Aggravation of Inappropriate Luteinizing Hormone Secretion by Bromocriptine in Polycystic Ovary Syndrome with Elevated Serum Dehydroepiandrosterone Sulfate

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Abstract

Ten clomiphene-resistant, normoprolactinemic women with polycystic ovary syndrome (PCOS) were treated by continuous and increasing administration of bromocriptine (Brc), and changes in hormonal profiles as well as therapeutic efficacy were examined. Ovulation was restored in four patients (responders), and two of them became pregnant, whereas the other six patients did not ovulate with Brc alone (non-responders). Endocrine analyses revealed distinct differences between responders and non-responders: 1) pretreatment serum levels of dehydroepiandrosterone sulfate (DHAS) in non-responders were significantly higher than those in responders: 2) exaggerated LH secretion was definitely aggravated with Brc therapy in non-responders, but unchanged or slightly reduced in responders: 3) basal PRL secretions showed a marked reduction in both groups, whereas this response to TRH in responders decreased more markedly than in non-responders with the therapy.

It is concluded that low DHAS group patients of PCOS are likely to respond to Brc, whereas high DHAS group patients appear contraindicated for this treatment due to its aggravating effect on LH secretion.

Although the precise etiology of polycystic ovary syndrome (PCOS) is still to be elucidated, recent studies have suggested that hypothalamic dopamine (DA) deficiency may be involved in causing inappropriate gonadotropin secretion characteristic of PCOS (Quigley *et al.*, 1981, Cumming *et al.*, 1984). Based upon this

hypothesis, normalization of hypothalamic dopamine turnover in PCOS patients has been attempted by several investigators using a potent dopamine agonist, bromocriptine (Brc). However, the effectiveness of this drug in PCOS patients through improving inappropriate LH secretion has remained controversial, since some investigators have successfully induced ovulation and corrected excess secretion of LH and androgens with this treatment (Spruce *et al.*, 1984, Falaschi *et al.*, 1986), while others have failed to achieve such an effect (Buvat *et al.*, 1986). In this study, on the basis

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that the endocrine status of PCOS patients may not be homologous (Yen 1980, Coney 1984, Futterweit 1984) especially in terms of adrenal function (Lachelin *et al.*, 1979, Loughlin *et al.*, 1986), we performed long-term Brc therapy in clomiphene-resistant PCOS patients in order to clarify the changes in endocrine profiles as well as clinical efficacy associated with Brc administration with the aim of obtaining some predictable indicators of clinical efficacy of this drug.

Materials and Methods

Patient Selection and Treatment Protocol

Ten clomiphene-resistant anovulatory patients, aged from 25 to 34, visiting the Infertility Clinic at the Department of Gynecology and Obstetrics of Kyoto University Hospital were diagnosed as PCOS by clinical symptoms and laboratory evidence of hyperandrogenemia and hypersecretion of LH as essentially described by Yen (1980). These patients did not ovulate even after clomiphene treatment (100 mg/day for 5 days starting on the 5th day of the induced menstrual cycle) for at least 3 consecutive cycles. All of these patients were amenorrheic with ultrasonographically confirmed polycystic ovaries (Parisi *et al.*, 1984, Orsini *et al.*, 1985). Hirsutism is rare in Japanese women with PCOS (Kurachi *et al.*, 1971, Aono *et al.*, 1977), and none of our patients were hirsutes. Hypersecretion of LH was determined either by elevated basal LH (>23 mIU/ml) or excess response to GnRH (>81 mIU/ml), as described below. Hyperandrogenemia was evaluated from elevated serum levels of $\Delta 4$ -androstenedione (ASD) (>1.4 ng/ml) and/or testosterone (T) (>0.40 ng/ml). These values were set as the mean $\pm 3/2SD$ of the measurements in our laboratories for the control subjects. Patients with hyperprolactinemic PCOS (basal PRL >25 ng/ml) were excluded to avoid confusion, because the effect of Brc on PRL secretion and accompanying changes in LH and androgens could induce ovulation. Eight informed volunteers with regular menstrual cycles served as control subjects.

The patients received Brc continuously at three different dose levels of 1.25, 2.5, and

5 mg daily for 4 weeks for each dosage. Starting from the lowest dose, effective dosage for inducing ovulation was maintained thereafter. If ovulation was not induced by the highest dose of Brc alone, 100 mg clomiphene daily was combined with this drug from day 5 of the menstrual cycle for 5 days in the subsequent cycles. The patients who demonstrated restored ovulatory cycles with Brc were referred to as responders, and those who remained anovulatory with this drug alone as non-responders. Ovulation was evaluated by ultrasonographic observation of follicles and serum levels of progesterone.

Blood Sampling and Hormone Measurements

To avoid the effects of daily fluctuations and circadian variations in each patient (Rebar *et al.*, 1976), blood samples for the measurements of basal hormonal levels were taken from 9:30 to 10:30 A. M. as often as possible with 6.7 mean sampling times before Brc administration and 3.9 times in the last treatment cycle during the Brc treatment for each patient, and mean basal levels were calculated. All samplings were performed soon after induced withdrawal bleeding or early in each treatment cycle.

A double loading test with simultaneous intravenous injection of 100 μ g GnRH and 250 μ g TRH (Tanabe Pharmaceuticals Co. Ltd., Osaka, Japan) was performed before treatment and at the end of every treatment cycle as previously described (Lin *et al.*, 1986). The net increase in LH and FSH for the first 30 minutes after loading GnRH was defined as ΔLH and ΔFSH , respectively. Likewise, ΔPRL was designated as the net increase in PRL for the first 15 minutes after the injection of TRH. In 6 patients, in whom the pulsatile secretion pattern of LH, FSH, and PRL was studied, blood sampling was performed every 15 minutes for 3 to 5 hours before, during, and at the end of the treatment.

Serum levels of LH, FSH, and PRL and those of progesterone (P), estradiol (E_2), and T were measured by RIA using commercial kits purchased from Daiichi Radioisotope Laboratories, Ltd. (Tokyo, Japan) and CIS (the Commissariat A L'Energie Atomique, France), respectively (Lin *et al.*, 1986). Dehydroepiandrosterone sulfate (DHAS), dehydroepiandrosterone (DHA), ASD, and estrone (E_1) were measured by the methods reported by Kokubu

et al. (1978) and Ohara *et al.* (1987).

The intrassay coefficients of variation were 5.5% for LH, 6.5% for FSH, 6.8% for PRL, 5.0% for E₂, 6.5% for E₁, 5.7% for P, 6.7% for T, 8.2% for DHAS, 5.4% for DHA, and 6.5% for ASD, respectively. The interassay coefficients of variation were 10.7% for LH, 10.5% for FSH, 9.5% for PRL, 5.7% for E₂, 11.0% for E₁, 11.5% for P, 9.9% for T, 8.9% for DHAS, 10.2% for DHA, and 8.7% for ASD, respectively.

Statistical comparison was performed using analysis of variance, followed by Duncan's multiple range test.

Results

Four out of ten patients demonstrated restored ovulatory cycles with Brc therapy (responders), and two of them became pregnant. After the initiation of this therapy, the first ovulations occurred in 0.6–2.6 months with an average period of 1.4 months, in the course of treatment periods which ranged from 1.5 to 8.0 months, with an average of 4.4 months. The other six patients did not respond to Brc and remained anovulatory (non-responders) during treatment periods ranging from 3 to 6 months with an average of 3.9 months. However, when clomiphene was added to Brc treatment in non-responders, two of them responded.

Table 1. Hormonal profiles of normal subjects and patients with Polycystic Ovary Syndrome (PCOS) before and after bromocriptine treatment

	Controls (n=8)	Total PCOS (n=10)	Responders ^a (n=4)		Non-responders (n=6)	
			Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Basal LH (mIU/ml)	16.7 ± 1.3	42.3 ± 4.1 ^d	45.9 ± 6.5	40.7 ± 5.5	39.9 ± 5.0	50.3 ± 5.6
ΔLH (mIU/ml)	38.7 ± 4.5	197.2 ± 23.1 ^d	187.9 ± 29.0	149.9 ± 22.8	193.2 ± 34.2	281.2 ± 45.8
Basal FSH (mIU/ml)	10.8 ± 0.6	11.8 ± 0.8	12.2 ± 1.8	10.3 ± 1.1	11.5 ± 0.2	12.0 ± 0.5
ΔFSH (mIU/ml)	7.6 ± 0.8	15.8 ± 1.8 ^e	15.2 ± 3.0	10.4 ± 1.9	16.6 ± 2.2	12.6 ± 1.8
LH/FSH	1.6 ± 0.1	3.7 ± 0.3	3.9 ± 0.4	4.0 ± 0.3	3.5 ± 0.5	4.2 ± 0.4
Basal PRL (ng/ml)	12.4 ± 1.5	12.7 ± 1.3	14.2 ± 2.6	6.6 ± 1.6 ^e	11.7 ± 1.0	5.0 ± 0.3 ^f
ΔPRL (ng/ml)	64.4 ± 8.3	116.3 ± 17.8 ^b	107.6 ± 20.8	8.1 ± 3.7 ^e	122.2 ± 25.9	28.5 ± 8.6 ^f
T (ng/ml)	0.32 ± 0.03	0.50 ± 0.04 ^e	0.50 ± 0.04	0.45 ± 0.07	0.50 ± 0.05	0.56 ± 0.08
DHAS (ng/ml)	842.0 ± 66.3	1262.5 ± 128.6 ^b	862.0 ± 76.8	880.9 ± 78.5	1529.5 ± 116.8 ^g	1275.1 ± 128.9
DHA (ng/ml)	2.90 ± 0.40	3.12 ± 0.15	2.81 ± 0.23	3.01 ± 0.41	3.32 ± 0.14	3.03 ± 0.47
ASD (ng/ml)	0.98 ± 0.09	1.58 ± 0.15 ^e	1.51 ± 0.23	1.94 ± 0.53	1.64 ± 0.18	1.87 ± 0.30
E ₁ (pg/ml)	86.5 ± 6.0	115.7 ± 10.4 ^b	116.5 ± 10.3	123.0 ± 6.2	115.2 ± 15.9	137.7 ± 12.2
E ₂ (pg/ml)	54.5 ± 4.4	63.4 ± 5.1	71.4 ± 7.0	88.9 ± 18.6	52.3 ± 7.3	61.4 ± 3.8
E ₁ /E ₂	1.64 ± 0.18	2.03 ± 0.16	1.72 ± 0.24	1.70 ± 0.42	2.27 ± 0.17	2.26 ± 0.20

Values are the mean ± SEM. T, testosterone; DHAS, dehydroepiandrosterone sulfate; DHA, dehydroepiandrosterone; ASD, Δ₄-androstenedione; E₁, estrone; E₂, estradiol.

^a: Patients ovulating in response to bromocriptine administration

^b: $P < 0.05$; ^c: $P < 0.01$; ^d: $P < 0.001$ (when compared with controls)

^e: $P < 0.05$; ^f: $P < 0.01$ (when compared with pre-treatment values)

^g: $P < 0.01$ (when compared with responders)

The hormonal profiles of responders and non-responders before and after Brc treatment are shown in Table 1 together with %changes (comparison of post-treatment values with pre-treatment values) in Fig. 1. Among pretreatment values of the hormones measured, only DHAS in non-responders (1529.5 ± 116.8 ng/ml) was significantly higher ($P < 0.01$) than that of responders (862.0 ± 76.8 ng/ml). Though not significant, DHAS tended to decrease after Brc administration in non-responders only. Basal LH concentrations tended to decrease in responders with Brc administration, in contrast to an increasing tendency in non-responders. This discrepancy became clearer when the % decrease in responders ($89.7 \pm 5.7\%$) was compared to the % increase in non-responders ($130.7 \pm 15.2\%$) with a

significant difference ($P < 0.05$) between these two figures. Likewise, there was a significant difference between the % decrease in Δ LH in responders and % increase in Δ LH in non-responders ($73.4 \pm 1.1\%$ and $163.9 \pm 29.4\%$, respectively). As in the case of basal LH, testosterone levels tended to fall in responders with Brc in contrast to the increasing tendency in non-responders. No discernible change was recognized with basal and Δ FSH. With Brc treatment, basal PRL was significantly decreased and Δ PRL markedly decreased, both in responders and non-responders. Though there was no significant difference in the % decrease in basal PRL in the two groups, the % decrease in Δ PRL in responders ($6.3 \pm 3.3\%$) was significantly smaller ($P < 0.05$) than that in non-responders ($21.4 \pm 4.6\%$).

Fig. 1. Percent changes ($\pm$ SEM) in basal LH, Δ LH, basal FSH, Δ FSH, basal PRL and Δ PRL after bromocriptine treatment in PCOS patients.

Percent changes signify comparison of post-treatment values with pre-treatment values. Δ LH and Δ FSH signify increases in LH and FSH after GnRH administration, respectively. Δ PRL signifies the increase in PRL after TRH administration.

Fig. 2. Change in the pulsatile LH secretion pattern in PCOS patients before and after bromocriptine therapy.

Blood sampling was performed every 15 minutes. In cases 1 and 2 ovulation was restored with bromocriptine therapy (responders). Cases 3 to 6 were unresponsive to bromocriptine therapy (non-responders).

The change in the pulsatile LH secretion pattern before and after Brc treatment is shown in Fig. 2. In responders, the baseline of LH secretion was almost unaffected (case 1) or slightly reduced (case 2) with the treatment, while the baseline and amplitude of LH secretion in non-responders even increased markedly.

Discussion

The present investigation unexpectedly demonstrated the existence of two subsets

of clomiphene-resistant PCOS with different responses to Brc in terms of restoring ovulation and hormonal changes.

Brc, at the inception of its use for patients with PCOS, was welcome as a novel tool to restore ovulatory cycles (Spruce *et al.*, 1984, Falaschi *et al.*, 1986) in line with the concept of relative insufficiency of DA inhibition of LH secretion with this syndrome (Quigley *et al.*, 1981, Cumming *et al.*, 1984). Recently, this therapy has been criticized, because of the lack of significantly higher clinical effectiveness in PCOS patients than in the control subjects

as shown by a large-scale randomized double blind study (Buvat *et al.*, 1986). However, it should be carefully noticed that randomly selected patients in the whole spectrum of heterologous PCOS were included in that study. In our present study, though fundamental diagnostic criteria of menstrual disorder, LH hypersecretion and hyperandrogenemia, were common to the previous study, ovulation was successfully induced with Brc in responders if a fraction of PCOS was selected by the additional criterion of clomiphene-resistancy. Since clomiphene-resistance may signify a more severe or advanced state among overall cases of PCOS, this fact seems informative in the clinical sense that Brc can be a choice as a treatment to induce ovulation in these clomiphene-resistant PCOS patients before stepping up to hMG-hCG treatment which has been shown widely to elicit severe ovarian hyperstimulation syndrome in PCOS (Raj *et al.*, 1977, Wang *et al.*, 1980).

Increased serum DHAS in non-responders before treatment was one of the conspicuous endocrine features in contrast to normal DHAS levels in responders. This observation might suggest the existence of a link to adrenal hyperfunction in these patients. Increased circulating levels of DHAS (Carter *et al.*, 1977, Kandeel *et al.*, 1978) without increased ASD (Vermeulen *et al.*, 1977, Bassi *et al.*, 1977) in hyperprolactinemic women has been well documented, and a positive correlation between PRL and DHAS has also been found (Jones *et al.*, 1980). Though hyperprolactinemic PCOS was excluded from the present study, it was noteworthy that differences between percent changes in the increase in PRL (Δ PRL) in response to TRH became significantly greater in non-responders than in responders after a long-term period of Brc treatment, suggesting a relative lack of response to Brc of PRL secretion in the former.

Aggravation of LH hypersecretion in non-responders, but not in responders was

another feature of hormonal changes induced by Brc treatment. Although a marked change was observed in pulsatile secretion pattern of LH after this treatment, the difference in LH secretion in responders and non-responders was apparent when comparing the percent changes in basal as well as Δ LH in the two groups, both of which became significantly different after the treatment. This aggravating effect of Brc on LH secretion in non-responders is unexpected, when one considers the available data concerning dopaminergic mechanisms in controlling LH secretion that have been controversial (Rosen & Lobo 1987), with the reports of inhibitory effects of DA and its agonist on LH secretion either in normal or hyperprolactinemic woman (Leblanc *et al.*, 1976, Lachelin *et al.*, 1977). Other reports deny such an inhibitory action in normal (Tolis *et al.*, 1975, Polansky *et al.*, 1976) and in hyperprolactinemic women (Evans *et al.*, 1980).

There has been only one study that reported a differential action of DA and Brc on LH secretion (Martin *et al.*, 1981), in which Brc was shown to slightly but definitely stimulate LH secretion, while DA lowered LH levels in normal women. The authors explained this discrepancy as a consequence of Brc binding to presynaptic receptors of multiple DA receptors in the hypothalamus. This, in turn, blocks the tonic inhibitory action of endogenous DA via postsynaptic receptors that is directly involved in GnRH secretion, as has recently been demonstrated *in vitro* in humans (Rasmussen *et al.*, 1986).

In conclusion, the increase in circulating DHAS can serve as a clinical index to predict the efficiency of Brc for patients with clomiphene-resistant PCOS. In PCOS patients with increased serum DHAS, Brc is not only ineffective in ovulation induction but also has an aggravating effect on LH secretion.

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