Although levodopa has provided a major advance in the treatment of parkinsonism, its maximum benefits have not yet been realised, in part because of its complicated pharmacokinetics. This review summarises the available pharmacokinetic data involving levodopa, especially as it relates to therapeutic response of parkinsonian patients.

A large number of factors, including protein intake, gastric emptying time, pyridoxine ingestion, and dopa decarboxylase activity, affect plasma levels of levodopa attained following oral administration of this drug. Other variables influence the rate of brain uptake of levodopa from the blood. Even so, plasma levodopa concentration correlates significantly with dosage size in a large parkinsonian population and also coincides with therapeutic response in many, but not all, patients. Therefore, in certain instances, valuable information may be derived by correlating clinical response with plasma levodopa concentration.

Cerebrospinal fluid levels of homovanillic acid, a major metabolite of dopamine, may have some value in predicting clinical response to levodopa. This relationship, however, has not been firmly established. Concentration of homovanillic acid or levodopa in body fluids may also be closely related to certain adverse side-effects, including abnormal involuntary movements, gastric discomfort and psychiatric disturbances.

Evidence indicates that a clearer understanding of levodopa pharmacokinetics may improve the clinical management of parkinsonism.
not correlate significantly with therapeutic response or toxic side-effects. It would be useful if a body fluid concentration of levodopa or one of its metabolites could be correlated with, or used to predict, the subsequent clinical response of the patient. Such estimations may provide valuable information leading to an improvement in therapeutic response achieved with levodopa. These associations already have been established for many other drugs. The purpose of this review is to summarise available pharmacokinetic data for levodopa which pertain to this important topic.

I. The Parkinsonian Syndrome and Rationale for Levodopa Therapy

Parkinson’s disease is a major crippling neurological disorder that usually appears in the latter decades of life, producing slowly increasing disability in movement. The disease commonly manifests four major clinical features: bradykinesia, tremor, rigidity, and disturbance of posture. In advances stages of parkinsonism, loss of motor function causes a variety of other signs and symptoms, such as impairment of postural reflexes, reduced blinking, micrographia, and microphonia. Microscopically, the disease is characterised by cell loss in the substantia nigra (Greenfield, 1963) and a reduction of dopamine in the corpus striatum, with an increase in the sensitivity of the striatal postsynaptic dopaminergic receptors (Bernheimer et al., 1973). The relationship between disease manifestations, dopamine deficiency, and nigra cell loss has been established (Bernheimer et al., 1973).

While dopamine does not cross the pial-glial barrier, its immediate metabolic precursor, levodopa, does. When levodopa is administered in therapeutic dosages, a portion is converted to dopamine in the striatum by means of cerebral L-aromatic amino acids decarboxylase (dopa decarboxylase) thereby replenishing the deficient dopamine stores. The following statements summarise the efficacy of levodopa:

a) Approximately 75% of parkinsonian patients respond at least reasonably well to levodopa. Therapeutic response in some patients is very gratifying, especially at the onset.

b) Essentially, all parkinsonian symptoms (including bradykinesia, rigidity, tremor, postural defect, muscle weakness, salivation, and increased sebum secretion) can be improved by levodopa.

c) Bradykinesia and rigidity generally respond better and more promptly than does tremor. In some patients, however, tremor is also markedly improved by this drug.

Levodopa treatment of parkinsonism consists of two phases, an initial induction period (lasting 2 to 6 weeks) and a subsequent, long-term maintenance phase (Yahr, 1975). During the induction phase, the daily dosage of levodopa is increased slowly in order to minimise the appearance of certain side-effects such as insomnia, nausea and anorexia, which appear more rapidly than signs of clinical improvement. Some patients, however, improve minimally or not at all. In these cases, CSF-HVA level determinations may be of some prognostic value in estimating future clinical improvement (Hinterberger and Andrews, 1972).

Although levodopa is established as the most effective agent for the treatment of Parkinson’s disease, clinical improvement is often less than optimal due to the appearance of dose limiting side-effects. These include cardiac arrhythmias, orthostatic hypotension, nausea, vomiting and anorexia. The two major limiting factors of long-term levodopa therapy are the development of dyskinesias and the ‘on-off’ phenomenon, both of which may coincide with high levodopa plasma levels (Fahn, 1974; Sweet and McDowell, 1974a). It is not clear why these undesirable side-effects of levodopa generally do not appear until the later maintenance phase.
2. Variations in the Clinical Presentation of Parkinsonism

Clinical observations of patients on chronic levodopa therapy indicate that different subpopulations exist, each characterised in part by their differences in response to levodopa. Marsden and Parkes (1976) describe the following categories of fluctuating clinical presentation, any one or more of which may occur in a patient:

a) Early-morning akinesia — characterised by akinesia, rigidity and tremor upon awakening, this phenomenon is due to low circulating levels of levodopa. It is simply parkinsonism, unrelieved by drug therapy.

b) Freezing episodes — this classical parkinsonian symptom has been termed ‘akinesia paradoxica’, ‘start hesitation’, or ‘freezing’. It presumably is not related to levodopa therapy but may be helped for a period of time by such treatment.

c) End-of-dose deterioration — deterioration in clinical status coincident with a fall in plasma levodopa levels is a common form of fluctuating disability. It usually develops after 1 or more years of levodopa therapy, during which time, the period of clinical improvement afforded by each dose of levodopa progressively diminishes.

d) Peak-dose dyskinesia — dose-related abnormal involuntary movements commonly occur 1 to 2 hours after each dose of levodopa at the time of maximum beneficial response.

e) Peak-dose akinesia — this is a rare symptom involving akinesia and dysphonia without tremor 1 to 2 hours after levodopa administration. It may result from either depolarisation blockage of striatal dopamine receptors by excess dopamine or ineffective partial agonist activity by dopamine metabolites.

f) ‘Yo-yo-ing’ — another type of fluctuating disability; this phenomenon occurs at unpredictable times throughout the day and appears to be unrelated to the timing of doses or the levels of circulating levodopa. It may result from progression of the end-of-dose phenomena or from chronic overdosage of levodopa (Barbeau, 1974).

Other authors have grouped these same clinical phenomena somewhat differently. Barbeau (1974) describes four patterns of fluctuating clinical response in patients on long-term levodopa therapy. His first three correspond to variations within the end-of-dose deterioration category, and the fourth is similar to the ‘yo-yo-ing’ phenomenon, both described above. To further complicate the diversity of therapeutic response to levodopa, certain parkinsonian patients respond to low dosages of levodopa with non-fluctuating, low blood concentrations of the drug and sustained clinical improvement. Others, who take large doses of levodopa, do not respond in a beneficial way, despite maintaining relatively high plasma levels of the drug (Tolosa et al., 1975).

3. General Factors Affecting Serum Levels of Levodopa

3.1 Gastro-Intestinal Absorption

Since levodopa is usually administered orally, interference with gastro-intestinal absorption may alter blood levels and the subsequent therapeutic response. Levodopa is an aromatic amino acid absorbed primarily in the small bowel by a special carrier transport mechanism. Other aromatic amino acids in the diet may compete successfully for this same carrier mechanism. Consequently, ingestion of levodopa with a high protein diet may decrease both the circulating plasma concentration of levodopa and the subsequent clinical improvement. Sweet and McDowell (1974a) compared plasma levodopa concentrations in nine parkinsonian patients on a regular diet and eight of these
same patients on a low protein diet (<10mg per day). Patients on the low protein diet achieved significantly higher plasma levels of levodopa (2.05 ± 0.11 versus 1.20 ± 0.92µg/ml; p < 0.001) than when ingesting a normal diet.

3.2 Local Metabolism by Gastric Mucosa

The enzyme L-aromatic amino acids decarboxylase has a ubiquitous distribution with high activity residing in the gastric mucosa. It has been established by Rivera-Calimlim et al. (1971), that minces of gastric mucosa from animals, everted gastric pouches of rats, and gastric mucosa of parkinsonian patients (studied in situ) all rapidly metabolise levodopa. Since levodopa is metabolised by the gastric mucosa, the rate of gastric emptying may alter greatly the blood concentration of levodopa achieved following oral administration (Rivera-Calimlim et al., 1971; Mearrick et al., 1974). For example, in parkinsonian patients with markedly slowed gastric emptying rates, levodopa may not provide adequate treatment of parkinsonism, because a significant portion of the orally administered drug is inactivated during its prolonged exposure to the gastric mucosa. In parkinsonian patients with sluggish gastric emptying coupled with markedly acid gastric juice (pH < 2), alkalinisation of the gastric contents to approximately pH 4 may hasten gastric emptying and thereby enhance the rate of levodopa absorption. Furthermore, the co-administration of anticholinergic drugs with levodopa may delay gastric emptying and thus decrease the net absorption of levodopa in the small bowel.

3.3 Pyridoxine Enhancement of Extracerebral Levodopa Metabolism

Once absorbed, approximately 99% of the serum levodopa is metabolised to dopamine by peripheral aromatic L-amino acids decarboxylase. This peripheral (extracerebral) metabolism of levodopa in parkinsonian patients is enhanced by pyridoxine (Yahr et al., 1972; Hsu et al., 1973). High pyridoxine dosages (750 to 1,000mg/day) completely abolish the antiparkinsonian effect of levodopa, but a normal daily diet containing less than 1mg pyridoxine does not interfere with its effectiveness (Yahr and Duvoisin, 1972b). The data of Hsu et al. (1973) suggest that pyridoxine enhances or accelerates the decarboxylation of levodopa to dopamine in parkinsonian patients but not in normal subjects. In 5 parkinsonian subjects who served as their own controls, urinary excretion of levodopa was significantly lower (by 55%; p < 0.01) and excretion of dopamine significantly higher (by 41%; p < 0.02) 4 hours after the simultaneous administration of pyridoxine and levodopa, as compared with the ingestion of levodopa alone. The difference in pyridoxine-induced levodopa metabolism between parkinsonian patients and normal control subjects may reflect an adaptive alteration in the decarboxylase system due to chronic administration of levodopa (Mars, 1975). This alteration may result from an increased cellular ability to synthesise pyridoxal-5-phosphate, the biologically active form of pyridoxine.

3.4 Peripheral Aromatic Amino Acids Decarboxylase Inhibitors

These agents, which include carbidopa and benserazide, have recently provided a major advance in the treatment of parkinsonism. In therapeutic dosages, they do not penetrate the blood-brain barrier, but act peripherally to block the conversion of levodopa to dopamine, thereby allowing a greater portion of administered levodopa to reach the brain. Co-administration of levodopa and a dopa decarboxylase inhibitor may decrease daily levodopa requirements by 80% (Morgan and Bianchine, 1971; Yahr and Duvoisin, 1972a; Cotzias, 1969).

Numerous studies (Bianchine et al., 1972; Messina et al., 1972; Dunner et al., 1971; Tissot et al., 1969) describe the pharmacokinetics of levo-
dopa administered both alone and in combination with a dopa decarboxylase inhibitor. In these investigations, levodopa dosage was held constant. Plasma levels of levodopa were higher, and half-life was longer, following co-administration of a decarboxylase inhibitor and levodopa compared with levodopa alone.

Fahn (1974) compared levodopa tolerance curves in 3 patients taking levodopa alone with tolerance curves obtained in these same patients taking levodopa (with an 80% reduction in dosage) plus carbidopa. These two dosage forms were therapeutically equivalent and yielded roughly similar plasma levodopa concentrations. Half-life determinations with and without dopa decarboxylase inhibitor were similar. Fahn's data differ from that of the investigators cited above. He suggests that his data more closely reflect levodopa tolerance curves found in the clinical setting because he administered therapeutically equivalent levodopa dosages to each group. However, this is the only report which indicates that a decarboxylase inhibitor does not alter plasma levodopa half-life.

The clinical advantages of co-administration of a dopa decarboxylase inhibitor with a lower dosage of levodopa include minimising certain dose-limiting adverse side-effects such as nausea and vomiting. On the other hand, other complications of levodopa such as psychiatric disturbances and abnormal involuntary movements are not affected by this combination (Morgan and Bianchine, 1971; Yahr and Duvoisin, 1972; Barbeau et al., 1972). Various side-effects accompanying levodopa treatment and their relationship to concentrations of levodopa and/or its metabolites in the body fluids are discussed in section 8.

3.5 Other Factors Influencing Serum Levels of Levodopa

Dopamine formed extracerebrally does not cross the blood-brain barrier, but serves as the precursor of other metabolic pathways, such as O-methylation, β-hydroxylation, oxidative deamination, conjugation, melanin formation, N-acetylation, and Schiff's base formation (fig. 1). Selective blockade of the catecholamine metabolising enzymes such as monoamine oxidase inhibitors may enhance the level of serum levodopa and thus ultimately augment cerebral dopamine concentration. However, their effect is difficult to control and usually results in undesirable or untoward effects. These factors, as well as drug interactions with levodopa which affect both peripheral and central levels of levodopa and its metabolites, have been reviewed by Bianchine and Sunyapridakul (1973).

4. Correlation Between Oral Dose and Plasma Levodopa Concentrations

While many variables affect the blood concentration of levodopa achieved following its oral administration, most investigators have established a statistically significant positive correlation between dosage size and blood level. This direct relationship has been demonstrated by Tyce et al. (1970) (p < 0.01; number of patients studied, n = 15), by Rinne et al. (1973b) (p < 0.01; n = 58), and by Muenter and Tyce (1971) (p < 0.01; n = 28). Muenter and Tyce (1971) also found the dosage to correlate positively with the concentration of levodopa in plasma over 4 hours (p < 0.01; n = 23).

On the other hand, two reports fail to confirm the above relationship. Hare et al. (1973) found no significant relationship between peak serum levels of levodopa and dosage administered. However, their population of 11 patients may be too small to allow cancellation of inherent variables. Pilling et al. (1975) reported that plasma levodopa concentration did not correlate significantly with the dosage used in a group of 27 outpatients. They noted, however, that part of the wide variation in plasma concentration of levodopa found between
patients 'stems from the difficulty of obtaining plasma samples at a fixed time interval after the last dose of L-dopa in an outpatient population'. Considering the short half-life of levodopa, it is clear that even seemingly small deviations from protocol regarding sampling times can interfere significantly with the dose-blood level relationship.

A careful consideration of all evidence available to date suggests that a significant positive correlation does exist between dosage size of levodopa and subsequent blood levels of levodopa.

5. Plasma Levodopa Levels and Therapeutic Response

From the above section it appears that most, but not all, investigators agree that there is a positive correlation between the size of levodopa dosage and subsequent blood level of levodopa achieved. However, as might be expected, attempts to correlate plasma levodopa levels with therapeutic response has generated considerable differences of opinion among investigators. The clinical response of parkinsonian patients to orally administered levodopa is extremely variable and depends on many factors. This diversity in response, and its relationship to plasma levodopa concentration, is summarised in this section. Only one fact seems clear — it is very important to define carefully each subject prior to pharmacokinetic study. Failure to do this almost totally negates the value of such studies.

5.1 Studies That Fail to Find Correlation Between Plasma Dopa Concentrations and Clinical Response to Levodopa

Attempts by four research groups to correlate plasma levels of levodopa with clinical response in parkinsonian patients were unsuccessful. Muetter and Tyce (1971) described two types of improvement which may result from levodopa therapy, one of short duration lasting 1 to 5 hours and the other of long duration lasting 3 to 5 days. Either

---

**Fig. 1.** Important catabolic pathways of levodopa. Major pathways are shown by heavy arrows; minor pathways by light arrows. AD, aldehyde dehydrogenase; COMT, catechol-O-methyltransferase; DBH, dopamine-β-hydroxylase; DC, aromatic L-amino acids decarboxylase; MAO, monoamine oxidase (reprinted with permission from Franz, 1975).
### Table I. Comparison of parkinsonian symptoms with concomitant plasma levodopa concentration in selected patients

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Patient symptoms</th>
<th>Plasma levodopa concentrations (µg/ml)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Sustained, nonfluctuating improvement</td>
<td>&lt;1 (nonfluctuating)</td>
<td>Tolosa et al. (1975)</td>
</tr>
<tr>
<td>11</td>
<td>Fluctuating improvement coinciding with plasma levodopa concentration</td>
<td>0.5–11 (fluctuating)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Minimal improvement</td>
<td>&lt;5 (fluctuating)</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Fluctuating improvement and dyskinesia coinciding with plasma levodopa concentration</td>
<td>0.5–3 (fluctuating)</td>
<td>Woods et al (1973)</td>
</tr>
<tr>
<td>31</td>
<td>Sustained, nonfluctuating improvement with no dyskinesias</td>
<td>1.5–2.0 (constant iv infusion)</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>Fluctuating improvement coinciding with plasma levodopa concentration</td>
<td>1.5–5.5</td>
<td>Shoulson et al. (1975)</td>
</tr>
<tr>
<td>51</td>
<td>Sustained, nonfluctuating improvement</td>
<td>2–2.5 (constant iv infusion)</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Clinical improvement (‘on’)(^2)</td>
<td>1.29 ± 1.08</td>
<td>Sweet and McDowell (1974a)</td>
</tr>
<tr>
<td>51</td>
<td>Akinesia (‘off’)(^3)</td>
<td>0.62 ± 0.59</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Reduced akinesia and increased hyperkinesia</td>
<td>Rising of &gt;2</td>
<td>Fahn (1974)</td>
</tr>
<tr>
<td>31</td>
<td>Increased akinesia and reduced hyperkinesia</td>
<td>Falling of &lt; 2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Clinical improvement with dyskinesia (‘on’)(^2)</td>
<td>&gt;1</td>
<td>Yahr (1974)</td>
</tr>
<tr>
<td>11</td>
<td>Neither clinical improvement nor dyskinesia (‘off’)(^3)</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>Less than maximal benefit in patients who respond well to levodopa</td>
<td>&lt;0.5</td>
<td>Allen (1973)</td>
</tr>
<tr>
<td>—</td>
<td>Associated dyskinesias in patients who respond well to levodopa</td>
<td>&gt;2.5</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Improved phonation, mental status, and kinesia (‘on’)(^2)</td>
<td>1–2</td>
<td>Calne et al. (1974)</td>
</tr>
<tr>
<td>11</td>
<td>Deterioration in phonation, mental status, and kinesia (‘off’)(^3)</td>
<td>&gt;4</td>
<td></td>
</tr>
</tbody>
</table>

1 Indicates that patients served as own controls.
2 ‘On’ indicates ‘on’ phase of ‘on-off’ phenomenon.
3 ‘Off’ indicates ‘off’ phase of ‘on-off’ phenomenon.
Fig. 2. Relationship between plasma levodopa levels and disability scores (0 = absent, 12 = maximal disability) in 2 patients with sustained improvement throughout the day (a, b); one patient with short duration of improvement (c); another with irregular response to each levodopa dose (d); and two who responded with only minimal improvement to the drug (e, f) [reprinted with permission from Tolosa et al., 1975].
or both types of clinical improvement may occur in any patient taking levodopa. They found no significant correlation between the short- or long-term therapeutic responses and either peak plasma concentrations of levodopa or concentration of levodopa over 4 hours. Hare et al. (1973) found no correlation between peak plasma levels of levodopa and clinical response in 11 patients. Pilling et al. (1975) likewise demonstrated no significant correlation between plasma levels and clinical improvement scores in 27 patients. However, they reported difficulty in 'obtaining plasma samples at a fixed time interval after the last dose of L-dopa'. Finally, Rinne et al. (1973b) showed that clinical improvement during chronic levodopa administration was not correlated significantly with total circulating levels or peak concentrations of levodopa in 173 patients.

These four reports have one or two points in common. First, all studies except Rinne et al. (1973b) involve a relatively small population of parkinsonian patients. As mentioned above, small populations are often not adequate for statistical analysis. Secondly, all four reports attempt to correlate levodopa plasma levels with therapeutic outcome in a diverse population of parkinsonian patients with little or no differentiation into meaningful subgroups [Muentener and Tyce (1971) do, however, differentiate between short- and long-term responders]. In fact, clinical observations of a large number of parkinsonian patients demonstrate the presence of a number of subpopulations whose clinical presentations may be intimately related to plasma levodopa concentrations (see section 2).

5.2 Studies That Find Positive Correlation Between Plasma Levodopa Concentrations and Clinical Improvement

Many reports indicate that short term (i.e. hour to hour) therapeutic response of certain selected parkinsonian patients is directly related to hour by hour fluctuation in plasma concentration of levodopa (see table I). Tolosa et al. (1975) described three groups of patients classified according to their clinical response to treatment with levodopa alone or in combination with carbidopa. In one group, three patients showed sustained clinical improvement with nonfluctuating low levels of plasma levodopa, which were often less than 0.1 μg/ml (fig. 2a, b). In another group, patients' plasma concentrations fluctuated between low (less than 0.5 μg/ml) and high (above 10 μg/ml) levels. Improvement in clinical disability coincided with higher plasma levodopa concentrations; parkinsonian symptoms reappeared when these concentrations fell below certain minimal levels (fig. 2c, d). For these patients, there was a significant positive correlation (r = 0.4, p < 0.05) between plasma levodopa concentration and clinical improvement. In addition, a more sustained clinical improvement was maintained when plasma levodopa concentration was kept above a certain minimal level (fig. 3a, b, c). In this particular case, higher plasma levodopa levels and increased motor ability were maintained by increasing levodopa dosage and altering its dosage schedule. In the third group, patients took large oral doses of levodopa yielding high levodopa plasma levels, but they exhibited only minimal clinical improvement (fig. 2e, f).

In 8 of the 16 patients described by Tolosa et al. (1975) abnormal involuntary movements were closely related to plasma levodopa levels (fig. 4a, b). In contrast to the findings of Rinne et al. (1973b) and Reid et al. (1972), Tolosa found no significant correlation between plasma levodopa and dyskinesia for the entire group of patients, considered together.

Woods et al. (1973) observed in three parkinsonian patients that peak plasma levels of levodopa achieved following oral administration coincided with maximum suppression of parkinsonian symptoms and the appearance of abnormal involuntary movements. Low circulating levels of the drug were associated with decreased clinical
improvement and the disappearance of abnormal involuntary movement. When constant levodopa plasma levels (1.5 to 2μg/ml) were maintained by intravenous infusion in these same patients, sustained clinical improvement with no interfering dyskinesia resulted.

Similar findings were reported by Shoulson et al. (1975). In 7 patients, there was a direct relationship between plasma levodopa and improved clinical state (fig. 5) and an inverse relationship between severity of parkinsonism and severity of abnormal involuntary movements. In each patient, declining levels of levodopa were associated with increased hypokinesia, and rising levels were coincident with decreased parkinsonism and increased hyperkinesia. However, this association between plasma levodopa levels and the amplitude of variation in clinical status was not statistically significant. When plasma levodopa was maintained at approximately 2μg/ml by slow intravenous infusion, both fluctuation in clinical state and severity of hypokinesia were markedly reduced (fig. 6).

Sweet and McDowell (1974a) measured plasma levodopa concentrations during ‘on’ (mobile and dyskinetic) and ‘off’ (akinetic and/or tremulous) episodes in 10 patients on chronic levodopa therapy. Levodopa levels were significantly higher during ‘on’ than ‘off’ periods (1.29 ± 1.08 versus 0.61 ± 0.59μg/ml; p < 0.001). Clinical improvement usually correlated closely with plasma levodopa levels, but this was not a constant finding since some patients occasionally showed good motor function when plasma levodopa was low.

Fahn (1974) observed that three parkinsonian patients, in whom plasma levodopa levels were either rising or higher than 2μg/ml, generally manifested hyperkinesia. When levels were falling or less than about 2μg/ml, these same patients were usually akinetic.

Yahr (1974) noted instances in which there was an ‘intimate relationship’ between plasma levodopa concentration and therapeutic response. He described a patient in whom ‘off’ periods were