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Pharmacodynamic and Pharmacokinetic Features of Cabergoline

Rationale for Use in Parkinson's Disease

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Summary

The appearance of late motor complications is the major drawback of long term levodopa therapy in patients with Parkinson's disease. Although disease progression may be a factor in the aetiology of these complications, unfavourable properties of levodopa may promote their development. These include competition with amino acids for gastrointestinal absorption and passage through the blood-brain barrier; and a short duration of action with a rapid peak plasma concentration and rapid clearance, producing strong receptor stimulation that rapidly alternates with neurotransmitter vacancy and nonselective stimulation of all dopamine receptors. Moreover, advanced neurodegeneration results in loss of the anatomical substrate responsible for dopamine uptake and transport, whereas the postsynaptic dopamine receptors (the therapeutic target of dopamine agonists) are relatively spared.

In theory, long-acting direct dopamine D_2 receptor agonists that also stimulate the D_1 receptor should provide a satisfactory alternative to levodopa without the above-mentioned drawbacks. Cabergoline possesses all the prerequisites for testing the hypothesis that steady stimulation of D_2 receptors may be able to minimise the development of late motor complications in patients with Parkinson's disease. It has an appropriate receptor affinity profile, with potent and long-lasting dopaminergic stimulatory effects in 6-hydroxydopamine-lesioned rats and in MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine)-lesioned primates; it has a consistent pharmacokinetic profile, with a very long mean plasma elimination half-life of 65 to 110 hours, and its absorption and excretion are unaffected by food, age or renal or hepatic disease; moreover, when given concomitantly, cabergoline does not influence levodopa pharmacokinetics. Initial clinical studies have demonstrated that the efficacy of cabergoline is comparable to that of levodopa in patients with Parkinson's disease. The preliminary results of a long term study of initiation of treatment with cabergoline or levodopa in patients with Parkinson's disease are in keeping with the hypothesis that steady receptor stimulation diminishes late motor complications.

1. Drawbacks of Levodopa Therapy in the Management of Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. The introduction, by Birkmayer and Hornykiewicz,[1] of levodopa replenishment therapy for the management of Parkinson's disease, to compensate for the loss of the neurotransmitter dopamine in the neostriatum (a consequence of the accelerated death of neurons in the substantia nigra), has revolutionised the approach to the treatment of this condition. Moreover, it has also stimulated investigation of other neurodegenerative diseases, prompting the search for their biochemical cause.

At present, the initial treatment of a patient with Parkinson's disease is varied, depending on the treating physician.[2] The majority of neurologists initiate therapy with levodopa, with most of the remainder choosing a dopamine agonist as first-line therapy. A minority start therapy with a monoamine oxidase B inhibitor[3] (although recent data have cast doubts on the safety of this approach[4]) or anticholinergic agents. Ideally, the therapeutic strategy should be tailored for the individual patient, on the basis of clinical, social and economic factors.

It is well known that the major drawback of levodopa treatment is the appearance after a variable number of years of a complex of effects commonly referred to as motor fluctuations.[5,6] Although the cause of these is unknown, a number of theoretical explanations have been proposed. These fall into two major categories: one linked to the pathophysiology of disease progression and the other to the pharmacodynamic and pharmacokinetic properties of levodopa.

1.1 Factors Related to Disease Progression

- In advanced neurodegeneration, the anatomical substrate that is responsible for dopamine uptake (i.e. the neostriatal dopaminergic terminals of neurons from the substantia nigra) disappears, whereas the postsynaptic dopamine receptor is left relatively intact. This results in diminished levodopa storage capacity.[7-11]
- Dopaminergic receptor upregulation occurs, potentially resulting in an abnormal response to the neurotransmitter.[12,13]
- With advanced disease, there is an imbalance between the two major motor outputs from the neostriatum: the direct and the indirect (via the pallidum and subthalamic nucleus) pathways.[14] The descending D_2-mediated GABA/enkephalin-containing indirect pathway shows abnormalities [15] and increased transcription of the gene encoding for enkephalin within the putamen.[16]

These changes are believed to contribute to the genesis of late motor complications in levodopa-treated animal models of, and patients with, Parkinson's disease.

1.2 Factors Related to the Pharmacology of Levodopa

- Levodopa has a short duration of action (plasma elimination half-life ≈90 minutes) with a rapid peak plasma concentration and rapid clearance, resulting in intermittent receptor stimulation.[17-19]
- Levodopa nonselectively stimulates all dopaminergic receptors, including those of the mesolimbic system, which are thought to be responsible for the cohort of psychiatric adverse effects of levodopa therapy.
- Levodopa is a precursor of noradrenaline (norepinephrine). Thus, a partial precursor effect should occur during therapy. This aspect of the levodopa therapy has been neglected and has not been taken into consideration in clinical practice.
- Levodopa is metabolised by oxidative deamination and is subject to auto-oxidation. Thus, production of free-radicals increases during levodopa therapy, increasing the risk of peroxidative neuronal damage,[20-24] (for reviews see Olanow[25] and Jenner & Olanow[26]). Substantial experimental evidence and some clinical observations suggest that oxidative stress

may be an important pathogenic factor in Parkinson's disease.[27]
- Levodopa competes with amino acids for both gastrointestinal absorption and passage through the blood-brain barrier.[23,24]

2. Rationale for the Use of Dopamine Agonists in Parkinson's Disease

It is believed that the combined action of all the undesirable effects of levodopa described in the previous section may be a contributing factor in the development of late motor complications. Treatment from the beginning with an agent that avoids intermittent receptor stimulation may prevent or reduce these complications.[28-30]

The reasons for preferring initial treatment with a dopamine agonist over levodopa can be divided into theoretical and practical. Theoretical reasons include the following:
- The therapeutic target of dopamine agonists (the postsynaptic receptor) is relatively spared by the disease.[31]
- In general, dopamine agonists provide more sustained and consistent receptor stimulation.[32]
- Oxidative stress resulting from dopamine metabolism would be minimised. Moreover, several dopamine agonists have shown antioxidant properties in *in vitro* and *in vivo* studies.[33,34]

Practical reasons for preferring dopamine agonists include the following:
- There is the possibility of significantly reducing the dosage of levodopa needed.[35-38]
- The absorption and passage of dopamine agonists through the blood-brain barrier are unaffected by the dietary intake of amino acids and vitamins. Thus, there is no need for the dietary restrictions that are recommended with the aim of improving levodopa effects.

There are also some drawbacks to be taken into account when choosing to initiate treatment with dopamine agonists, including the less dramatic motor response and the higher rate of adverse effects associated with these agents compared with levodopa.[2,39] One even more controversial issue is the possibility that treatment with dopamine agonists might increase survival in parkinsonian patients. Indeed, a recent multicentre multinational study with bromocriptine was terminated prematurely, as it appeared that patients in the levodopa monotherapy arm had a significantly higher death rate than patients in the dopamine agonist arm.[40] Although this finding is not conclusive and the claim of a cause-effect relationship between treatment and mortality is unwarranted, it is clear that studies specifically designed to test the hypothesis of prolonged survival after dopamine agonist treatment should be performed.

A dopamine agonist capable of inducing a clinical motor response similar to that produced by levodopa and a prolonged duration of action, which avoids the 'rollercoaster' effect on dopaminergic receptors, would appear ideal to test the validity of the previously mentioned hypotheses. A direct D_2 receptor agonist that also stimulates the D_1 receptor subtype might be particularly advantageous, as D_1 receptor stimulation is recognised as playing a synergistic role.[41-45]

Table I. *In vitro* binding of cabergoline and other agents to rat brain tissue[47]

Receptor	^{3}H-Ligand	Brain region	IC_{50} (μmol/L)		
			cabergoline	pergolide	bromocriptine
Dopamine D_1	SCH 23390	Striatum	0.560	0.600	2.0
Dopamine D_2	Spiroperidol	Striatum	0.003	0.004	0.006
Dopamine D_3	7-OHDPAT	Nucleus accumbens	0.004	0.006	0.015
α_1-Adrenoceptor	Prazosin	Frontal cortex	3.2	0.4	0.13
α_2-Adrenoceptor	Yohimbine	Frontal cortex	0.28	1.6	0.35
Serotonin 5-HT_1	5-HT	Hippocampus	0.17	0.1	0.36
Serotonin 5-HT_2	Ketanserin	Prefrontal cortex	1.0	0.14	0.28

Abbreviations: IC_{50} = concentration required to inhibit binding of ligand by 50%.

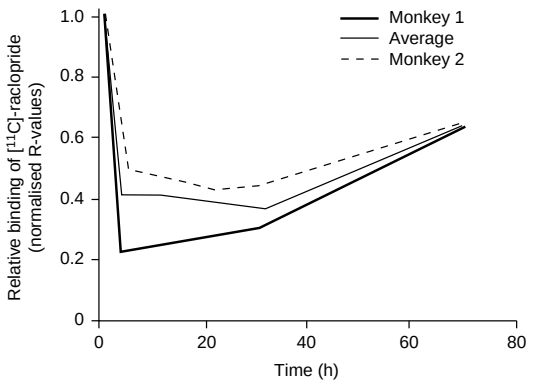

Fig. 1. Cabergoline binding to dopamine D_2 receptors *in vivo*: Positron Emission Tomography (PET) study used [^{11}C]-raclopride to study dopamine D_2 receptor occupancy in striatal tissue in monkeys. After a single 1-hour intravenous infusion of cabergoline 1 mg/kg uptake of [^{11}C]raclopride markedly decreased. Dopamine D_2 receptor occupancy in striatal tissue was 59, 56 and 37% after 4, 28 and 68 hours, respectively.[46]

3. Rationale for the Use of Cabergoline

3.1 Pharmacodynamic Properties

Cabergoline is a relatively selective dopamine D_2 agonist that shows prolonged steady ligation to the receptor *in vivo* and *in vitro* for at least 72 hours.[46] Radioligand receptor binding studies in rat brain tissue showed that cabergoline had high affinity for dopamine D_2 and D_3 receptors, which was similar to that of pergolide and greater than that of bromocriptine. All 3 compounds had lesser affinity for D_1 receptors, with cabergoline and pergolide showing very similar affinity and bromocriptine the lowest (concentration required to inhibit binding of ligand by 50%, 2 μmol/L) [table I]. The concentration of cabergoline required to inhibit specific binding of [^{3}H]-spiroperidol to rat striatal tissue and 7-OHDPAT to the nucleus accumbens by 50% was 3 and 4 nmol/L, respectively. Cabergoline had negligible affinity for adrenergic and serotonergic receptors.[47]

Positron Emission Tomography (PET) studies in monkeys used radiolabelled raclopride to determine dopamine D_2 receptor occupancy. These studies showed that cabergoline crosses the blood-brain barrier, with receptor binding that remained significant for more than 3 days after a single 1 hour intravenous infusion at a dose of 1 mg/kg (fig. 1).[46] Dopamine D_2 receptor occupancy by cabergoline in the striatum was 59, 56 and 37% at 4, 28 and 68 hours, respectively, postadministration.

When given subcutaneously at a dosage of 0.5 or 1 mg/kg, cabergoline induced contralateral rotational behaviour in 6-hydroxydopamine-lesioned rats. At 6 hours postdose, cabergoline (particularly at the higher dosage) induced a greater number of contralateral turns than apomorphine (0.5 mg/kg), quinpirole (0.05 mg/kg), pergolide (0.1 mg/kg) or bromocriptine (1 mg/kg). At 24 hours postdose, cabergoline showed increased activity in this model, whereas the effects of the other agents had ceased.[47] Single or multiple doses of cabergoline (0.1 mg/kg subcutaneously or 2 mg/kg orally) ameliorated parkinsonian symptoms induced by administration of MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) to cynomolgus monkeys and restored normal motor function without dyskinesias. Antiparkinsonian activity was evident for 48 to 72 hours after administration of cabergoline. This model is considered very valid in terms of predicting clinical efficacy in Parkinson's

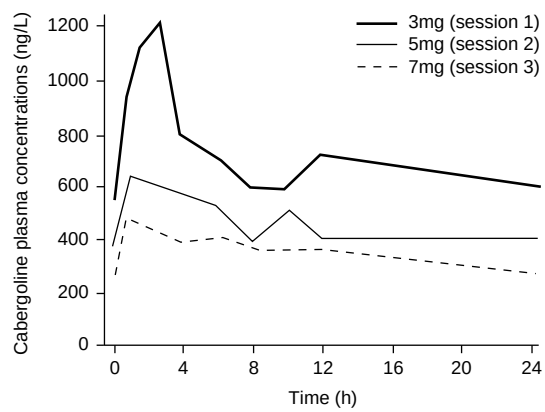

Fig. 2. Pharmacokinetic profile of cabergoline: plasma concentrations of cabergoline at steady-state after oral administration of doses ranging from 3 to 7mg once daily to groups of 6 parkinsonian patients in a parallel-group study.[56]

disease.[48] In a similar study from another laboratory, the motility-restoring effects of cabergoline in MPTP-treated cynomolgus monkeys were confirmed.[49] In addition, the coadministration of cabergoline and levodopa prolonged the beneficial effects of each drug given alone and abolished levodopa-induced hyperactivity and dyskinesia.

Initial clinical studies have demonstrated that the efficacy of cabergoline is comparable to that of levodopa in patients with Parkinson's disease. In an early phase II study,[50] 12 of 32 patients receiving cabergoline 2 mg/day achieved a UPDRS (Unified Parkinson's Disease Rating Scale) global score reduction of >50%, a result that compares favourably with optimal levodopa therapy. In a larger study, the proportion of patients showing clinical improvement with cabergoline did not differ from that seen with levodopa.[51] In addition, cabergoline has antioxidant properties.[52]

3.2 Pharmacokinetic Properties

Cabergoline achieves peak plasma concentrations within 1 to 2 hours of administration,[53,54] with extensive distribution into body tissues, including brain tissue, and has a very long elimination half-life of 65 to 110 hours (fig. 2). It is extensively metabolised, mainly by hydrolysis, and is excreted mainly in the bile and faeces. The pharmacokinetic profile of cabergoline is linear within the dosage range of 3 to 7 mg/day and is not affected by food intake (table II), age, or impaired renal or hepatic function.[55,56] Moreover, concomitant administration of cabergoline does not affect the pharmacokinetics of levodopa. The plasma levodopa concentration-time curves in 12 patients with advanced Parkinson's disease during treatment with levodopa alone and during treatment with levodopa plus cabergoline (4 mg/day) were virtually superimposable (fig. 3).[57]

Table II. The pharmacokinetic profile of cabergoline (mean ± SD) after administration of a single oral 1mg dose, before and after food, in 12 healthy volunteers[56]

	Fasting	Postprandial
C_{max} (ng/L)	54 ± 40	44 ± 18
t_{max} (h)	2.5	2.5
$AUC_{0\text{-}336}$ (ng • h/L)	5531 ± 3940	6392 ± 4461
$Ae_{0\text{-}168}$ (% of dose)	1.2 ± 1.1	1.3 ± 0.7
$t_{½\beta}$ (h)	100.4 ± 22.1	109.7 ± 41.2

Abbreviations: $Ae_{0\text{-}168}$ = fraction of dose excreted in the urine over 168 hours; $AUC_{0\text{-}336}$ = area under plasma concentration-time curve from 0 to 336 hours; C_{max} = maximum plasma concentration; $t_{½\beta}$ = terminal elimination half-life; t_{max} = time to C_{max}.

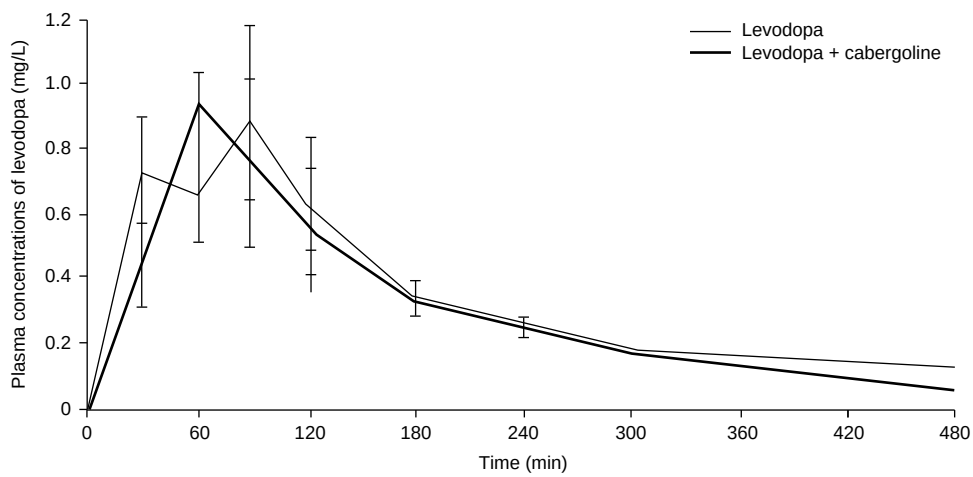

Fig. 3. Effects of concomitant cabergoline therapy on the pharmacokinetics of levodopa: plasma levodopa concentration-time curves in 12 patients with advanced Parkinson's disease during treatment with levodopa alone (625 to 875 mg/day in divided doses) and during treatment with levodopa plus cabergoline (4 mg/day) [from Del Dotto et al.[57] with permission].

4. Conclusions

Almost 40 years after Birkmayer and Hornykiewicz used this approach to treat the first patient,[1] levodopa still remains the cornerstone of treatment of Parkinson's disease. However, practical and theoretical reasons have stimulated the search for new treatment approaches. The appearance of late motor complications after several years of levodopa administration is a major concern that has prompted a sizeable number of neurologists on both sides of the Atlantic to delay levodopa administration in patients with Parkinson's disease.[28] Disease progression may be a major factor in the development of late motor complications, but other causes appear to be linked to levodopa itself.

Cabergoline is a selective and potent dopamine agonist, with higher affinity for dopamine D_2 and D_3 than D_1 receptors *in vitro*. It has potent and long-lasting dopaminergic activity in animal models of Parkinson's disease. Cabergoline has a prolonged plasma elimination half-life and linear pharmacokinetics over the therapeutic dose range; its pharmacokinetic profile is not affected by food intake, age, or renal or hepatic impairment. It appears to be the ideal candidate to test the postulated role of intermittent receptor stimulation in the pathogenesis of tardive motor complications in Parkinson's disease. Studies investigating this hypothesis are being conducted at present, and, to date, results supporting the hypothesis have been found.[30]

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