Limitations of Long Term Use of Antiparkinson Drugs

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ABSTRACT: Effective control of parkinsonian symptoms can be achieved in a substantial number of patients by the judicious use of dopaminergic agents. To a considerable extent these drugs produce optimal therapeutic effects during the first 3-5 years of their use. Subsequently, efficacy diminishes with reemergence of parkinsonian symptoms as well as a number of untoward responses. The nature, frequency and mechanisms underlying the limitations of long term use of presently available anti-parkinson agents are discussed in this presentation.

RÉSUMÉ: Le contrôle efficace des symptômes Parkinsoniens peut se faire chez un nombre important de patients par l'emploi judicieux d'agents dopaminergiques. Ces médicaments produisent leur effet thérapeutique optimal durant les 3 à 5 premières années d'emploi. Par la suite l'efficacité diminue et les symtômes du Parkinson réapparaissent, ainsi que se développent certaines réactions indésirées. Dans cette présentation, nous discutons de la nature, de la fréquence et des mécanismes des limitations de l'emploi à long-terme des agents anti Parkinsoniens disponibles.

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Over the past 15 years significant advances have been made in controlling the devastating effects of Parkinson's disease. Not only are symptoms of the disorder more effectively controlled and the quality of life for those afflicted improved, but the excess mortality rate which markedly shortened life expectancy has been substantially reduced. (Yahr, 1975; Diamond et al., 1975; Zumstein and Siegfried, 1976; Bauer et al., 1980). Of the numerous factors which have contributed to alleviating the plight of the parkinsonian, the most significant is the establishment of a rational pharmacological basis for the development of new agents for control of symptoms. This has led to the introduction of levodopa, the various dopamine receptor agonists, and other drugs capable of altering storage or catabolism of dopamine. All have played a role in contributing to the improved outlook for sufferers of parkinsonism, for when used judiciously, these agents can provide considerable relief of symptoms for extended periods of time. However, they do have inherent shortcomings some of which relate to their inability to control all of the pleomorphic symptoms of the parkinson process and others which develop as a result of their long-term administration. This report will deal primarily with the problems which emerge after long-term administration of dopaminergic agents, particularly levodopa which over the past 10 years has been the drug of choice in the treatment of Parkinson's disease.

Present day treatment of parkinsonism relies considerably on the concept that the primary biochemical abnormality in Parkinson's disease is a decreased availability of dopamine in the nigrostriatal complex. The severity of symptoms relates to the degree of this defect (Hornykiewicz, 1982), and the mechanism by which symptoms are produced results from a disturbance of dopaminergic relationships with other neurotransmitters, particularly that which reciprocally exists with acetylcholine. All drugs presently in use are directed toward reestablishing normal neurotransmitter function to the affected brain region, since their primary pharmacological effects are to either increase dopaminergic or decrease cholinergic activity. However, none of these agents are capable of doing so with the precision required by the intricate mechanisms at play in the human nervous system, nor are there presently methods for restricting delivery of these agents to the precise area of the brain where their effects are most desired. Further, since treatment is neither directed toward eliminating the cause of Parkinson's disease, which is still unknown, nor halting the progressive underlying morphological abnormalities, it must be regarded as symptomatic and pallative. It is therefore not surprising that numerous limitations regarding the use of pharmacological agents exist. Those most frequently encountered in the course of treating patients with Parkinson's disease using the drugs presently available for its control are indicated in Table 1. The six major problems indicated occur with sufficient frequency to warrant being designated as the major limitations in our present therapy of Parkinson's disease. Some relate to symptoms of the disease which are poorly controlled by drugs and tend to occur with increasing severity as the disease progresses, others are due to a direct interaction of the medication with the underlying disease substrate. Each of these will be discussed separately.

Table 1: Major therapeutic problems after 3 years of levodopa

1. Decreased control of parkinsonian symptoms
2. Increased involuntary movements
3. Alterations in mentation
4. Increased diurnal fluctuations; "on-off" periods
5. Episodes of akinetic freezing and "crisis"
6. Increased fatigue and neurasthenia

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Less Effective Control Of Parkinsonism

With the passage of time, most parkinsonians using dopaminergic agents tend to lose a substantial amount of the initial therapeutic benefits. This appears to be the case for levodopa and bromocriptine, both of which have been studied in a sufficient number of patients and for time intervals long enough to assess their full efficacy. For levodopa in particular, 30% to 40% of the initial level of improvement is lost in approximately 60% of patients who have been under treatment for more than 3 years. A similar pattern of deterioration has been reported for bromocriptine (Stern, 1981). This reemergence of parkinsonian symptoms has been interpreted in varying fashion. It has been suggested by some that it represents the natural progression of the disease (Marsden and Parkes, 1977), that is, the expected progressive rate of decompensation of the involved structures and their loss of responsivity to pharmacological agents. Since this rate of progression is variable among patients they differ in their degree and duration of responsiveness to treatment. It is doubtful that this is the only basis since in studies comparing patients with differing degrees of severity of the disease, when entering treatment and the duration of optimal beneficial effect, one finds that they show a similar pattern of deterioration (Yahr, 1977). That is, after an initial optimal beneficial response deterioration of therapeutic efficacy sets in a uniform time frame regardless of degree of severity of parkinsonism at time of initiating treatment. Further, reports from those utilizing drug holidays in patients where over time a loss of optimal therapeutic effect occurred indicate that after a period in which drugs are withheld, reinstating treatment allows some patients to recapture such benefits. All these data suggest that the drugs themselves, and the time interval over which they are administered, play a significant role in this altered response. In support of this concept are post-mortem studies of receptor sensitivity (Lee et al., 1978), which indicate a loss of supersensitivity of dopaminergic receptors in those treated intensively with levodopa as compared to parkinsonians who have not received this agent. Using physostigmine as a pharmacologic probe to determine the state of reactivity of the cholinergic system, we have been impressed with a resurgence of its predominance after long term use of dopaminergic agents (Yahr et al., 1982). Hence, one cannot dismiss a pharmacodynamic action between drug administration and the underlying pathophysiological substrate in parkinsonism which is altered over time and leads to a loss of therapeutic effectiveness.

Regardless of the nature of the underlying mechanism, one of the major limitations of presently available dopaminergic agents is the restricted period in which they exert their optimal antiparkinson effects. At present it would appear unlikely that one can extend the total duration of effective therapeutic action by dopaminergic agents alone of the type presently available and administered by conventional methods. Whether combined use of these agents will avoid the cumulative effects of high dosage of single drugs or alternate routes of administration will provide more uniform levels of bioavailability remains to be determined.

Induced Involuntary Movements

The second limiting aspect of long term treatment is the induction of unacceptable levels of involuntary movements. This has primarily occurred with the use of levodopa and less so with the ergoline derivatives. Though data regarding the incidence of induced movements is not readily available, it is probably safe to estimate that few parkinsonians on levodopa for more than 5 years do not have some elements of dyskinetic phenomena. It appears to be a product of the degree of alteration of the morphological substrate, the potency, duration of administration, and the dosage level of the dopaminergic agent which is used. That is, the longer one has been treated and the higher the dose used, the more frequent the occurrence of, and the more severe the involuntary movements. Once involuntary movements appear they may then be induced by much lower doses of these agents. In fact, some patients eventually become intolerate of even exceedingly small doses of levodopa. The mechanism for such reactions is yet to be defined although receptor supersensitivity is a good possibility. The overriding question is which receptors and where are they located? At present, no effective means other than dose reduction or elimination of the dopaminergic agents exists for the control of these movements. Agents which have been tried to date are numerous (Table 2), and are those capable of altering one or another of the neurotransmitter systems. None have been effective and indeed this has been a fruitless and frustrating experience.

Table 2: Drugs administered for control of abnormal involuntary movements (AIM)

	AIM	Parkinsonism
Anti-ACH	0	▼
Stelazine	▼	▼
Haloperidol	▼	▼
Imipramine	0	▼
Disulfram	▲	▲
Pyridoxine	▼	▼
L-Tryptophane	0	0
L-5-HTP	0	0
L-Methionine	0	0
Parachlorophenylalanine	0	0
Dilantin	0	0
Barbiturates	0	0
Reserpine	▼	▼
Clonazepam	0	0
Di-n-proplylacetate	0	0
Deanol	0	▼
Lithium	0	0
Choline	±	▲
Progabide	▲	▲

0 — No Effect
▲ — Increased Response
▼ — Decreased Response
± — Equivocal Response

Alterations in Mentation

The long term effects of drugs in altering intellect and personality in parkinsonism is not readily assessed. In part, it relates to the controversy regarding these changes as being an intricate feature of Parkinson's disease itself. Reports vary regarding the incidence and degree of cognitive change and even more so concerning the occurrence of dementia in Parkinson's disease. To a considerable extent much of our confusion in this area arises from the fact that most studies have been retrospective. Hence they fail to take into account the changing concept of parkinsonism as a nosological entity nor can accurate data regarding drug effects be readily retrieved, analyzed and substantiated by appropriate testing. There are a few facts, however, that have emerged over the years. The induction of confusional

states and frank psychotic episodes are not infrequent with the long-term administration of anticholinergics but are less frequent with dopaminergic agents. When they do occur with use of the latter they tend to appear early on in treatment and more so in those whose parkinsonism is characterized as having atypical features, rather than being of the classical Parkinson's disease variety (Sroka et al., 1981). As regards late occurrence of these phenomena, age of the patient, daily dosage and again evidence of disease more widespread than that involving the striatum, are all factors. In all instances, to my knowledge, discontinuing the use of dopaminergic agents has always resulted in reversal of the abnormal behavioral state.

Diurnal Fluctuations

It is not unusual for parkinsonian symptoms to occur throughout the day in a variable and capricious manner. Such fluctuations appear to be an inherent characteristic of the disorder. With the introduction of levodopa however, the degree and severity of such phenomena has been seen with greater frequency and in more dramatic fashion. It is beyond the scope of this report to describe all of the features which some authors include under the fluctuating state. There are, however, two responses which appear directly related to long-term use of dopaminergic agents. One is the so-called "wearing off" or end-dose, start-dose phenomena which bears a relationship to the time of ingestion of the medication. The second occurs randomly and has been termed "on-off" response. Some evidence exists that the former, which tends to appear during the 3rd or 4th year of treatment, is a prelude to the latter. In this regard, it is of some interest that in both situations challenging the patient with injected apomorphine during a period when parkinson symptoms have recurred, (i.e. off period) causes a rapid reversal of such symptoms. Similar responses can be obtained by continuous infusion of levodopa. These pharmacological responses suggest that the essential mechanisms for controlling these fluctations and obtaining an effective response are all present and operative but are not being appropriately activated by orally administered drugs. Whether alteration in transport across the various barriers which must be traversed to reach the appropriate site or alterations in catabolism of drugs or other factors play a role, is presently unknown.

Akinetic Freezing and "Crisis"

One of the most bedeviling of the parkinsonian symptoms is the sudden occurrence of inability to initiate movement of the lower limbs when walking. These freezing episodes which leave the individual rooted in place and lead to falling on attempted movement have been relatively resistant to drug therapy. It has been suggested that they are related to a deficiency of noradrenaline in the parkinsonian brain which is not readily rectified by the use of levodopa. Recent reports suggest that threo-dops, which acts as a precursor of noradrenalin, will control freezing episodes. This finding has yet to be validated by other investigators before it can be commented upon in a positive manner. Hopefully it will prove to be a new therapeutic modality.

Akinetic crisis in which patients become totally immobilized yet maintain consciousness have been seen more frequently in recent years. Some have considered these as extended "off" periods, others have reported that they represent total failure of the striatal dopaminergic system and are indicative of an end stage of the Parkinson's disease process. The latter concept is based on a limited number of autopsies in which biochemical assay has shown little residual striatal dopamine and morphological changes involving both pre- and post-synaptic components of the dopaminergic system. Undoubtedly such occurs but we have been impressed that some patients in such crisis do recover with supportive measures and go on to be responsive, to a degree, to the administration of dopaminergic agents. Further, we have seen crisis occur in patients who have on their own precipitiously stopped the use of medication or involved themselves in drug holiday programs with drastic and rapid dose reduction of anti-parkinson drugs. Reinstituting treatment has resulted in reversal of the crisis.

Fatigue and Neurasthemia

Such symptoms are not frequently included in most descriptive material on Parkinson's disease. Yet in our experience, a considerable number of patients include this complaint with a frequency equal to that of dysfunction of the motor system. In many, it continues unabated despite optimal usage of anti-parkinson medication. In some, it actually intensifies despite control of the other major symptoms of the disorder. The biochemical basis for this symptom is obscure. It does not respond to drugs whose action mimics that of amphetamine.

Conclusions

The discovery that the administration of levodopa was capable of reversing the symptoms of parkinsonism marked a milestone in therapeutics of neurological disorders. Untold numbers of patients have benefited from its use not only by extended longevity but improving the quality of life as well. Unfortunately, long term administration of levodopa revealed a number of shortcomings in its use. Though this has generated the development of additional agents, none have as yet proven capable of being more potent or eliminating the limitations of levodopa. Hopefully, as additional insights regarding the intricate biological mechanisms of the basal ganglia become available, more effective methods for dealing with these limitations will be possible.

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