Drug treatment of pituitary tumours

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Summary

The primary therapeutic aims in the management of pituitary tumours are to correct the excess hormone secretion and to reduce tumour size to prevent damage to normal pituitary tissue and adjacent structures such as the optic chiasma. Treatment of pituitary tumours has been improved by advances in transphenoidal surgery and radiotherapy and by the development of effective drug therapy for prolactinoma and acromegaly. Dopamine agonists are first-line treatment in prolactinomas, and somatostatin analogues are often used in the management of acromegaly.

Key words: acromegaly, dopamine agonists, prolactinoma, somatostatin analogues.

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Introduction

Pituitary tumours are almost always benign adenomas classified by size and cell of origin. Lesions smaller than 1 cm are classified as microadenomas, and larger lesions are macroadenomas. Prolactin, adrenocorticotrophic hormone, thyroid-stimulating hormone, luteinising hormone, follicle stimulating hormone and growth hormone are all secreted by cells in the anterior pituitary and the tumour may arise from any of these cell types. Patients with pituitary tumours may therefore present with:

- hormonal hypersecretion (for example prolactinoma, Cushing's disease, acromegaly)
- symptoms of mass effect due to tumour compression of adjacent structures (for example visual field defects)
- hormone deficiencies caused by the tumour damaging other cell types in the pituitary.

Tumours may also be an incidental finding on radiological imaging.

Investigations

The diagnosis of pituitary tumours rests on biochemical assessment and magnetic resonance imaging (MRI). Specific tests can be organised to assess secretory abnormalities or hormonal deficiencies.

Management

The management options for pituitary tumours include neurosurgery, medical therapy or irradiation, depending on the clinical presentation and type of pituitary tumours. Drug treatments can be used as first-line therapy for prolactinomas and acromegaly.

Prolactinoma

Stress, renal failure and drugs can cause mild to moderate hyperprolactinaemia, but a greatly increased concentration is usually caused by a pituitary adenoma. Prolactinomas are the most common hormone-secreting pituitary adenomas, accounting for approximately 60% of functioning tumours. Over 90% of prolactinomas are small, benign intrasellar tumours that rarely increase in size.[1]

Dopamine agonists

Dopamine agonists are usually the first therapy for patients with either prolactin-secreting microadenomas or macroadenomas. The aim of treatment is to normalise prolactin concentrations, restore gonadal function and shrink the tumour. Not all patients with prolactin-secreting microadenomas require treatment with dopamine agonists. Premenopausal women with normal menstrual cycles or postmenopausal women with tolerable galactorrhoea can be monitored with 6–12 monthly measurements of serum prolactin. Women treated with dopamine agonists who do not desire pregnancy but require contraception may take an oral contraceptive provided that there is tight control and monitoring of serum prolactin because oestrogen may stimulate lactotroph growth.

Patients with prolactin-secreting macroadenomas, including those with associated visual field defects, can be safely treated with dopamine agonists. Tumour shrinkage often occurs within 1–2 weeks of commencing therapy, and may continue for many months to years.

The dopamine agonists currently available in Australia are bromocriptine, cabergoline and quinagolide. If the patient cannot tolerate the first dopamine agonist prescribed, or serum prolactin does not normalise, it is reasonable to switch to another dopamine agonist. Transphenoidal surgery is reserved

for patients who are either resistant or intolerant to medical therapy.

Cabergoline

Cabergoline is an ergot derivative with a very prolonged duration of action. It is preferred to bromocriptine as it is more potent and effective in achieving normoprolactinaemia. Cabergoline is given once or twice weekly and the usual maintenance dose is 0.5–2 mg weekly. It is better tolerated than bromocriptine and may be effective in patients resistant to bromocriptine.

There is an increased risk of cardiac valve regurgitation with the use of cabergoline in patients with Parkinson's disease.[2] The doses used to treat prolactinomas are much smaller, but it may be reasonable to offer echocardiograms to patients who have been on prolonged treatment with cabergoline.

Bromocriptine

Bromocriptine is an ergot alkaloid and suppresses prolactin secretion by directly binding to D_2 dopamine receptors within the anterior pituitary. Therapy should be started at 0.625 to 1.25 mg at night to minimise the adverse effects of nausea, vomiting, dizziness and postural hypotension with the initial dose. The dose can be gradually increased to a maintenance dose of 2.5 mg twice or three times daily. Bromocriptine normalises prolactin and reduces tumour mass in 80–90% of patients with microadenomas and in 70% of patients with macroadenomas.[1]

Quinagolide

Quinagolide is a non-ergot, well-tolerated, oral dopamine agonist. If patients cannot tolerate bromocriptine or cabergoline, it is best to switch them over to quinagolide as it may be better tolerated given its specificity for the D_2 dopamine receptor. Quinagolide is given once daily and a starter pack is used to gradually increase the dose over seven days to a maintenance dose of 75 microgram daily. The dose can be increased further to 150–300 microgram daily if required.

Monitoring patients with prolactinoma

Serum prolactin should be checked one month after starting a dopamine agonist and then 3–6 monthly as clinically indicated. Once hyperprolactinaemia is normalised, serum prolactin can be monitored annually. When prolactin has been normal for more than two years and the reduction in tumour size is more than 50%, the dose of dopamine agonists can be gradually decreased to the lowest maintenance dose.[1] However, cessation of treatment may lead to tumour regrowth and recurrence of hyperprolactinaemia. Follow-up of these patients is important with regular (3–6 monthly) monitoring of serum prolactin.

Patients with microadenomas whose serum prolactin concentrations have been suppressed for more than 1–2 years by dopamine agonist therapy may be able to stop their medication. It is also reasonable to withdraw treatment in those patients with macroadenomas and no evidence of residual tumour on MRI, but the dopamine agonists should be gradually tapered before cessation. Serum prolactin should be monitored every three months during the first year of drug withdrawal.[3] Therapy should be continued in patients with any tumour mass on MRI.

Pregnancy

Once pregnancy is confirmed, bromocriptine or cabergoline are often withdrawn in patients with microadenomas, but dopamine agonists may be continued in patients with macroadenomas. Patients are asked to report headaches and visual disturbances during pregnancy as prolactinomas, especially macroadenomas, may grow during pregnancy under continued oestrogen stimulation.

Bromocriptine has an extensive safety record in pregnancy and emerging experience suggests cabergoline may also be safe in early pregnancy. Insufficient safety data on quinagolide preclude its use during pregnancy.

Acromegaly

Growth hormone secreting adenomas account for 20% of functional pituitary tumours. The aims of treatment in acromegaly are to:

- remove the tumour and resolve symptoms due to tumour mass
- normalise growth hormone and insulin-like growth factor (IGF-1) secretion
- prevent progressive disfigurement, bone expansion and osteoarthritis
- improve cardiovascular and metabolic abnormalities.

Transphenoidal surgery is the mainstay of treatment, with surgical cure achieved in more than 80% of patients with microadenomas.[4] However, only 50% of patients with macrodenomas can be cured surgically and this rate is significantly reduced in patients with invasive macroadenomas. Cure is defined biochemically as normalisation of IGF-1 within the age-related reference interval or a random growth hormone concentration less than 2.5 microgram/L (5 mU/L) or adequate suppression of growth hormone secretion during an oral glucose tolerance test.

Medical treatment with somatostatin analogues has assumed a prominent role in the management of acromegaly and is successful in the control of hormone excess in about 60% of patients.[4] It has often been used as adjuvant therapy after unsuccessful surgery, but more recently somatostatin analogues have been proposed as first-line therapy. Studies have shown that biochemical control of acromegaly and tumour shrinkage can be achieved when somatostatin analogues are used as first-line therapy, especially when surgical cure is not possible for invasive macroadenomas.[5] Somatostatin analogues may also be used in preoperative treatment of patients with significant

obstructive sleep apnoea or cardiovascular disease, to attempt to rapidly lower growth hormone concentrations and possibly reduce perioperative complications.

The availability of long-acting depot preparations of somatostatin analogues has improved the ease of administration and patients' compliance. Octreotide and lanreotide are currently available in Australia. Patients resistant to medical therapy are often referred for radiotherapy.

Octreotide

Octreotide is an eight-amino acid synthetic somatostatin analogue. The short-acting form is available as subcutaneous injections, given as 100–200 microgram three times daily. The modified-release, long-acting formulation of octreotide is given as a monthly intramuscular injection. Gastrointestinal adverse effects, due to drug-induced suppression of gastrointestinal motility and secretion, occur in one-third of patients. These effects include nausea, abdominal discomfort, fat malabsorption, diarrhoea and flatulence, but are often short-lived. The most significant adverse effect involves the formation of gallstones and in symptomatic patients cholecystectomy may be required. Mild glucose intolerance may develop due to transient suppression of insulin secretion.

Lanreotide

Lanreotide is a cyclic octapeptide analogue of somatostatin. Lanreotide acetate is given as fortnightly intramuscular injections. The availability of lanreotide as a gel in a pre-filled syringe (60, 90, 120 mg) has further improved the ease of administration. This is given as a deep subcutaneous injection every four weeks. Extended dosing with 120 mg every 6–8 weeks may be as effective for patients established on 60–90 mg every 4 weeks. The adverse effect profile is similar to that of octreotide.

Dopamine agonists

Dopamine agonists may suppress growth hormone secretion in patients with acromegaly and some growth hormone-secreting adenomas may co-secrete prolactin. These drugs are often used in conjunction with somatostatin analogues for an additive suppressive effect when biochemical cure is not achieved with somatostatin analogues alone. Dopamine agonists alone are rarely effective in the treatment of acromegaly.

Pegvisomant

Pegvisomant is a pegylated recombinant analogue of human growth hormone which acts as a growth hormone receptor antagonist. It normalises IGF-1 in over 90% of patients with acromegaly. Pegvisomant is given as subcutaneous injections. This drug can be used in patients with active acromegaly not cured by surgery and resistant to somatostatin analogues. Pegvisomant, as a growth hormone antagonist, does not act on the tumour and is unlikely to influence tumour growth and secretion. It is well tolerated and long-term safety data are gradually accumulating, but it may cause elevated transaminases on liver function tests. This treatment is not readily available in Australia.

Future directions

The development of new therapies and the availability of long-acting depot formulations have provided improved therapeutic options in the management of growth hormone- and prolactin-secreting pituitary tumours. Further drug development for the management of pituitary tumours should enable more patients with hormone-secreting adenomas to be successfully treated medically.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

3. Dopamine agonists are first-line therapy for prolactin-secreting microadenomas.
4. Gallstones are an adverse effect of octreotide.