

Using midwives to supervise and top-up epidural analgesia undoubtedly encourages more anaesthetists and obstetricians to insert the catheter initially for induction of analgesia, as they do not have to be in virtually continuous attendance during the labour. Supervision and topping up of epidurals, however, cannot safely be left in the hands of medical or nursing personnel unless they have been fully trained and can maintain their skill in dealing with complications and emergencies that may include the need for urgent endotracheal intubation. Therefore, providing a 24-hour rota of midwives trained to undertake this work should be considered. Any training course must include full and practical instruction in possible resuscitation procedures; thereafter, there must be continuing inservice opportunities to practise these skills. It would also help if the resources for epidural analgesia were concentrated in centres that could offer a 24-hour service. Patients asking for epidural analgesia could then be booked at such units, the personal cost of their preference being the need to travel to a centre perhaps not so conveniently situated geographically.

The public demand for epidural analgesia stems from the knowledge of its efficacy. In only a few cases are there potential

medical benefits from epidural analgesia. Thus in attempting to provide every mother with the comfort and safety that is her right during childbirth we should also develop more effective methods of pain relief, widely applicable in the present and foreseeable context of obstetric practice.

We should like to thank all the obstetricians and anaesthetists who contributed data on which this study is based.

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(Accepted 26 July 1979)

Effects of bromocriptine on pituitary tumour size

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British Medical Journal, 1979, 2, 700-703

Summary and conclusions

In a prospective study designed to assess the influence of bromocriptine on pituitary tumour size 12 patients with pituitary tumours, eight of whom had suprasellar extensions, were treated for three months with 20 mg of bromocriptine daily after a gradual increase to this dose. The group comprised eight women and four men, five with prolactin-secreting adenomas, four with acromegaly, two with functionless adenomas, and one with Nelson's syndrome. All five patients with prolactin-secreting adenomas showed a reduction in pituitary tumour size as assessed by computerised tomography and metrizamide cisternography accompanied by a fall in prolactin concentrations and clinical and biochemical improvement in their hypopituitarism. One patient in this group had a visual-field defect before treatment, and this resolved. There was no radiological evidence of reduction in tumour size in the remaining seven patients, though this might reflect the fairly short duration of treatment, particularly in view of the ancillary evidence of clinical, biochemical, and visual-field improvement in some of the patients.

These results emphasise the potential value of bromocriptine in treating patients with large prolactinomas or

recurrences of such tumours after previous chiasmal decompression and conventional external megavoltage irradiation to the pituitary.

Introduction

The management of patients with pituitary tumours, particularly macroadenomas, remains unsatisfactory.¹ The development of prolactin radioimmunoassays² has shown that about two-thirds of the so-called "non-secretory chromophobe adenomas" are, in fact, prolactinomas.³ This finding, along with the introduction of bromocriptine, an ergot derivative⁴ with long-acting dopamine agonist properties⁵ that inhibits prolactin secretion, has added a new dimension to the treatment of pituitary tumours. While transsphenoidal surgery may result in high cure rates for patients with small prolactinomas (microadenomas), the cure rate falls with increasing tumour size.⁶⁻¹⁰ Conventional irradiation alone rarely lowers prolactin concentrations into the normal range,^{10 11} though results of long-term follow-up of patients treated by this method are awaited.

Several reports are now available on using bromocriptine in patients with hyperprolactinaemia irrespective of cause¹²⁻¹⁴ and show a rapid restoration of normal gonadal function, with fall of prolactin concentrations. Many of these patients have been receiving treatment for up to seven years without ill effect. With return of gonadal function an increasing number of women have become pregnant^{15 16} with no evidence of teratogenicity in their offspring. While bromocriptine has made a dramatic impact on the treatment of hyperprolactinaemia, its precise role in managing prolactinomas, particularly large tumours, has remained controversial, largely owing to uncertainty about its influence on tumour growth. The tendency has therefore been to treat such patients with surgery or irradiation to the pituitary, supplementing this treatment when necessary with bromocriptine.

The antitumour effect of ergot alkaloids on prolactin-secreting adenomas in the rat is well recognised.¹⁷⁻¹⁹ A similar

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effect has been reported in man,²⁰⁻²⁶ though most of the data have been based on indirect and subjective evidence of change in tumour size, such as improvement in visual fields. By taking advantage of the excellent visualisation of the pituitary gland made possible by computerised tomography (CT scanning) with intravenous iohalamic acid or intrathecal metrizamide contrast enhancement²⁷ and using the additional technique of metrizamide cisternography, we have investigated the effect of bromocriptine on pituitary tumour size in man.

Patients and methods

Eight women and four men with pituitary tumours, eight of whom had suprasellar extensions, were treated with a gradually increasing dose of bromocriptine to a total of 20 mg daily. They underwent full pituitary assessment, including visual-field testing, immediately before and three months after starting bromocriptine. They were followed up closely as outpatients throughout the treatment to permit early recognition of tumour progression. Table I shows their clinical features before treatment.

RADIOLOGY

Skull radiographs and CT scans (both without and with administration of intravenous iodinated contrast medium) were obtained in all patients before and after treatment. In two patients the extrasellar extension of the pituitary tumour was shown to be large on the CT scan, and no further investigations were performed before treatment. In the remaining patients the water-soluble contrast medium metrizamide was introduced intrathecally to enhance the intracranial subarachnoid spaces, especially the suprasellar cistern. Lateral radiographs (metrizamide cisternograms) and CT scans (metrizamide CT cisternograms) of the sella and juxtaseellar regions were obtained. In the follow-up studies, performed three months to one year after the start of treatment, similar metrizamide studies were done and skull radiographs and CT scans obtained in all but one patient.

We now use methods using intrathecal metrizamide instead of the more conventional pneumoencephalogram in assessing extrasellar extension of pituitary tumours. The indications, technique, results, and complications are described elsewhere²⁸ and are similar to those reported by others.²⁹ In general we find that this method is simpler and more easily tolerated by the patient than pneumoencephalography,

and the information obtained is often superior. When repeat examinations are required to show the effects of treatment, as in this study, then patient tolerance is especially important, and two metrizamide studies were carried out in nine of the 12 patients in this series. Indeed, one patient underwent metrizamide cisternography three times in seven months, which would rarely be tolerated by anyone undergoing pneumoencephalography.

HORMONAL STUDIES

Three basal samples taken 30 minutes after cannulation were measured for serum prolactin concentration by radioimmunoassay³⁰ (RIA) using MRC human prolactin 71/222 as standard. The mean of the three samples is reported. Serum thyroxine concentration was measured by RIA in unextracted serum.³¹ Thyroid-stimulating hormone (TSH) concentration was measured by RIA using MRC human TSH 68/38 as the standard,³² and the TSH response to 200 µg of thyrotrophin-releasing hormone (TRH) was assessed.³³ The responses of luteinising hormone (LH) and follicle-stimulating hormone (FSH) to 100 µg of luteinising hormone-releasing hormone (LHRH) given intravenously were measured by RIA using MRC standards 68/40 LH and 69/104 FSH respectively.³⁴ Plasma testosterone concentration was measured by RIA using a Sigma standard.³⁵

An insulin tolerance test was performed with measurement of blood concentrations of glucose, plasma 11-hydroxycorticosteroids,³⁶ and serum growth hormone (GH) by a specific RIA³⁷ using the international reference standard 66/217 (WHO) GH. In the patients with acromegaly serum GH concentrations were measured during a glucose tolerance test. Corticotrophin (ACTH) was assayed by RIA using a purified human ACTH standard.³⁸

Results

Table II summarises the overall response to bromocriptine in the 12 patients. Side effects were minimal and transient, and in no case interfered with the therapeutic regimen. Throughout the period of treatment there was no evidence of tumour progression.

CLINICAL RESPONSE

Ten of the 12 patients reported symptomatic improvement. The most dramatic and rapid change was seen in the patient in case 1

TABLE I—Clinical features of patients studied

| Case No | Age | Sex | Presenting symptoms | Previous treatment | Diagnosis |
|---------|-----|-----|---|--|---|
| 1 | 28 | M | Impotence, deteriorating vision, headache, and vomiting | 1974: surgery and external irradiation | Prolactinoma |
| 2 | 29 | M | Impotence, galactorrhoea | 1972: surgery and external irradiation | Prolactinoma |
| 3* | 60 | M | Impotence, headache | 1976: surgery and external irradiation | Prolactinoma |
| 4* | 54 | M | Impotence | | Prolactinoma |
| 5 | 34 | F | Galactorrhoea, amenorrhoea | | Prolactinoma |
| 6 | 31 | F | Amenorrhoea, headache, galactorrhoea | | Acromegaly and hyperprolactinaemia |
| 7 | 30 | F | Infertility, galactorrhoea, headache | 1969: yttrium implant | Acromegaly and hyperprolactinaemia |
| 8* | 33 | F | Irregular menstruation, headache | | Acromegaly and hyperprolactinaemia |
| 9* | 48 | F | Headache, enlarging hands and feet | | Acromegaly and hyperprolactinaemia |
| 10 | 60 | F | Deteriorating vision, headache | | Nelson's syndrome and hyperprolactinaemia |
| 11 | 34 | F | Amenorrhoea after taking oral contraceptive | | Functionless adenoma |
| 12 | 45 | F | Deteriorating vision, headache | 1964: surgery and external irradiation | Functionless adenoma |

*No suprasellar extension before treatment.

TABLE II—Response to bromocriptine

| Case No | Diagnosis | Presenting symptoms resolved | Improvement in impaired visual fields | Biochemical improvement in hypopituitarism | Radiological evidence of tumour regression |
|---------|----------------------|------------------------------|---------------------------------------|--|--|
| 1 | Prolactinoma | + | + | + | + |
| 2 | Prolactinoma | + | NA | + | + |
| 3 | Prolactinoma | + | NA | + | + |
| 4 | Prolactinoma | + | NA | + | + |
| 5 | Prolactinoma | + | NA | + | + |
| 6 | Acromegaly | + | + | + * | - |
| 7 | Acromegaly | + | + | + * | - |
| 8 | Acromegaly | - | NA | - | - |
| 9 | Acromegaly | - | NA | - | - |
| 10 | Nelson's syndrome | + | + | - | - |
| 11 | Functionless adenoma | + | NA | - | - |
| 12 | Functionless adenoma | + | + | - | - |

- = No change. + = Improved. NA = No abnormality detectable before treatment.

*Fall in fasting growth hormone concentration and in growth hormone concentration during a glucose tolerance test.

(reported fully elsewhere²³), in whom symptoms of raised intracranial pressure had resolved within one week after starting treatment and signs of a bitemporal hemianopia had disappeared by one month. Visual-field defects also improved in four other patients. Galactorrhoea stopped in four patients. All four men with prolactinomas noted return of libido and an appreciable improvement in potency. Menstruation returned in the single woman with a prolactinoma, in one with acromegaly (case 6), and in one of the two patients with a functionless adenoma (case 11). The two patients who showed no clinical improvement had acromegaly; their GH concentrations did not fall in response to bromocriptine.

HORMONAL RESPONSE

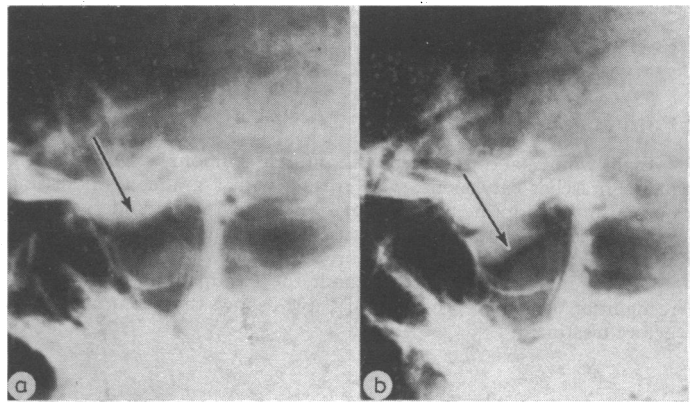
Irrespective of their mean pretreatment basal prolactin concentration all 12 patients showed a fall in prolactin in response to bromocriptine, which was greatest, as expected, in the patients with prolactinoma. Other than this fall in prolactin concentration there was no biochemical response to treatment in the two patients with functionless adenomas or the patient with Nelson's syndrome; in the latter the ACTH concentrations remained raised at over 700 ng/l (normal less than 80 ng/l). Of the four patients with acromegaly, those in cases 8 and 9 showed no fall in their fasting GH concentration in response to bromocriptine. In case 6 the fasting GH concentration fell and the minimum GH concentration during a glucose tolerance test fell from 88 mU/l to 40 mU/l after bromocriptine. Case 7 showed a fall in the minimum GH concentration during a glucose tolerance test from 230 mU/l to 40 mU/l three months after starting bromocriptine.

Table III shows the hormonal pattern in the five patients with prolactinoma. While the most dramatic change in all five was the fall in mean basal prolactin concentrations, they all showed an improved cortisol response to insulin-induced hypoglycaemia (though the influence of more-severe biochemical hypothyroidism before treatment in cases 1-3 cannot be excluded). Serum thyroxine concentration rose; the TSH response to TRH and LH response to LHRH improved in cases 1, 2, and 3; and in cases 2, 3, and 4 the plasma testosterone concentration rose though remained subnormal in cases 2 and 3.

RADIOLOGY

Plain skull x-ray films showed asymmetrical or global enlargement of the pituitary fossa in all patients. There was no change in the size of the fossa during treatment, though the duration of treatment was too brief for this to be expected. While symptomatic, visual-field, or

biochemical improvement in hypopituitarism was shown in 10 patients, the size of the pituitary tumour as assessed by radiology changed detectably in only the five patients with prolactinomas. In all five of these patients the size of the tumour was shown to have decreased by CT scanning alone or by metrizamide studies combined with CT scanning (figure). The examinations with metrizamide were



Metrizamide cisternogram before (a) and three months after (b) starting treatment with bromocriptine in case 4. The pituitary fossa is slightly enlarged and does not change. In (a) the diaphragma sellae is in its normal position (arrow), but in (b) it has dropped down into the fossa (arrowhead), indicating the development of a partial "empty sella" owing to tumour regression.

well tolerated by all patients. The side effects included headache, nausea, and occasional vomiting, these being only mild or moderate in severity and responsive to analgesics and intramuscular metoprolol. No other complications occurred.

Discussion

Of the 12 patients with pituitary tumours treated with bromocriptine for three months, five showed evidence of a decrease in the size of their tumour as assessed by CT scanning and metrizamide cisternography. All five patients had prolactin-secreting adenomas. In all of them there was clinical and biochemical evidence of improvement in their associated

TABLE III—Hormonal response to bromocriptine in five patients with prolactinomas. Responses of LH, FSH, and TSH measured after 0, 20, and 60 minutes

| Case No | Mean basal serum prolactin (mU/l) | | Plasma testosterone (nmol/l) | | Serum LH + FSH response to LHRH 100 µg IV (U/l) | | | | Serum TSH response to TRH 200 µg IV (mU/l) | | Serum thyroxine (nmol/l) | | Insulin-induced hypoglycaemia | | | |
|--------------|---|----------------|------------------------------|-------|---|-------------------|-------|----------|--|--------|--------------------------|-------|-------------------------------|-------|-------------------------------|-------|
| | Before | After | Before | After | Before | | After | | Before | After | Before | After | Peak serum GH (mU/l) | | Peak plasma cortisol (nmol/l) | |
| | | | | | LH | FSH | LH | FSH | | | | | Before | After | Before | After |
| 1 | 8730 | 2960 | 5.3 | 4.7 | 3.6 | 1.1 | 3.5 | 1.2 | 2.1 | 2.1 | 40 | 59 | <1 | <1 | 300 | 500 |
| | | | | | 3.5 | 2.0 | 4.9 | 2.0 | 1.4 | 3.7 | | | | | | |
| | | | | | 3.7 | 1.9 | 6.0 | 3.0 | 2.0 | 4.0 | | | | | | |
| 2 | 7596 | 81 | 5.9 | 8.0 | 0.8 | 0.2 | 2.9 | 0.8 | 1 | 2.1 | 47 | 57 | <1 | <1 | 410 | 670 |
| | | | | | 1.3 | 0.4 | 3.9 | 1.3 | 1.7 | 5.3 | | | | | | |
| | | | | | 1.2 | 1.0 | 5.0 | 1.4 | 2.1 | 8.3 | | | | | | |
| 3 | 8190 | 79 | 0.9 | 6.1 | 0.4 | 0.5 | 1.8 | 0.9 | 1 | 1.6 | <13 | 28 | <1 | <1 | 220 | 430 |
| | | | | | 1.3 | 0.4 | 1.3 | 1.1 | 1 | 2.0 | | | | | | |
| | | | | | | | 1.7 | 1.1 | 1 | 1.8 | | | | | | |
| 4 | 2112 | 120 | 9 | 23 | 9 | 13.8 | 16.3 | 12.4 | 3.4 | 3.2 | 103 | 93 | 50 | 103 | 300 | 830 |
| | | | | | 46 | 20 | 45.2 | 22.8 | 12.0 | 12.0 | | | | | | |
| | | | | | 34 | 26 | 45.4 | 33.5 | | 10.5 | | | | | | |
| 5 | 8960 | 2420 | | | 3 | 0.8 | ≥4 | 4.5 | 2.4 | 1.7 | 85 | 85 | 17 | 28 | 440 | 580 |
| | | | | | 46 | 6.6 | >50 | 11.0 | 12.5 | 13.6 | | | | | | |
| | | | | | 37 | 8.7 | >50 | 21.0 | | | | | | | | |
| Normal range | 70-270 (men) 70-700 (premenopausal women) 70-350 (postmenopausal women) | 8.5-27.5 (men) | | | Men: Women: Follicular phase 1-6 Luteal phase 1-3 Mid-cycle Postmenopausal | LH 1-6 FSH 1-7 | | Basal <6 | | 60-150 | | >20 | | >500 | | |

LH = Luteinising hormone. FSH = Follicle-stimulating hormone. LHRH = Luteinising hormone-releasing hormone. TSH = Thyroid-stimulating hormone. TRH = Thyrotrophin-releasing hormone. GH = Growth hormone. IV = Intravenously.

Conversion: SI to traditional units—Plasma testosterone: 1 nmol/l ≈ 28.8 ng/100 ml. Serum thyroxine: 1 nmol/l ≈ 0.078 µg/100 ml. Plasma cortisol: 1 nmol/l ≈ 0.036 µg/100 ml.

hypopituitarism, and this together with the return of hyperprolactinaemia in two of the patients on stopping treatment would make secondary tumour infarction an unlikely explanation for the observed radiological regression. More probably, when space-occupying lesions regress there is early evidence of return of function of residual normal pituitary tissue.

Not surprisingly, four of our patients with prolactinomas were men, since they tend to present later than women and consequently are more likely to have larger tumours.³⁹ Previous treatment by transfrontal craniotomy and subsequent irradiation in three of the patients was not curative, which is almost certainly explicable in terms of tumour bulk. The argument that the changes in tumour size after bromocriptine treatment cannot be separated from the long-term effects of the destructive treatment given previously is unlikely to apply, since in all three cases clinical and hormonal deterioration occurred before the start of bromocriptine treatment.

Improvement in visual-field abnormalities after bromocriptine treatment for acromegaly has been reported.²¹ While two of our patients with acromegaly reported symptomatic improvement associated with improvement in visual fields and decreases in both prolactin and GH concentrations after bromocriptine treatment, no change in tumour size could be shown radiologically. This might reflect insensitivity of the radiological techniques used. The duration of treatment was too short to exclude an antitumour effect in these patients, and it is therefore interesting that Wass *et al*,²⁶ following up such patients for up to six years, showed a reduction in pituitary fossa size after bromocriptine treatment.

In the two patients with functionless adenomas and the one with Nelson's syndrome the tumours appeared to be responsive to bromocriptine. The visual-field improvement in two of these patients would again suggest some influence on tumour size, although this could not be shown radiologically. Reports on the influence of bromocriptine on the course of Nelson's syndrome have been conflicting.⁴⁰⁻⁴¹ The explanation for the possible reduction in the size of the adenoma in case 12 is uncertain. Without histological evidence the possibility that this patient had a secretory adenoma that had lost its ability to produce hormone or was producing abnormal, unrecognisable hormone or perhaps normal hormone in small quantities cannot be excluded.¹⁰

The role of bromocriptine in therapeutic regimens for pituitary tumours is still being evaluated, particularly with regard to dosage, duration of treatment, and any long-term side effects. Besides lowering prolactin and GH concentrations, bromocriptine probably also inhibits tumour growth, and this is probably quite rapid for prolactinomas. Reassessment of its role in managing prolactinomas is needed. While transsphenoidal surgery with microadenectomy seems to offer a high cure rate for small prolactinomas with modestly raised prolactin concentrations,⁶⁻¹⁰ the management of larger tumours is still unsatisfactory.⁴² The traditional use of transfrontal craniotomy for chiasmal decompression together with postoperative megavoltage irradiation is palliative in most and curative in few. The finding that bromocriptine can reduce these tumours and in doing so both decompress the chiasm and resolve the hyperprolactinaemia indicates a more satisfactory treatment.

We suggest that bromocriptine should be used in managing large prolactinomas, which can thus be reduced in size and then more satisfactorily treated by a transsphenoidal approach. More importantly, as in three of the cases reported here, a group of patients exists in whom transfrontal craniotomy and postoperative irradiation fail to cure the disease. Further destructive treatment is contraindicated in such patients, and bromocriptine may then be life saving.

We are indebted to Professor J Hankinson for permission to study his patients, to Mr W Ross and Professor A Crombie for advice on managing these patients, and Miss A Kellett for help with the photography.

MM and MFS are in receipt of MRC training fellowships.

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(Accepted 26 July 1979)

ONE HUNDRED YEARS AGO An appeal has been made by a Calcutta Baboo, named Rajendianath Datta, for a sum of 2,00,000 rupees, wherewith to found a "Free Ayur Veda College for the education of Hindoo physicians." The prospectus states "that in India treatment according to the Hindoo system of medicine is generally more efficacious than that according to a foreign one. As our bodies are formed and nourished by Indian materials, it would be against Nature if medicines brought from foreign countries suit our constitution in time of illness. It is a fact greatly to be deplored that, owing to the influence of various social changes to which India has been subject, the hard-earned gems of Hindoo medical science have become dim and soiled by disease and are about to be lost and forgotten." If the Baboo cannot get the whole amount asked for, he is content to start on a smaller scale. That he relies strongly on the "gems of Hindoo science" is evidenced by the item in the monthly estimates for the purchase of "rare medical works from distant places," twenty-five rupees; which would certainly, at the present rate of exchange, represent a very modest library fund. (*British Medical Journal*, 1879.)