BROMOCRIPTINE IN THE TREATMENT OF HYPERPROLACTINEMIA AND INFERTILITY*

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It is well recognised that Bromocriptine, the anti-prolactin agent effectively corrects the gonadal dysfunctions associated with hyperprolactinemia, and is the most physiological approach to the management of infertility of hyperprolactinemic origin. We employed Bromocriptine to induce pregnancy in 20 hyperprolactinemic infertile patients investigated for secondary amenorrhoea, oligomenorrhoea or anovulation. Investigations included endocrine evaluation and sella study. Bromocriptine was administered in a dose of 5 to 7.5 mg/day for 2 to 6 months or more, except in 2 patients who received cyclical therapy (2.5 mg/day for 20 days in a cycle) for 6 cycles. Ovulation was restored (B.B.T. evidence) in 10 of the 13 patients (76.90%), excluding the 7 patients who have not completed 6 months treatment. Among the 10 patients who responded, husbands of 2 patients were concurrently treated for severe oligospermia. Considering the other 11 patients, 6 became pregnant (54.55%). Two patients conceived after the 2nd month of treatment, 2 after 4 cycles, 1 after 5 cycles and 1 after 9 months of treatment. Side effects were minimal and were experienced only on initiation of therapy. The patients successfully treated included one subject with suspected prolactinoma (as revealed by Sellar X-ray), and she is on Bromocriptine (7.5 mg/day) therapy during pregnancy. Another successfully treated patient was a subject undergoing unsuccessful attempts at artificial donor insemination. On Bromocriptine therapy she conceived by the 4th cycle of insemination. The first patient to achieve pregnancy delivered a healthy male baby by caesarean section.

Introduction

One of the most important advances in reproductive endocrinology is the identification of 'prolactin' as a distinct anterior pituitary hormone (Hwang *et al*, 1972), and the knowledge that hyperprolactinaemia produces disturbances of gonadal function resulting in amenorrhoea, oligemenorrhoea, anovulation and luteal insufficiency (Archer *et al*, 1974; Corenblum *et al*, 1976; and Chang, 1978). This syndrome complex has gained much clinical importance and interest, partly due to the development of a sensetive radioimmunoassay for prolactin (Hwang *et al* 1972), and equally, due to the simultaneous development of Bromocriptine, a pharmacological agent that can effectively

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Accepted for publication on 12-8-82.

suppress the unphysiological level of prolactin (Lloyd *et al*, 1975 and Thorner *et al*, 1974).

Female infertility due to anovulation and accompanied by hyperprolactinemia has been successfully treated with bromocriptine (Parlodel), a long acting dopamine agonist, by effectively suppressing the prolactin level (Wiebe *et al*, 1977; Parkes, 1977; Archer, 1977; Badano *et al*, 1979, Vaughn and Hammond, 1980; Kinch, 1980 and Pepperell, 1981). Not only in functional hyperprolactinaemia, but also in patients with prolactin-secreting pituitary adenomas pregnancies have been induced by bromocriptine commonly, and successful outcome for pregnancy doccumented (Corenblum, 1979; Gemzell and Wang, 1979; Marshall, 1980; and Canales *et al*, 1981). Considering the safety of the drug and easy administration, bromocriptine has also been employed in the treatment of euprolactinemic infertile subjects with amenorrhoea, anovulation or idiopathic infertility (Tolis and Naftolin, 1976; Moggi *et al*, 1979; Jacobs and Wright, 1978).

Bromocriptine treatment of infertile women was initiated in our Infertility Unit from June, 1981. The study was designed to determine the scope of bromocriptine treatment ovulatory disorders of normoprolactinaemic subjects and patients with idiopathic infertility, in addition to the established role in hyperprolactinaemic anovulations (Rajan and Sreedevi, 1982). However, in the present paper we confine ourselves to our experience with bromocriptine (Parlodel) in the management of hyperprolactinaemic infertile patients with secondary amenorrhoea, oligomenorrhoea and anovulatory cycles. The report relates to 20 such patients who had a detailed infertility work-up which included all basic investigations, evaluation of pelvic factors by HSG/Laparoscopy/Laparotomy. complete endocrine profile and skull X-ray for evidence of pituitary tumour.

Material and Methods

In our infertility work-up prolactin assay was considered mandatory for subjects with secondary amenorrhoea, oligomenorrhoea, anovulation and luteal insufficiency, particularly when they fail to respond to ovulation induction by clomiphene citrate (Fertyl). If the menstrual dysfunction was associated with significant galactorrhoea and or hypoestrogenism no ovulation inducing drugs were administered prior to prolactin assay. In addition to prolactin a complete hormone profile was obtained before starting the medication.

In 20 patients with secondary amenorrhoea, oligomenorrhoea or anovulation endocrine evaluation revealed an abnormally elevated lefel of prolactin. All those patients were considered for bromocriptine therapy. Before treatment was initiated, all patients had undergone the following examinations: (1) General, physical and vaginal examination, and examination of the breast for galactorrhoea. (2) A radiological examination, a lateral view skull X-ray, was performed to study the sella turcica. (3) A complete survey for other causes of infertility, including the male factor. (4) Determination of thyroid function by serum T_3 and T_4 values, particularly to exclude hypothyroidism. (5) determination of serum F.S.H. and L.H. values, and urinary oestrogens, androgens and pregnanediol falues. (6) All patients recorded their basal body temperature prior to therapy and during the entire period of treatment.

The usual treatment schedule was 5 mg of bromocriptine/day, taken in two devid-

ed doses with food. The treatment was started with a small dose of 1.25 mg/day and gradually increased to 5 mg. In 2 patients, however, cyclical therapy with 2.5 mg/day for 20 days starting from the 5th day of the cycle was given. If the patient did not respond as revealed by menstruation and biphasic BBT, the dose was increased to 7.5 mg. The average duration of treatment was 6 months. Side effects included mild nausea with occasional vomiting, dyspepsia, constipation and mild postural hypotension. All these problems could be easily managed by gradually increasing the dose, administering with food, and proper diet habits. Moreover, the side effects were seen only in the initial phase of the treatment.

Results

Among the 20 patients treated, 12 had galactorrhoea, 8 had secondary amenorrhoea, 3 had oligomenorrhoea and 9 had anovulatory cycles. Excluding the 7 patients who had not completed atleast 6 months treatment, among the 13 subjects 10 responded by showing evidence of ovulation and menstruation (BBT charts I to VI). In this group 2 subjects had male factor in the form of severe oligospermia (being treated with HCG). Eliminating all these patients, among the 11 patients receiving bromocriptine regularly and where a male factor did not operate, 6 became pregnant within 2 to 9 months of treatment (54.55%) (Table I).

Conception occurred in 2 patients after the 2nd month of treatment, and both were patients with secondary amenorrhoea (patients No. 4 and 10). Both responded by menstruation after the first month of treatment, patient No. 4 by ovulatory menstruation and patient No. 10 by anovulatory cycle. The BBT of the patient No. 4 of the 2nd cycle of treatment in which she conceived.

Two patients became pregnant after 4 cycles of treatment, and one (patient No. 6) was treated for secondary amenorrhoea with 5 mg/day for 3 months. She did not even menstruate, but when the dose was enhanced to 7.5 mg in the 4th cycle she showed a biphasic BBT and conceived without ever menstruating. The other patient who became pregnant by the 4th month was having anovulatory infertility and was undergoing A.I.D. under clomiphene regulation without any results. She also had 3 months treatment with 5 mg and 4th month enhanced dose of 7.5 mg during which period she conceived by A.I.D.

One patient conceived after 5 cycles of treatment. She was oligomenorrhoeic and developed ovulatory cycles with 5 mg/day schedule, and in the same dose she became pregnant after the 5th cycle. Another patient who was anovulatory but having almost regular cycle was treated by cyclical treatment schedule with 2.5 mg/day for 20 days/4 months and 5 mg/day for 20 days/2 months without any response, started regular ovulation with 7.5 mg/day continuous therapy and subsequently conceived after 9 months of treatment.

Among those who had no pregnancy, 4 subjects had regular ovulation following bromocriptine treatment, either 5 mg or 7.5 mg/day and of them 2 patients had male factor in the form of severe oligospermia. There was no occasion to discontinue the drug in any patients because of side effects.

The first patient (No. 1) to have become pregnant in the present series delivered a healthy male baby at term by caesarean

TABLE I
Bromocryptine for Hyperprolactinaemia

Age	Infertility	Menstrual cycles	Galactorrhoea	Skull	Prolactin ng/ml.	Dose and duration of treatment (mg/day)	Results and Remarks
35 yrs	10 yrs	Oligomenorrhoea	+	Normal	280 ng/ml	5 mg/day/5 cycles	*Pregnancy* Caesarean section Healthy Male baby (Total: 190 tablets)
26 yrs	5 yrs	Regular	Nil	Normal	65 ng/ml	2.5 mg/20 days/4 cycle (Cyclical) 5 mg/20 days/2 cycles (Cyclical) 7.5 mg/day/3 cycles	*Pregnancy*—10 weeks (Total: 430 tablets)
35 yrs	6 yrs	Secondary Amenorrhoea	+	Normal	85 ng/ml	5 mg/day/2 months 7.5 mg/day/4 months	Monophasic B.B.T. menstruation (Total: 480 tablets)
30 yrs	6 yrs	Secondary Amenorrhoea	+	Normal	26 ng/	5 mg/day/1 month 5 mg/day/1 month	Ovulatory cycle and menstruation *Pregnancy*—32 weeks (Total: 120 tablets)
34 yrs	6 yrs	Delayed cycles	+	Normal	1114mg/1	5 mg/day/6 cycles 7.5 mg/day/3 cycles	Regular ovulatory cycles (Total: 630 tablets)
35 yrs	11 yrs	Secondary Amenorrhoea	Nil	Normal	75 ng/ml	5 mg/day/3 months 7.5 mg/day/1 month	No periods BBT—Biphasic and *Pregnancy* No follow up (Total: 270 tablets)
34 yrs	5 yrs	Regular cycles	Nil	Normal	33 ng/ml	5 mg/day/4 cycles 7.5 mg/day/5 cycles	Regular ovulatory cycles) (Total: 540 tablets)

Age	Infertility	Menstrual cycles	Galactorrhoea	Skull	Prolactin ng/ml.	Dose and duration of treatment (mg/day)	Results and Remarks
35 yrs	6 yrs	Secondary Amenorrhoea	Nil	Normal	105 ng/ml	5 mg/day/1 month 7.5 mg/day/7 months	No menstruation (Total: 690 tablets)
25 yrs	4 yrs	Delayed cycle	+	Normal	115 ng/ml	5 mg/day/3 cycles 7.5 mg/day/1 cycle	A.I.D. Ovulatory cycles *Pregnancy* No follow up (Total: 270 tablets)
26 yrs	2 yrs	Secondary Amenorrhoea	++	Slight enlargement of sella	27 ng/ml	5 mg/day/1 month 7.5 mg/day/1 month	*Pregnancy*—12 weteks (Total: 150 tablets) Menstruated (Monophasic BBT)
30 yrs	6 yrs	Secondary Amenorrhoea	+	Normal	55 ng/ml	5 mg/day/6 months	No response (Total: 360 tablets)

section. Patient No. 10 who was successfully treated had radiological evidence of pituitary tumour (Fig. 1). She complained of visual disturbance at 12 weeks of pregnancy which was confirmed by visual field charting. Since then she has been on bromocriptine treatment in a dose of 7.5/mg/day and is being carefully followed.

Discussion

Since a clinically applicable assay of prolactin has become available, it has been possible to ascertain the aetiology of many of the menstrual disorders and anovulations unsuccessfully treated by ovulation inducing drugs such as clomiphene citrate. Moreover, the almost simultaneous development of the new anti-prolactin agent, bromocriptine, has offered a medical approach to the successful induction of ovulation and pregnancy in hyperprolactinaemic infertile subjects. In our preliminary study we could induce regular ovulation in 76.90% of hyperprolactinaemic infertile women investigated for secondary amenorrhoea, oligomenorrhoea or anovulation, and achieve pregnancy in 54.55% of them. The results are commendable because many of the patient were above the age of 30 years (oldest being 35 years) and were having long period of infertility, many between 6 to 11 years. Moreover a good number of them were treated with various ovulation inducing drugs and declared intractable with no hope of further treatment. Since recent studies document successful outcome for pregnancy in patients with prolactin producing pituitary tumours (Corenblum, 1979; and Canales *et al* 1981) and tumour regression with bromocriptine treatment (Corenblum, and Hanley, 1981), we had attempted induction of pregnancy in the one patient who had radiological and

endocrine evidence of a pituitary prolactinoma.

Acknowledgement

We are grateful to Dr. V. Vasudeviah, Pharmacological division of Sandoz (India) P. Ltd., for supporting this study on Bromocriptine in our infertility unit. We thank the endocrinologists, Dr. C. B. Sridhar of St. John's Medical College, Bangalore, and Dr. P. Govindarajulu of Taramani Institute of Basic Medical Sciences, Madras, for their valuable help in endocrine evaluation. We are also indebted to Dr. K. C. Joseph, Associate Professor of Radiology, Medical College, Kottayam for the radiological evaluation of the patients. Our thanks are due to the Superintendent, Medical College Hospital, Alleppey, for his kind permission to analyse the Hospital records.

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See Fig. on Art Paper VII