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New Delivery Systems for Antiparkinsonian Drugs

Peter A. LeWitt and *Alberto Albanese

Clinical Neuroscience Program, Sinai Hospital, West Bloomfield, Michigan;
Departments of Neurology, Psychiatry, and Behavioral Neuroscience, Wayne State University School
of Medicine, Detroit, Michigan; *Istituto di Neurologia, Università Cattolica del Sacro Cuore,
Rome, Italy; and *Centre pour les Maladies Neurologiques Dégénératives, Service de Neurologie,
Université de Lausanne, Lausanne, Switzerland.

LEVODOPA PREPARATIONS

Although standard oral preparations of levodopa (L-DOPA) give satisfactory symptomatic relief for most patients with Parkinson's disease (PD), some experience disabling motor fluctuations that are amenable to changes in their medication regimen. Patients who have developed "wearing-off" from each dose of immediate-release L-DOPA can achieve more "on time" and less precipitous "off states" from therapies lengthening the actions of L-DOPA. Several pharmacologic strategies have been devised to extend the benefits from each dose of L-DOPA (1). Among these are sustained-release L-DOPA preparations (2,3), enteral infusions of an L-DOPA suspension (4,5,6), monoamine oxidase type B (MAOB) inhibition, and the recently developed inhibitors of catechol-O-methyltransferase (COMT) (7). These strategies have been especially useful for managing problems that often develop after long-term L-DOPA therapy. Some patients experience undesirable peak-effect responses such as dyskinesias or painful dystonic spasms (8,9,10). To control these problems, pharmacologic methods lessening the abruptness of rise and fall in striatal dopaminergic stimulation can be beneficial.

In addition to strategies mentioned above, sustained duration of action can help to lessen nocturnal wearing-off of medication, which would otherwise precipitate awakenings in some patients. Controlled-release formulations of medications for PD may have other important applications as well. There has been experimental evidence that pulsatile dopaminergic

agonism at striatal receptors results in different effects in the rat than would be produced by more continuous stimulation (11). These findings may have implications for the long-term therapy of PD with L-DOPA. If intermittent dosing with dopaminergic drugs were to be a factor promoting the development of motor fluctuations and dyskinesias, regimens producing more constant drug effects might yield better long-term clinical results. Extrapolation of this animal research to PD management has generated considerable controversy (12). Speculations regarding the value of constant dopaminergic stimulation are unproven, as demonstrated by a recently completed clinical trial with sustained-release L-DOPA (13). However, if constant dopaminergic stimulation is shown to be better for long-term symptomatic control of parkinsonism, medications capable of sustained dopaminergic stimulation will be needed to replace currently available formulations of L-DOPA. Two new dopaminergic agonists with long half-lives, cabergoline (14) and pramipexole (15), each could serve in this role, as might the use of the COMT inhibitor tolcapon with L-DOPA (10).

Extension of Levodopa Effect

There has been extensive research into ways that the pharmacokinetic and pharmacodynamic profile of L-DOPA can be tailored to improve results in controlling motor fluctuations (2,17). The development of improved formulations of this drug and other products for improving consistency of effect has faced

several challenges. The ideal dose range ("therapeutic window") of an antiparkinsonian medication can become very narrow for some patients. To achieve optimal effects from L-DOPA or other antiparkinsonian drugs, dosing may need to be highly individualized. For example, optimal daily intake of dopaminergic ergots can vary over a tenfold range, primarily because of the effects of first-pass hepatic metabolism (18). The route of drug delivery via the gastrointestinal tract is intrinsically problematic for achieving consistency. Water-soluble drugs like L-DOPA are not absorbed in the stomach, so their uptake can be delayed while digestion of meals is ongoing. As an L-aromatic neutral amino acid, L-DOPA leaves the gut by an active transport process that competes with dietary amino acids. Drugs absorbed through the gastrointestinal tract face renal clearance of hepatic metabolism, and their distribution throughout the body limits the fraction of an ingested dose that actually reaches the brain. In the case of L-DOPA, 2% or less of an ingested dose enters the brain. These factors can have a major impact on how useful and reliable antiparkinsonian medications can be.

The first demonstrations of an antiparkinsonian effect with L-DOPA used the intravenous route of administration (19). Subsequent studies have used L-DOPA infusions to demonstrate that some types of motor fluctuation can be lessened by maintaining a constant L-DOPA plasma concentration (10,20,21). Although promising as a research tool, intravenous L-DOPA administration is impractical for several reasons, among them the large volume of solution which would need to be infused because of the low aqueous solubility of L-DOPA. Because it can be prepared in more concentrated form, L-DOPA methylester in solution has been proposed for long-term intravenous use (22,23). The L-DOPA methylester, which is readily hydrolyzed to release L-DOPA, can "smooth out" motor fluctuations during constant infusion (24). Similar investigations have been conducted with jejunal infusion of L-DOPA ethyl ester (25). Preparations of carbidopa/L-DOPA in suspension form have allowed some patients to drink optimized doses of this medication to achieve effects not possible with marketed pill forms.

Some patients have achieved more constant plasma L-DOPA concentrations with enteric infusions of carbidopa/L-DOPA suspension. Since slowed or erratic gastric emptying of medication may be a contributing account for some fluctuations in antiparkinsonian control, direct infusion of L-DOPA has been tried in which the suspension is delivered directly to the duodenal surface by a continuous-flow pump. This ap-

proach has given significant benefit for apparent L-DOPA-nonresponders and for patients unable to improve further by adjustment of oral L-DOPA intake (6,26). Enteral infusion requires surgical insertion of a feeding tube and requires that the patient carry a portable pump and L-DOPA suspension. The percutaneous insertion of the feeding tube can be performed without abdominal surgery, and ambulatory patients can make use of this system for years. Enteral infusion permits small adjustments to be made in rate of L-DOPA infusion, and bolusing of extra doses with more rapid response than achieved by ingesting pill forms of this medication. It also permits infusion of L-DOPA throughout the night, if needed.

Other strategies for improving delivery of L-DOPA have been devised using various transient derivatives of L-DOPA. These derivatives prevent metabolism before or during absorption process to improve bioavailability (27,28). Chelating L-DOPA to certain divalent metals has been another means for enhancing L-DOPA transport into the brain (29). In animal studies, Cu^{++} or Zn^{++} chelated to L-DOPA increased its transport into the brain by 100% to 150% (30).

Controlled Drug Release of Levodopa

An impressive array of drug delivery systems has been developed by the pharmaceutical industry to achieve controlled release of medications (31). For PD therapeutics, there are only a few examples of drugs formulated as other than immediate-release tablets or capsules. Amantadine HCl is available in a liquid form that allows titration of intake of multiple daily dosing. Until recently, the anticholinergic trihexyphenidyl has been available in North America in the form of a sustained-release tablet. Two sustained-release preparations of L-DOPA have been marketed for several years. Sinemet CR, a product in which carbidopa/L-DOPA is dispersed within a polymer matrix, was developed from a group of five sustained-release prototypes (3). Madopar HBS retards the release of L-DOPA and benserazide by transformation of its gelatin capsule into a mucous body which floats in the stomach and permits slow diffusion outward of the two drugs (32). The less abrupt rise and fall of plasma L-DOPA concentration with these sustained-release preparations may improve the consistency and lessen wearing-off medication responses.

Recently, a new L-DOPA formulation combining two drug-release systems has undergone clinical development (32). The Geomatrix concept involves a sandwich of two or more drug retention materials (34). The thickness, surface area, and diffusion char-

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Release of Levodopa

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acteristics of the matrices determine release of L-DOPA and benserazide. In the product tested, the discharge of drug from the immediate-release and sustained-release components of the Geomatrix tablet were activated simultaneously. The result is a pharmacokinetic profile of L-DOPA representing the maximal capabilities of the gastrointestinal tract to deliver the drug in a constant manner to the bloodstream. The dopaminergic agonist bromocriptine has been prepared as a sustained-release form (Parlodel SRO). This formulation was successful in achieving a longer duration of action than the immediate-release product, and the more gradual release of the dopaminergic compound may also help in the development of tolerance (35).

INFUSION OF LISURIDE

The development of dopaminergic compounds has permitted assessment of alternative routes for delivery of antiparkinsonian medications. One example is lisuride, a dopamine receptor 2 (D₂)-like receptor agonist developed as an adjunct to L-DOPA (36). Although currently marketed as an oral tablet, lisuride is water soluble and has undergone testing using the subcutaneous route for continuous infusion (37). The most extensive experience with lisuride infusions has been reported by Vaamonde et al. (38). In their study of 70 patients, half were followed for more than a year (and seven of them for more than 2 years). The infusion rate of lisuride (slightly more than 100 mg/hour) greatly lessened "off time" and permitted reduction in daily L-DOPA dose (Table 75-1). Although this strategy can give improved control of motor fluctuations in advanced PD, often, lisuride is not well tolerated, and the demands of using a subcutaneous pump system are sometimes impractical. Patients needed to discontinue use of subcutaneous lisuride infusion for a variety of reasons, including

psychiatric side effects (hallucinations of a mostly visual nature, and psychosis), nausea, vomiting, and skin nodules at the site of injection (39). Further trials of lisuride infusion have ceased because the sponsor (Schering AG, Berlin, Germany) has discontinued production of lisuride for parenteral injection. However, therapeutic principles learned from the use of lisuride infusion are applicable to apomorphine, as described below.

INFUSION OF APOMORPHINE

Apomorphine, first administered as an antiparkinsonian drug more than 40 years ago, has received increasing attention in recent years. This drug is one of the most effective ways to reverse the parkinsonian state and has shown the ability to counteract an "off state" occurring even during a constant infusion of L-DOPA (20). Apomorphine is most widely used via subcutaneous injection for immediate rescue of patients from a "frozen" state. To establish the optimal dose, patients usually start with injections of 1.5 to 3 mg subcutaneously administered during predictable off periods. This dose can be built up to 5 mg or more per dose. The duration of effect can be up to 3 hours. When used in this manner three to four times per day, apomorphine can control wearing-off responses and other types of motor fluctuation. For simplicity in achieving its immediate effects, patients can administer apomorphine by means of a recently developed storage-injection device capable of delivering precisely measured doses.

Apomorphine is not effective as an oral medication because of oxidation in the acid environment of the stomach and extensive first-pass hepatic metabolism. It may be possible to shield the oxidation of the parent compound in the gastrointestinal tract if the drug is conjugated to acetyl, propionyl, or benzoyl groups by ester bonds at the catechol hydroxyl sites. Apo-

TABLE 75-1. Continuous infusion of lisuride allowed reduction of levodopa by approximately 30% but was discontinued in a high proportion of patients because of the occurrence of side effects^a

	Before infusion	After 5 weeks	After 20 months	After 27 months
No. of patients	36	36	27	7
L-DOPA (mg/day)	1,038.7	729.6	784.7	401.0
No. of daily doses	6.2	4.5	4.6	4.0
Lisuride (μg/h)		113.3	109.9	100.8
Off, h/day	7.3	0.9	1.5	2.0
KCH score "on"	19.1	16.6	16.4	27.4
KCH score "off"	61.1	30.7	34.6	45.5

KCH, Kings College Hospital reading score.

^aFrom ref. 49, with permission.

morphine can also be taken up by other parenteral routes, including intranasal (40) and sublingual (41) absorption, and via rectal suppository (42). Recently, there have been studies in which apomorphine was administered from a transdermal patch system employing an electric current to drive the drug through the skin (43). Over the period of 1 hour, this iontophoretic technique could deliver enough apomorphine to achieve a plasma drug concentration in the usual therapeutic range.

Like lisuride, apomorphine has had extensive testing as a therapy by the route of continuous subcutaneous infusion. Figure 75-1 shows the daily response pattern of a patient receiving apomorphine by continuous subcutaneous infusion. In this example, the treatment resulted in an "on state" for most of the day, although it did not abolish all fluctuations. A trend to worsening as the day progressed and a predictable "off state" postprandially were not corrected by the continuous apomorphine infusion. These results, typical of the experience with apomorphine infusions and other attempts to enhance constancy of drug effect in managing PD, emphasize that factors other than improvement of pharmacokinetics may be necessary for better therapies in the future. Continuous apomorphine infusion can be limited by the development of skin nodules or local inflammatory reactions at the injection sites (although this problem can be lessened by use of an apomorphine concentration of not more than 5 mg/mL).

Some studies of apomorphine infusion have indicated that some patients can improve greatly on a

long-lasting basis. For example, Hughes et al. (44) reported on subcutaneous apomorphine administration for up to 5 years in PD patients with severe motor fluctuations. The researchers observed a marked reduction of "off time" without the occurrence of tolerance or decline in benefit over time. The limits to continuous infusion of apomorphine included increasingly severe "on-state" dyskinesias and the development of postural instability. Some tolerance to the effects of apomorphine develop within hours after the start of continuous administration of apomorphine, as shown by decreased response to bolus test doses as compared with responses before the infusion (45). Comparisons of clinical outcomes from continuous infusions of lisuride and of apomorphine have shown that the latter drug is better tolerated and more efficacious (46,47).

TRANSDERMAL PREPARATIONS

Future therapeutics for PD have the opportunity to draw from a variety of technological advances in delivery systems to improve upon the manner in which drugs will work. For example, near-constant plasma concentrations and enhanced duration of action of certain antiparkinsonian drugs can be achieved through the transdermal route. A variety of transdermal drug delivery systems have been developed (48). This option is not possible for L-DOPA because of the quantity of drug which would have to be transferred for achieving useful clinical effects. The concept of transdermal delivery of a

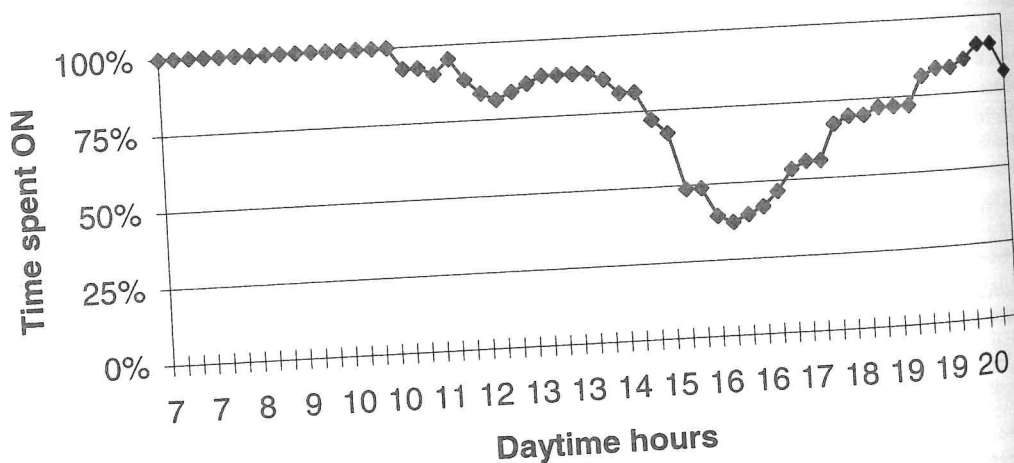
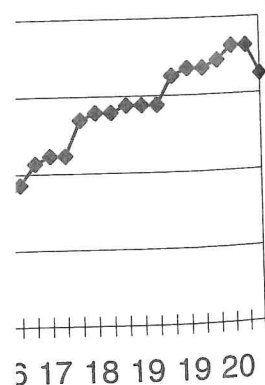


FIG. 75-1. Apomorphine continuous infusion (6.6 mg/h): average time spent "on," measured daily for 21 consecutive days. It is observed that daytime worsening and postprandial "off state" occur notwithstanding a continuous daytime infusion.

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dopaminergic compound was first explored with (+)4-propyl-9-hydroxynaphthoxazine (PHNO; also known as MK-458 or naxagolide). PHNO is the most potent D₂ dopaminergic compound known and is readily absorbed through the skin. Although administration of PHNO in an oral sustained-release form showed potent antiparkinsonian effectiveness (49), this drug was discontinued from further development before the transdermal delivery route could be tested in human subjects.

Transdermal administration is currently under investigation with another dopaminergic compound, N-0923 (Discovery Therapeutics, Richmond, VA). N-0923 is an aminotetralin with selective D₂ dopaminergic agonism has recently been shown to achieve therapeutic doses after application of a skin patch formulation. Initial clinical trials with this compound by the intravenous route demonstrated it could lessen parkinsonian features. Based on this experience, transdermal patches were developed, each containing 10, 20, or 30 mg of N-0923 and releasing it over 30 hours. Tests in nine patients revealed 19% to 53% improvements in scores on a modified Columbia University Parkinsonism Rating scale (50,51). The maximal effect began at 5 hours and lasted up to 24 hours. A second study of three transdermal doses of N-0923 tested tolerability and effectiveness over 3 weeks. An interim analysis of results in this placebo-controlled, double-blind study in 25 patients showed that N-0923 could fully replace prior dopaminergic agonist therapy with pergolide or bromocriptine, and permitted reduction of L-DOPA dose by 20% to 30% without decline in control of parkinsonism. Motor fluctuations were lessened, dose titration of N-0923 was not necessary, and adverse effects were minimal. Further development of this compound for transdermal administration is planned.

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