A Rationale for Dopamine Agonists as Primary Therapy for Parkinson's Disease

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ABSTRACT: Levodopa is the most potent symptomatic treatment for Parkinson's disease but adverse reactions are common and the initial response is not maintained. Further there is recent evidence that suggests that free radicals generated from the oxidative metabolism of dopamine may contribute to the pathogenesis of Parkinson's disease. This raises the possibility that levodopa therapy by way of its conversion to dopamine may promote free radical formation and accelerate the rate of neuronal damage. Levodopa sparing strategies designed to minimize the cumulative levodopa dosage employed over the course of the disease seem a rational way to treat Parkinson patients in face of current information. Such a strategy would include the use of dopamine agonists as primary symptomatic therapy, the introduction of levodopa as an adjunct when dopamine agonists can no longer sufficiently provide satisfactory clinical control and the use of the lowest dose of levodopa that will provide satisfactory clinical control. In this way symptomatic control is not compromised on theoretical grounds, but the cumulative levodopa dose is minimized in an effort to reduce the likelihood of free radical formation with their potential adverse consequences on disease progression.

RÉSUMÉ: Justification de l'utilisation des agonistes de la dopamine comme thérapie de première ligne dans la maladie de Parkinson. La lévodopa est le traitement symptomatique le plus puissant dans la maladie de Parkinson, mais ses effets secondaires sont fréquents et la réponse initiale n'est pas maintenue. De plus, des données récentes suggèrent que les radicaux libres générés par le métabolisme oxydatif de la dopamine peut contribuer à la pathogenèse de la maladie de Parkinson. Ceci soulève la possibilité que la thérapie par la lévodopa, par sa conversion en dopamine, peut promouvoir la formation de radicaux libres et accélérer le dommage neuronal. Les stratégies d'épargne de la lévodopa, destinées à minimiser la dose cumulative de lévodopa employée au cours de l'évolution de la maladie, semblent une façon rationnelle de traiter les parkinsoniens, compte tenu de l'information courante. Une telle stratégie inclurait l'utilisation d'agonistes de la dopamine comme thérapie symptomatique de première ligne, l'introduction de la lévodopa comme thérapie d'appoint quand les agonistes de la dopamine ne procurent plus un contrôle clinique satisfaisant et l'utilisation de la plus faible dose de lévodopa qui procure un contrôle clinique satisfaisant. Par cette stratégie, le contrôle symptomatique n'est pas compromis sur une base théorique et la dose cumulative de lévodopa est minimisée dans l'espoir de réduire la probabilité que des radicaux libres soient formés, évitant leurs conséquences adverses potentielles sur la progression de la maladie.

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Dopamine agonists are a diverse group of drugs with differing chemical and physical properties. They share the capacity to stimulate dopamine receptors and to provide an anti-parkinsonian response. They differ from levodopa in that they are independent of the degenerating presynaptic neuron and do not depend on a pool of decarboxylase enzyme for conversion into the active product. They also tend to be more stable and to have a longer half-life than levodopa. Perhaps most importantly, they do not undergo oxidation and thus avoid the potentially toxic by-products of levodopa metabolism. The two dopamine agonists which have been best studied and are approved for use in the United States are bromocriptine (Parlodel) and pergolide (Permax).

Dopamine agonists were originally introduced as a substitute for levodopa and later as an adjunct for patients with advanced Parkinson's disease who had a reduced response to levodopa and who had developed adverse effects such as dyskinesia and motor fluctuations.[1-3] More recently, they have been employed either as monotherapy or in early combination with levodopa based on studies which demonstrate that such an approach is associated with a reduced incidence of adverse reactions compared to patients treated with levodopa alone.[4-6]

Recent information has strengthened the rationale for using dopamine agonists early in the treatment of Parkinson's disease as part of a levodopa sparing strategy. This is based on the notion that the pathogenesis of Parkinson's disease may be related to free radicals generated from dopamine metabolism.[7,8] Dopamine is metabolized either enzymatically or by auto-oxidation to form a pool of hydrogen peroxide:

a) **Enzymatic Oxidation**

$$DA + O_2 + H_2O \xrightarrow{MAO} 3,4\ Dihydroxyphenyl\text{-}acetaldehyde + NH3 + H_2O_2$$

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b) **Auto-oxidation**

$$DA + O_2 \longrightarrow \cdot SQ + O_2^- + H^+$$

$$DA + O_2^- + 2H^+ \longrightarrow \cdot SQ + H_2O_2$$

In the normal brain, hydrogen peroxide is cleared by glutathione in a reaction catalyzed by glutathione peroxidase (See Below).

$$2\,GSH + H_2O_2 \xrightarrow{\text{Glutathione Peroxidase}} GSSG + 2H_2O$$

However, excess hydrogen peroxide which is not cleared by the pool of glutathione can be further reduced in the presence of iron to form the hydroxyl free radical.[8]

Fenton Reaction

$$H_2O_2 + FE^{2+} \longrightarrow \cdot OH + OH^- + Fe^{3+}$$

Hydroxyl Free Radical

Oxidative damage is primarily mediated by the hydroxyl free radical in reactions which are dependent on the regional concentration of iron; increased concentrations of iron enhance oxidation and the formation of free radicals while removal of iron by chelation retards and may even abort the oxidation reaction.[9-11]

A free radical is a molecule which contains one or more unpaired electrons in its outer orbital(s). These are highly unstable molecules which react almost instantaneously with neighboring biological molecules in order to extract an electron so as to complete their orbital.[8] The molecule which "donates" the electron is thus oxidized and potentially damaged by the process. Free radicals can damage a wide variety of organic molecules including proteins, lipids, carbohydrates and DNA.[9,11,12] The brain appears to be particularly vulnerable to oxidative damage because of its relatively high concentration of iron and impoverished defense mechanisms.[13,14] Further, because of the abundance of polyunsaturated lipids in neuronal membranes, free radicals in the brain are likely to interact with lipids and induce a chain reaction (lipid peroxidation) leading to alteration in the functional integrity of the cell membrane and ultimately cell death.[7,8] This is a particular concern in the substantia nigra where alterations in dopamine metabolism could favor the production of free radicals and expose dopamine neurons to damage leading to Parkinson's disease. Circumstances which favor the formation of free radicals in the substantia nigra include: i) An increase in the metabolic rate of dopamine leading to an increased production of hydrogen peroxide; ii) A decrease in the pool of glutathione thereby limiting the capacity to protect against free radical formation; iii) An increase in the local concentration of iron which enhances the rate at which free radicals are formed.

It is now becoming apparent that the environment *within the substantia nigra* of patients with Parkinson's disease is conducive to the formation of free radicals and that free radicals are in fact being formed. Evidence includes: i) *Increased iron* which promotes the formation of free radicals;[15-18] ii) *Decreased ferritin* which normally binds iron and thus limits its capacity to promote oxidation.[19] The finding of increased iron and decreased ferritin suggests that iron is present in an unbound state and in the form in which it can promote free radical formation. This finding also raises the possibility that in Parkinson's disease there is a defect in the capacity of iron to induce the mRNA for ferritin; iii) *Alterations in the Fe^{2+}/Fe^{3+} ratio* suggesting the presence of oxidative stress and increased formation of hydroxyl radical;[17] iv) *Decrease in levels of glutathione*; this is the primary mechanism responsible for clearing H_2O_2 and protecting against the formation of free radicals within the substantia nigra;[20-22] v) *Decreased mitochondrial complex I* which may diminish ATP synthesis and thereby limit necessary cellular metabolic processes including the capacity to generate glutathione;[23,24] vi) *Increased lipid peroxidation* indicative of membrane damage due to free radical formation.[25]

While it is possible that these findings may be the consequence rather than the cause of cell damage, an environment is nonetheless established which could lead to secondary oxidative damage to the cell.[26] Secondary oxidative damage can occur in the presence of increased iron, decreased glutathione, decreased complex I, etc. even if they occur as the result of some other primary cause of tissue damage. We have recently demonstrated that iron infusion into the pars compacta results in a loss of neurons and striatal dopamine markers.[27]

Recent clinical trials based on the hypothesis that oxidation reactions contribute to the pathogenesis of Parkinson's disease have sought to determine whether antioxidant therapy with the MAO-B inhibitor L-deprenyl could influence the rate of disease progression.[28,29] Untreated patients with mild Parkinson's disease were randomly assigned to L-deprenyl or placebo to determine whether disability necessitating the introduction of symptomatic therapy (*endpoint*) could be forestalled by the introduction of deprenyl as compared to placebo. Both studies demonstrated in a highly significant manner that the addition of deprenyl delayed the development of disability consistent with the notion that deprenyl exerts a protective effect by blocking the MAO-B enzymatic metabolism of dopamine and thereby the formation of free radicals. The possibility that this delay in reaching endpoint is due to symptomatic effects of deprenyl cannot be absolutely excluded as deprenyl is associated with an increase in dopamine availability, amphetamine by-products and a possible anti-depressant effect. While minor symptomatic effects were observed with drug wash-in, it seems likely that deprenyl also provides a protective effect in view of the magnitude of the clinical observation and the lack of clinical deterioration following drug wash-out.[28] Nevertheless, studies to confirm that deprenyl delays progression by a protective mechanism are required. If it can be unequivocally established that deprenyl has a protective effect, it implies that an oxidant mechanism contributes to the pathogenesis of Parkinson's disease. As deprenyl does not prevent hydrogen peroxide formation from dopamine oxidized by MAO-A or by autooxidation, alternative antioxidant therapies such as iron chelation might be even more effective.

If Parkinson's disease is due to cell damage related to oxidant mechanisms it seems rational to design symptomatic therapy which minimizes oxidant stress and the likelihood of forming free radicals. In this regard, one must question the consequences of levodopa therapy. Levodopa is decarboxylated to form dopamine which increases both the formation of hydrogen peroxide and the risk of free radical formation as illustrated.

(1) L-Dopa $\xrightarrow{\text{Dopa-Decarboxylase}}$ DA + CO_2

(2) Dopamine + O_2 + H_2O $\xrightarrow{\text{MAO}}$ 3,4 Dihydroxyphenyl-acetaldehyde + NH_3 + H_2O_2

(3) H_2O_2 + 2 GSH $\xrightarrow{\text{Glutathione Peroxidase}}$ GSSG + 2 H_2O

(4) $H_2O_2 + FE^{2+} \longrightarrow FE^{3+}$ + .OH (HYDROXYL RADICAL) + OH (HYDROXIDE ION)

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This may be particularly relevant to patients with Parkinson's disease where protective mechanisms may be compromised. Cohen et al. have demonstrated that levodopa administration induces an oxidant stress as evidenced by an increase in the percentage of oxidized glutathione.[30] This can be eliminated by the co-administration of an MAO inhibitor indicating that the oxidant stress associated with levodopa administration is related to its conversion to dopamine and subsequently hydrogen peroxide. Large doses of levodopa also impair survival of fetal dopamine neurons in tissue culture.[31] Further, dopamine depletion protects against ischemia-induced cell death of striatal neurons thought to be due to free radicals generated by dopamine metabolism.[32] Administration of large doses of levodopa to animals[33,34] and non-parkinsonian humans[35] has not been demonstrated to induce dopamine neuronal damage but there are obvious differences between these examples and patients with Parkinson's disease in whom the capacity to withstand oxidant stress may be altered. It thus seems reasonable to question whether L-dopa therapy in parkinsonian patients can adversely affect dopamine neurons and disease progression.

Since the introduction of levodopa, studies clearly indicate improved survival for L-dopa treated Parkinsonian patients.[36,37] It must be remembered however, that this effect could be a function of symptomatic benefits provided by levodopa and does not exclude the possibility that levodopa administration adversely affects surviving dopamine neurons. The question is whether a putative dopamine agonist which provides symptomatic effects comparable to levodopa but does not undergo oxidative metabolism would be a preferable drug. It is noteworthy that numerous studies have observed that adverse reactions are decreased in patients treated with dopamine agonists alone or used in combination with low doses of levodopa.[4-6] It has further been observed that patients receiving high doses compared to low doses of levodopa have a greater incidence of adverse reactions and a shorter latency until adverse reactions develop.[38,39] While other retrospective studies do not support these observations,[40] it is nonetheless interesting to speculate on whether the reduced incidence of adverse reactions observed with dopamine agonists and low doses of levodopa is related to avoiding toxic by-products generated by dopamine metabolism.

Chase and his colleagues have postulated that adverse effects are a function of the number of residual striatal dopamine terminals and their capacity to store dopamine.[41,42] L-dopa has a relatively short half-life (approximately 90 minutes). The prolonged anti-parkinsonian response observed following a single dose of levodopa is thought to be related to the capacity of striatal dopamine neurons to store and tonically release dopamine. With disease progression, there is a reduction in the number of striatal dopamine terminals and hence a decreased capacity to store dopamine. This leads to an increased dependence on the peripheral availability of levodopa and the development of motor responses which fluctuate in concert with changes in the plasma levodopa concentration. Under these circumstances, dopamine receptors are exposed to alternating high and low concentrations of dopamine instead of the constant dopamine levels which occur under physiologic conditions. Exposure of dopamine receptors to alternating high and low concentrations of dopamine in animal models induces receptor changes and leads to motor fluctuations and dyskinesia.[43,44] We have recently performed pharmacokinetic studies on levodopa and its metabolites in the ventricular CSF of patients with Parkinson's disease.[45,46] In those patients with advanced Parkinson's disease, the motor response correlates precisely with the appearance and disappearance of levodopa in the ventricular CSF (Figure 1A). The inability to sustain a clinical response in the presence of a falling levodopa level is consistent with the notion of reduced central storage of dopamine.

By contrast, the patient who was the least disabled demonstrated motor improvement which persisted following the decline in CSF levodopa (Figure 1B) and is consistent with the notion that dopamine storage is relatively preserved in patients with milder parkinsonism. These observations support the hypothesis that adverse events are related to the number of remaining dopamine terminals and raises the question of whether the increased incidence of adverse events seen in patients treated with levodopa as compared to dopamine agonists might be due to an accelerated loss of dopamine terminals due to the toxic metabolites of dopamine. If this interpretation is correct it would suggest that the decreased incidence of adverse events seen in patients treated with dopamine agonists may be related to the relative reduction in levodopa consumed by these patients. That dopamine agonists might have a protective effect is also suggested by the report of Felten et al.[47] They report that rats fed the dopamine agonist Pergolide had a decrease in the age related decline of nigral dopamine neurons, an increase in dopamine fluorescent staining in the striatum, and a decrease in the lipofuscin content of the striatum. The mechanism responsible for these "protective" effects is thought to be the capacity of pergolide to decrease dopamine turnover and thereby oxidant stress.

It thus seems reasonable to treat patients with Parkinson's disease with a strategy which minimizes the cumulative levodopa dose which the patient consumes over the course of their disease so long as symptomatic control is not compromised. Such a strategy might be expected on theoretical grounds to reduce oxidant stress and to minimize adverse consequences of free radicals on disease progression. Clearly levodopa is the most potent of the available anti-parkinson agents. However dopamine agonists can provide some clinical benefits in patients with early Parkinson's disease[48] and permit a reduction in the levodopa dose in more advanced patients.[49] Dopamine agonists can thus be used to implement a *levodopa sparing strategy* designed to minimize the dose of levodopa and the risk of oxidant stress in the following ways: i) *Initiate therapy with deprenyl* at time of diagnosis to provide possible protective benefits and to delay need for symptomatic therapy; ii) *Initiate dopamine replacement therapy with dopamine agonists* rather than levodopa and continue for as long as satisfactory clinical benefit can be maintained; iii) *Add levodopa as an adjunct* when satisfactory clinical results cannot be obtained with dopamine agonists and deprenyl alone; iv) *Use the lowest dose of levodopa* that will provide satisfactory symptomatic control. If larger doses are necessary to achieve the desired clinical result, then levodopa dosage can be titrated upward accordingly. In this way symptomatic control is not compromised based primarily on theoretical considerations. On the other hand, large doses of levodopa are avoided if they are not necessary in order to obtain the desired clinical effect.

This levodopa sparing strategy provides symptomatic control while minimizing the cumulative levodopa dose and the risk of

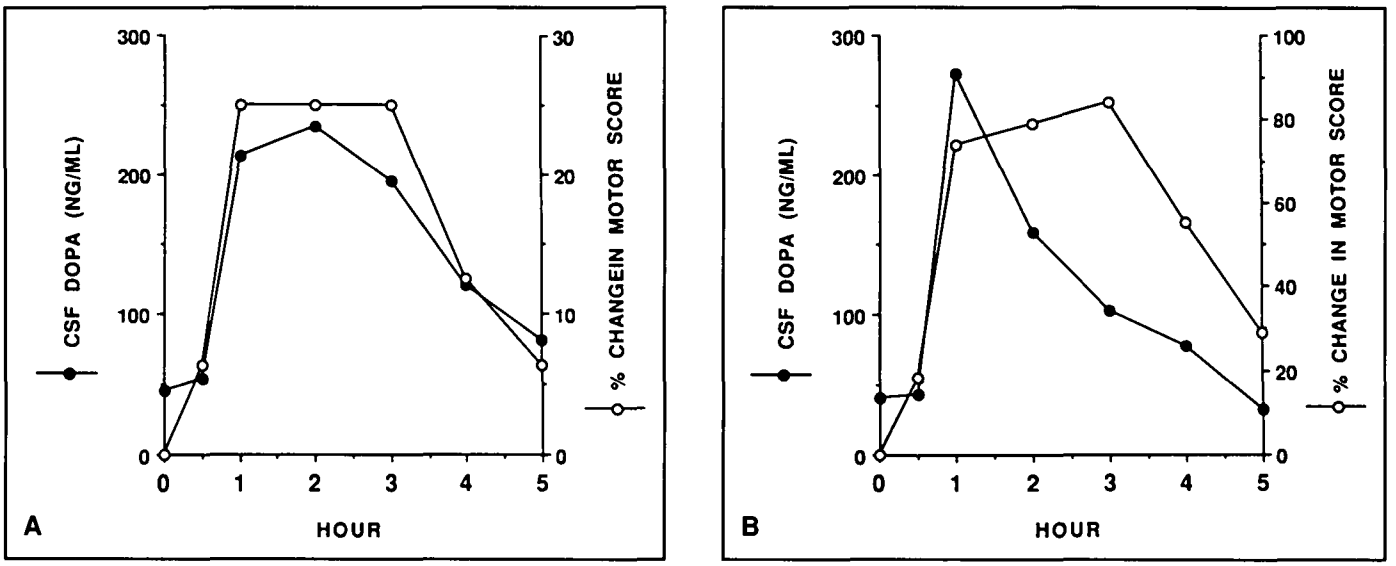

Figure 1 — A) Comparison of ventricular CSF concentration of levodopa with the change in motor performance following a dose of levodopa/carbidopa (25/250) in a patient with advanced Parkinson's disease. Note the precise relationship between the appearance and disappearance of levodopa and the rate of change in motor performance. The inability to sustain motor benefits following the disappearance of levodopa from the ventricular CSF is in keeping with the notion of a reduced capacity for central storage of dopamine in patients with advanced Parkinson's disease. B) A comparison of the ventricular CSF concentration of levodopa with the change in motor performance following a dose of levodopa/carbidopa (25/250) in a patient with moderate Parkinson's disease. Note that motor performance persists following disappearance of levodopa from the ventricular CSF. This is in keeping with the notion that central storage of dopamine is relatively preserved in patients with moderate rather than advanced Parkinson's disease.

free radical formation with their potentially deleterious effect on disease progression. Ideally, it would be preferable to use a dopamine agonist with comparable potency to levodopa. Limitations in dopamine agonist potency may relate to their dopamine receptor profile which differs from that of dopamine. The development of a new dopamine agonist with a receptor profile which more closely approximates that of dopamine may allow for symptomatic effects which are comparable to levodopa with the advantage of a drug which is not oxidized and does not favor free radical formation. Recent cloning of the D_1 and D_2 receptors may facilitate the development of such a dopamine agonist. While new therapies which can stop the progression of Parkinson's disease and restore neuronal activity are the ultimate goal of therapy, for the present, a dopamine sparing approach appears to be the most rational way to provide symptomatic therapy for patients with Parkinson's disease while minimizing the risk of adversely influencing disease progression.

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