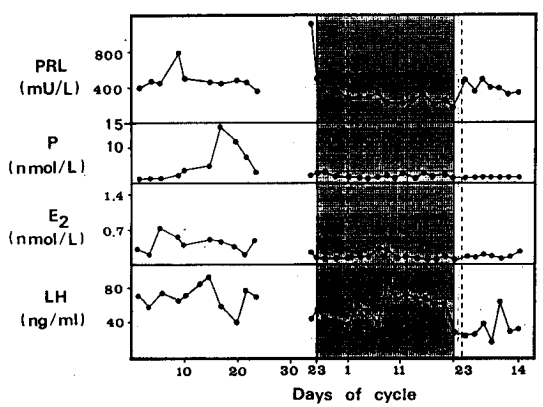
7C : Monkey Nº. 74



7D : Monkey Nº. 29



7E : Monkey Nº. 24



Discussion

The galactorrhea monkeys in the colony were found to display two types of menstruation : irregular cycles (# 11 and 58) and regular cycles (# 74, 29 and 24). Both types of galactorrhea were accompanied by hyperprolactinemia, as serum PRL levels of all galactorrhea monkeys were about three times higher than the levels found in the normal control (Figures 6 and 7 A-E). The findings were in agreement with those reported studied in humans[1,2,16].

Prior to bromocryptine treatment, the first two galactorrhea monkeys with irregular cycles (# 11 and # 58) showed hormonal patterns of anovulation throughout 100 days of amenorrhea. Both monkeys had high serum PRL levels, had neither preovulatory LH nor E_2 peaks and low P levels throughout the study period (Figure 7 A, B). When these results are combined with the absence of menses, it is quite clear that no ovulation occurred in these two monkeys. These anovulatory patterns of galactorrhea-amenorrhea conditions are widely seen in most hyperprolactinemic patients[12,17]. This phenomenon may be due to dysfunction of the hypothalamic-pituitary-ovarian axis. The absence of LH and E_2 peaks may be due to the high PRL levels found in hyperprolactinemia in women[17,18,19]. However the exact mechanism of this phenomenon is still unknown.

In the regular cycle galactorrhea monkeys, only two monkeys (# 74, 29) exhibited a normal length of menstrual cycle of 30-33 days, while monkey # 24 had the shorter cycle period lasting only 24 days. With regard to the hormonal profiles found in these monkeys (Figures 7 C-E), it was shown that they exhibited similar patterns of E_2, LH and P profiles compared to those found in the normal monkeys but with peaks at lower levels. The E_2 and LH surges were absent in monkey # 24. All monkeys had high levels of PRL. The higher levels of PRL may cause decrease in pituitary LH and ovarian E_2 secretions, as reported in hyperprolactinemic women[17,18,19]. The lower levels of E_2 and LH may be insufficient to induce ovulation in these monkeys. It is of interest that monkey # 24 inspite of showing a regular cycle, the cycle lasted only 24 days. She had neither E_2 surge nor preovulatory LH surge and exhibited low luteal P level, which lasted only 9 days and may be due to her luteal function insufficiency. These phenomena are in agreement with those found in hyperprolactinemic woman[8,20] and with the *in vitro* study reported by McNatty[21] that human granulosa cells produced lesser amounts of P in the presence of higher concentrations of PRL. This similar pattern was also seen in the hyperprolactinemic baboon induced by sulpiride[10].

All these galactorrhea monkeys were more than 10 years old. All monkeys except # 24 had records of normal deliveries of normal babies at least twice during the last five years prior to the onset of this study. The monkey # 74 delivered the last baby in 1981. Since then she has failed to conceive and has had galactorrhea. Monkeys # 11 and 29 have not been pregnant for more than five years. Therefore, it is possible that besides

galactorrhea, old age and a long duration of nonpregnancy may play a role in causing infertility in these monkeys, since 5-10 year-old female monkeys in this colony were reported to have fertile mating with successful pregnancies throughout the year[22].

Gaclactorrhea monkeys were administered with bromocryptine at the dose of 2.5 mg/day as the minimum effective dose used in humans[1-3, 23]. Our results showed that, during 30 days of bromocryptine treatment, PRL levels returned to the normal levels in all five galactorrhea monkeys (Figures 7A-E). This effect did not depend on the day of menstrual cycle since bromocryptine was administered on different days of the cycle in each monkey. Bromocryptine may exert its direct effect on PRL secretion in monkeys in the same manner as in humans, since this drug is a dopamine agonist[16,23,24] and mimics dopamine action by binding to dopaminergic receptors on lactotrophs resulting in suppression of PRL secretion[2,3]. It has also been reported to increase hypothalamic dopamine content[24]. In anovulatory monkeys # 11 and 58 (irregular cycle), during the 30 day period of bromocryptine treatment, there seemed to be an LH surge together with E_2 surge, both of which were not present before the treatment. Interestingly, these phenomena were followed by a substantial rise in P levels for approximately 14 days, as typically seen in the luteal phase. It seemed that in these two monkeys, bromocryptine may have induced a regular cycle even though the numbers of days shifted from normal cycle i.e. ovulation may have occurred approximately on day 27 in # 11 and day 26 in # 58 (see Figures 7A, B). In the group with regular cycles, bromocryptine did not alter the pattern of LH, E_2 and P in monkey # 74, while it seemed to induce E_2 and LH surges in monkey # 29. However, the E_2 and LH levels increased by bromocryptine in monkey # 29 were still lower than those found in normal ovulatory monkeys. Therefore it was not clear whether bromocryptine could really induce ovulation in this monkey unless ovulation could be determined by the laparoscopic technique.

It is of interest that in monkey # 24, which exhibited a shorter luteal phase, bromocryptine could lower serum PRL levels as found in other treated monkeys but suppressed E_2 and P secretions, while it seemed to induce LH surge (Figure 7 E). The results obtained may be due to the individual response to bromocryptine, since this monkey was the only galactorrhea monkey in the group which was 15 years old and had never been pregnant. Due to the unusual response of this monkey to bromocryptine, the study on the effect of bromocryptine on fertility improvement in this monkey was therefore omitted.

We found that, after 30 days of treatment, the serum PRL levels in galactorrhea monkeys returned to the high levels right after bromocryptine withdrawal. This effect may be due to the rapid rate of bromocryptine clearance[2,24]. For PRL levels to be completely restored to the normal range after drug withdrawal, a longer time of treatment may be required since 11% of hyperprolactinemic patients treated bromocryptine for one year had their PRL levels returned to normal levels with no sign of recurrence of hyperprolactinemia after drug withdrawal[25]. Our results also showed that during 30 days of bromocryptine

treatment, galactorrhea was reduced and disappeared within 15 days of the treatment in all monkeys except for monkey # 74. These phenomena are consistent with those reported in patients[23]. Galactorrhea recurred in all monkeys within one or two days after bromocryptine withdrawal. The recurrence may be due to the increment in PRL levels[26].

Bromocryptine treatment was continued for 3 months in four monkeys (# 11, # 58, # 74 and # 29). Despite non-pregnancy after being mated with fertile male on every mid-cycle period during the treatmet, the receptive mating behavior in all treated monkeys seemed to improve. A high successful pregnancy rate in hyperprolactinemic patients using bromocryptine has been reported[3,4,16,27]. The failure of pregnancy in our monkeys may be due to the short period of bromocryptine treatment or to the age of the monkeys used. The actual cause of infertility besides hyperprolactinemia in these galactorrhea monkeys will need to be further investigated.

The following conclusions may be drawn from the present studies. Firstly, galactorrhea may occasionally occur spontaneously in some old cynomolgus monkeys and is accompanied by hyperprolactinemia which suppressed the preovulatory LH surge, leading to menstrual disorder and infertility. Secondly, bromocryptine suppressed PRL secretion in all hyperprolactinemic monkeys resulting in increased pituitary LH and ovarian E_2 and P secretions. Thirdly, withdrawal of bromocryptine after the first 30 days of treatment caused prompt recurrence of high serum prolactin levels associated with galactorrhea. Finally, three months of continuous bromocryptine treatment at the dose of 2.5 mg/day was capable of improving the receptive mating behavior to a certain degree but was unable to improve fertility in these aged and galactorrhea monkeys.

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References

1. Thorner, M.O., McNeilly, A.S., Hagen, C. and Besser, G.M. (1974). Long-term treatment of galactorrhea and hypogonadism with bromocryptine. *Brit. Med. J.* **4**, 419-422.

2. Thorner, M.O., Schran, H.F., Evans, W.S., Rogol, A.D., Morris, J.L. and Macleod, R.M. (1980). A broad spectrum of prolactin suppression by bromocryptine in hyperprolactinemic woman : A study of serum prolactin levels after acute and chronic administration of bromocryptine. *J. Clin. Endocrinol. Metab.* **50**, 1026-1033.

3. Kinch, A.R. (1980). The use of bromocryptine in obstetrics and gynecology. *Fertil. Steril.* **33**, 463-470.

4. Thorner, MO., Besser, G.M., Jones, A., Dacie, J. and Jones, A.E. (1975). Bromocryptine treatment of female infertility : report of 13 pregnancies. *Brit Med. J.* **4**, 694-697.

5. Skrabanek, P., McDonald, D., Meagher, D., de Valera, E., Carrol, C., Lanigan, O. and Powell, D. (1980). Clinical course and outcome of thirty-five pregnancies in infertile hyperprolactinemic women. *Fertil. Steril.* **33**, 391-395.

6. Edwards, C.R.W., Forsyth, I.A. and Besser, G.M. (1971). Amenorrhea, galactorrhea and primary hypothyroidism with high circulating levels of prolactin. *Brit. Med. J.* **3**, 462-464.

7. Seppala, M., Hirvonen, E., Ranta, R., Virkkumen, P. and Leppaluoto, J. (1975). Raised serum prolactin levels in amenorrhea. *Brit. Med. J.* **2**, 305.

8. Seppala, M., Hirvonen, E. and Ranta, T. (1976). Hyperprolactinemia and luteal insufficiency. *Lancet* **1**, 229-230.

9. Varavudhi, P. and Yodyingyuad, V. (1980). Hormonal changes during the menstrual cycle in the crab eating monkey, *Macaca fascicularis.* In *Non-Human Primate Models for Study of Human Reproduction,* Satellite Symposium, 7th Congress Int. Primatol. Soc. (Anand Kumar, T.C. ed.), pp. 55-60 Karger, Basel.

10. Aso, T., Matsuoka, M., Su, J., Horie, K., Taü, S., Motohashi, T. and Nishimura, T. (1982). Influence of sulpiride induced hyperprolactinemia on baboon menstrual cycle. *J. Med. Primatol.* **11**, 20-34.

11. Cuellar, F.G. (1980). Bromocryptine mesylate (Parlodel) in the management of amenorrhea/galactorrhea with hyperprolactinemia. *Obstet. Gynecol.* **55**, 278-284.

12. Rachmen, I.A., Soebijanto, S., Jacob, T.Z., Surjama, E.J. and Samil, R.S. (1982). The use of bromocryptine (Parlode(R)) in hyperprolactinemic cases. *J. of ASEAN Federation of Endocrine Societies* **2**, 61-62.

13. Varavudhi, P., Tanpraprutgul, P., Yodyingyuad, V. and Lamsa-ad. P. (1982). Regulation of corpus luteum function in *Tupia glis* and *Macaca fascicularis. J. of ASEAN Federation of Endocrine Societies 2,* 91-102.

14. World Health Organization Collaborating Centre for Research and Reference Services in the Immunoassay of Hormone in Human Reproduction (1981) Method Manual : 5th edition.

15. World Health Organization Collaborating Centre for Research and Training in Human Reproduction : Radioimmunoassay of rhesus luteinizing hormone and rhesus follicle-stimulating hormone (1984). Method Manual.

16. Besser, G.M. and Edward, C.R.W. (1972). Galactorrhea. *Brit. Med. J.* **1**, 280-282.

17. Robyn, C.M., Vekemans, M., Canfriez, A. and L. Hermite, M. (1976). Effects of sulpiride induced hyperprolactinemia on circulating gonadotropins and sex steroids during menstrual cycle. *Int. Res. Commun. System. Med. Sci.* **4**, 14.

18. London, D.R. Glass, M.R., Shaw, R.W. Butt, W.R. and Edward, R. (1977). The modulation of ovarian hormones of gonadotropin release in hyperprolactinemic woman. In *Prolactin and Reproduction,* pp. 119-124, ed. P.G. Crosignani and C. Robyn, Academic Press London.

19. Tyson, J.E., Khajandi, M., Huth, J., Smith, B. and Thomas. P. (1975). Inhibition of cycle gonadotropin secretion by endogeneous human prolactin. *Am. J. Obstret. Gyne.* **121**, 375-379.

20. Muhluastedt, D., Bohnet, H.G., Hanker, J.P. and Schneider, H.P.G. (1978). Short luteal phase and prolactin. *Int. J. Fertil.* **23**, 213-218.

21. McNatty, K.P., Sawyers, R.S. and McNatty, A.S. (1974). A possible role for prolactin in control of steroid secretion by the human Graafian follicle. *Nature* **250**, 653-655.

22. Tangpraprutgul, P. and Varavudhi, P. (1982). Lack of breeding seasonality in the *Macaca fascicularis* studied in Bangkok environment. *J. Steroid Biochem.* **17**, xci.

23. Kleinberg, D.L. and Franz, A.G. (1977). Galactorrhea. A study of 235 cases : including 48 with pituitary tumors. *M. Eng. J. Med.* **296**, 589-600.

24. Fuxe, K., Fredholm, B.B., Orgen, S.O., Agnati, L.F., Hokfelt, T. and Gustafsson, J.A. (1978). Pharmocological and biochemical evidence for the dopamine agonistic effect of bromocryptine. *Acta Endocrinol. Suppl.* **216**, 27-58.

25. Moriondo, P., Travaglini, P., Nissim, M., Conti, A and Falia, G. (1985). Bromocryptine treatment of microprolactinoma : evidence of stable prolactin decrease after drug with-drawal. *J. Clin. Endocrinol. Metab.* **60**, 764-770.

26. Leblance, H., Lachelin, G.C.L., Abu-Fadil, S. and Yen, S.S.C. (1976). Effect of dopamine infusion on pituitary hormone secretion in humans. *J. Clin. Endocrinol. Metab.* **43**, 668-674.

27. Franks, S., Jacob. H.S., Steele, S.J. and Nabarro, J.D.N. (1977). Management of hyperprolactinemic amenorrhea. *Brit. J. Obstet. Gyne.* **84**, 241-253.

บทคัดย่อ

จากการศึกษาถึงระดับฮอร์โมนในซีรัมลิงเพศเมียอายุเกิน 10 ปี ที่เกิดภาวะกาแลคตอเรีย (อาการน้ำนมไหลและมีลูกยาก) ขึ้นเองโดยธรรมชาติในหน่วยวิจัยไพรเมต จุฬาลงกรณ์มหาวิทยาลัย พบว่าลิงทุกตัวมีระดับ PRL ในเลือดสูงกว่าระดับปกติอย่างเห็นได้ชัด (154-1154 มิลลิยูนิต/ลิตร เทียบกับ 109-224 มิลลิยูนิต/ลิตร) แต่ระดับ E_2 และ LH ในช่วงกลางของรอบประจำเดือนจะต่ำหรือไม่มีเลย

เมื่อใช้โบรโมคริบตินในการทดลองรักษาเป็นเวลา 30 วัน โดยให้กินวันละ 2 ครั้ง ขนาด 2.5 มิลลิกรัมต่อวัน พบว่าลิงทุกตัวมีระดับ PRL ลดลงสู่ระดับปกติ และอาการน้ำนมไหลก็จะหายไปภายใน 15 วัน ของการให้ยา ขณะเดียวกันก็พบว่า LH, E_2 และ P ก็เพิ่มระดับขึ้นกว่าเดิมเล็กน้อย หลังจากหยุดยาแล้วจะมีอาการน้ำนมไหลอีก และระดับ PRL ก็จะสูงขึ้นภายใน 1-2 วัน ได้ทดลองให้ยานี้ติดต่อกันเป็นเวลา 3 เดือน เพื่อดูผลต่อการมีลูก พบว่าลิงเหล่านี้มีการยอมรับการผสมได้ดีขึ้น แต่ก็ไม่มีลิงตัวใดตั้งครรภ์ได้เลย