Bromocriptine

**Introduction**

Bromocriptine (2-bromo-alpha-ergocriptine) is a potent ergot alkaloid derivative which is an agonist at D2 dopamine receptors. Ergot alkaloids were first developed in the 1960s and were investigated for their anti-fertility properties and considered a potential commercial rival to the hormonal contraceptive pill. One of the compounds, CB-154 (later named bromocriptine) was found to have an anti-prolactin effect in animals. It was structurally similar to apomorphine, a known dopaminergic agonist, and was originally trialled and successfully used to treat non-puerperal galactorrhoea. Presently, we have greatest familiarity with its use by endocrinologists in the management of pituitary disease, as well as by neurologists and geriatricians for the treatment of parkinsonism.

**Pharmacology**

Bromocriptine is a centrally acting agent which directly activates dopamine receptors in the striatum. It is in the same chemical class as the hallucinogen LSD. It is a D2 agonist and a D1 antagonist. The specific effects of D2 receptor stimulation include inhibition of cyclic AMP production which increases dopamine release and blockade of the D1 receptor leads to activation of adenylyl cyclase and modulation of D2 mediated events. It also interacts with various serotonin receptors and it inhibits the release of glutamate, by reversing the GLT-1 transporter.

In 2009, bromocriptine mesylate was approved by the FDA for the treatment of patients with type 2 diabetes (T2DM). It is not currently known what the underlying mechanism of action is for improving glycaemic control. It has been shown to reduce HbA1c by ~0.5%. It has been postulated that it works by inhibiting glucose stimulated insulin secretion by direct activation of the α2-adrenergic receptors in pancreatic beta cells, the suggestion being that this ‘promotes beta cell rest’ through reduction of insulin hypersecretion. However, it may also be through its effects on reducing growth hormone and IGF-1 production directly at the site of the pituitary. Interestingly, many years ago, hypophysectomy used to be considered an efficacious treatment for...
advanced diabetic retinopathy and other vascular complications of diabetes, the theory being that removal of pituitary hormones especially ACTH and GH ameliorates the natural progression of poorly controlled diabetes (the Houssay phenomenon of increased insulin sensitivity after hypophysectomy).

The opposite situation of dopamine receptor stimulation may also provide some clues. The relationship between antidopaminergic drugs and glucose has not been extensively studied, but it is recognized that chronic neuroleptic treatment causes hyperinsulinemia in normal subjects and is associated with diabetes in psychiatric patients. The most common side effects of bromocriptine are nausea, vomiting, headache, nasal congestion, fatigue and dizziness. These tend to improve after two to three weeks of therapy and can be minimized by starting with a low dose at night-time and by taking the drug with food. Later side effects include digital vasospasm, constipation, blurring of vision and some neuropsychiatric effects such as confusion and behaviour change. It is contraindicated in patients with syncopeal migraine and actually increases the risk of a hypotensive episode in these patients.

It now appears to have taken on a new role for a potentially very large market, that of suppressing hyperglycaemia in the context of diabetes mellitus; although it has a novel pharmacological action different from the plethora of other oral hypoglycaemic agents available, its effect on HbA1c reduction appears rather small. Ultimately, it will be interesting to see if it takes off as a useful therapy and whether regulatory authorities will advise on the use of routine echocardiography in the context of screening for valvular fibrosis in patients taking bromocriptine for diabetes.

Key points

- Bromocriptine is a safe, generally well tolerated drug used for a variety of endocrine, neurological and psychiatric disorders
- It has now been approved for use in the context of diabetes; although its exact mechanism of action is unclear, it reduces HbA1c by an average of 0.5%
- There is still concern about the potential risk of fibrotic complications from ergot alkaloid drugs, although the doses used in endocrine disease (and now diabetes) are much less than those used in conditions such as idiopathic Parkinson’s disease

Discussion

Bromocriptine appears to have fallen out of favour in recent years: both among endocrinologists as it has been mostly replaced by the longer acting agent cabergoline for prolactin related disorders and by somatostatin analogues for acromegaly, as well as among neurologists who prefer non-ergot derivatives for the management of movement disorders.

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Drug notes

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References