PREDICTION OF RESPONSE TO BROMOCRIPTINE IN ACROMEGALY

by

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BROMOCRIPTINE was first used in the treatment of acromegaly in 1974 (Liuzzi et al, 1974 a). Not all patients show lowered human growth hormone in response to the drug (Liuzzi et al, 1974 a; Thorner and Besser, 1975; Sachdev et al, 1975). We have performed a series of tests on acromegalic patients in an attempt to discover if any test could predict those patients likely to show long-term response to the drug.

MATERIAL AND METHODS

Eleven active acromegalics, eight with normal adrenal and thyroid status and three on adequate replacement therapy, were studied. Three patients had had no previous treatment. Three had undergone external pituitary irradiation, three had had courses of chlorpromazine, one transfrontal hypophysectomy and another transfrontal hypophysectomy followed by yttrium-90 implantation.

Each patient had a 50g oral glucose tolerance test (OGTT), a 30g arginine infusion, and also an intravenous insulin tolerance test (0.3U/Kg) if the patient had a normal pituitary-adrenal axis. All tests were performed between 9.00 and 11.00 a.m. Human growth hormone, hGH (except during arginine infusion), glucose, insulin, secretin and glucagon were measured during each test by standard radioimmunoassay techniques. Insulin-induced hypoglycaemia was considered adequate if blood sugar fell to less than 50 per cent of the original value, and/or there was a sharp rise in plasma cortisol.

Human growth hormone was measured hourly for 4 hours after a 2.5mg oral dose of bromocriptine. Long-term treatment with bromocriptine was then commenced and dosage increased gradually on the basis of random hGH estimations. Dosages from 5 to 20mg daily were used. After three months the tests were repeated.

RESULTS

Ten of the 11 patients reported subjective improvement varying from improved wellbeing to increased muscle strength and diminished sweating. Five patients experienced side effects. These were exacerbations of pre-existing Raynaud’s phenomenon (two patients) and nausea, epigastric discomfort and vasovagal attack each occurring in one patient. In all cases side effects were mild, not necessitating drug withdrawal.
Bromocriptine resulted in a marked fall in hGH levels during an oral GTT (Fig. 1). Mean fasting levels fell (69.5mU/1 to 23.2mU/1) as did the levels at 60 and 90 minutes (75.4 and 80.8 to 32.6 and 29.8 respectively). These results were statistically significant (P≤0.05). Individual analysis showed that some patients responded biochemically as measured by mean hGH during the second OGTT while others failed to do so (Table 1). Biochemical response was defined as a fall in mean plasma hGH during the second OGTT to less than 25 per cent of the mean value during the first OGTT. This response showed no correlation with sella size, length of history, previous mode of therapy or pattern of glucose response to arginine infusion.

Fig. 2 shows pattern of hGH response to the first glucose load. We considered whether those patients who suppressed partially during an OGTT might eventually be either responders or non-responders. This was not so. Likewise, a paradoxical rise in hGH during the oral GTT did not delineate response or non-response.

Fig. 3 shows the results following a 2.5mg test dosage of bromocriptine. In five of seven patients the response to this was accurate as a prediction of eventual response. In two cases, one a responder and another a non-responder, the test was unhelpful. However, the test may still be of use (see below).
Table 1: Mean hGH (mU/1) during 50g GTT before and after treatment

| Patient | Before Therapy | After Therapy | After Therapy x 100 | Category |
|---------|----------------|---------------|---------------------|----------|
| M.B.    | 170            | 11            | 6.5                 | R        |
| J.O’N.  | 49             | 8             | 16.0                | R        |
| J.O’H.  | 46             | 63            | 137.0               | NR       |
| G.R.    | 126            | 18            | 14.0                | R        |
| A.S.    | 40             | 26            | 65.0                | D        |
| S.S.    | 69             | 79            | 115.0               | NR       |
| C.M.    | 24             | 16            | 75.0                | D        |
| S.A.    | 159            | 6             | 4.0                 | R        |
| M.M.    | 46             | 11            | 24.0                | R        |
| B.H.    | 26             | 25            | 96.0                | NR       |
| A.F.    | 120            | 134*          | 112.0               | NR       |

R: Responder.  
D: Doubtful.  
NR: Non-responder.  
* Mean outpatient values at review.

Fig. 2: Fasting, maximal and minimal human growth hormone values during first 50g oral glucose tolerance test in eventual biochemical responders and non-responders.
FIG. 3: Human growth hormone response to a 2.5mg trial dosage of bromocriptine showing correlation with eventual biochemical response to long-term therapy with the drug. R: eventual responders - NR: eventual non-responders.

Table 2 shows hGH response to insulin-induced hypoglycaemia. This was of predictive value. Eventual responders showed a much more marked rise in hGH than non-responders whose hGH level remained flat during the test. In our small group of patients it was uniformly predictive of eventual response to bromocriptine.

Our results also showed that in acromegalics mean glucagon-89, glucagon-57 and secretin were all within the normal range during both OGTTs (Table 3). When biochemical responders and non-responders were analysed separately for each glucose tolerance test, there was no variation so that neither bromocriptine nor falling hGH affect circulating levels of these hormones. In responders there was a fall in peak insulin during the second OGTT from 102 to 52uU/ml, probably on the basis of a lower plasma glucose.

**Table 2: hGH Levels during Insulin-Induced Hypoglycaemia**

| Patient | hGH Fasting | Maximal Fasting | Maximal Value x 100 | Category |
|---------|-------------|-----------------|---------------------|----------|
| M.B.    | 133         | 220             | 165                 | R        |
| G.R.    | 100         | 176             | 176                 | R        |
| S.A.    | 223         | 280             | 125                 | R        |
| M.M.    | 14          | 220             | 1571                | R        |
| J.O'H.  | 31          | 34              | 109                 | NR       |
| B.H.    | 38          | 40              | 105                 | NR       |
| A.F.    | 142         | 146             | 103                 | NR       |

R: Responder. NR: Non-responder.
Table 3: Mean fasting G.I. hormones before and after therapy

|          | Before       | After        |
|----------|--------------|--------------|
| Glucagon-89 | 66.2 pg/ml   | 54.2 pg/ml   |
| Glucagon-57  | 118.5 pg/ml | 108.5 pg/ml  |
| Secretin    | 15.2 pg/ml   | 12.7 pg/ml   |
| Insulin     | 11.4 uU/ml   | 10.1 uU/ml   |

Discussion

Wass et al (1977) reported that 21 per cent of a group of acromegalic patients did not respond to bromocriptine. Sachev et al (1975) similarly reported two of 21 cases who showed no response. They also stated that the optimum therapeutic daily dose was 20mg or less and that no further significant fall was seen in most of those given higher dosage. Since bromocriptine is an expensive drug, we have looked for possible means of predicting likely response to the drug in reasonable dosage (less than 20mg daily).

Our results have shown that in seven cases out of seven the response to insulin-induced hypoglycaemia was predictive. Patients who showed a marked response in terms of rise in hGH became long-term responders, while those whose hGH remained flat failed to do so. In another series (Liuzzi et al, 1974 b) response of hGH to a test dosage of 2.5mg bromocriptine was compared with various tests, including hypoglycaemia, but no uniform correlation was found. In that series only a single dose of bromocriptine was assessed and an hGH “response” to hypoglycaemia was accepted only when the hGH level doubled. Although our results show 100 per cent uniformity, this might well not be so in a larger series.

The bromocriptine test dosage may also be helpful in the long term; in our series, five of seven were accurate predictors, while two were not. This test may not be uniformly reliable or it may be that the two misleading cases were fortuitous. The eventual non-responder was still on a relatively small dose while the other patient may not have been compliant in drug taking.

The question of using predictive tests before starting bromocriptine is unresolved. It may be that all patients on the drug show changes in ratios of molecular sizes of growth hormone (Besser et al, 1976) or in somatomedin concentrations. If this proves to be so, it would be worthwhile to treat all acromegalis who show activity of the disease process. At present it remains our policy to give all patients a trial of bromocriptine in reasonable dosage. We feel that both insulin-induced hypoglycaemia and a 2.5mg oral dosage of the drug are useful in predicting likely long-term response. If both tests suggest non-response, then at present it would appear pointless to proceed to massive dosage of the drug.

Summary

Eleven active acromegalis were studied before and after bromocriptine therapy. Five clearly responded biochemically to the drug (mean hGH during second OGTT less than 25 per cent of value obtained during first test). Four did
not (mean 96-137 per cent of original) while response in two was doubtful (mean 65-75 per cent). Ten of the 11 claimed subjective improvement.

A four-hour profile of hGH following 2.5mg bromocriptine given orally predicted likely response to long-term treatment in five out of seven cases but in two was misleading. hGH response to insulin-induced hypoglycaemia predicted eventual response in all cases studied, a brisk rise (125-1500 per cent of fasting levels) being seen in responders. Non-responders did not show this feature (103-109 per cent).

Insulin-induced hypoglycaemia may be of value in predicting response to bromocriptine though numbers studied are small.

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