

BROMOCRYPTIN AND EPIGESTROL IN MAP-NEGATIVE SECONDARY AMENORRHEAS

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SUMMARY

18 patients, between 18 and 24 years of age, affected by normoprolactinemic secondary amenorrhea and still MAP-negative after three successive Epimestrol cycles underwent five cycles of a combined treatment (Bromocryptin and Epimestrol).

Before and after the first cycle of combined treatment, in all patients FSH, LH, E₂ and PRL were measured. Progesterone was evaluated three days after the thermic rise. The basal temperature was measured daily.

In all the examined patients the combined treatment produced the appearance of the menstrual flow after the third therapeutical cycle. In 13 out of the 18 examined patients ovulation was observed.

The hormonal dosage highlighted a clear increase in Gonadotropins and Estradiol levels.

Recent studies have highlighted the high effectiveness of Epimestrol – a weak estrogen – in cases of normoprolactinemic amenorrhea or ovarian micropolycystosis^(1, 2, 3).

However, many amenorrheal patients draw no benefit from treatments with this drug and remain MAP-negative.

Del Poro⁽⁴⁾, Seppala⁽⁵⁾ and Tolis⁽⁶⁾ observed that Bromocryptin treatments produce positive responses in about 50% of normoprolactinemic amenorrhea cases. Furthermore, Wolf⁽⁷⁾ pointed out that a Bromocryptin therapy makes a previous negative response to a Clomiphene treatment, positive, thus establishing a normal FSH-LH ratio and producing a consequent increase in plasmatic Estradiol and in Progesterone.

The therapeutical result can be explained by examining the three possible action levels of Bromocryptin: ovarian, hypophyseal and hypothalamic.

Therefore, our study aims at verifying whether the association of Bromocryptin and Epimestrol in patients who have remained MAP-negative after three successive Epimestrol cycles, can make them MAP-positive.

MATERIAL AND METHODS

18 patients, between 18 and 24 years of age, affected by normoprolactinemic secondary amenorrhea, presenting minimal gonadotropinic values and still MAP-negative after three successive cycles of Epimestrol treatment (10 mg/die per 10 days) underwent 5 cycles of a combined Bromocryptin-Epimestrol treatment. The following therapeutical programme was used: 2.5 mg/die of Bromocryptin together with 10 mg/die of Epimestrol over the first 10 days.

When the menstrual flow did not occur within 35 days from the beginning of the treatment, the MAP test was performed (150 mg).

In case of negative result, a second therapeutical cycle was started after eight days.

In case of positivity or spontaneous flow, Bromocryptin and Epimestrol were administered starting from the third day.

In all patients, prior to the beginning of this therapy and on the first day of the second cycle, FSH, LH, Estradiol and PRL plasma levels were evaluated.

Table 1.

Cases	FSH m I.U./ml			LH m I.U./ml			E ₂ pg/ml			PRL ng/ml		
	A	B	C	A	B	C	A	B	C	A	B	C
1	4.2	4.8	6.6	3.1	3.2	7.4	25	32	64	9.6	10	8.9
2	3.5	4	7.1	4.3	4	8	36	44	75	12	14	10
3	2.9	3.6	7.5	5.2	5.4	7	40	36	85	9	12	12
4	5.1	4.8	7.3	5	5.1	7.6	46	35	90	9.4	10	11
5	2.4	2.8	5.6	2.9	3.4	6.1	15	20	60	7	8.2	10
6	3.2	3.4	7.8	3	3.2	7.2	24	30	74	6.5	7	7
7	6.4	6.6	7.2	2.5	2.8	6.4	38	40	65	6	6	7.6
8	5.9	6.1	7.6	3.4	3.2	7.1	40	36	70	5.8	7.2	9
9	4.8	4.6	8	3.6	3.8	7.2	42	48	88	6	7	8.4
10	6.7	6.6	7.5	3.2	3.4	7.1	30	34	72	7	7	9
11	3	3.5	6.8	3.9	4.2	4.8	25	32	40	8	8.4	8
12	6.5	6.7	7.2	4	4.3	6.9	32	28	66	9	8	10.2
13	3.9	4.1	8.3	9	8.5	8.1	48	55	94	12	10	12.5
14	5.3	5	7.6	4	4	6.8	40	38	75	9	12	12
15	6.7	6.8	7	3	3.1	6.4	34	40	76	7	8.5	9
16	4	3.6	5	3.2	3.4	4.3	22	30	44	6.5	7	8
17	7.4	7.2	7.8	2.5	2.8	6.9	29	41	84	7	8.5	8
18	4.7	4.3	8.2	4	3.8	7.3	32	34	90	9	9.5	10
	4.8±	4.8±	7.3±	3.8±	3.9±	6.8±	33.2±	3.6±	73±	8±	9±	9±

A = Basal values, $M \pm sD$, of the patients examined before Epimestrol treatment.

B = Basal values, $M \pm sD$, after 3 Epimestrol cycles.

C = Basal values, $M \pm sD$, at the 3rd day of the 2nd Bromocryptin-Epimestrol treatment.

The examined patients measured their basal temperature daily. In case of thermic rise after three days, blood samples were taken for Progesterone dosage.

FSH, LH, PRL, E₂ and Progesterone evaluated according to the RIA method (Kits: Biodata Serono).

RESULTS

The Gonadotropin dosage highlighted the increase of FSH and LH basal levels (tab. 1) after one therapeutical cycle.

On the average, the two Gonadotropins increased by 150% (FSH) and 176% (LH) (taking 100 as the mean basal value before the combined treatment).

The ratio between FSH and LH average levels passed from 1.23 to 1.06 after the first therapeutical cycle. Estradiol mean values increased by 219%.

Progesterone plasma levels exceeded 10 mg/ml (fourth day of thermic rise, with biphasic curve of basal temperature and normal duration) in 10 cases, in the first cycle, in 12 in the second and third, 13 in the fourth and fifth cycles (tab. 2).

After just one therapeutical cycle, the association of Bromocryptin and Epime-

Table 2. — Responses to Bromocryptin-Epimestrol treatment in the 18 examined patients.

	Map.-negative Menstruation Ovulation		
1st cycle (18 cases)	3	15	10
2nd cycle (18 cases)	1	17	12
3rd cycle (18 cases)	0	18	12
4th cycle (18 cases)	0	18	13
5th cycle (18 cases)	0	18	13

strol produced the appearance of menstruations in 15 out of the 18 examined patients. No patient was still amenorrheal after three therapeutical cycles; 12 had normal ovulations whereas 2 showed luteinic insufficiency (lower thermic rise at the 10th day) (tab. 2).

Only three patients (cases 5, 11, 16; tab. 1) showed negative MAP-test results after the first therapeutical cycle. Case 16 remained negative for three cycles. Ovulation never occurred, in these patients, during the 5 cycles of combined therapy.

DISCUSSION

The association of Bromocryptin and Epimestrol changed MAP responses from negative to positive and normalized the cycles of 13 out of the 18 examined patients. This effect of Bromocryptin had already been pointed out in Clomiphene and cyclophenile treatments of normoprolactinemic amenorrhea.

The increase in Gonadotropins average values, after the first therapeutical cycle, indicates that these two substances mainly act at the hypothalamo-hypophysial level.

They are thought to produce an increase hypothalamic and hypophysial stores.

According to Genazzani and Coll. ^(2, 6, 8), Epimestrol causes an increase in the Gonadotropin hypophysial stores. According to Fuxe and Coll. ⁽⁹⁾, Bromocryptin exerts

a short, inhibiting action on LH-RF casting off, thereby further increasing hypophysial stores.

However, Bromocryptin mainly facilitates Gonadotropin cyclical secretions ⁽¹⁰⁾.

The successful Epimestrol-Bromocryptin treatment of these patients suggests that Bromocryptin enhance Epimestrol effectiveness in increasing hypophysial stores and producing Gonadotropin cyclical secretions.

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