Bromocriptine in the Management of Infertile Men after Surgery of Prolactin Secreting Adenomas

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This study evaluated bromocriptine treatment in nine patients with prolactin secreting adenomas who continued to have elevated circulating levels of prolactin after surgery, and who were interested in improving their sperm counts. These patients were brought into the study 3.2 ± 1.8 years (mean ± SD) after surgery. All of them presented with high circulating levels of prolactin, and eight of the patients had oligozoospermia (range 0–10 × 10^6 spermatozoa/ml). LH and testosterone levels were low in seven patients, and eight patients had low FSH values. All patients were treated for 90 days with 7.5 mg/day of bromocriptine. After treatment, prolactin levels decreased significantly in all patients, while sperm counts increased significantly in five of them. Testosterone levels increased in four subjects. Bromocriptine therefore seems useful in the management of this type of patient because of the observed decline in prolactin levels and the increase in sperm counts. Possible mechanisms involved in this action are discussed.

Key words: prolactin, hypophysis adenomas, spermatogenesis, bromocriptine treatment.

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It is known that some patients with pituitary prolactin secreting adenomas continue to have high circulating levels of prolactin and gonadal insufficiency after surgery (Prescott et al, 1982). This is seen more often in patients with large adenomas which cannot be completely excised (Derome et al, 1979). The continued elevation of prolactin levels with gonadal insufficiency is of major importance to those men who are interested in recovering their fertility. The existence of drugs such as 2 Bromo-α-ergocriptine (BEC), which reduce prolactin levels, offers a therapeutic approach to this problem (Thorner and Besser, 1977; Nagulesparen et al, 1978). The aim of this trial was to evaluate the results of bromocriptine therapy in a group of men who had had surgery for chromophobe adenomas, and who continued long after surgery to have elevated prolactin levels as well as oligozoospermia with asthenospermia.

Materials and Methods

Nine patients out of a total population of 21 were chosen for the study. These patients were selected because of their interest in fathering children. The other 12, who were not included in the evaluation, had rejected having semen analyses. All of them had had surgery for a chromophobe pituitary adenoma. The age range at the time of surgery was 16 to 42 years.

The evaluation was performed 3.2 ± 1.8 years ($\bar{x}$ ± SD) after surgery. Two patients (nos. 6 and 9, Table 1) showed adrenal insufficiency, and patients 3 and 6 had thyroid insufficiency. At the time of this study, all of them were under specific substitutive medication and were clinically compensated. Patients 2, 3, 5, 6, 7, and 8 had mild to severe sexual dysfunction. Patients 4 and 5 had galactorrhea and gynecomastia. The following determinations were performed in all patients at the beginning of the study: LH, FSH, prolactin, testosterone. Basal serum levels were determined at 8:00 a.m. after a night's rest and an 8-hour fast. LH and FSH responses to a 50 μg i.v. injection of synthetic LHRH were also recorded. Blood samples were obtained under basal conditions 30 and 60 minutes after the injection.

LH and FSH levels were determined by RIA (Midgley Jr, 1966, 1967), and their values were expressed in mUI/ml in terms of the 2nd IRP–HMG. Prolactin and testosterone levels were also determined by RIA (Sinha et al, 1973; Ismail et al, 1972), and their values were expressed in ng/ml. Coefficients for intra and interassay variations

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TABLE 1. Hormonal Results and Sperm Counts Before and After Administration of Bromocriptine*

	Serum Prolactin ng/ml		Plasma Testosterone ng/ml		Plasma Gonadotropins												Sperm Count Millions/ml	
					Before BEC Therapy						After BEC Therapy							
					LH (mIU/ml)			FSH (mIU/ml)			LH (mIU/ml)			FSH (mIU/ml)				
Patients	Before	After	Before	After	B†	30′‡	60‡	B	30′	60′	B	30′	60′	B	30′	60′	Before	After
1	45	15	3.3	3.8	11.9	43	43	1.5	2.7	2.7	19	38	87	2	2	2	5	60
2	160	3.5	1.2	4.2	4	12	11	0	0	5	2.6	8.5	36	3.9	3	4	1	45
3	48	20	1.1	3.3	3.2	8.5	8.4	3.5	1.4	4.2	3.8	3.2	9.5	3.2	2	2	1.5	33
4	640	160	3.7	3.9	10	15	11	6	6	6.5	20	63	55	7.7	5.2	21	10	89
5	200	80	0.1	4.4	1	4	5	3.5	8.5	4.5	1	8	6	4.3	3.5	9.5	7.5	91
6	82	11.5	0.6	1.1	0.2	0.2	0.2	0	0	0	0.5	0.2	0.7	0	0	0	0	0
7	150	115	1.9	2	4.3	6	10	3.3	1.7	2.5	3	8	10	4.3	4.7	2.3	3	0
8	150	42	0.6	1.8	1	1	1	0	0	0	0	9.4	5	1.4	4.8	2.1	0	0
9	150	74	2.6	4.3	2.2	3.5	2.5	3.1	3.4	1.7	3.2	3.8	4	4.9	4.8	3.3	69	90

* 7.5 mg/day for 90 days.
† Basal gonadotropin level.
‡ 30 min and 60 min responses to LHRH stimulation (50 μg i.v. in a 100 μl/ml dilution).

were 8% and 16%, respectively. Semen analysis was performed in all patients after four days of sexual abstinence with specimens obtained by masturbation. Because of ethical and/or clinical reasons, it was possible to perform only one semen analysis before treatment and one after 90 days of BEC therapy. Semen analyses were performed according to a technique previously described (McLeod, 1965).

All patients were treated with bromocriptine at a dose of 7.5 mg per day for 90 days. This course of treatment was established according to the time frame for spermatogenesis in man. After treatment, basal and post-LHRH prolactin, testosterone, LH and FSH determinations, as well as sperm counts, were repeated. After the evaluation, all patients continued with bromocriptine therapy. Those patients who had above normal prolactin values at evaluation were given increased dosages of up to 15 mg per day.

Results

Table 1 shows the results of hormonal determinations and sperm counts before and after bromocriptine treatment. All patients had elevated prolactin levels before treatment and experienced a significant decrease afterwards. Moreover, four of them entered the normal range.

Before treatment, basal levels of LH were low (<5 mIU/ml) in seven patients and normal in two of them. The LH response to LHRH was significantly increased in two patients and low in the remaining seven. After treatment, basal LH values and in response to LHRH were not significantly changed. FSH basal values before treatment were low in eight patients, and the response to LHRH was low in the same eight patients. After treatment, FSH levels were not significantly modified. Testosterone levels were low before treatment in seven patients (<3 ng/ml). The two patients with normal testosterone levels (1 and 4) remained within the normal range after therapy; four patients (2, 3, 5, and 9) who had low T levels entered the normal range after treatment, while three patients (6, 7, and 8) still had low circulating testosterone levels.

Sperm concentration in the ejaculate was low or nil in all but one patient before treatment. After treatment, five patients had significantly increased sperm concentrations of 20×10^6/ml and total sperm numbers in the ejaculate exceeding 120×10^6. These values are generally considered to be within the normal range (McLeod, 1951; Amelar et al, 1973). No significant correlation was observed between LH and FSH values and sperm counts. Those patients with normal levels of testosterone after treatment (two with initially normal values and four who had increased testosterone levels after treatment) were the ones who achieved significant increases in sperm concentrations which brought them into the normal range. Only one patient (2) fathered a child after four months of treatment. With the exception of patient 6, all patients with previous sexual dysfunction improved their sexual potency. No correlation was found between improved sperm counts after bromocriptine therapy and the degree of functional pituitary deficiency prior to treatment.

Discussion

The main conclusions of this study are 1) the clear efficacy of BEC in reducing prolactin levels in those patients who continued to have high prolactin values after surgery; 2) the improvement in sperm counts in most patients; and 3) the enhancement of testosterone circulating levels in four patients who prior to treatment had T values that were clearly below the normal range.

The persistence of elevated prolactin levels after surgical removal of pituitary adenomas has been previously described (Franks et al, 1978). The decrease in prolactin levels in these patients after bromocriptine therapy is merely a confirmation of the properties of this drug (del Pozo and Fluckiger, 1973). However, there are only a few reports on the effectiveness of bromocriptine treatment for the recovery of fertility in patients with oligozoospermia after pituitary surgery. Carter et al (1978) observed that the administration of BEC in hypogonadic patients following the removal of pituitary adenomas resulted in a rise in testosterone levels and some improvement of impotence in some of the patients, even though there was almost no modification of LH levels.

The results of this study, in which bromocriptine was the only therapy, suggest that the improved sperm counts could be attributed to the decline in prolactin levels. A direct effect of this drug on the testis could not be ruled out, but evidence for this hypothesis is still weak (Bartke and Lackritz, 1981).

In patients 4 and 5, prolactin values decreased with bromocriptine but remained above the upper limits of the normal range. In spite of this, these patients experienced a significant improvement in sperm counts. This fact is hard to explain. It is possible that the decrease in prolactin could have been sufficient to improve gonadotropin secretion (case 4) or else the testicular response to gonadotropins (case 5).

It was obvious that the effect of the treatment did not significantly affect LH and FSH levels. Thus the improved sperm counts hardly seem attributable to a mechanism that would involve an increase in gonadotropin secretion, the only exception being patient 4. Other authors have also observed incongruent results; some of them found increased gonadotropin secretion (Seki and Seki, 1974) while others obtained results similar to ours (Franks et al, 1978).

It was interesting to note that testosterone levels increased in some patients but were not correlated with a parallel increase in gonadotropin secretion; one can speculate that the BEC-induced decline in prolactin levels increased the testicular response to LH (Perryman and Thorner, 1981).

Although the mechanisms involved remain unclear, the results of this study suggest that since bromocriptine decreases prolactin levels, it could be useful for increasing sperm counts in those patients who continue to have elevated prolactin levels after surgery for pituitary adenomas. Since LH values are not significantly modified by this treatment, the increase in sperm counts could be attributed to an increase in the testicular response to LH and/or an improvement of the intratesticular content of testosterone.

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References

Amelar R, Dubin L, Schoenfeld C. Semen analysis. Urology 1973; 2:605–611.

Bartke A, Lackritz R. Bromocryptine stimulates testosterone production by mouse testes in vitro. Fertil Steril 1981; 35:473–476.

Carter J, Tyson J, Tolis G, Van Vliet S, Faiman C, Friesen H. Prolactin-secreting tumors and hypogonadism in 22 men. N Engl J Med 1978; 299:847–852.

del Pozo E, Flückiger E. Prolactin inhibition: experimental and clinical studies. In: Pasteels JL, Robyn C eds. Human prolactin. New York: American Elsevier Publishing, 1973; 291–301.

Derome P, Peillon F, Bard R, Jedynak C, Racadot J, Guiot G. Adénomes á prolactine résultats du traitment chirurgical. Nouv-Presse Méd 1979; 8:577–583.

Franks S, Jacobs H, Martin N, Nabarro J. Hyperprolactinaemia and impotence. Clin Endocrinol 1978; 8:277–287.

Ismail A, Niswender G, Midgley A. Radioimmunoassay of testosterone without chromatography. J Clin Endocrinol Metab 1972; 34:177–184.

McLeod J. The semen examination. Clin Obstet Gynecol 1965; 8:115–120.

McLeod J. Semen quality in one thousand men of known fertility and eight hundred cases of infertile marriage. Fertil Steril 1951; 2:115–119.

Midgley Jr A. Radioimmunoassay: a method of human chorionic gonadotropin luteinizing hormone. Endocrinology 1966; 79:10–18.

Midgley Jr A. Radioimmunoassay for human polide stimulating hormone. J Clin Endocrinol Metab 1967; 27:295–299.

Nagulesparen M, Ang V, Jenkins J. Bromocryptine treatment of males with pituitary tumors, hyperprolactinaemia and hypogonadism. Clin Endocrinol 1978; 9:73–79.

Perryman R, Thorner M. The effects of hyperprolactinaemia on sexual and reproductive function in man. J Androl 1981; 5:233–241.

Prescott R, Kendall–Taylor P, Hall K, Johnston D, Crombie A, McGregor A, Hall R. Hyperprolactinaemia in men—response to bromocryptine therapy. Lancet 1982; 8266:245–248.

Seki M, Seki M. Successful ovulation and pregnancy achieved by CB 154 (bromoergocryptine) in a woman with Chiari–Frammel syndrome. J Clin Endocrinol Metab 1974; 38:508–509.

Sinha Y, Selby F, Lewis V, Vanderlaan W. A homologous radioimmunoassay for human prolactin. J Clin Endocrinol Metab 1973; 36:509–519.

Thorner M, Besser G. Hyperprolactinaemia and gonadal function: results of bromocryptine treatment. In: Crosignani PG, Robyn C eds. Prolactin and human reproduction. London: Academic Press, 1977; 285–301.