Clinical Reports

Six year remission of ACTH-dependent Cushing’s syndrome using bromocriptine

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Summary: A patient with ACTH-dependent Cushing’s syndrome remained in clinical and biochemical remission six years after pituitary irradiation and while on bromocriptine therapy. When bromocriptine was discontinued urinary free cortisol values became elevated, and were not suppressed by dexamethasone. After reintroduction of the drug, remission was again obtained. It is concluded that bromocriptine is responsible for continuing longterm remission in this case. The possible use of bromocriptine as an adjunctive therapy in ACTH-dependent Cushing’s syndrome is discussed.

Introduction

In many centres the first approach to therapy for pituitary-dependent Cushing’s syndrome is selective pituitary adenomectomy by the transphenoidal approach. Other approaches to therapy have been advocated – external or internal pituitary irradiation, total or subtotal adrenalectomy and various drugs. The latter have included the serotonin antagonist cyproheptadine (Krieger et al., 1975) and bromocriptine (Spark & Dickstein, 1979) a dopamine agonist which also has an antimitotic action on pituitary cells in vivo (Davies et al., 1974; Lloyd et al., 1975).

It has recently become apparent that transphenoidal surgery is not uniformly successful in controlling hypercortisolism. A recent review by Burch (1983) has revealed cure rates between 10 and 100% in various centres. A number of patients therefore require further treatment after unsuccessful or only partially successful microsurgery.

Since reports on the efficacy of bromocriptine at any stage of Cushing’s disease are relatively rare, and mostly of a short term nature (Lamberts & Birkenhager, 1976; Lamberts et al., 1977; Kennedy et al., 1978; Ambrosi et al., 1979; Lamberts et al., 1980; Pieters et al., 1982; Lamberts et al., 1982; Kapcala & Jackson, 1983), it is of interest to report in detail a prolonged remission (six years) of Cushing’s disease in a patient who concurrently received external pituitary irradiation. Various possibilities to account for this remission were considered. These were the effect of external pituitary irradiation, the effect of bromocriptine and finally the possibility of spontaneous remission, as previously described (Hayslett & Cohn, 1967). Bromocriptine therapy was therefore withdrawn and the patient carefully reassessed over a four month period.

Case report

A 34 year old man was referred with facial swelling, lack of energy, progressive muscle weakness, impotence, depression and polydipsia. On examination he was clinically cushingoid. He had profound hypokalaemia (2.5 nmol/l). Serum cortisol values were markedly elevated – 08.00 h 1446 nmol/l, 23.00 h 1690 nmol/l. The corresponding plasma ACTH values were high at 187 ng/l and 116 ng/l respectively. Serum cortisol at 09.00 h, after four days of dexamethasone, 8 mg/day, was not suppressed at 1180 nmol/l.

Urgent medical therapy was instituted using aminoglutethamide, 250 mg twice daily and metyrapone, 750 mg six hourly. Two weeks later, bromocriptine, 2.5 mg, three times daily was introduced. Four weeks after the start of therapy, aminoglutethamide and metyrapone were withdrawn and bromocriptine therapy alone continued. External pituitary irradiation was commenced eight weeks after presentation, the patient receiving a total of 4500 rads in 20 doses over a four week period. Seventy weeks after the start of therapy the patient was in clinical remission (Kennedy et al., 1978) and the urinary free cortisol and

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serum cortisol were within the normal range.

Six years later the patient remained in remission on bromocriptine (2.5 mg b.d.) alone. Urinary free cortisol was 182 and 255 nmol/24 h on two occasions (normal under 450 nmol/24 h). Bromocriptine therapy was withdrawn and the patient carefully reassessed over a four month period. The protocol was explained in detail to the patient who gave informed verbal consent for the reassessment.

Methods

Blood, for plasma ACTH estimation, was withdrawn into tubes containing EDTA. The samples were promptly centrifuged and the plasma stored at −20°C until estimation of plasma ACTH by radioimmunoassay (RIA), using reagents supplied by Immuno Nuclear Corporation. The normal range was found to be <75 ng/l. The between batch coefficient of variation was 7.1% with a mean value of 98 ng/l. Serum cortisol samples were stored at −20°C until estimation by a direct radioimmunoassay featuring a 125I radioligand and a solid phase antibody (Riad-Fammy et al., 1979). On completion of all 24 hour urine collections the volume was measured and aliquots were stored at −20°C. For estimation of urinary free cortisol, the urine was extracted with dichloromethane and assay for free cortisol performed (RIA) on the dried solvent residue (Riad-Fammy et al., 1979).

Results of reassessment

After cessation of bromocriptine therapy the patient was monitored by measuring the 24 hour urinary free cortisol (UFC) output. At no stage did the patient have return of the clinical features described previously. After two months, UFC became elevated (1250 nmol/24 h) and a standard low dose dexamethasone test (0.5 mg, six hourly for 48 h) was performed. Urinary free cortisol was not suppressed (Day 2 – 802 nmol). There was similar lack of suppression during a standard high dose test (2 mg, six hourly for 48 h) (Day 2 – 1890 nmol).

Two weeks later the patient was admitted to the Metabolic Unit and a two hourly profile of plasma ACTH and serum cortisol was obtained over 24 hours. Bromocriptine, 2.5 mg, 12 hourly was then restarted and the same measurements made over 24 hours (Figure 1). There was a statistically significant fall in both cortisol and ACTH as compared to the control day (P < 0.001 and P < 0.001 respectively). The patient returned home on 2.5 mg bromocriptine twice daily and one month later was readmitted for a further 24 hour profile (Figure 1). On this occasion urinary

![Graph](http://pmj.bmj.com/)

**Figure 1.** 24 hour profile of plasma ACTH and serum cortisol on a control day (○), during the first day of therapy (△) with bromocriptine 2.5 mg twice daily at 08.00 and 20.00 and (▲) after one month of therapy. (▽ denotes time of dosage).
free cortisol was 339 nmol/24 h and serum cortisol and plasma ACTH values were still significantly lower as compared to the previous control day ($P < 0.001$ and $P < 0.001$ respectively).

The patient remains in remission. Recently, while on bromocriptine, a DR 3 Somatom (Siemens) 4th generation computed tomographic (CT) scan has shown normal sized adrenal glands, normal lung fields (8 mm thickness cuts at 10 mm intervals) and evidence of a small microadenoma occupying the left anterior portion of the sella turcica, thus providing evidence that the ACTH overproduction originated from the pituitary gland.

Discussion

This report demonstrates that bromocriptine can be responsible for long term remission in Cushing's disease. Only seven patients have previously been studied after treatment for more than a month (Kapcala & Jackson, 1983). The present case is the longest known of remission of Cushing's disease on bromocriptine. Since the plasma ACTH levels on no treatment after bromocriptine withdrawal were lower than those at presentation it can be inferred that external pituitary medication also had an effect. However, urinary free cortisol values rose over some months after bromocriptine was stopped and it remains a possibility that ACTH and cortisol values had not reached a plateau when the drug was restarted.

If bromocriptine is advocated as either a primary or an adjunctive therapy in Cushing's disease it is of some importance to know how many patients are likely to respond. Most studies have concentrated on the acute response to bromocriptine therapy. The largest series is that of Pieters et al. (1982), who found a statistically significant fall in plasma cortisol over a four hour period in three of 17 patients following a 5 mg test dose. Three others had falls which were not significant. However, most series, including that of Pieters, have not had adequate control data, not having studied cortisol levels across a day when the drug was not given. Combining a number of studies (Kennedy et al., 1978; Ambrosi et al., 1979; Lamberts et al., 1980; Pieters et al., Lamberts et al., 1982; Kapcala et al., 1983) it would appear that a distinct fall in cortisol can be expected in, at the very most, between 32 and 40% of cases. These figures may be falsely high for three reasons - the lack of control data, the fact that results for two papers by Lamberts et al. are cited and thus some patients may be included twice, and finally the fact that positive results are more likely to be reported than negative ones.

It is of interest to note that in all studies in which there has been a more chronic assessment of the drug, patients who have initially responded to it have subsequently escaped from control. The explanation for this escape has not been clear. In the present case there is a difference in the ACTH and cortisol response at Day 1 of reintroduction and that seen after one month of treatment (Figure 1). There is an elevation of both cortisol and ACTH between 8 and 12 hours after each bromocriptine dose on the latter occasion. It is possible that this escape prevents our patient from becoming hypoadrenal, as has been previously reported (Lamberts et al., 1977). However, the escape seen in our patient may also explain some of the more serious escape phenomena described in the literature. Perhaps careful analysis of response of cortisol to bromocriptine throughout 24 hours would allow remission to be regained in such cases by adjustment of dose and dose intervals.

The present report documents that bromocriptine is responsible for a six year remission of ACTH-dependent Cushing's syndrome. Each dose causes sustained depression of ACTH and cortisol over eight hours. Since some patients with pituitary-dependent Cushing's syndrome are not cured by transphenoidal surgery (Burch et al., 1983) and since bromocriptine can cause remission in some cases of the disease (at the very most 40%) it would appear worthwhile to carefully assess the drug's effect in that group. Its use may obviate the necessity for reoperation or for bilateral adrenalectomy. To achieve optimal responses careful attention should be paid to dose and to dosage intervals.

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