

# The on-off phenomenon

A J LEES

*From the National Hospital for Nervous Diseases, London UK*

**SUMMARY** The on-off phenomenon is an almost invariable consequence of sustained levodopa treatment in patients with Parkinson's disease. Phases of immobility and incapacity associated with depression alternate with jubilant thaws. Both pharmacokinetic and pharmacodynamic factors are involved in its pathogenesis, but evidence is presented to indicate that the importance of levodopa handling has been underestimated and that progressive reduction in the storage capacity of surviving nigrostriatal dopamine terminals is not a critical factor. Re-distribution of levodopa dosage which may mean smaller, more frequent doses, or larger less frequent increments, may be helpful in controlling oscillations in some patients. Dietary protein restriction, the use of selegiline hydrochloride and bromocriptine may also temporarily improve motor fluctuations. New approaches to management include the use of subcutaneous apomorphine, controlled-release preparations of levodopa with a peripheral dopa decarboxylase inhibitor and the continuous intra-duodenal administration of levodopa.

The on-off phenomenon comprises profound diurnal fluctuations in the psychomotor state of patients with Parkinson's disease treated with levodopa. Each swing usually lasts for one to three hours, but occasionally several oscillations may occur over the course of 30 minutes. It was first reported in the very first study using high doses of levodopa in 1969<sup>1</sup> and the term was coined by a patient of Duvoisin's<sup>2</sup> who likened the glow of the levodopa awakening to the switching on of a light and the equally abrupt return of Parkinsonian darkness to the light going off. The American drug subculture has also introduced to the English language the terms "switched on" and "switched off" to indicate either an individual who is energetic, sophisticated and streetwise or conversely one with a nostalgic dinosaur mentality. Although our concepts of the nature of this remarkable disturbance have developed substantially over the last 20 years and disagreements remain even with respect to its definition, the on-off phenomenon is easily understood by patients and the term still in most common usage to describe levodopa-related motor swings. It is the most important therapeutic challenge in the long-term management of Parkinson's disease and its occurrence has permitted the concurrent study of behavioural effects related to dopaminergic stimulation and dopaminergic deficiency. It may also permit some insight into the progression of the

underlying disease process seen during the "off" state which can then be compared with the period of "on" mobility seen even after 20 years of chronic levodopa treatment. The rapidity, severity of change and frequency of this phenomenon is unique.

Greater understanding of the individual's response to such violent and capricious biological changes may shed light on other cyclical disease states such as bipolar depressive illness, periodic psychosis, brittle diabetes mellitus and catamenial epilepsy.

## *Historical introduction*

In their pioneer high dose levodopa study Cotzias and his colleagues<sup>1</sup> reported minor transitory episodes of sub-optimal performance usually in the afternoon, and also noted significant fluctuations in motor performance in some patients. On stopping levodopa and starting placebo those patients who had shown clinical fluctuations reverted to a severe Parkinsonian state much more rapidly than those showing a stable response. In some patients the nadir did not occur until two weeks of placebo treatment. Yahr and colleagues<sup>3</sup> also reported that abrupt withdrawal of levodopa was followed by a gradual loss of effect over several days. These observations were difficult to marry with the short half-life of about one hour for levodopa and a first phase half-life of no more than five to ten minutes. Single-dose levodopa tolerance tests led to the notion of two types of therapeutic response; a short or medium duration effect measured in minutes or hours and generally related to the rise

Address for reprint requests: Dr A J Lees, The National Hospital for Nervous Diseases, Queen Sq, London WC1N 3BG, UK.

Accepted January 1989

and fall in plasma dopa levels. Those patients with noticeable swings in motor performance were considered to have a short duration motor response whereas others who were unaware of their medication taking effect or wearing off were considered to have a long duration response lasting days. The long duration response was also used to explain the delay in deterioration following levodopa withdrawal.<sup>4</sup> By the mid-1970s most authorities recognised two apparently distinct types of motor fluctuations. The commoner of these was named "end-of-dose deterioration" or the "wearing-off effect" and was characterised by relative predictability and a relation to falling plasma dopa levels. In our original study with high dose levodopa started in 1969, 65% of 178 patients with a range of pre-treatment disease severity had significant wearing-off effects after six years of continuous therapy.<sup>5</sup> Progression of the underlying disease process leading to a progressive reduction in the capacity to store dopamine in surviving nigrostriatal terminals was believed to be the most likely explanation. At this time the on-off effect was restricted by many, to a much rarer see-sawing effect in which vicissitudes from mobility to immobility occurred repeatedly over minutes for up to half an hour. These seemingly unpredictable fluctuations were also sometimes termed akinesia paradoxa or yo-yoing. In our study, after six years we considered about 10% of patients to have this disturbance.<sup>5</sup> Excessive levodopa dosage was believed to be at least partly responsible for this effect.

Differences in terminology between different research groups bedevilled the study of levodopa fluctuations throughout the 1970s making it extremely difficult to compare long-term follow-up data from different centres. A generally accepted rule of thumb, however, was that approximately 10% of patients would develop troublesome fluctuations per treatment year so that after ten years treatment virtually all cases would be affected. Careful in-patient studies with single oral doses of levodopa has revealed that many patients believed on the basis of their description in out-patient clinics to have unpredictable swings do in fact have dose-related oscillations. It is also now clear that most of the apparently complex fluctuating responses are artefactual and related to complex overlapping dosage schedules. Akinesia paradoxa has never been reported in patients receiving supra-threshold intravenous infusions or in single dose oral studies and their occurrence may in fact be due to overlap effects of serial doses or rebound deterioration following each dose of dopa. It may also occur if the dose of levodopa is relatively small, producing plasma dopa levels close to or around threshold levels. No convincing evidence exists to suggest that wearing-off effects and akinesia paradoxa differ pathophysiologically.

### *The clinical picture*

*An extract from a letter received in 1983 from a patient with the on-off phenomenon:*

"It is in fact difficult now to stick to the 2-hour regime because of this apparent unreliability. If for instance I find myself "over", suffering from so-called involuntary movements, my limbs behaving as if controlled by a drunken marionette master, I am reluctant to take a pill in the midst of these side-effects. So I postpone it. And then before I know where I am I am "off". "On" is quite simply normal; I can survive a dinner party, drive a car, write a fair, round hand, my voice is normal. I can fall asleep rather easily unless I am trying not to. "Off" on the other hand is very unpleasant. I lose almost all motor power in my legs; and this paralysis increasingly now spreads to my arms. Sometimes odd pains and cramps move round the body. There is no position in which I am comfortable. I can't write, I can't type, my speech is slurred and low powered. The "off" comes on with increasingly little warning. One can adopt strategies to save oneself from various kinds of embarrassment; I have a radio taxi account or if one goes "off" badly in the street one holds on to a lamp post until a taxi comes past. People are extraordinarily sympathetic and helpful. I find an aluminium walking stick useful as it is a sign that something is wrong and holding on to a lamp post is not necessarily because one is drunk. I find my "offs" are accompanied by a curiously deep and malevolent depression. It isn't suicidal; I actually feel as if I am dying. Almost as bad is the boredom and the frustration of not being able to work. I find I am tetchy and intolerant and that it is difficult not to be bitter and sarcastic".

A gratifying response to levodopa therapy occurs in most patients with Parkinson's disease leading to a considerable reduction in disability. Most patients with mild disease before the onset of treatment are therefore unaware of any specific effects from each dose of treatment, but appreciate what appears to be a sustained effect with an improvement in all the cardinal signs of the disease. Tremor, however, is generally the last major sign to come under control and postural instability when prominent may also linger. As treatment continues, more and more patients begin to become aware of the pharmacological effect of individual doses. Inexplicable episodes of stiffness, slowness or tremor occur, lasting several hours, especially in the afternoon or evening. Patients begin to complain that they are becoming allergic or immune to the treatment and accuse their physician of switching them to placebo. Their lives now become dominated by the clock and great care has to be taken in the timing of each dose. Some patients claim that their levodopa seems to be working for a progressively shorter period of time and the frequently quoted

duration of benefit from each dose once the problem has set in is two to three hours, compared to six hours to eight hours at the outset of treatment. The morning dose almost invariably works better than subsequent doses later in the day and a few patients report clear but truncated responses of only 30 minutes to an hour in the afternoon. Once the tablet is working, however, most patients say that the effect is as good as when they started treatment, although their families may note increasing fidgetiness and restlessness due to dyskinesia. The duration of benefit from individual doses is increased when the patient is relaxed and at rest, and when excited and involved in an enjoyable pastime, many hours may pass without the tell-tale warnings of pain, shaking or slowness down one side which indicate that the "battery is running low". On the other hand if the patient is acutely stressed or involved in intense physical exercise the duration of benefit is often shortened. These effects generally become apparent after 2 to 5 years of treatment and at this time too, patients may become aware of the time taken for the first tablet to work in the morning which is usually between 20 and 90 minutes. Smaller, extremely frequent doses of levodopa throughout the waking day often reduce the severity of drug-induced dyskinesias, but may actually sometimes make the oscillations more capricious and baffling. Marked diurnal mood swings and precarious balance add to the patients' difficulties. As the disease continues to progress the severity of the fluctuations becomes more striking. At this stage half the day may be spent in a mobile, hypomanic, choreic state while the remainder of the day is spent in a mute, akinetic, straitjacket accompanied by feelings of dejection and hopelessness. After 10 years of treatment the islands of motor response become less satisfactory usually as a result of increasingly violent volleys of chorea, ballismus, stereotypies or dystonia, or associated psychiatric side-effects particularly visual hallucinations, hypomania, schizophreniform psychoses or confusion. During off periods in addition to all the classical parkinsonian signs, a number of other less frequently recognised disabilities are often prominent including severe pain in the limbs and back, torsion of the limbs, particularly the feet, urinary retention, anismus and distressing dysphagia sometimes with intractable belching. Although absence of responsiveness to levodopa rarely occurs even after 20 years of treatment, the quality of the motor response deteriorates as a result of secondary effects and escape of particular symptoms and signs, especially postural instability and speech.

#### *Clinical pharmacological observations*

The post-synaptic dopaminergic striatal apparatus

appears to remain intact and sensitive throughout akinetic off periods. The subcutaneous administration of the dopamine receptor agonist apomorphine, reliably and rapidly eliminates off periods.<sup>6</sup> Positron emission tomography and post-mortem neurochemical studies have both failed to show any definite abnormalities of the D2 receptor following long-term treatment with levodopa.<sup>7,8</sup> Bromocriptine, a dopamine receptor agonist, does not cause significant oscillations in performance when given as monotherapy to previously untreated patients.<sup>9</sup> This may, however, be in part artefactual because the drug is less potent than levodopa and the difference between the on and off response is therefore substantially less.

There is marked inter-subject variability in levodopa pharmacokinetics<sup>10</sup> and many investigators have failed to find a consistent correlation between plasma dopa concentrations following a single oral loading dose and either the magnitude or the timing of the motor responses.<sup>11-14</sup> Difficulties in interpreting these studies include age and body weight differences, problems with the accurate diagnosis of Parkinson's disease, the effect of a concurrently administered peripheral dopa decarboxylase inhibitor, the frequency of blood sampling and sensitivity of scoring and whether the patients were fasting or not. Tolosa and colleagues,<sup>15</sup> however, were able to report that increasing the size and frequency of levodopa dosage could abolish motor fluctuations, but this was not a practical strategy because of the emergence of dose-limiting adverse reactions, particularly disabling dyskinesias.

We have recently re-examined the relative influence of pharmacodynamic and pharmacokinetic factors on the duration and quality of motor response to a single oral morning dose of 200 mg of levodopa with 50 mg of benserazide in 31 randomly selected, fasting, levodopa-treated patients. The duration of benefit of a single dose depended on the degree to which the plasma levodopa level had declined over 4 hours. The motor response wore off in each patient when the plasma level had dropped to about 50% of peak concentrations irrespective of the duration of the motor response. The duration of the response was not significantly different in patients with short duration of disease and treatment compared with those having long disease duration who had been treated often for more than ten years with levodopa. In contrast the amplitude of motor response, that is the difference between the Parkinsonian score on and off, increased progressively with duration of treatment. These results suggest that following a standard dose of levodopa above that needed to produce a minimum effective plasma concentration, duration of response appears to be determined by peripheral levodopa pharmacokinetics.<sup>16</sup> The evolution of motor oscillations would

be ideally studied by longitudinal studies over a number of years in the same group of patients as it is conceivable that peripheral pharmacokinetic handling of levodopa might change to some degree with chronic administration.<sup>17</sup>

We have also conducted another study in which Parkinsonian patients with marked asymmetry of basal ganglia signs fail to show a matching asymmetry in the duration of motor response to a single oral dopa dose. In a concurrent investigation using post-mortem material from a group of patients with asymmetrical physical signs at death there is a 10–20% difference in the number of pigmented nigral cells on the two brain sides.<sup>18</sup> This provides further evidence that dopamine storage capacity is not of major importance in determining the time course of levodopa motor responses.

Apparent increase in severity and frequency of the on-off phenomenon with progressively longer duration of treatment may therefore be illusory and related to the increase in disease severity revealed during off periods as the malady progresses. Patients with severe pre-treatment disease as frequently occurs in post-encephalitic parkinsonism and MPTP-induced Parkinson's syndrome have levodopa-induced fluctuations in the first few weeks of therapy, supporting this notion. Less prolonged striatal accumulation of fluorodopa has been demonstrated in vivo in oscillating patients compared with stable levodopa responders and normal controls.<sup>19</sup> However, the interpretation of these data is clouded by problems of not knowing which levodopa metabolites contain the isotope visualised at various times and by the fact that significant amounts of dopamine are known to be synthesised outside dopaminergic neurones.

Additional support for the importance of levodopa pharmacokinetics in the production of the on-off phenomenon comes from continuous intravenous levodopa infusion studies. In 1975 continuous intravenous infusions of levodopa given at a constant rate for several hours to five patients with on-off oscillations were sufficient to sustain mobility, but because the patients remained fasting and supine throughout the experimental period only limited conclusions could be drawn about the motor responses.<sup>20</sup> In a later controlled study in 12 severely oscillating patients using continuous subclavian vein infusions of levodopa for seven to twelve hours, sufficient to reach steady state plasma dopa levels, we were able to show that at infusion rates between 32 and 80 mg an hour a marked reduction in off periods occurred when compared with the patients' customary oral levodopa dose. The patients were encouraged to remain mobile throughout this study and had standard hospital meals. Plasma levodopa concentrations were maintained within a much narrower range than was seen during oral administration, the optimum therapeutic

concentration was between 0.3 and 1.6 mg per litre.<sup>6,21</sup> Using higher intravenous doses (70–143 mg/hour), well above threshold, it has also proved possible to eliminate completely diurnal off periods for up to five days.<sup>22,23</sup> These results clearly indicate that delivery of levodopa to the striatum is a critical determinant of therapeutic response. As an approach to management it is impracticable because of the quantity of solution required and its acidity. If the solution is administered via a peripheral vein thrombophlebitis develops rapidly, so administration through a central venous line has to be considered in long-term management. Levodopa methyl ester which is much more soluble and readily hydrolysed to levodopa, permits the volume of solution to be reduced by as much as 97% and its use in mini-pumps has been tried with encouraging results although concern exists about the long-term build-up of methanol levels in the blood.<sup>24</sup>

Nutt and his colleagues from Portland, Oregon, have also argued against the reduced dopamine storage capacity hypothesis. Using intravenous levodopa infusions of variable length and then plotting the decline of motor response and plasma dopa levels following abrupt discontinuation of the infusion they have shown that there is a minimum intravenous infusion rate and plasma dopa concentration required to produce a motor response in an individual patient, that there is a lag in the motor response with respect to the plasma dopa level and that the duration of response is directly related to peak plasma dopa concentrations. They have also emphasised that the magnitude of the motor response to levodopa is all or nothing and one cannot enhance the quality of therapeutic response by increasing the dose. Augmentation of the dose, however, increases the duration of motor response.<sup>25,26</sup> It is uncertain whether other dopamine receptor agonists with different pharmacological profiles may further improve the residual disabilities during the levodopa-induced motor response. The Portland group have also demonstrated that the duration of motor response after a two-hour intravenous infusion of levodopa administered in the fasting state does not differ between stable and clinically fluctuating patients and that a poor correlation exists between disease severity and motor response duration.<sup>27,28</sup> Swings might be entirely explained on the variable absorption, short plasma half-life and modifiable transport across the blood-brain barrier.

The frequent complaint of patients that they are worse following a motor response to levodopa than they are first thing in the morning before their first daily dose has also been confirmed in clinical pharmacological studies. It is proposed that this might be due to a biphasic action of dopa with inhibitory effects occurring at sub-threshold doses.<sup>29</sup> The

possibility of sleep benefit in the morning cannot, however, be totally excluded. Complete unresponsiveness to individual doses of levodopa, especially in the afternoons and even when food has not been taken at lunch, is a well-recognised phenomenon which has been suggested to be due in part to the erratic, intermittent absorption of levodopa.<sup>30</sup> It does not appear to be due to variations in diurnal receptor responsiveness throughout the day,<sup>31</sup> but it is possible that successive serial levodopa doses lead to pharmacodynamic changes or the build-up of toxic metabolites.

#### *Management of the on-off phenomenon*

The standard approach to the emergence of disabling Parkinsonian disabilities at the end of each interdose period is to add in one or two additional doses of levodopa with a peripheral dopa decarboxylase inhibitor thereby reducing the interdose interval. However, if the patient's on periods are also compromised because of disabling dyskinesias, balance problems or mild confusion, this incremental increase may be impossible. In this circumstance small, more frequent doses are given. Sometimes this is counter-productive because the response to each dose becomes shorter and more erratic because plasma dopa levels may be closer to, or even below, the minimum effective concentration, and if the plasma level is hovering around threshold, yo-yo effects may be seen. In some patients, particularly those with incapacitating onset and end-of-dose (biphasic) involuntary movements it may be better to settle for two to four larger doses of levodopa a day.

Levodopa is mainly absorbed from the proximal duodenum and enters the brain by a saturable carrier system which also transports large neutral aminoacids such as tryptophan, phenylalanine, tyrosine, leucine, isoleucine and valine. The transport of levodopa into the brain is dependent on plasma concentrations of these aminoacids and their elevation by dietary intake can reduce the therapeutic effect of levodopa.<sup>32</sup> Competition at the blood-brain barrier has been directly visualised by positron emission tomography when increasing plasma long chain aminoacids threefold prevents completely the entry of 18-fluoro-dopa into the brain.<sup>33</sup> Dietary protein competition might therefore explain the delayed action and occasional failure of response to some doses of levodopa and it would seem logical for patients with disabling fluctuations to avoid high protein meals. A reduction in off periods has been reported with stringent dietary protein restriction (less than 7 G a day up to a late evening dinner during which there is a free protein intake).<sup>35,36</sup> It is by no means certain, however, that this beneficial effect is related to the reduced level of

plasma neutral aminoacids. Elevation of dietary carbohydrate, changes in gastric emptying and levodopa absorption may also be important. If the start-up time in the morning is slow following the first daily dose of levodopa it is useful to instruct the patient to grind up or dissolve his first daily dose and imbibe it in a sweetened drink. This can improve the speed of response by up to thirty minutes. If readjustment of levodopa dosage and dietary protein restriction is unhelpful, selegiline hydrochloride (deprenyl), a selective Type B monoamine oxidase inhibitor, should be introduced in a dose of 5 mg in the morning and 5 mg at lunchtime. Partial substitution of levodopa by the longer acting bromocriptine or pergolide may also be temporarily effective in a minority of patients, but leads to a complicated drug regimen, control is often short-lived and side-effects may be frequent.<sup>38</sup> Nevertheless it is possible that the use of sub-maximum doses of levodopa in combination with bromocriptine from an earlier stage may reduce the severity of on-off oscillations as has been suggested by Rinne.<sup>39</sup>

#### *New therapeutic strategies*

(1) *Controlled release oral levodopa/peripheral dopa decarboxylase inhibitor preparations.* The first generation of sustained-release levodopa preparations were developed in the early 1970s in an attempt to reduce the frequency of gastrointestinal side-effects and drug-induced dyskinesias. Disappointing results occurred with the prototype preparations and this approach was not pursued.<sup>40</sup> The recent research with intravenous levodopa infusions which has shown that provided plasma dopa levels can be kept above a minimum effective concentration for an individual patient mobility is preserved, has encouraged physicians to put pressure on the pharmaceutical companies to develop a second wave of these preparations. Two galenical formulations have now been extensively tested throughout the world and one (Madopar CR) has already been marketed in several European countries including the UK. Madopar CR comprises hydrocolloids, soluble excipients, hydrogenated fat, lubricants and glidants as well as levodopa and benserazide. When the matrix comes into contact with gastric fluid, a hydrated boundary layer is formed and the drug is released slowly by diffusion. The exhausted boundary layer is continually dissipated and each successively exposed rim then becomes hydrated. The capsule remains floating on the top of the stomach contents after a standard meal for six to twelve hours.

Pharmacokinetic studies have shown that the drug is released and absorbed over 4 to 5 hours maintaining significant plasma concentrations for up to 8 hours. The plasma dopa level rises more slowly than with conventional preparations with a lower plateau peak

at 1.5 to 3 hours. The oral bioavailability of Madopar CR is 65% that of standard levodopa/benserazide. Madopar CR has been reported to benefit up to two-thirds of patients with fluctuations, but the results are much better in patients with a shorter duration of disease and duration of therapy. In order to achieve satisfactory results in oscillating patients it is essential to combine Madopar CR with a morning dose of conventional Madopar in order to give the patient a "kick start". A proportion of patients who have grown accustomed to the cycles they experience with conventional levodopa preparations find the striking change in motor response unacceptable. A mean 50% increase in total dosage is required to obtain good results in oscillating patients and there is no overall reduction with Madopar CR in the frequency of dosage. In our own study some patients experienced prolonged bouts of unresponsiveness followed by what we termed "time bomb effects" with sudden unanticipated relief of disability together with violent abnormal involuntary movements.<sup>42</sup> It remains to be shown whether treatment ab initio with controlled-release formulations will reduce the frequency of on-off oscillations and whether they will be able to produce better overall control of nocturnal disabilities than conventional levodopa.

A series of controlled-release prototypes of levodopa/carbidopa combinations have simultaneously been developed (Sinemet CR1-CR5) with Sinemet CR4 looking the most promising for further development. These are all formulated using a polymeric matrix which releases levodopa and carbidopa by surface erosion. Studies with these drugs have also indicated a reduced bioavailability (70% that of Sinemet) and the best effects in mild oscillators.<sup>43,44</sup> In a recent randomised study comparing Madopar CR with Sinemet CR4 in patients with on-off phenomenon, both preparations led to a reduction in dose-dependent motor fluctuations and there was no major difference between the two preparations. Both groups required considerably larger daily doses of levodopa when on controlled-release therapy (62% for the Madopar CR group and 52% for the Sinemet group).<sup>45</sup> It seems likely therefore that there is little to choose between these preparations and both may confer benefit in a few patients with otherwise refractory motor oscillations. The limiting factor however in their efficacy is the capricious gastric emptying time and the delay in onset of action.

(2) *Subcutaneous apomorphine.* The use of apomorphine in the treatment of Parkinson's disease was first proposed more than a century ago. It was not confirmed to have beneficial effects until 1954. Cotzias and his colleagues, following their report of the successful use of high doses of dopa in the treatment of Parkinson's disease, looked for other dopamine

agonists which might confer additional benefit and conducted some careful studies on apomorphine administering it both orally and parenterally. They were able to confirm that the drug had powerful anti-Parkinsonian properties and in some respects was seen to complement the effects of levodopa. For example, apomorphine appeared to be most effective in the relief of tremor and had sedative rather than alerting effects. It was also reported to reduce levodopa-induced dyskinesias and it abolished off periods seen during sustained levodopa therapy when given parenterally.

When it was given by mouth doses of several grams were required to obtain good effect and the studies had to be stopped because of reports of pre-renal uraemia. When it was given subcutaneously apomorphine was found to be short-acting and a high incidence of adverse reactions, particularly nausea, sedation and postural hypotensions occurred. Interest therefore faded and greater attention was paid to the development of longer acting orally administered dopamine receptor agonist drugs.

In 1982 we investigated the clinical pharmacological effects of subcutaneous apomorphine (1 mg) and compared it with lisuride, another water soluble dopamine receptor agonist (75–150 µg) and saline placebo in 13 patients with levodopa-provoked on-off effects. The pharmacological challenges were given 10 to 15 minutes after spontaneous off periods and 20 of 22 exposures to apomorphine produced positive responses with a rapid switch-on, compared to only 16 of 35 with lisuride and none from 39 with saline controls. The duration of effect with apomorphine lasted from between 45 minutes and 2 hours: the quality of response with lisuride was generally less good, some doses wearing off after only 5 to 10 minutes or producing intermittent or shifting effects.<sup>6</sup> Encouraged by these findings we embarked on a comparative study using continuous subcutaneous infusions of apomorphine and lisuride in refractory oscillators, using an ambulatory mini-pump system with a needle inserted into the abdominal wall. Our preliminary results seemed to show a clear difference in response between the two drugs with lisuride producing much less satisfactory therapeutic responses and a higher frequency of intolerable side-effects.<sup>46</sup> We therefore decided to concentrate on the use of apomorphine administered either as a single shot injection through a penject or by continuous pulsed subcutaneous administration. Domperidone (10–20 mg tds), a peripheral dopamine antagonist, was given as cover in the first few weeks of treatment after which it was often possible to withdraw this without rebound adverse reactions.

Initial long-term results showed that apomorphine produced a therapeutic response analogous to the

intravenous injection of levodopa and that it could markedly reduce the mean off time per day, transforming the lives of many previously severely handicapped individuals. The mean dose used in the pump system was 89 mg per day (24–207) and it was possible to reduce the mean levodopa dose by 200 mg (from 992–775 mg/day). Psychiatric side-effects were rare, the main complications being tender nodules and panniculitis with scab formation at the site of the infusion needle in the abdominal wall. Comparable results were obtained in patients with more predictable fluctuations using a penject system, (mean daily dose 10 mg (1–28 mg), mean number of injections 5 (2–18)), the only serious adverse reactions occurring in this group was one patient who broke the needle in the abdominal wall at the time of injection. Success with both approaches depended to a large extent on the anticipation of off periods with the use of the bolus demand system (2 mg boluses, mean 9/day) in the pump patients or the rapid use of the penject before immobility ensued.<sup>47,48</sup>

We have now given apomorphine to 21 patients by pump and 32 patients by penject for periods up to 2.5 years. With the pump patients, three patients are now receiving apomorphine alone, the majority continue to require some additional levodopa (overall 36% reduction in requirements). This is probably because most patients find that it is simpler to have a buffer of levodopa than use a low background continuous level of subcutaneous apomorphine and then have to continually use the booster at times of relative unresponsiveness. However, there may of course be additional pharmacological explanations. Some patients run their apomorphine continuously for 24 hours and have done so for many months without apparent loss of long-term responsiveness whereas others elect to remove the pump system on retiring to bed. No signs of tachyphylaxis have occurred with supra-threshold doses and a few patients have actually been able to reduce their apomorphine requirements with time despite keeping their levodopa levels the same. On the other hand, some patients using penject systems have had to increase their mean injection (dose range 1–5 mg) in order to consistently get an on response. In those patients receiving penjects who have always complained that the afternoon period is the worst time of the day for them, frequently the response to apomorphine is less gratifying at this time than earlier in the day.

Provided a patient's main disabilities occur in the off period, apomorphine is consistently of benefit and may help such varied disturbances as frequency of micturition, constipation, pain, dystonia and swallowing problems as well as the cardinal signs of the disorder. If, however, the on period is marred by postural instability and hypotonia or distressing biphasic dyskinesias the results are less good. Our

experience of biphasic dyskinesias has been that although one may get the patient through these into a good on, non-dyskinetic, phase rather more quickly there is a tendency for the involuntary movements to break through at successively higher doses and eventually transform into continuous dyskinesias during the "on" period.

Our present strategy is to try all oscillators on penject treatment first because of its relative simplicity and switch to the more expensive pump only if the number of injections required to produce smooth motor control is unacceptably large or the patient cannot react rapidly enough to the vagaries of his motor state. These encouraging results have now been confirmed by several other European groups.<sup>49,50</sup> Until a severely oscillating patient has tried subcutaneous apomorphine it would seem unethical to offer experimental implantation procedures.

(3) *Continuous duodenal infusions of levodopa.* Erratic gastric emptying may be a factor in the unpredictable absorption of orally administered levodopa and the continuous delivery of the amino-acid into the duodenum is one way of attempting to overcome this problem. Direct duodenal infusions of levodopa via a nasoduodenal tube and mechanical pump markedly reduced on-off effects and produced more stable plasma levels in three patients with resistant fluctuations.<sup>51</sup> In a further study continuous duodenal infusion of levodopa was found to be more effective than intermittent duodenal infusion or Sinemet CR4 in controlling offs and producing steady plasma levels.<sup>52</sup> Intolerance of the naso-duodenal tube has led to consideration of intestinal pouches for levodopa delivery.<sup>53</sup> Infusions have been given for several months through a gastrostomy in two patients with the tube fed on into the proximal duodenum. Local irritation occurred in one patient at the gastric insertion site, but the results were generally satisfactory. Interestingly, a biphasic reduction in levodopa requirements with continuing improvement occurred in both patients, a later more gradual dosage decline occurring over a sixty day period, raising the possibility of up-regulation of striatal dopamine receptors.<sup>54,55</sup> Although this approach may prove to be an interim measure for control of a few compliant, refractory oscillators it is more complex and less effective than subcutaneous apomorphine and does not get over the difficulty of protein competition with levodopa at the blood-brain barrier. The approach might stand a better chance of practical success if dopa methyl ester is used and percutaneous delivery systems to the proximal duodenum can be devised.

### Conclusion

Encouraging inroads are now being made on a

phenomenon which for some time was considered untreatable. Now that it is possible to reduce the disability induced by diurnal off periods in many patients the new challenge to long-term management has focused on ways of improving the quality of on time. Although levodopa-induced dyskinesias are closely yoked to the therapeutic response in most patients, it should be possible to devise selective anti-dyskinetic drugs which do not aggravate Parkinsonian disabilities. Experience with apomorphine shows that it is possible to have a drug with potent dopamine receptor stimulant effects which does not cause serious psychiatric morbidity. Postural instability appears to escape more readily from dopaminergic control than the other cardinal signs and this may ultimately prove to be the single most difficult management problem. Attempts to modify it with drugs acting on different neurotransmitter systems must be considered. It is possible that if a long-acting, powerful dopamine receptor agonist with pharmacological effects similar to those of apomorphine can be devised extension of duration of effective medical therapy in Parkinson's disease could be achieved. Whether continuous parenteral or even intraventricular delivery will prove to be more beneficial than oral administration remains to be determined.

## References

- Cotzias GC, Papavasiliou PS, Gellene R. Modification of parkinsonism—chronic treatment with L-dopa. *N Engl J Med* 1989;280:337–45.
- Duvoisin RC. Variations in the on-off phenomenon. In: McDowell F, Barbeau A, eds. *Adv Neurology Vol 5*. New York: Raven Press, 1974:339–40.
- Yahr MD, Duvoisin RC, Shear MJ, Barrett RE, Hoehn MM. Treatment of parkinsonism with levodopa. *Arch Neurol* 1969;21:343–54.
- Muenter MD, Tyce GM. L-dopa therapy of Parkinson's disease: plasma L-dopa concentration, therapeutic response and side-effects. *Mayo Clin Proc* 1971;46:231–9.
- Shaw KM, Lees AJ, Stern GM. The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980;49:283–93.
- Hardie RJ, Lees AJ, Stern GM. On-off fluctuations in Parkinson's disease. A clinical and neuropharmacological study. *Brain* 1984;107:487–506.
- Stahl SM, Leenders KL, Bowery NG. Imaging neurotransmitters and their receptors in living brain by positron emission tomography. *TINS* 1986;9:241–5.
- Guttman M, Seeman P, Reynolds GP, Riederer P, Jellinger K, Tourtellotte WW. Dopamine D2 receptor density remains constant in treated Parkinson's disease. *Ann Neurol* 1986;19:487–92.
- Lees AJ, Stern GM. Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1981;44:1020–3.
- Wade DN, Mearrick PT, Birkett DJ, Morris J. Variability of L-dopa absorption in man. *Aust NZ J Med* 1974;4:138–43.
- Winterberger A, Andrews CJ. Catecholamine metabolism during oral administration of L-dopa. *Arch Neurol* 1972;26:245–52.
- Bergmann S, Curzon G, Friedel J, Godwin-Austen RB, Marsden CD, Parkes JD. The absorption and metabolism of a standard oral dose of levodopa in patients with parkinsonism. *Br J Clin Pharmacol* 1973;1:417–24.
- Pilling JB, Baker J, Iversen LL, Iversen SD, Robbins T. Plasma concentrations of L-dopa and 3-methyldopa and improvement in clinical ratings and motor performance in patients with parkinsonism treated with L-dopa alone or in combination with amantadine. *J Neurol Neurosurg Psychiatr* 1975;38:129–35.
- Rosor MN, Watkins J, Brown MJ, Reid JL, Dollery CT. Plasma levodopa, dopamine and therapeutic response following levodopa therapy in parkinsonian patients. *J Neurol Sci* 1980;46:385–92.
- Tolosa ES, Martin WE, Cohen HP. Value of plasma dopa determinations in the management of Parkinson's disease. *Lancet* 1973;i:942.
- Kempster PA, Frankel JP, Bovingdon M, Webster R, Lees AJ, Stern GM. Levodopa peripheral pharmacokinetics and duration of motor response in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1989; (in press).
- Poewe WH, Bates IP, Kent A, Webster R, Lees AJ, Stern GM. The pharmacokinetics of levodopa before and after sustained therapy: a prospective study in six previously untreated patients. In: Streifler M, ed. *Adv Neurol. Proc Int Parkinson's Disease Symposium*, Jerusalem. New York: Raven Press, 1989.
- Kempster PA, Gibb WRG, Lees AJ, Stern GM. Asymmetry of substantia nigra loss in Parkinson's disease and its relevance to the mechanism of motor fluctuations. *J Neurol Neurosurg Psychiatry* 1989;52:72–76.
- Leenders KL, Herold S, Palmer AJ, et al. Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. *J Neurol Neurosurg Psychiatry* 1986;49:853–6.
- Shoulson I, Glaubiger GA, Chase TN. On-off response: clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. *Neurology* 1975;25:1144–8.
- Hardie RJ, Malcolm SL, Lees AJ, Stern GM, Allen JG. The pharmacokinetics of intravenous and oral levodopa in patients with Parkinson's disease who exhibit on-off fluctuations. *Br J Clin Pharmacol* 1986;22:429–36.
- Quinn N, Parkes JD, Marsden CD. Control of on/off phenomenon by continuous intravenous infusion of levodopa. *Neurology* 1984;34:1131–6.
- Marion M-H, Stocchi F, Quinn NP, Jenner P, Marsden CD. Repeated levodopa infusions in fluctuating Parkinson's disease: clinical and pharmacokinetic data. *Clin Neuropharmacol* 1986;9:165–81.
- Juncos JL, Mouradian MM, Fabbri G, Serrati C, Chase TN. Levodopa methyl ester treatment of Parkinson's disease. *Neurology* 1987;37:1242–45.
- Nutt JG, Woodward WR. Levodopa pharmacokinetics and pharmacodynamics in fluctuating parkinsonian patients. *Neurology* 1986;36:739–44.
- Nutt JG. On-off phenomenon: relation to levodopa pharmacokinetics and pharmacodynamics. *Ann Neurol* 1987;22:535–40.
- Gancher ST, Nutt JG, Woodward WR. Peripheral pharmacokinetics of levodopa in untreated stable and fluctuating parkinsonian patients. *Neurology* 1987;37:940–4.
- Gancher ST, Nutt JG, Woodward W. Response to brief levodopa infusions in parkinsonian patients with and without motor fluctuations. *Neurology* 1988;38:712–6.
- Nutt JG, Gancher ST, Woodward WR. Does an inhibitory action of levodopa contribute to motor fluctuations? *Neurology* 1988;38:1553–7.
- Melamed E, Bitton V, Zelig D. Episodic unresponsiveness to single doses of L-dopa in parkinsonian fluctuations. *Neurology* 1986;36:100–3.
- Gancher ST, Nutt JG. Diurnal responsiveness to apomorphine. *Neurology* 1987;37:1250–3.
- Nutt JG, Woodward WR, Hammerstad JP, Carter JH, Anderson JL. The on-off phenomenon in Parkinson's disease. Relation to

- levodopa absorption and transport. *N Engl J Med* 1984;**310**:483-8.
- 33 Leenders KL, Poewe WH, Palmer AJ, Brenton DP, Frackowiak RSJ. Inhibition of L-[<sup>18</sup>F] fluorodopa uptake into human brain by aminoacids demonstrated by positron emission tomography. *Ann Neurol* 1986;**20**:258-62.
- 34 Mena I, Cotzias GC. Protein intake and treatment of Parkinson's disease with levodopa. *N Eng J Med* 1975;**292**:181-4.
- 35 Pincus JH, Barry KM. Plasma levels of aminoacids correlate with motor fluctuations in parkinsonism. *Arch Neurol* 1987;**44**:1006-9.
- 36 Riley D, Lang AE. Practical application of a low protein diet for Parkinson's disease. *Neurology* 1988;**38**:1026-31.
- 37 Stern GM, Lees AJ, Hardie RJ, Sandler M. Clinical and pharmacological problems of deprenyl (selegiline) treatment in Parkinson's disease. *Acta Neurol Scand* 1983;**68**(suppl 95):123-6.
- 38 Lander CM, Lees AJ, Stern GM. Oscillations in performance in levodopa-treated parkinsonians: treatment with bromocriptine and L-deprenyl. *Clin Exp Neurol* 1979;**16**:197-203.
- 39 Rinne UK. Combined bromocriptine-levodopa therapy early in Parkinson's disease. *Neurology* 1985;**35**:1196-8.
- 40 Curzon G, Friedel J, Grier L, *et al*. Sustained release levodopa. *Lancet* 1973;i:1391.
- 41 Lees AJ. A hydrodynamically balanced controlled release L-dopa/benserazide formulation in the treatment of Parkinson's disease. In: Fahn S, Marsden CD, Calne DB, eds. *Recent Developments in Parkinson's Disease. Vol 2*. New Jersey: Macmillan, 1987:257-67.
- 42 Poewe WH, Lees AJ, Stern GM. Treatment of motor fluctuations in Parkinson's disease with an oral sustained-release preparation of L-dopa. Clinical and pharmacokinetic observations. *Clin Neuropharmacol* 1986;**9**:430-9.
- 43 Hutton JT, Morris JL, Roman GC, Imke SC, Elias JW. Treatment of chronic Parkinson's disease with controlled release carbidopa/levodopa. *Arch Neurol* 1988;**45**:861-4.
- 44 Goetz CG, Tanner CM, Shannon KM, *et al*. Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuations. *Neurology* 1988;**38**:1143-6.
- 45 Kleedorfer B, Birbamer G, Poewe WH. A randomised study comparing two oral sustained-release preparations of L-dopa in patients with the long-term L-dopa syndrome. In: Streiffler M, ed. *Adv Neurol*. New York: Raven Press, Jerusalem.
- 46 Stibe CMH, Lees AJ, Stern GM. Subcutaneous infusion of apomorphine and lisuride in the treatment of parkinsonian on-off fluctuations. *Lancet* 1987;i:871.
- 47 Stibe CMH, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988;i:403-5.
- 48 Stibe CMH, Kempster PA, Lees AJ, Stern GM. Subcutaneous apomorphine in Parkinson's disease. In: Przuntak H, Riederer P, eds. *Early Diagnosis and Preventive Therapy in Parkinson's Disease*. Berlin: Springer, 1988:349-55.
- 49 Poewe WH, Kleedorfer B, Gerstenbrand F, Oertel W. Subcutaneous apomorphine in Parkinson's disease. *Lancet* 1988;i:943.
- 50 Chaudhuri KR, Critchley P, Abbott RJ, Pye IF, Millac PAH. Subcutaneous apomorphine for on-off oscillations in Parkinson's disease. *Lancet* 1988;ii:1260.
- 51 Kurlan R, Rubin AJ, Miller C, Rivera-Calimlin L, Clarke A, Shoulson I. Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observations. *Ann Neurol* 1986;**20**:262-5.
- 52 Kurlan R, Nutt JG, Woodward WR, *et al*. Duodenal and gastric delivery of levodopa in parkinsonism. *Ann Neurol* 1988;**23**:589-95.
- 53 Sage JL, Trooskin S, Schuh LP, Duvoisin RC. Isolated intestinal pouches for levodopa delivery in parkinsonian patients with on-off phenomenon: successful experimental model in dogs. *Neurology* 1987;suppl 1:273.
- 54 Sage JL, Schuh L, Heikkila RE, Duvoisin RC. Continuous duodenal infusions of levodopa: plasma concentrations and motor fluctuations in Parkinson's disease. *Clin Neuropharmacol* 1988;**11**:36-44.
- 55 Sage JL, Trooskin S, Sonsalla PK, Heikkila R, Duvoisin RC. Long-term duodenal infusion of levodopa for motor fluctuations in parkinsonism. *Ann Neurol* 1988;**24**:87-8.