Rationale for Use of Dopamine Agonists in Parkinson's Disease: Review of Ergot Derivatives

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ABSTRACT: While dopamine agonists are still traditionally used as adjunct medications to improve performance and smooth out motor response complications in advanced levodopa-treated Parkinson's disease, they are increasingly used in monotherapy or early in combination with levodopa particularly in patients under 65 years of age. Long-term studies using bromocriptine showed efficacy in lowering the cumulative levodopa dose and reducing the early incidence of levodopa-related motor response complications. New dopamine agonists have recently shown efficacy as adjunct medications in short-term trials. While we now have more options to fit our individual patients' needs and tolerance, it is important to view the new agonists in the light of the results obtained with ergot derivatives. In this article, the rationale for use and efficacy profile of the ergolines are briefly reviewed.

R SUM : Indications de l'utilisation des agonistes dopaminergiques dans la maladie de Parkinson: les d riv s de l'ergot de seigle. Les agonistes dopaminergiques sont traditionnellement utilisés comme adjuvants dans le but d'améliorer la performance et réduire les fluctuations motrices observées chez les malades dopa-traités aux stades avancés de la maladie de Parkinson. Toutefois, ils sont de plus en plus prescrits précocément dans la maladie, en monothérapie ou en combinaison avec la L-DOPA, surtout chez les malades de moins de 65 ans. Les essais cliniques prolongés avec la bromocriptine ont bien montré son efficacité à réduire la dose cumulative de L-DOPA utilisée et à diminuer l'incidence précoce des complications motrices associées à la dopathérapie. De nouveaux agonistes non dérivés de l'ergot de seigle ont récemment démontré leur efficacité lors d'essais cliniques de courte durée, nous donnant davantage de choix pour maîtriser les signes et symptômes de la maladie et les problèmes d'intolérance précoce. Il apparaît opportun de revoir les indications du traitement agoniste et les effets des dérivés de l'ergot de seigle dans la maladie de Parkinson en attendant la publication d'études cliniques contrôlées comparant les nouveaux agonistes aux premiers mis sur le marché.

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The role and optimal timing of introduction of dopamine agonists in the symptomatic treatment of Parkinson's disease (PD) are still unsettled. Reevaluation of these issues is required in light of new experimental data published on crucial therapeutic issues revolving around the mechanisms of induction of motor response complications and cell death. In spite of suggestive animal evidence that levodopa may be harmful to compromised dopamine neurons *in vivo*,[1-2] there is no direct proof yet that levodopa results in irreversible dysfunction of the basal ganglia and catecholaminergic cell death in humans.[3] Nonetheless, strategies to reduce (adjunct agonist therapy) or even replace (agonist monotherapy *de novo*) levodopa early in the disease have been explored for many years in an attempt to reduce long-term adverse effects. The advantages of direct dopamine agonists in PD include the lack of competition with dietary amino acids for absorption and absence of necessary enzymatic metabolic steps, leading to more reliable and consistent effects, a long duration of efficacy, greater potency, potential alternative modes of delivery, a reduced incidence of early motor response complications and possible neuroprotective properties. The clinical efficacy of the ergot derivatives is briefly reviewed to provide useful information for comparing their effects with newer dopamine agonists.

PHARMACOLOGICAL PROPERTIES

Bromocriptine [2-bromo α-ergocryptine], pergolide mesylate [(8β)-8-[(methylthio)methyl]-6- propylergoline], lisuride hydrogen maleate (1,1 diethyl-3-(9,10-didehydro-6-methyl-8α-ergolinylurea) and cabergoline (1-[(6-allylergoline-8β-yl) carbonyl]-1-[3-(dimethylamino) propyl]-3- ethylurea) are all synthetic derivatives of lysergic acid (ergot derivatives) that differ from the newer, nonergoline dopamine agonists ropinirole and pramipexole (see elsewhere in this issue) in terms of their affinity for dopaminergic and nondopaminergic receptors. Ergot

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derivatives have a differential effect on the five dopamine receptor subtypes that have been characterized in the brain. All dopamine agonists bind to the D2 receptor subtype, a member of the D2-like receptors family which also includes D3 and D4 subtypes, a common feature generally linked to antiparkinsonian efficacy (Table). Studies suggest that ergot derivatives also display variable activity at the D1 receptor subtype with weak antagonism for bromocriptine,[4-6] partial antagonism/agonism for lisuride[7] and limited activity if any for cabergoline.[8] Pergolide is the only drug that displays mild agonist activity at the D1 receptor subtype,[9-11] but this has been disputed recently.[12] The net contribution of the D1 receptor to the antiparkinsonian efficacy of the ergot derivatives is uncertain. However, it is now clear that the D1 receptor is not a silent bystander and that its activation can enhance D2 receptor-mediated responses in rodent[13-16] and primate[17,18] models of PD, and may even provide effective motor relief by itself in parkinsonian primates[19-21] and PD patients.[22-24] Although ergoline compounds show no D2:D3 receptor subtype selectivity, they all have significant affinity for the D3 subtype but less so in the case of bromocriptine.[12,25] Whether this confers a definite advantage in terms of efficacy or adverse effect profile is unknown at present. Both pergolide and lisuride are 10 times more potent than bromocriptine on a milligram per milligram basis. Ergoline compounds also vary in terms of biological half-life (Table) but with the exception of cabergoline, their efficacy half-life appears to be more similar and to justify a TID dosing regimen.

Ergot derivatives display some affinity as well for other monoaminergic receptors. While bromocriptine binds preferentially to noradrenergic α_1 receptors, the other ergolines have more affinity for α_2 receptors and also show affinity for serotonergic 5-HT_1 and 5-HT_2 receptors, especially lisuride which is also a serotonin agonist.[11] The nonselectivity of ergolines for monoaminergic receptors likely contributes to their safety and adverse effect profile, although the most frequent side effects seen in parkinsonian patients, namely nausea, dizziness, hypotension, dyskinesia, somnolence and hallucinations, are probably due to peripheral and central dopaminergic stimulation. All ergot drugs also presumably differ from the newer dopamine agonists in their incidence of adverse reactions such as erythromelalgia[26] and fibrosis.[27] The prevalence of symptomatic pleuropulmonary fibrosis during chronic bromocriptine treatment has been estimated to be as high as 2-5% over 5 years.[27] Such complications appear infrequent with the other ergot derivatives and may affect less than 1 in 1,000 individuals treated with pergolide (Eli Lilly, data on file). These potentially serious complications are therefore uncommon within the recommended dose range and are largely reversible in most but perhaps not all cases upon drug withdrawal or reduction in dosage.

Dopamine agonists versus levodopa in animal models

In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys with moderately severe parkinsonism, bromocriptine provides an antiparkinsonian response of equal magnitude and longer duration compared with levodopa.[28] In these animals, the absence of severe dose-limiting adverse reactions allows a substantial oral dose (up to 5 mg/kg) to be administered. This proof of principle demonstration of the symptomatic efficacy of bromocriptine suggests that its apparent lower clinical efficacy compared with levodopa is related to low potency and an unfavorable therapeutic index. The MPTP-lesioned monkey has also allowed the dissection of the contribution of various dopamine receptor subtypes and nondopaminergic pathophysiological mechanisms responsible for levodopa-related motor response complications. Although the induction mechanisms responsible for such complications remain elusive, presynaptic and postsynaptic dopaminergic mechanisms are thought to contribute.[29] Postsynaptic dopaminergic changes probably play a greater role than heretofore believed and are potentially reversible since motor response complications were ameliorated by the continuous delivery of levodopa for up to 12 days in PD patients but only gradually returned to baseline once oral levodopa treatment was resumed;[30] continuous infusion for 3 months of the postsynaptic dopamine D2 receptor agonist lisuride was even more efficacious at increasing the antiparkinsonian benefit and therapeutic window (difference between threshold doses for clinical efficacy and side effects) of levodopa.[31] Animal studies have shown that levodopa accentuates striatal changes in neuropeptide content,[32] glutamic acid decarboxylase activity[33] and mRNA expression,[34] preproenkephalin mRNA[35] expression, ΔFosB-like protein(s) expression,[36] as well as pallidal changes in $GABA_A$ receptors[37] brought about by chronic nigrostriatal denervation. Thus, standard short-acting levodopa is not physiological and further compromises the physiology of dopamine-denervated basal ganglia circuits.

Levodopa priming can set the stage for dopamine agonists to produce dyskinesia, even early on, contrasting with the response profile observed with agonist monotherapy in PD (see below). Under primed conditions, pharmacological studies in dopamine-denervated animals have suggested a dominance of dopamine D2 receptor-mediated mechanisms with enhanced responsiveness to a D2 agonist in rats[38] and better reproducibility of levodopa-induced dyskinesia following acute challenge with D2 agonists in parkinsonian primates.[21,39] Thus, levodopa-treated parkinsonian monkeys display a full antiparkinsonian response with dyskinesias following acute challenge with bromocriptine (5 mg/kg orally),[21] whereas levodopa-naive animals remain free of dyskinesia after weeks of bromocriptine treatment.[28] The behavioral effect observed with bromocriptine as the first-line drug is similar to that

Table. Comparative pharmacological properties of ergot derivatives.

Agent	Half-life (hrs)	Daily dose (mg)	Dosing regimen	Dopamine receptor selectivity	Norepinephrine αreceptors	Serotonergic receptors
Bromocriptine	6	10 - 40	TID	D2 (D1-)	+	+
Pergolide	27	1 - 4	TID	D2,D3>D1	+	+
Lisuride	2-4	1 - 5	TID	D2,D3 (D1-)	±	++
Cabergoline	65	0.5 - 5	ID	D2	±	±

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obtained with a nonergoline selective D2 agonist administered continuously through a pump that also showed low dyskinesigenic potential. This response correlated in both cases with downregulation of putaminal D2 receptors[37,40] and, in the case of the continuous nonergoline drug treatment, no further increase in pallidal $GABA_A$ receptors compared with levodopa.[37] In drug-naive MPTP-lesioned parkinsonian monkeys treated with cabergoline, dyskinesias were less frequent, less severe and more transient compared with levodopa-treated animals.[41] This behavioral response also correlated with significant downregulation in putaminal D2 receptors. Thus, the low dyskinesigenic potential of bromocriptine and cabergoline may, at least in part, be related to longer duration of response compared with levodopa. Intuitively, long-acting pergolide would also be expected to provide similar results but this remains to be demonstrated. This response profile differs from that resulting from nonergoline short-acting dopamine D2 agonists that all showed great dyskinesigenic potential when chronically administered to drug-naive parkinsonian monkeys.[42] This suggests that when adequately stimulated in a context of chronic dopamine denervation, the D2 receptor subtype can modulate motor function without long-term complications.

The same conclusions apply to the selective pharmacological stimulation of D1 receptors. Levodopa-treated parkinsonian primates showed dyskinesia but of lesser severity when acutely challenged with selective D1 agonists compared with the precursor levodopa.[21] This is similar to PD patients administered infusions of the novel dopamine D1 receptor pro-agonist ABT-431.[23] These observations are unlikely to result from changes in dopamine D1 receptor striatal binding since postmortem and positron emission tomography studies have failed to document consistent differences between dyskinetic and nondyskinetic cases. However, repeated administration of a short-acting D1 agonist to drug-naive parkinsonian monkeys rapidly produced a wearing-off effect and dyskinesia,[43] while the same agonist administered continuously through a pump resulted in early and profound tachyphylaxis.[44] Thus, it is highly unlikely that motor response complications result from abnormal regulation and sensitization of a single dopamine receptor subtype in the basal ganglia. The mode of dopamine receptor occupancy is likely of greater importance.

Monotherapy in early Parkinson's disease

Levodopa eventually leads to a short, fluctuating response associated with various dyskinesias in a substantial proportion of patients, particularly in young[45] and more parkinsonian[46,47] individuals. Although one recent study comparing immediate- and continuous-release levodopa preparations reported an unusually low incidence of motor fluctuations and dyskinesias of 20% over a 5-year period,[48] such complications can still arise rapidly in otherwise stable parkinsonian conditions[46,49-51] and are therefore felt to be directly related to chronic levodopa oral intake.

Dopamine agonists (bromocriptine and lisuride in most studies) used in monotherapy in mild PD patients produce definite antiparkinsonian efficacy and seldom produce motor response complications.[52-57] The improvement of motor disability resulting from bromocriptine may be greater than 50% in some patients and similar[58,59] or only slightly inferior[60] to levodopa in early PD. The magnitude of the response is dose-related and has been as high as 76% in patients administered daily doses of bromocriptine over 100 mg,[61] far exceeding the generally recommended and tolerated dose range for this drug. In levodopa-treated patients showing good tolerance, single optimal doses of pergolide[62] and lisuride[63] have compared advantageously with levodopa in terms of acute antiparkinsonian efficacy. In another study comparing cabergoline and levodopa, patients able to remain on monotherapy were improved to the same extent in both groups and, similar to lisuride, 62% of patients administered cabergoline did not require levodopa during the first year of treatment.[64] Only a few patients developed dyskinesia in each group. In long-term studies, one in six patients could be managed satisfactorily with bromocriptine monotherapy for 5 years[53,57] and about one in ten patients were satisfactorily treated with lisuride monotherapy for over 5 years[65] with few adverse motor response complications. Bromocriptine monotherapy combined later with levodopa significantly delayed the emergence (4.9 vs. 2.7 years from first treatment; $p<0.01$) and incidence (14/25 patients vs. 26/29 patients; $p<0.01$) of motor response complications in PD patients compared with patients administered levodopa alone.[21] This therapeutic strategy did not appear to put individuals at undue risk of developing early dyskinesias, which became manifest after a similar average latency once levodopa is added.[55] The initiation of levodopa in far more advanced and severe patients may accelerate dyskinesias as the experience of MPTP-intoxicated subjects with severe parkinsonism suggests.[46] Unfortunately, the dropout rate for bromocriptine and lisuride at one year averages 40-50% due to low tolerance or lack of efficacy, while it is approximately 27% for pergolide[66] and only 7% in one study for cabergoline.[67]

A similar rationale underlies the early ("primary") combination of a dopamine agonist with levodopa. Most studies have used bromocriptine. Advocates of this strategy have argued that it reduces long-term motor response complications[68-70] and mortality,[71] while others have disagreed and criticized the methodologic flaws of previous studies.[72] Nonetheless, early co-treatment with dopamine agonists can significantly lower the daily dose of levodopa administered (by 40% in one study with bromocriptine).[70] Chronic low-dose levodopa may delay the incidence of motor response complications, at least for several years, compared with high doses.[73,74] Given the benefit provided by dopamine agonist monotherapy in early PD, even beyond the first year of treatment in a fraction of patients (see above), "primary" combination therapy (within 3 months) cannot be recommended as a general strategy and should be utilized only in those with a low tolerance for dopamine agonists despite gradual titration and the use of domperidone.

Adjunct therapy in advanced Parkinson's disease

The traditional indication for dopamine agonist use is to overcome motor response complications in advanced PD patients as adjunct therapy. These drugs are useful in the majority of patients but results have varied as greatly as the daily dose administered. When added to levodopa, ergot derivatives generally reduce total daily "off" time enough to allow a reduction in levodopa dosage by approximately 30%. Co-treatment with bromocriptine has reduced levodopa dosage by 10%[75] to 71%.[76] In a review of 9 studies,[77] bromocriptine adjunct therapy improved "on" time in 71% of patients. Long-term results are

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usually less impressive. Similar results were obtained with pergolide with total daily dose of levodopa and total "off" time usually reduced by 25-40%.[66,78,79] The impact on dyskinesia is variable as persistence, emergence or increase in dyskinesia is reported. In general, an increase in dyskinesia produced by adjunct dopamine agonist therapy can be managed by a reduction in levodopa dosage without significant increase in motor disability. In one long-term study, dyskinesia significantly decreased after 3 years of pergolide treatment in spite of stable levodopa daily dosage.[80] Ergot derivatives may also be beneficial for "off" period leg dystonia. In selected patients with advanced PD and severe levodopa-induced dyskinesia, high-dose pergolide almost completely replaced levodopa intake and substantially reduced dyskinesia with reasonable control of PD symptoms.[81] It is also worth noting that patients no longer responding to bromocriptine may still benefit from a trial of pergolide.[82,83] Other limited and indirect evidence gathered in small patient populations also suggested that pergolide is clinically more effective in decreasing total "off" time than bromocriptine.[84] Comparative studies between the new nonergoline agonists and pergolide are lacking.

Similar clinical results have been reported with lisuride (available in Europe) which reduced total "off" time by 70-130% and daily levodopa intake by 20-50% following daily doses up to 5 mg.[7] All parkinsonian features were improved, with some authors arguing that tremor was particularly responsive. Lisuride was also superior to bromocriptine in some studies.[84] In 17 patients with motor response complications, the improvement in disability resulting from pergolide and lisuride use was similar but the impact on total "off" time was more significant with pergolide.[84] The effect on dyskinesia was variable. Like levodopa-treated parkinsonian monkeys challenged with selective dopamine D2 agonists,[21] levodopa-treated PD patients exhibited peak dose dyskinesia following the acute intravenous administration of lisuride.[85] Given the duration of clinical efficacy and thrice daily dosing regimen of most ergot derivatives (Table), the development of a practical means to deliver agonist therapy continuously would be advantageous. This strategy has been pursued with long-acting cabergoline which reduces total "off" time and disability and allows a reduction in levodopa dosage.[67,86] This drug is currently not available for clinical use in PD in Canada.

The issue of neuroprotection

Some experimental *in vivo* studies suggest that ergot derivatives may be neuroprotective. Indeed, chronic treatment with pergolide prevented the age-related attrition of midbrain dopamine neurons in rats[87] while in mice, oral bromocriptine prevented the striatal dopamine loss produced by diethyldithiocarbamate and MPTP[88] and intracerebroventricular bromocriptine protected mice against 6-hydroxydopamine-induced cell death.[89] The mechanisms of action are not fully elucidated but direct free radical scavenging effect and stimulation of dopamine autoreceptors (reducing dopamine turnover and possibly the formation of neurotoxic radicals) may be involved. Some inconclusive preliminary studies suggest that lisuride and pergolide may be neuroprotective in PD.[65,83,90,91] While there is no direct proof of levodopa neurotoxicity,[3] all dopamine agonists also allow a nonspecific reduction in cumulative levodopa dose, thereby reducing the lifetime exposure to possibly neurotoxic free radicals. These hypotheses are certainly worth pursuing in prospective clinical trials.

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