Levodopa, melanoma, and Parkinson's disease

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Article abstract—Previous reports and the Physicians' Desk Reference caution against the use of levodopa in Parkinson's disease (PD) patients with melanoma. A critical review of the literature reveals only anecdotal evidence to support a link between levodopa and melanoma. In fact, levodopa has an antitumor effect on melanoma. We report nine patients with PD and melanoma who were treated with levodopa/carbidopa (L/C). Current evidence suggests that L/C can be used safely in PD patients with a history of melanoma.

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Levodopa/carbidopa (L/C) continues to be the best symptomatic treatment for Parkinson's disease (PD). Parkinsonian patients who are unable to take L/C encounter severe motor dysfunction earlier in their illness, and the decision to withhold L/C is one with major impact on the patient. This paper will examine the practice of withholding L/C from PD patients who have a history of melanoma.

Shortly after levodopa's release, a patient was reported[1] who developed recurrent melanoma after 4 months of levodopa therapy for newly diagnosed PD. A cause-and-effect relationship between the initiation of levodopa therapy and the recurrence of a melanoma was postulated. Despite the fact that L/C has never been reported to stimulate the pigmentary system, a series of case reports followed (table 1), and the anecdotal evidence that levodopa stimulated the growth of malignant melanoma increased.[2-14]

These reports resulted in the pharmaceutical companies listing the following warning in the Physicians' Desk Reference (PDR) under contraindications for both Sinemet and levodopa: "Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma."[15] This warning first appeared in 1976 and continues to be renewed on a yearly basis.

We present a critical review of the reported cases of purported association between L/C, melanoma, and PD. We also present nine additional PD patients who have been treated with L/C despite a diagnosis of melanoma.

Methods and Results. We present nine patients who were evaluated at the University of Miami Department of Neurology Movement Disorders Clinic between 1985 and 1992. Their parkinsonian symptoms were treated successfully with Sinemet, despite a history of melanoma or the development of melanoma during Sinemet therapy (table 2). Four patients with a history of melanoma were treated with Sinemet and no patients developed recurrent melanoma. Five patients were diagnosed with melanoma after beginning Sinemet therapy. Four continued Sinemet without developing recurrent melanoma. One patient had a local recurrence 2 years later.

Discussion. *Review of previously reported cases.* Skibba et al[1] in 1972 first raised the possibility of a link between levodopa therapy and recurrence of melanoma. Others expanded this relationship to include induction of a newly diagnosed melanoma after the onset of levodopa therapy, and a total of 21 cases have been reported. Eight of these can be critically reviewed.

In patient 1 (table 1), the course of levodopa was relatively short (4 months) prior to recurrence of melanoma.[1] A critical reexamination of this original case report was published 8 years later.[16] The authors concluded that the lesions in the original case report were epidermotropic metastases and that levodopa played no part in the progress of the tumor.

Patient 2 (table 1) noted a discharge from a nevus prior to the initiation of a 21-day course of levodopa. Therefore, it is likely that malignant transformation of this congenital nevus bore no relation to the onset of levodopa therapy.

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Table 1. Previously reported cases of Parkinson's disease and melanoma

Pt no.	Age/Sex	Site of primary melanoma	Previous nevus at melanoma site	Time from Rx L-dopa to melanoma recurrence (Dx)*	Time from Dx melanoma to Rx L-dopa	Authors advise L-dopa with melanoma	Ref
1	55/M	Skin	>6 mo	4 mo	4 yr	?	1
2	50/M	Skin	Since birth	9 mo	0	No	2
3	70/M	Skin	20 yr	(18 mo)	N/A	No	3
4	62/M	Skin	Unknown	3 mo	1 yr	No	3
5	62/M	Skin	Unknown	No recurrence	2 yr	No	3
6	71/M	Skin	No	(L-dopa withheld)		No	4, 5
7	—	—	Unknown	(L-dopa withheld)		Caution	5
8	—	—	Unknown	(8 yr)	N/A	Caution	5
9	48/M	Skin	15 yr	(6 yr)	N/A	Yes	6
10	74/F	Skin	Unknown	(10 yr)	N/A	No	7
11	69/F	Choroid	No	(7 yr)	N/A	?	8
12	53/F	Choroid	No	(4 yr)	N/A	?	8
13	70/F	Ciliary body	No	(1 yr)	N/A	?	8
14	67/M	Choroid	No	(1 yr)	N/A	?	9
15	58/M	Skin	Since birth	(14 mo)	N/A	Caution	10
16	72/M	Skin	15 yr	(5 yr)	N/A	No	11
17	67/M	Skin	No	(18 mo)	N/A	Yes	12
18	66/F	Skin	Unknown	(11 yr)	N/A	Yes	12
19	65/F	Mets	N/A	(9 yr)	N/A	Yes	12
20	59/F	Skin	>45 yr	(5 mo)	N/A	No	13
21	38/M	Skin	Unknown	No recurrence	12 yr	Yes	14

* Times are from onset of L-dopa therapy to melanoma recurrence. Times in parentheses are for patients who had the initial diagnosis of melanoma made after beginning L-dopa, and therefore did not have recurrent disease.
? Authors make no recommendation on L-dopa's use in patients with melanoma.
N/A Not applicable. These patients were diagnosed with melanoma after starting L-dopa and did not have recurrent disease.

Patient 4 (table 1) developed an intracerebral mass presumed to be metastatic melanoma and died. An autopsy was not performed, and histologic confirmation was not made. It is not possible to draw a cause-and-effect relationship because recurrent disease was not documented.

Patients 5, 11, and 21 (table 1) showed no evidence of melanoma recurrence despite levodopa therapy.[3,8,14] Although reported with other cases of recurrence, these patients' successful courses on Sinemet support the position that L/C can be used safely in patients with melanoma.

Patients 6 and 7 (table 1) had levodopa therapy withheld due to concern for safety. They were reported along with patient 8 (table 1), who was diagnosed with melanoma 8 years after beginning Sinemet.[4,5] Because Sinemet was withheld in these two patients, they have no bearing on the relationship between levodopa and melanoma.

The remaining 13 patients reported between 1972 and 1992 developed melanoma, or had a recurrence of previously diagnosed melanoma, after the onset of levodopa therapy. We propose several alternative explanations for these remaining reports.

Levodopa and melanoma. The possibility of development of a second primary melanoma coincidental with the onset of levodopa therapy must be considered. There is a critical differentiation between primary nonmetastatic melanoma and metastatic malignant melanoma. Multiple primary melanomas occur in 3%[16] to 4%[7] of patients with primary melanoma, usually within 5 years of the original surgical resection. This increased risk of a secondary primary melanoma makes it difficult to assess the importance of levodopa's effect in multi-

Table 2. Currently reported cases of Parkinson's disease and melanoma

Pt no.	Age/ Sex	Time from Rx L-dopa to melanoma recurrence (Dx)†	Time from Dx melanoma to Rx with L-dopa	Years of follow-up on L-dopa after recurrence (or Dx)
1	69/M	None	6 yr	8 yr
2	78/M	(4 yr)	N/A	1 yr
3	79/F	(1 yr)	N/A	4 yr*
4	53/M	None	17 yr	<1 yr
5	74/F	(3 yr)	N/A	2 yr
6	61/F	None	10 yr	15 yr
7	54/F	(6 yr)	N/A	2 yr
8	63/M	None	13 yr	<1 yr
9	80/F	(17 yr)	N/A	1 yr

* Initial diagnosis of melanoma made 1 year after L-dopa therapy. Patient followed for 4 more years with recurrence during 2nd year.
† Times are from onset of L-dopa therapy to melanoma recurrence. Times in parentheses are for patients who had the initial diagnosis of melanoma made after beginning L-dopa, and therefore did not have recurrent disease.
N/A Not applicable. These patients were diagnosed with melanoma after starting L-dopa and did not have recurrent disease.

ple primary tumors.

The natural history of melanoma is for late recurrence and irregular growth patterns. Malignant melanoma has continued to increase in incidence over the last several decades and 5-year survival now exceeds 80%. In 1979, it was estimated that there were 350,000 patients with PD and that the melanoma incidence was 9 per 100,000; therefore, 31 new cases per year of melanoma in patients with PD would be expected.[17] Substituting current figures of an estimated 500,000 patients with PD and a melanoma incidence of 13 per 100,000,[18] 65 new cases of melanoma in patients with PD would be expected in 1990. The original contention first made in 1979 that the number of PD patients reported with melanoma was small remains true today.

Sober and Wick[6] prospectively examined 1,099 patients in a multicenter study of melanoma cases and found only one patient taking levodopa. The authors concluded that the risk of developing melanoma could not be substantial and that there was little evidence to support a cause-and-effect relationship.

Melanoma cells possess a unique mechanism for the biochemical formation of melanin that includes levodopa as an intermediate. Exogenous levodopa was presumed to stimulate melanogenesis and melanoma growth. If a peripheral decarboxylase inhibitor was given in addition to levodopa, the quantity of unchanged levodopa to reach pigmented cells would be increased, and therefore increase the incidence of melanoma growth or recurrence.

Although the basis for this hypothesis was correct, levodopa's effect on melanoma has been the opposite of that proposed by authors of early case reports. Levodopa and other precursors in the biosynthetic pathway of melanin have a toxic effect on melanoma.

After the initial case reports of the link between PD and melanoma, a series of in vitro studies revealed that levodopa was selectively incorporated into pigmented cells and inhibited their growth.[19,20] Peripheral decarboxylase inhibitors used in conjunction with levodopa enhance incorporation of levodopa into melanoma and enhance the antitumor effect.[21]

Because of the success of preclinical studies, four patients with advanced malignant melanoma were studied with intravenous infusion of dopamine. Cardiovascular side effects were significant and dose limiting. However, each patient showed a significant reduction in the labeling index of tumor cells following treatment.[22]

Clinical trials utilizing L/C as an antimelanoma treatment have yielded some clinical responses and have been nonconclusive.[23,24] Contrary to the previous anecdotal reports, there was no evidence for accelerated progression of melanoma. The major limitation of the therapeutic use of levodopa is the inability to achieve cytotoxic concentrations in vivo without side effects.

There are several hypotheses for the mechanism of action of the antitumor effect of melanin precursors (ie, levodopa, dopamine, and their analogues). These compounds selectively inhibit thymidine incorporation soon after exposure to the drug. The inhibition is suggested to be at the stage of DNA synthesis, and the site of action is proposed to be at DNA polymerase.[25] These compounds are also oxidized to quinone forms, which are electrophiles that can interfere with cellular metabolism.[26] Recent work has also suggested that the antitumor effect may be mediated through the immune system.[27]

Conclusion. The evidence for a link between levodopa therapy and growth or recurrence of malignant melanoma is purely anecdotal and not well documented. Review of the previously reported cases that suggest a link between levodopa and melanoma reveals alternative explanations. Nine patients are presented whose parkinsonian symptomatology was successfully treated with L/C despite a history of melanoma. Levodopa has an antitumor effect on melanoma. Although a warning remains in the PDR, and the association remains in the literature, L/C should not be withheld if clinically indicated in parkinsonian patients with a history of melanoma.

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Clinical experience with controlled-release carbidopa/levodopa in Parkinson's disease

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Article abstract—We converted 158 Parkinson's disease (PD) patients on stable doses of standard carbidopa/levodopa (Std-L) to controlled-release carbidopa/levodopa (L-CR). Of the 141 patients who completed the study, 103 (73%) preferred L-CR, 26 (18.5%) preferred Std-L, and 12 (8.5%) had no preference. One hundred fourteen patients elected to continue L-CR, and we performed the primary data analysis on this group. Following conversion to L-CR, patients reported an increase in length of benefit from each dose and an increased "kick-in" time. There was a decrease in the total number of doses, "off" periods, sleep interruptions per night, dose failures, and sleep disturbances. Conversion to L-CR resulted in a significant increase in total levodopa dose. There was no significant change in the dyskinesias. However, early-morning dystonia resolved in eight of 14 patients. Our findings suggest that L-CR is particularly effective in decreasing motor fluctuations, reducing nocturnal problems, and minimizing levodopa dose failures in PD.

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Levodopa is the most efficacious drug currently available for the symptomatic treatment of Parkinson's disease (PD).[1] However, chronic therapy with levodopa is associated with dyskinesias and motor fluctuations, which limit the use of this drug.[2] In some patients, the complications of the therapy can be more disabling than the parkinsonian symptoms. Loss of dopamine storage capacity may lead to end-of-dose deterioration[2,3] with oral administration. A slow-release oral formulation of levodopa was developed to provide a more constant plasma levodopa level with the intent of decreasing fluctuations and minimizing long-term complications associated with standard levodopa use. Clinical trials during drug development indicated that controlled-release carbidopa/levodopa (L-CR, Sinemet CR) resulted in fewer doses, reduced "off" time, and in some patients less dyskinesia[4] compared with standard formulation. To further investigate the specific benefits from L-CR, we have documented our clinical experience when converting patients from standard carbidopa/levodopa (Std-L) to L-CR.

Methods. One hundred fifty-eight PD patients on stable doses of Std-L were converted to L-CR. A stable dose was defined as that dose providing optimal control of symptoms, ie, patients did not have significant functional disability, or, if they did, any further increase in levodopa dose, in the opinion of the examiner, could cause undesirable adverse effects. Subjects were on stable Std-L dose for 6 or more weeks prior to study entry. The following

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