Current Status of Dopamine Agonists in Parkinson’s Disease Management

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Summary

The occurrence of late side effects of long term levodopa therapy (fluctuations in motor performance, abnormal movements, and symptoms unresponsive to dihydroxyphenylalanine) led to the search for novel anti-Parkinsonian drugs. Dopamine agonists are one of the newer families of anti-Parkinsonian agents, and they include ergot derivatives and apomorphine, which can be used in the different stages of Parkinson’s disease.

Ergot derivatives (bromocriptine, lisuride, pergolide) are believed to act independently of the dying cells of the substantia nigra, acting instead directly on postsynaptic dopamine receptors in the striatum. They are usually used in combination with levodopa when late side effects occur, especially ‘wearing-off’ or decreased efficacy of levodopa. They can also be prescribed earlier in combination with levodopa in de novo Parkinsonian patients, and in this setting are thought to delay the occurrence of late adverse motor effects. In some patients, monotherapy with relatively high doses of ergot derivatives can be used as initial treatment. However, their efficacy often decreases after 1 to 3 years, thus justifying a late combination with levodopa.

Apomorphine is a non-ergot derivative dopamine agonist, which is used subcutaneously for the treatment of severe ‘off’ refractory periods, in combination with other dopaminergic drugs without changing the patient’s routine drug regimen.
Over the last 25 years, few topics in medicine and pharmacology have surpassed Parkinson's disease in terms of progress in our understanding of the mechanisms involved and pharmacological treatment.

In the late 1960s, the discovery of the dopaminergic nigrostriatal pathway and the decrease in striatal dopamine levels in patients with Parkinson's disease led to the introduction of levodopa therapy which remains the 'gold standard' of treatment. However, the initial therapeutic success of levodopa is blunted by the development of motor side effects, such as abnormal movements or fluctuations in performance, and adverse mental effects after a few years of treatment (Montastruc 1991; Obeso et al. 1989a).

Because of the limitations of levodopa, the pharmacological treatment of patients with Parkinson's disease has been recently expanded to incorporate 3 different approaches: (a) the development of dopamine agonists; (b) the search for agents which may prevent or slow the underlying pathological process (e.g. selegiline) [see review by Chrisp et al. 1991]; and (c) studies of the feasibility of brain tissue transplants (Montastruc 1991).

Dopamine agonists are a heterogeneous group of drugs which share the capacity to exhibit an antiparkinsonian effect through the activation of dopamine receptors. They were first developed in the early 1970s, and to date bromocriptine (Lieberman & Goldstein 1989a), lisuride (Gopinathan et al. 1989) and pergolide (Langtry & Clissold 1990; Markham & Diamond 1989) have undergone extensive clinical trials and are now used in clinical practice, although many other dopamine agonists, like piribedil (Jenner 1992) have been studied. Several compounds such as lergotrile, mesulergine, aboerphine and CQA-206291 have been withdrawn from investigation because they are no more effective than other currently available agents, or show human or animal toxicity.

Bromocriptine and related compounds were first introduced as add-on therapy to levodopa in patients experiencing motor fluctuations. More recently, they were proposed either as monotherapy or in early combination with levodopa. In the late 1980s, apomorphine, a non-ergot dopamine agonist, was rediscovered and introduced for the treatment of complications of levodopa (especially severe 'off' refractory periods) in patients with advanced disease.

1. Ergot Derivatives
1.1. Clinical Pharmacology

1.1.1 Mechanism of Action
Bromocriptine, lisuride and pergolide are ergot derivatives with a complex pharmacology (fig. 1). They act directly on postsynaptic dopamine receptors. However, their binding profile at dopamine D1- and D2-receptors differs slightly (table I). Bromocriptine stimulates only D2-receptors and is a partial agonist at D1-receptors (Lieberman & Goldstein 1989a), and lisuride is a potent D2-agonist with only some action at D1-receptors (Gopinathan et al. 1989). Pergolide stimulates D2- more than D1-receptor activity (Markham & Diamond 1989).

This pharmacological profile suggests certain theoretical advantages of ergoline compounds over levodopa (Olanow 1989, 1992; Rascol et al. 1982): (a) they stimulate postsynaptic dopamine receptors directly, thus bypassing the degenerating nigrostriatal neurons; (b) they do not depend on a pool of decarboxylase enzyme for conversion into the active transmitter; (c) they do not produce toxic metabolites (e.g. 6-hydroxydopamine from levodopa); and (d) their use will not result in the formation of free radicals, with potential adverse consequences on disease progression.

Besides their effects on D1- and D2-receptors, these ergot derivatives are also able to bind to amnergic [α-adrenergic and serotoninergic (5-HT)] receptors. Lisuride is a potent 5-HT agonist. It also exhibits a lower affinity for α-adrenoceptors than bromocriptine (Gopinathan et al. 1989). Thus, some authors have suggested that lisuride is more likely to produce neuropsychiatric side effects through its activity at 5-HT receptors, and less likely to cause postural hypotension through α-receptor stimulation than bromocriptine, although this has not been supported by any sound clinical evidence.