Medical Intelligence

Parkinsonism, Levodopa, and Anesthesia

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Parkinsonian symptoms (akinesia, rigidity, and tremor) have their pathogenesis in deficiency of dopamine in the basal ganglia. Levodopa crosses the blood–brain barrier and is converted to dopamine in the brain. Its efficacy is far superior to that of anticholinergic drugs or thalamectomy. Motor functions improve in two thirds of patients treated with levodopa. Apomorphine and amantadine can also ameliorate parkinsonian symptoms, the former through activation of dopaminergic receptors and the latter through increased release of dopamine. Levodopa has a short half-life in the body, being metabolized to 3-methoxydopa, dopamine, and homovanillic acid. For optimal effects levodopa (2–8 g, daily) is administered in four or more divided doses. Major adverse reactions include abnormal movements and psychic and cardiovascular disturbances. These are apparently the result of increased formation of catecholamines centrally and peripherally. Advances are being made to improve the efficacy of levodopa therapy and to reduce its side-effects. Inhibition of peripheral decarboxylase with hydrazine derivatives (MK 486 or Ro 4-4602) makes levodopa more available to the central nervous system, reduces the dose needed, and attenuates some of the peripheral side-effects. In surgical patients being treated with levodopa, therapy should be continued until the night before operation and resumed as soon as possible postoperatively. The anesthesiologist should be familiar with the actions of levodopa to assure a smooth perioperative course. In more than 40 anesthetic procedures major difficulties were encountered in only one case, in which severe rigidity and pulmonary edema occurred after administration of droperidol and fentanyl. (Key words: Amantadine; Apomorphine; Catecholamines; Decarboxylase inhibitors; Dopamine; Levodopa; Parkinsonism.)

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Parkinsonism is a progressive, debilitating disease. Its principal manifestations are akinesia, rigidity, and tremor. Until a few years ago, treatment consisted of anticholinergic drugs and/or thalamectomy, the long-term results of which were not encouraging. Since the pioneering work of Hornykiewicz and associates1,2 and Barbeau et al.,3 levodopa (L-3,4-dihydroxyphenylalanine, L-dopa, Larodopa, Dopar) has been found effective in alleviating parkinsonian symptoms in approximately two thirds of the patients being treated.4–5 Advances are still being made to improve the efficacy of levodopa therapy, based upon basic knowledge of neurochemistry and neuropharmacology gained since the 1950's.

This review summarizes the rationale of levodopa therapy in parkinsonism, pharmacology of levodopa, some recent developments, and complications associated with the disease and its therapy relevant to the conduct of anesthesia. More extensive discussions on this subject have been published as proceedings of symposia held in 1969,10 1970,11,12 and 1971,13 and a review by Hornykiewicz.14

Rationale of Levodopa Therapy—Mechanism of Action

Levodopa, a naturally-occurring aromatic amino acid, is the immediate precursor of dopamine. Figure 1 shows the pathways of synthesis and metabolism of catecholamines. Studies of the biochemistry and pharmacology of biogenic amines (norepinephrine, dopamine, and serotonin) laid the experimental foundation for the clinical use of levodopa as a drug. It is now well established that dopamine exists in the animal and human brain in high concentrations in the basal ganglia (the caudate nucleus and the putamen). The
basal ganglia receive ascending tracts, considered to be dopaminergic, from the substantia nigra. Dopamine exerts an inhibitory effect on the basal ganglia in controlling extrapyramidal functions. In parkinsonian patients there is a consistent degeneration of the substantia nigra. Dopamine concentrations in the basal ganglia are lower than normal, as are those of its principal metabolite, homovanillic acid (HVA). This deficiency of dopamine would result in "release" symptoms such as rigidity and tremor, hallmarks of parkinsonism.

Early studies in animals showed that reserpine depletes tissue catecholamine stores and causes akinesia and sedation. Levodopa restores brain dopamine levels and reverses reserpine-induced symptoms. Based upon these observations and biochemical findings in parkinsonism, Birkmayer and Hornykiewicz and Barbeau et al. took the logical step in trying to increase brain dopamine concentrations with levodopa. Administration of small doses of levodopa did indeed relieve parkinsonian symptoms.

Levodopa, being an amino acid, crosses the blood-brain barrier to reach the brain. The rate-limiting step in the synthesis of catecholamines (hydroxylation of tyrosine, reaction 1, fig. 1) is bypassed, and conversion of levodopa to dopamine (decarboxylation, reaction 2, fig. 1) proceeds at a rapid rate. In parkinsonism patients, HVA concentrations in the cerebrospinal fluid are lower than normal. Levodopa causes large increases, indicating that a part of the administered dose is indeed being converted to dopamine in the brain, with subsequent metabolism of dopamine to HVA (reactions 3 and 4, fig. 1).

Birkmayer and Hornykiewicz also considered other possible mechanisms of action of levodopa. Pretreatment with a monoamine oxidase inhibitor (MAOI) considerably poten-
iated the effects of levodopa. As MAOI does not directly interfere with the metabolism of aromatic amino acids, but inhibits that of biogenic amines, the clinical action of levodopa probably is mediated through the amines formed from levodopa. Intravenously-injected dopamine does not have antiparkinsonian actions, as it cannot cross the blood–brain barrier, nor does the alternate metabolite of levodopa, 3-methoxydopa. Finally, administration of another aromatic amino acid, threo-3,4-dihydroxyphenylserine (threo-dops), has no effect on parkinsonian symptoms. Threo-dops, different from levodopa only by the presence of a hydroxy group on the beta carbon atom, can be converted (decarboxylation) directly to norepinephrine. All of these results point to dopamine as the active metabolite of levodopa having its effects centrally.

**Pharmacology of Levodopa**

The current regimen consists of rather large doses of levodopa (2–8 g, daily) given by mouth in four or more divided portions. The initial dose is small, 0.1 g administered three times a day, and is increased gradually to the final level. The build-up of an optimal therapeutic dose may take weeks, and is frequently slowed because of side-effects such as nausea, vomiting, and faintness. The need for careful titration of the dose and time schedule of administration for each patient to achieve maximal therapeutic benefit with the least side-effects has been stressed. Side-effects, mostly minor but disturbing, occur in more than 90 per cent of patients.

This rather cumbersome therapeutic regimen and the high incidence of side-effects are related to the pharmacokinetics of levodopa and the pharmacologic actions of dopamine, which affect almost all systems.

In the mouse, more than half of $^{14}$C-labelled DL-dopa is metabolized during the first 20 minutes after its intraperitoneal injection, the major metabolites being 3-methoxydopa and HVA. After 20 and 60 minutes less than 0.1 per cent of $^{14}$C-catechols present in the body are found in the brain. In the dog, following an intravenous injection of $^{14}$C-levodopa (50 mg/kg), the plasma half-life is approximately 40–60 minutes. When given orally, only 22–30 per cent of the administered dose reaches the general circulation. The remainder is either not absorbed (10–20 per cent) or degraded in the gastrointestinal tract and/or metabolized in the liver during its first passage (approximately 60 per cent). In Parkinsonism patients, absorption of orally administered $^{14}$C-levodopa is complete. However, after an hour approximately 50 per cent of the radioactivity in the blood is present as acid metabolites, with less than 10 per cent present as unchanged dopa. Therefore, only a small fraction of levodopa is available to the brain, explaining the necessity for frequent administration and the relatively large doses needed.

Methylation of levodopa to 3-methoxydopa by catechol-O-methyltransferase (reaction 3, fig. 1) accounts for only a part of levodopa degradation. The pharmacologic activity of 3-methoxydopa is largely unknown. However, as methylation of levodopa (and dopamine) requires a methyl-group donor, the availability of methionine and S-adenosylmethionine (SAMe) is of interest. Wurtman et al. showed that in rats 30–100 mg/kg levodopa decreases the concentration of SAMe in the brain. They speculated that depletion of SAMe might enhance the action of cerebral dopamine (through a decreased rate of metabolism). They also expressed concern about the possibility of long-term nutritional deficiencies of methionine, owing to its utilization during levodopa therapy. Methionine is essential for the function of nucleotides and synthesis of certain proteins. It has been suggested that chronic levodopa therapy may produce some changes of macromolecules in the brain.

The ubiquitous presence of aromatic L-amino acid decarboxylase results in conversion of levodopa to dopamine in peripheral tissues. The pharmacologic actions of dopamine have a number of side-effects. Nausea and vomiting occur frequently, especially during the early phase of therapy. These can usually be avoided by slow, gradual increases in the daily dose. Administering levodopa with food also helps, suggesting that gastric irritation is the cause of nausea and vomiting. However, in dogs intravenous injection of levodopa causes vomiting. Similarities in the
effects of levodopa and apomorphine in relieving parkinsonian symptoms and causing nausea and vomiting have led to the suggestion that dopamine acts on the chemoreceptor trigger zone (area postrema) to elicit vomiting.21-28

Faintness is a common complaint. This could be related to postural hypotension (see below) or to amputation after prolonged inactivity. Of more concern are psychic disturbances and abnormal movements (choreoathetoid dyskinesia) during levodopa therapy. Patients may become euphoric, aggressive, or depressed. Confusion, hallucinations, and attempted suicides have been reported.8,9 The incidences of psychic disturbances, minor and major, have ranged from 30 to 43 per cent,6,8 necessitating reduction of the dose of levodopa and sedation in major episodes. The basis for these mental changes is not clear, but they are probably related to levodopa-induced alterations in cerebral biogenic amines. Indeed, levodopa has been tried for the treatment of depression.29

Dyskinesia is an annoying and sometimes disabling complication, involving all segments of the body. The dose of levodopa producing dyskinesia is very close to or even less than that needed for effective therapy of parkinsonism. Carlsson suggested that dyskinesia is probably related to activation of dopamine or norepinephrine receptors in the neostriatum.50 Reducing the dose of levodopa alleviates dyskinesia but compromises the effectiveness of therapy.

Cardiovascular side-effects consist primarily of postural hypotension and less frequently, episodes of arrhythmias or hypertension.5,6,8,9 It seems likely that these latter actions of levodopa are mediated through its metabolite, dopamine, which is known to increase arterial blood pressure and heart rate, although it is much less potent than norepinephrine. Prior inhibition of peripheral decarboxylase prevents the conversion of levodopa to dopamine and abolishes the immediate hypertensive and tachycardia responses to intravenously-administered levodopa in pithed rats (Krenis et al.: to be published) and anesthetized dogs.31,32 Propranolol blocks the positive inotropic and chronotropic effects of levodopa.32

Hypotension, asymptomatic or associated with syncope and dizziness upon standing, occurs with variable incidence. Several mechanisms have been suggested. Levodopa causes accumulation of dopamine with concurrent loss of norepinephrine stores in the peripheral adrenergic nerve terminals, lasting as long as four hours.33 Conceivably, dopamine, which is less potent than norepinephrine, could act as a false transmitter, interfering with sympathetic function. In cats and dogs the carotid sinus reflex is obtunded during levodopa infusion; in dogs, stimulation of the lumbar sympathetic trunk no longer causes vasoconstriction in the femoral vascular bed.34 Whitnack et al. also reported that levodopa interferes with chronotropic responses to postganglionic sympathetic (cardioaccelerator) nerve stimulation in dogs.35 However, the central action of levodopa or its metabolites (catecholamines) has also been suggested. In dogs and in man37 pretreatment with a peripheral decarboxylase inhibitor, MK-486 (L-α-methyldopa hydrazine) or MK-485 (racemic mixture of MK-486) did not prevent the levodopa-induced hypotension.

Two additional possible mechanisms of hypotension during levodopa therapy should be mentioned. Finlay et al. showed that in patients with parkinsonism or congestive heart failure levodopa in single doses of 1 to 2 g increases glomerular filtration rate, renal plasma flow, and electrolyte excretion, probably through the action of dopamine.38 The markedly increased sodium excretion (from a mean of 116 to 289 µEq/min) could accentuate orthostatic hypotension. These effects of levodopa on renal function have been suggested to be of potential value in the treatment of congestive heart failure and hypertension.58 Barbeau et al. observed that in parkinsonism patients' plasma renin activity is lower than normal. Levodopa therapy uniformly decreases plasma renin further, to undetectable levels.39

Other actions of levodopa have been observed. Paulson and Tafrate noted that levodopa considerably increases the minute ventilatory volume in parkinsonian patients, probably related to the improvements in posture and rigidity of the chest muscles.40 Levodopa
increases the levels of plasma growth hormone significantly and suppresses serum prolactin levels, probably through the action of dopamine on the hypothalamus. The clinical significance of these changes in endocrine function is not clear at present.

In rats, chronic treatment with large doses of levodopa (1 g/day) decreases tyrosine hydroxylase activity in the adrenal gland by 50 per cent, but does not decrease that in the brain. The increased concentrations of catecholamines cause an end-product inhibition of this rate-limiting enzyme. The rate of recovery of tyrosine hydroxylase activity has not been studied. It is possible that sudden withdrawal of levodopa therapy may leave patients with a diminished capacity to synthesize catecholamines in peripheral adrenergic tissues.

Recent Developments in the Treatment of Parkinsonism—Drug Interactions and Alternate Drugs

Combined therapy with levodopa and a peripheral decarboxylase inhibitor, MK-186 (L-α-methyl-levodopa hydrazine) or Ro 4-4602 (N,N-di-n-propyl-L-3,4-dihydroxyphenylalanine) has been under trial. In rats, pretreatment with Ro 4-4602 markedly increases plasma concentration of levodopa and its half-life. In the caudate nucleus the increase in dopamine concentration following levodopa and Ro 4-4602 is approximately thirtyfold compared with that after treatment with levodopa alone. In parkinsonian patients the dose of levodopa needed to relieve akinesia and rigidity is only a tenth to a sixth that needed when levodopa is given alone. The reduced dose requirement has several advantages. A therapeutic plateau is achieved sooner, with fewer oscillations in daily and long-term performance. There are fewer side-effects such as hypotension, nausea, and vomiting. The frequency of dosing with levodopa is reduced, making handling easier. However, abnormal movements still occur and may even have on earlier onset, suggesting that dyskinesia is the result of increased synthesis of catecholamines in the central nervous system. Studies of Mena et al. support this view. They administered fusaric acid, an inhibitor of dopamine-β-hydroxylase (enzyme for reaction 5, fig. 1) to parkinsonism patients. Some were treated with levodopa alone, others with levodopa in combination with a peripheral decarboxylase inhibitor. Inhibition of dopamine-β-hydroxylase prevents the conversion of dopamine in norepinephrine. A marked reduction in abnormal movements occurred without apparent change in the control of parkinsonian symptoms.

Vitamin B₆, pyridoxal phosphate, strikingly reversed the effect of levodopa on parkinsonism. Pyridoxine is a coenzyme of dopa decarboxylase. Increased decarboxylation of levodopa to dopamine in the periphery would make levodopa less available to the brain. High doses of pyridoxine, such as that present in therapeutic vitamin capsules, should be avoided during levodopa therapy. However, this action of pyridoxine has been exploited. It is being used to relieve abnormal movements during levodopa therapy. Paradoxically, pyridoxine, administered together with levodopa and MK-486, seems to improve the efficacy of levodopa and to shorten the time needed to establish the therapeutic dose level of levodopa. The rationale for this combined therapy is that with peripheral inhibition of decarboxylase, pyridoxine is thought to accentuate the action of levodopa through facilitation of decarboxylation centrally.

As mentioned above, apomorphine has actions similar to those of levodopa in relieving parkinsonian symptoms. The duration of action is brief, 30–180 minutes. Because apomorphine is destroyed in the intestine, it must be given parenterally. These limitations, together with its emetic action, make the use of apomorphine impractical.

Schwab et al. first discovered that amantadine (Symmetrel), an antiviral agent, can also ameliorate symptoms of parkinsonism. About two thirds of patients treated with amantadine showed various degrees of improvement. The quality of improvement appears inferior to that obtained with levodopa, but the incidence of side-effects is lower. Based upon results of animal studies, amantadine probably acts by enhancing release of dopamine in the basal ganglia.
Anesthetic Management of Parkinsonism Patients Being Treated with Levodopa

With the increasing usage of levodopa in treating parkinsonism, anesthesiologists will become increasingly involved in the management of these patients during surgical procedures. Knowledge of the pharmacologic actions of levodopa, as discussed above, is necessary to avoid complications during anesthesia and to assure a smooth perioperative course.

The relatively short half-life of levodopa in the body dictates that drug therapy should be maintained if possible. Although parkinsonian symptoms do not always recur immediately upon withdrawal of levodopa, akinesia, tremor, and rigidity can be quite disturbing to the patient. The so-called "minor" symptoms, ventilatory insufficiency owing to rigidity of chest muscles and salivation from difficulty in swallowing, may become major problems.

On the other hand, the reported cardiovascular effects of levodopa, particularly arrhythmias and hypotension, are causes for concern. Goldberg voiced caution in respect to the administration of cyclopropane and halothane within four hours of levodopa administration. The presence of high concentrations of dopamine in the peripheral adrenergic tissues could lead to ventricular arrhythmias upon its release. Possible development of hypotension from loss of peripheral norepinephrine stores, natriuresis, or reduced renin activity necessitates awareness and precautions, as with patients being treated with reserpine, alpha-methylidopa, or other antihypertensive drugs.

We have anesthetized more than 40 parkinsonian patients receiving levodopa. The majority underwent orthopedic or urologic operations. In 1968, levodopa therapy was discontinued two days or more prior to anesthesia and operation because of uncertainty concerning cardiovascular side-effects. Since 1969, the patient's usual dose of levodopa has been maintained preoperatively and resumed as soon as possible postoperatively. The last dose of levodopa is given the night before operation. If the procedure takes place in the afternoon, one dose of levodopa is administered in the morning. We reason that six hours or more following the administration of levodopa, very little dopamine would remain in peripheral adrenergic tissues. So far we have not encountered unexpected cardiovascular complications during anesthesia using a variety of anesthetics, including cyclopropane and halothane. Serious arrhythmias have not been observed. We have not had to use lidocaine or propranolol. Of course, our experience is still limited, necessitating continued surveillance.

On theoretical grounds, the use of butyrophenone derivatives, haloperidol and droperidol, would seem to be contraindicated in patients on levodopa therapy. Haloperidol antagonizes the action of dopamine. We have reported that in one patient droperidol and fentanyl may have caused severe rigidity and pulmonary edema, interfering with ventilation during and following anesthesia. However, Norinder anesthetized a patient on levodopa therapy with droperidol, fentanyl, succinylcholine, and nitrous oxide, without incident.

Combined therapy with levodopa and a peripheral decarboxylase inhibitor should reduce the likelihood of cardiovascular complications, as less dopamine is then being formed in the periphery. However, as mentioned above, the central action of levodopa in causing hypotension has been suggested. The long-term effects of peripheral decarboxylase inhibitors are not known. Experience with patients on combined therapy is even more limited. Thus far, we have anesthetized three patients receiving levodopa and MK 486, without difficulties.

It should be stressed, however, that many parkinsonian patients are receiving other drugs for various complaints or coincidental diseases. Examples relevant to anesthetic management may include vasopressors, tricyclic antidepressants, tranquilizers, sedatives, anticholinergic agents, and digitalis preparations. Drug interaction through their effects on the catecholamine system or on enzyme induction may pose additional problems for the anesthesiologist.

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