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DRUGS AFFECTING MOVEMENT DISORDERS

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INTRODUCTION

In 1974 Barbeau (1) reviewed drugs affecting movements disorders in this journal. This review updates the previous one, covering the considerable expansion of pharmacological tools for studying these disorders in the last few years. Unfortunately, Dr. Barbeau was only able to draw the outline for this article before his premature death. We hope that the completed version reflects his extraordinary experience and skill in the treatment of movement disorders.

In the previous review Barbeau (1) defined "movement disorders," a term that could include most, if not all, neurological diseases. Currently, movement disorders are defined as the so-called extrapyramidal diseases in which either the exclusive, the primary, or the essential lesion is located in the basal ganglia. We refer the reader to the 1974 article for more discussion of these introductory remarks. That review centered on the main extrapyramidal symptoms: akinesia, tremor, rigidity, and dyskinesias. In this review we report the considerable number of new drugs according to the main clinical disorders: Parkinson's disease, dystonic syndromes, Huntington's disease, Wilson's disease, and Gilles de la Tourette's disease. In fact, although drugs for movement disorders are mainly symptom specific, some drugs display a disease-specific dose and treatment pattern. This pattern occurs, for example, with anticholinergic drugs in Parkinson's disease and dystonic syndromes. Furthermore, levodopa (L-DOPA), which in the early 1970s was used on a symptom-based rationale (2) to treat several extrapyramidal disorders with

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different results, is today used almost exclusively for treating Parkinson's disease. To avoid repetition, general considerations of each drug are reported only the first time it is mentioned.

PARKINSON'S DISEASE

Since L-DOPA was introduced in the treatment of Parkinson's disease (PD) we have gradually reached an understanding of both its mechanism of action and the consequences of its long-term use. More recently other dopamine agonists, particularly ergot derivatives, have considerably increased our therapeutic arsenal. At present, the treatment of PD results from careful evaluations of the following aspects: (*a*) the type of PD syndrome (akineto rigid, tremor dominant, balanced); (*b*) the stage of the illness (early, intermediate, advanced); (*c*) the patient's age (onset may range from the mid-twenties to late old age); and (*d*) the individual response to the different drugs. Conflicting points of view remain concerning the implications of the stage of the illness and patient's age in PD treatment. We cannot provide a detailed examination of these clinical problems here and refer the reader to a recent paper for a review of this topic (3). However, we emphasize that the increased number of drugs for treating PD has also increased the need for the physician to possess a thorough knowledge of their properties, side effects, and interactions. Achieving good therapeutic results with as few adverse effects as possible is today a fairly complex procedure that requires enduring and skillful care. Patients with PD must be regularly followed as outpatients throughout their illness, at two–six month intervals according to the treatment phase. On one hand, the neurologist must modify the pharmacological regimen when necessary, but on the other hand he must sometimes counteract the attraction of some patients for frequent drug changes and therapeutical novelties.

We now describe the different drugs for PD.

Levodopa

Barbeau reported much about L-DOPA in the previous review (1). After 13 years L-DOPA is still the most useful and effective treatment for PD, although several important side effects of its long-term administration are now recognized. At present L-DOPA is most often given in a combined form, i.e. with a peripheral decarboxylase inhibitor (PDI) that increases its availability in brain tissue. The term "peripheral" indicates that the commonly used dose of PDI is effective on dopa-decarboxylase of peripheral tissues, mainly the small intestine. PDI does not, at that dose, affect brain capillary decarboxylase, i.e. the enzymatic blood-brain barrier (4–6). The two PDIs currently available in commercial preparations are benserazide and carbidopa, the former in a 1:4

ratio, the latter in 1:4 and 1:10 ratios, to L-DOPA. The clinical efficacy of L-DOPA plus benserazide and L-DOPA plus carbidopa does not differ significantly, except in individual cases (7, 8). The combined administration of L-DOPA plus a PDI eliminates or greatly reduces the peripheral side effects of L-DOPA, but does not change the central, i.e. neurological and psychiatric, side effects. The 1:4 ratio of a PDI to L-DOPA reduces peripheral side effects more effectively than 1:10 ratio (8, 9).

We discuss next some important aspects of the treatment with L-DOPA.

FACTORS INFLUENCING BRAIN AVAILABILITY OF L-DOPA Many factors influence L-DOPA bioavailability in brain tissue. Several studies demonstrate that plasma levels of L-DOPA and modification of parkinsonian symptoms are correlated (10, 11). "Off" fluctuations and episodic unresponsiveness are related to low plasma levels of L-DOPA (10, 12). Therefore, absorption from the gut and plasma levels of L-DOPA appear very important in the clinical fluctuations during L-DOPA therapy of parkinsonian patients. The following factors reduce the gut absorption and/or availability of L-DOPA in the brain: (*a*) several aromatic and branched amino acids from dietary proteins (i.e. protein-rich meals) compete with L-DOPA for the transport carrier system at two subsequent levels, the intestinal mucosa and the brain capillary endothelial cells (13–16); (*b*) some factors reducing gastric emptying time, such as meals, anticholinergic drugs, dopamine agonists, and antidepressants with anticholinergic properties, increase the gastric absorption of L-DOPA (17, 18); (*c*) an increase of gastric acidity also increases absorption of L-DOPA (16); (*d*) physical exercise in patients who are still active reduces mesenteric blood flow and, consequently, the intestinal absorption of the drug (19); and (*e*) 3-O-methyldopa, a metabolite formed from L-DOPA by catechol-O-methyl-transferase, competes with L-DOPA for brain uptake and can also inhibit L-DOPA metabolism in rat brain (20, 21). Parkinsonian "nonresponders" have high plasma levels of 3-*O*-methyldopa (22), which are not modified by addition of a PDI (6).

The following factors increase the absorption and/or availability of L-DOPA: (*a*) a carbohydrate-rich meal reduces the plasma concentration of branched chain amino acids, indirectly favoring the uptake of aromatic amino acids such as L-DOPA by the brain (23); (*b*) metoclopramide, a neuroleptic drug used to improve gastro-intestinal motility, enhances gastric emptying increasing intestinal absorption of L-DOPA (24). However metoclopramide, because of its central action, is also a parkinsongenic drug (25); and (*c*) gastrectomy favors the intestinal absorption of L-DOPA (26, 27).

EFFECT OF LEVODOPA ON THE NATURAL COURSE OF THE DISEASE In the years after its introduction as a substitution therapy for PD, it was unclear

whether L-DOPA could affect the natural course of the disease. Subsequently, some aspects of this question have been well documented. First, disease progression after the initial clinical improvement with the drug is similar to that observed before the initiation of treatment, suggesting that L-DOPA does not interfere with the natural course of the disease (28, 29). Second, overall clinical improvement declines slowly over several years of treatment, with an increasing sensitivity to the drug. Daily dosage must be reduced and/or subdivided and redistributed over 24 hours (28, 30). Similarly, length of clinical effect after a single dose gradually decreases with later onset ("start-up" periods; 31) and earlier ending ("wearing-off" phenomenon; 32). Also, daily fluctuations in clinical improvement can be managed by i.v. infusion of L-DOPA (33). Finally, L-DOPA increases the life span of patients with PD, giving them a greater resistance to intercurrent illnesses (29, 30).

Another point is still widely discussed. After several years of treatment some psychiatric symptoms appear, such as dementia, psychosis, and a psychiatric symptom complex heralded by sleep disruption (34). These symptoms were relatively rare before L-DOPA was used. Whether these symptoms belong to the natural course of the disease (disclosed by the increased life span) or are caused by L-DOPA is unclear. The answer probably lies midway between these two possibilities. The symptoms are probably triggered by a dopaminergic overactivity on a background of advanced neuronal degeneration. This problem is one aspect of the "long-term Levodopa syndrome" we discuss below.

THE LONG-TERM LEVODOPA SYNDROME After a variable period in which clinical results are evident with or without peripheral side effects, the parkinsonian patient treated with L-DOPA begins to experience "central" side effects, in particular abnormal involuntary movements (AIM's; 35). AIM's are mainly of choreic and dystonic type, but athetotic and ballic dyskinesias can also be observed (30). According to their time of occurrence they can be divided in two main groups, peak-dose dyskinesia and diphasic, or onset and end-of-dose, dyskinesia. The relationship with plasma levels of L-DOPA is evident: peak-dose dyskinesia occurs in close relation with L-DOPA peak in plasma, diphasic dyskinesia occurs at the beginning and at the end of the therapeutic effect when plasma level of L-DOPA is within a critical range either before or after the peak. An increased striatal homovanillic acid/dopamine ratio (HVA/DA) indicates that in PD patients treated with L-DOPA the remaining nigrostriatal neurons are overactive (36). Klawans et al (37) proposed that the development of AIM's is dependent on supersensitivity of the striatal DA receptors. However, in untreated parkinsonian patients the density of D_2 receptors in the striatum is increased, and treatment with L-DOPA reverses this pattern (38, 39). Agid et al (40) pointed out that a decrease of presynaptic autoreceptors might mask a high density of postsynaptic receptors. Therefore, the possibility that AIM's depend on a

supersensitivity of striatal DA receptors is not ruled out. Agid et al (40) proposed that diphasic dyskinesias are explained by the activation of one type of supersensitive DA receptor with a high affinity for L-DOPA. In this case AIM's would cease when another type of receptor with a low affinity inhibited the high-affinity receptors. AIM's seem to occur more frequently in young patients; these AIM's include a disabling akineto-rigid variant of PD and a high degree of initial improvement with L-DOPA (33). Another type of AIM, early morning dystonia, which occurs late in the long-term L-DOPA syndrome, is not related to plasma peak of L-DOPA and probably has a different pathogenesis (41).

AIM's are closely correlated with fluctuations or oscillations in performance. At the beginning of treatment with L-DOPA the patient often experiences an even level of improvement during the whole day. Later, parkinsonian symptoms reappear between two consecutive doses (wearing-off phenomenon and start-up delay) with increasingly clear-cut limits. These oscillations in performance are commonly called on-off phenomena, but this term was originally used to indicate a particular type of oscillation[2]. We prefer the term *wearing-off* as a general, comprehensive designation. When wearing-off begins to appear, AIM's may still be absent or if present, they appear briefly in a randomized fashion during "well" periods. In an advanced stage, AIM's start and end in close relation to the reduced length of "well" periods.

Oscillations in performance are considered as a function of the pharmacokinetics of L-DOPA. In fact, i.v. infusion of L-DOPA greatly reduces or abolishes oscillations (33). However, an additional mechanism might play a role. Experimental data in animals show that apomorphine and L-DOPA have a dual effect, i.e. low doses decrease, and high doses increase, motor activity (45). L-DOPA may have a similar effect in patients with PD, thus enhancing "off" periods when its level in plasma is not high enough to improve the patient's condition. To counter their oscillations in performance, some patients become L-DOPA abusers, taking high daily doses of the drug in spite of severe AIM's (46).

MANAGEMENT OF THE LONG-TERM LEVODOPA SYNDROME We already mentioned that a useful way to manage both AIM's and oscillations in performance is fractionating, redistributing, and eventual reducing L-DOPA

[2]Dr. Barbeau described the on-and-off phenomenon as characterized by a rapid changeover from the free to the rigid condition, or the inverse changeover. He described also another phenomenon called hypotonic freezing or akinesia paradoxica. These changes occur in a continuous flow of fluctuations during chronic L-DOPA treatment. Barbeau summarized those changes in four graphs (1, 30, 32, 42–44). For these and his other contributions to our knowledge of the "long-term Levodopa syndrome," we would like to suggest that Dr. Barbeau's name be attached to it: *Barbeau's syndrome*.

daily dosage. In some patients small doses every two hours, sometimes even during the night, are helpful. However, in our experience the best treatment is prevention: low doses of L-DOPA must generally be administered from the beginning of treatment. These doses should rarely exceed 600 mg of L-DOPA and 150 mg of PDI per day. If the improvement is not sufficient, other drugs can be added (see next sections). A similar preventive stategy may be used to avoid some psychiatric side effects. In general, sleep disrupted by vivid dreams, nightmares, and night terrors precedes the onset of hallucinations. The patient maintains a clear sensorium and remains critical of his hallucinations (hallucinosis). In the following stage it is possible to observe a delusion of paranoid type, in some instances accompanied by a confusional state (47). When such a progression is becoming evident, it is worthwhile to reduce or withdraw drugs in the therapeutic regimen in the following order: (*a*) anticholinergic drugs; (*b*) ergot derivatives; (*c*) amantadine; and (*d*) L-DOPA. This order reflects an increasing therapeutic index. Sometimes it is necessary to continue the treatment with only L-DOPA at a reduced dose. It has been suggested that, if it is not possible to reduce dopaminergic drugs without a worsening of parkinsonian symptoms, a "drug holiday" of four to seven days is worthwhile (48). This procedure is not free of dangers and must be carried out with hospitalized patients only. (For a review of practical guidelines, benefits, and risks, see 47.)

A few drugs were reported to be helpful in the management of some side effects of the long-term L-DOPA syndrome. It was reported that baclofen reduces foot dystonia (49), naloxone decreases AIM's (50), methysergide counteracts acute psychotic symptoms, and amitriptyline relieves symptoms of sleep disruption and emotional depression (51). However, we think that prevention, and not the addition of another drug, is the best avenue by which to treat Barbeau's syndrome.

LEVODOPA WITHDRAWAL Acute withdrawal of L-DOPA may be very dangerous. Several reports indicated that an acute withdrawal, caused by lack of drug, negligence, psychiatric problems, or intercurrent illnesses, may induce a syndrome similar to that observed in neuroleptic malignant syndrome (52–55). If absolutely necessary, L-DOPA withdrawal must be carried out gradually over several days under medical supervision.

LEVODOPA AND MELANOMA At least nine parkinsonian patients treated with L-DOPA were reported to have developed cutaneous or uveal melanoma after a mean treatment length of 46 months (see 3). Another three patients showed a relapse of a skin melanoma diagnosed before L-DOPA treatment. It is not clear whether L-DOPA administration and melanoma are causally related because experimental data point to an antimelanoma effect of L-DOPA

(56). Until this issue is clarified, L-DOPA treatment should be avoided in patients with a previous diagnosis of melanoma.

Anticholinergic and Antihistamine Drugs

Anticholinergic drugs introduced in the 1940s were the first modern drugs for PD. Nevertheless, we still know relatively little about their pharmacokinetics and mechanism of action. They are able to block central muscarinic receptors (57), and some of them inhibit dopamine uptake in striatal synaptosomes (58). Anticholinergic drugs used commonly in the treatment of PD are benztropine mesylate, trihexyphenidyl HCl, procyclidine HCl, cycrimine HCl, biperiden HCl, ethopropazine HCl, bornaprine HCl, and methixene HCl. It is impossible to state, from a clinical point of view, the order of their relative potency. They differ slightly in their target symptom also, although they mainly act on rigidity and tremor. Trihexyphenidyl is more potent than L-DOPA on parkinsonian tremor (59). The overall clinical benefit given by anticholinergics is mild (about 30% improvement) but they can be very useful in the initial stages of PD and in a combined treatment with other drugs. The simultaneous administration of more than one anticholinergic drug is not useful.

The therapeutic index of anticholinergic drugs is sometimes low because of their side effects. The side effects happen mainly in patients over 65 years of age. The most dangerous and insidious of the side effects is mental deterioration with memory loss, which can evolve into a dementialike syndrome. In several patients with PD, choline acetyltransferase levels decrease to 60% of normal central levels in the frontal cortex (60); this cholinergic deficit can be exacerbated by anticholinergic drugs to a symptomatic state (61). Therefore the use of anticholinergics must be avoided in patients who have a previous history of psychiatric symptoms and/or who are over 65 years old. Other relevant contraindications are prostatic hypertrophy, glaucoma, and stenosis of the pylorus, which can be acutely worsened by these drugs.

The combined treatment of anticholinergic drugs plus L-DOPA may have two side effects: (*a*) by slowing gastric emptying, they reduce intestinal absorption of L-DOPA (18), and (*b*) by potentiating L-DOPA effect and cholinergic hypofunction, they can increase AIM's (62). An acute withdrawal of anticholinergics may be dangerous, and may bring on a sudden worsening of parkinsonian symptoms, even when their effect appeared to be mild or absent (63, 64). Acetylcholine receptor supersensitivity with increased density of muscarinic receptors in the frontal cortex (60) probably plays a role in this exacerbation of parkinsonian symptoms on anticholinergic withdrawal.

Antihistamines are similar to, but less potent drugs than, anticholinergics. Since their side effects are considerably limited, antihistamines can be used instead of anticholinergics when it is necessary to withdraw the latter drugs. Antihistamines used commonly for PD are diphenhydramine HCl, chlorphe-

noxamine HCl, and orphenadrine HCl. They belong to the H_1 receptor blocking agents and also have a mild antimuscarinic effect. Their central mechanisms of action and distribution are not well known.

Amantadine

Amantadine HCl was reviewed in the previous article (1), to which we refer the reader. Since its introduction in 1969 amantadine has been a valid pharmacological tool with a well-defined place in the treatment of PD. Its mechanism of action has been investigated in recent years. Amantadine increases dopamine (DA) release and synthesis (65, 66), inhibits DA reuptake (67) and probably has also a direct stimulating effect on DA receptors (68, 69). However, these actions were observed in animals with high doses not comparable with the commonly used dose in humans. Furthermore, amantadine does not modify homovanillic acid (HVA) levels in cerebrospinal fluid of patients with PD (70). Its mechanism of action in man remains controversial, even if several beneficial effects and side effects suggest its inclusion among DA agonists. An argument in favor of the dopaminomimetic effect of amantadine in man is its ability to antagonize partially the neuroleptic-induced extrapyramidal syndrome (71, 72). The increase of DA release seems to be the pharmacological action of amantadine that fits well with its clinical effect in parkinsonian patients. In fact, amantadine tends to lose a part of its efficacy within a few months of treatment (70). It can again elicit some benefit after a withdrawal period (73).

Many clinical results support the statement that the dose of amantadine with a good therapeutic index is between 100 and 200 mg per day. The drug has a long plasma half-life of 10–28.5 hours (hr) (74), and 200 mg can be given in two administrations at 8–12 hr intervals. With doses higher than 200 mg, side effects are frequent. The more long-lasting and dangerous side effects are ankle edema and livedo reticularis (75, 76), and psychiatric symptoms, such as hallucinations and confusion (77). With psychiatric symptoms, amantadine can cause the same side effects induced by anticholinergic drugs (77). This effect must be remembered when a combined treatment is started and the dose of anticholinergics should be reduced or kept low. We observed AIM's analogous to those caused by L-DOPA in one patient treated with 300 mg of amantadine (70).

The percentage of benefit obtained with amantadine in PD is similar to that given by anticholinergics, but amantadine probably works more uniformly on all parkinsonian symptoms, including bradykinesia. There is not a general agreement about the decay of efficacy of the drug (75). However, amantadine can be used alone in the initial stages of PD (stages I–III of Hoehn & Yahr, 78) or can be added to L-DOPA in severely affected patients with whom L-DOPA dosage must be kept at suboptimal levels because of its side-effects.

Ergot Derivatives

A new category of potent antiparkinsonian drugs was developed in the last decade after the first reports of Calne et al on the action of bromocriptine (79). These drugs are ergolines or ergot derivatives with dopaminergic activity (80). They act on postsynaptic DA receptors by a hormonelike action that is independent of the production of axonal impulse (81). This mechanism of action seemed a promising complement to L-DOPA action, particularly in patients with an advanced degeneration of the nigrostriatal pathway. Ergot derivatives have partially met these expectations. In fact, when given in combination with L-DOPA they can reduce oscillations in performance (wearing-off) and AIM's (82). However, they gradually lose efficacy over several years of treatment and cannot counteract disease progression. A striatal receptor down-regulation may also explain this decay of efficacy (83).

Such ergolines as bromocriptine mesylate and lisuride hydrogen maleate are agonists of D_2 dopamine receptors and antagonists of D_1 receptors. Only pergolide mesylate is an agonist of both D_1 and D_2 receptors (81). An oral dose equivalent has been established for the commonly used drugs: 30 mg bromocriptine = 2.5 mg lisuride = 2.5 mg pergolide (81). Other ergot derivatives with a well-defined antiparkinsonian effect are no longer used for human treatment because they have some dangerous side effects. Lergotrile mesylate cannot be used because it shows alterations in liver function tests (84); mesulergine HCl was withdrawn because it induces testicular tumors in one strain of rats (80).

Bromocriptine is the ergoline most thoroughly investigated clinically. Several authors reported that bromocriptine must be given in high doses (i.e. 30–130 mg/day) for maximum efficacy in PD, with a dose–disease stage relationship (85, 86). Unfortunately, severe side effects may impair these beneficial effects, requiring reduction of daily dose or withdrawal of the drug. Side effects of bromocriptine are similar to those of L-DOPA and other dopaminomimetic drugs, but AIM's are rare and psychiatric symptoms are relatively frequent. Nausea and vomiting may be particularly severe, but domperidone, a blocker of peripheral DA receptors, effectively reduces them (87). Also, orthostatic hypotension may be particularly severe. In this case, slow rise from supine position, elastic stockings, and an increase in sodium intake may help the patient. For these problems a slow titration of bromocriptine has been suggested, increasing the dose from 1.25 to 2.5 mg per week (88). Several authors also claimed that low doses of bromocriptine (5–15 mg) are useful (88), but there is no general agreement on this point. A relatively low dose is probably sufficient when bromocriptine is added to L-DOPA. Rinne (82) obtained better results after three years of treatment with the combination of L-DOPA and bromocriptine at a mean daily dose of 16.6 mg

than with L-DOPA alone at a higher dose. When bromocriptine is added to L-DOPA in advanced cases, the clinical results are controversial (89, 90). Lander et al (91) reported that a single dose of bromocriptine at bedtime relieves morning akinesia and dystonia.

In recent years lisuride and pergolide joined bromocriptine as effective ergolines in the treatment of PD. Lisuride and bromocriptine have comparable clinical effects, but the effective dose of lisuride is about one-twelfth that of bromocriptine (81, 92). A disadvantage of lisuride is its additional property as a central serotonin agonist, which probably causes enhanced psychiatric side effects in comparison to bromocriptine (92). The most interesting use of lisuride seems to be its continuous subcutaneous administration by means of a portable miniinfusion pump, in addition to oral L-DOPA plus a peripheral decarboxylase inhibitor (PDI) (93). Oscillations in performance and the overall parkinsonian picture were considerably reduced in three patients with an advanced long-term L-DOPA syndrome (93). Pergolide in acute studies has a powerful and long-lasting effect, which lasts more than twice as long as that induced by L-DOPA (94). Its therapeutical dose is equal to, or somewhat smaller than, that of lisuride. There is some controversy about the loss of efficacy of pergolide in chronic treatment of PD. Goetz et al (95) found that pergolide was still effective after five years of treatment; Lieberman et al (96) reported a 35% decrease of efficacy after a mean of 16 months of treatment in a large population of patients. Since such a decrease of efficacy is not dose related and is not restored after a drug holiday, it seems caused by the natural course of the disease more than by receptor down-regulation (97). Side effects of pergolide are similar to those of the other dopamine agonists. A particular drawback seems to be the occurrence of episodes of sudden freezing (97). On the other hand, pergolide lacks cardiac toxicity in parkinsonian patients with cardiac disease (98).

In conclusion, ergot derivatives are a new, important class of antiparkinsonian drugs. Their relatively long-lasting action on postsynaptic DA receptors, essentially of D_2 type, is a useful complement to the pharmacological action of the other antiparkinsonian drugs, in particular L-DOPA. A treatment with one ergoline plus one or more of L-DOPA, amantadine, and an anticholinergic drug is possible and useful in certain circumstances, once the previously mentioned indications, side effects, and interaction of these drugs are considered.

Other Drugs

Several drugs with a potent antiparkinsonian effect were dropped from clinical use in the last few years for different reasons. For instance, apomorphine HCl is not used because of its short duration of action and side effects, whereas MIF [PLG (Pro-Leu-Gly-NH_2)], a synthetic tripeptide that potenti-

ates L-DOPA effects, is not used because it is effective only intravenously, not orally (99). Moreover the cost of these drugs is high, and in light of their clinical usefulness, it does not justify their current use.

Other drugs have not yet been submitted to a thorough pharmacological and clinical evaluation. A new, interesting approach to the therapy of PD is based on the introduction of an inhibitor of monoamine oxidase-B (MAO-B), L-deprenyl. L-Deprenyl selectively inhibits DA catabolism (100), and a single oral dose induces a long-lasting (up to three days) dopaminergic potentiation (101). Some clinical studies demonstrated that L-deprenyl, when added to L-DOPA, potentiates L-DOPA's effect. This further improvement is still evident after several years of combined treatment (101, 102). L-Deprenyl is administered orally in a 5–10 mg dose, and the dose of L-DOPA in this combined treatment may be reduced to avoid an increase of AIM's. But some recent experimental data challenge these clinical results. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a potent neurotoxin, causes a typical parkinsonian syndrome in man and animals (see 103 for a review), and MAO-B is essential to transform MPTP to its active metabolite MPP^+. L-Deprenyl is a good candidate to counteract this transformation. However, Bradbury et al (104) showed that L-deprenyl potentiates DA depletion caused by MPP^+ in mouse striatum. Therefore, these experimental data seem to conflict with clinical experience and require further investigation of the pharmacological properties of this drug.

Another drug, DL-threo-dihydroxyphenylserine (DOPS), a β-hydroxylated form of DOPA that is converted to norepinephrine (NE) by DOPA-decarboxylase, was suggested to improve transient freezing (105), but a subsequent report did not confirm these results (106). The usefulness of a central NE stimulant for some particular symptoms of PD is still uncertain. Recently, Stoessl et al (107) reported that (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) is an effective antiparkinsonian drug. This observation is interesting and deserves further attention, since PHNO is a new type of DA agonist, not related structurally to morphine and ergolines.

Some drugs introduced many years ago for indications other than PD can help in the management of PD, particularly tremor. Propranolol HCl, a well-known β-adrenergic blocker useful in the treatment of essential tremor, is effective on the postural tremor that sometimes occurs in PD (108). Also nadolol, a β-blocker active only peripherally, has a therapeutic effect on the different types of tremor in PD (109). This finding raises the possibility that parkinsonian tremor can be influenced by a peripherally acting drug. Finally, clonazepam, a benzodiazepine thoroughly used for the treatment of epilepsy, relieves PD tremor when given at a dose of 3 mg per day (110).

In conclusion, the pharmacological means of treating PD have been continuously increasing in the last twenty years. Today, the neurologist has the

responsibility of choosing the treatment properly and making the decision of when to give a drug, at which dose, and with what combination of other drugs. Mistakes in the treatment are giving too many drugs at the same time or increasing one drug to the maximum tolerated level to obtain the best result possible. Since PD is a chronic disease, we must be careful in trying to achieve perfect results immediately. A 60–70% improvement should be considered a satisfying and prudent achievement, and the physician should aim to keep the improvement as stable as possible in the following years. Patients with PD sometimes appear to tolerate AIM's very well, but they do indeed become seriously handicapped. Therefore, long-term treatment of PD is essentially a problem of maintaining equilibrium between the present and the future: the easily achievable, immediate benefit and the long-term functional results.

DYSTONIC SYNDROMES

Dystonic syndromes (DS) are fairly common, heterogeneous disorders that may occur idiopathically, as an inherited trait, or secondarily to various brain lesions. They are also encountered within a number of complex degenerative diseases (111). The more frequent idiopathic syndromes are torsion dystonia, cranial dystonia (Meige's syndrome), spasmodic torticollis, and focal dystonia (writer's cramp). The pathological bases and the biochemical abnormalities of DS are unknown. Therefore, the pharmacology of these syndromes is very limited and developed essentially from clinical observations and therapeutic trials. Since some drugs may be beneficial, we report these attempts.

Barbeau (112) suggested that L-DOPA in low doses could improve some DS. He based this suggestion on the well-known dystonic reactions that occur mainly in young people after the administration of neuroleptic drugs and on the consideration that dystonic symptoms are a common feature in postencephalitic parkinsonism. Several clinical trials demonstrated that L-DOPA is not useful in most DS, but in the hereditary Segawa variant with diurnal fluctuations, the drug was reported to cause a sustained improvement of dystonia (113, 114). L-DOPA seems effective in young patients at low doses, not combined with a PDI. A DA agonist, bromocriptine, was reported to have improved three patients with DS when given at high doses (115, 116). Bassi et al (117) obtained a significant improvement in 6 out of 7 patients with DS with another ergot derivative, lisuride (see "Ergot Derivatives"). These results were confirmed by Quinn et al (118), who observed improvement of 8 of 31 patients with idiopathic DS (26%) when they were given lisuride at doses ranging from 0.4 to 5 mg (mean = 3 mg). These authors suggested, however, that lisuride could act on DS because of its serotonergic effect, not

because of its dopaminergic properties. Since little is known about the possible involvement of the serotonergic system in DS, this question remains open.

The results with L-DOPA and DA agonists appear to contradict various reports on the beneficial effects of neuroleptics such as haloperidol and tetrabenazine (119–121). Tolosa & Lai (122) based their hypothesis of a striatal DA preponderance in a particular form of dystonia, Meige's syndrome, on this effect. However, neuroleptic drugs may have a highly aspecific, sedative-type effect, which is observed to varying degrees in all the hyperkinetic syndromes.

The most interesting and extensive reports on the treatment of DS concern anticholinergic drugs (AC). Fahn (123) matched the observations on the dystonic reactions caused by neuroleptics (which are reversed by AC) with the therapeutic principle of a slow dose titration to avoid side effects. He also treated 75 patients with DS with trihexiphenidyl (THP) and ethopropazine (EP) (see "Anticholinergic and Antihistamine Drugs") and found significant benefit in 61% of children and 38% of adults. Several reports followed Fahn's contribution, confirming his positive findings in almost the same percentage of patients. We calculated the overall results of 11 reports on patients with idiopathic DS (119, 121, 124–132). Out of 245 patients treated with THP, EP, or benztropine (BT) 105 (43%) showed a clear-cut improvement. The dose of AC varied considerably; for instance, for THP its range was between 2 and 80 mg per day. The main conclusions that can be drawn from these studies are the following: (*a*) improvement is more frequent in children than in adults because children can tolerate higher doses of AC. (*b*) THP seems most effective, but it is very difficult to go beyond the dose of 30 mg per day in patients over 40 years old. EP and BT can be used in adults, when THP is not well tolerated. However, the maximum dose tolerated must be very gradually obtained by increases over several months of treatment. (*c*) The treatment with AC is less effective in patients with symptomatic or secondary DS (such cases are not included in the data given above). (*d*) Spasmodic torticollis, torsion dystonia, and Meige's syndrome show the best results, while writer's cramp responds less often to AC. (*e*) The clinical result appears inversely correlated with the length of the disease (132). (*f*) The value of i.v. AC administration as a predictive test of response to oral administration is controversial. Probably several factors, dose, difference between oral and i.v. administration, patients studied, affect the results. In patients with severe dystonia where THP is not effective, Marsden et al (130) suggested a combined treatment of THP with tetrabenazine and pimozide. In conclusion, although unpredictable and of benefit to a limited percentage of patients only, AC treatment appears the most effective pharmacological tool for DS at the moment. The effect of AC suggests that a cholinergic overactivity occurs in

DS. However, from the available data we cannot infer which neurotransmitter imbalance would be responsible for this "functional" overactivity.

HUNTINGTON'S DISEASE

The main pathological changes in Huntington's disease (HD), i.e. a degeneration of the small cholinergic and GABAergic neurons in the striatum, have been known for several years. We also know that the concentrations of GABA, glutamic acid decarboxylase (GAD), and choline acetylase (ChAc) are lowered in several regions of the HD brain (133, 134). Nevertheless, several therapeutic approaches similar to the "replacement" strategy used in Parkinson's disease, i.e. increasing brain levels of GABA and acetylcholine (ACh), have failed to give substantial results to date. Moreover, the administration of GABA and acetylcholine receptor agonists, which are active in the absence of nerve impulse from degenerated axons, failed to improve choreic hyperkinesias and dementia, the two cardinal symptoms of HD. We briefly review these reports.

Growdon et al (135) gave choline, the ACh precursor, in high doses of 8 to 20 g per day to 10 patients with HD. Although choline levels in cerebrospinal fluid (CSF) were increased, no consistent clinical improvement was observed after 19–125 days (mean = 50 days) of treatment. Arecoline, a potent, short-acting muscarinic agonist, was given to 6 patients in another study and resulted in the exacerbation of choreic movements (136). On the contrary in acute studies physostigmine, an anticholinesterase agent, was reported to improve chorea in 13 out of 23 patients (see 137 for references). Nutt (138) reported that some AC, such as scopolamine and benztropine, paradoxically improve chorea, but he pointed out that the effect of both physostigmine and AC may depend on their aspecific sedative effect, not on their cholinergic or anticholinergic action. In fact, scopolamine and benztropine reduced chorea but worsened incoordination in patients with HD, showing that these effects are dissociated. In therapeutic trials scoring only chorea, not coordination, an important component of the dyskinetic syndrome is certainly missed. In conclusion, the results obtained with drugs active on central cholinergic systems show that this approach cannot presently be used for HD. However, most of these results were obtained in acute, short-term studies in which drug action was observed on abnormal movements, not on psychiatric symptoms.

The GABAergic approach has not been more encouraging than the cholinergic one. Perry and coworkers (139) gave high doses of isoniazide (INH) to 6 patients with HD. They observed a gradual benefit on both dyskinetic and psychiatric symptoms in 3 patients. INH dose was related to the acetylation phenotype of each patient, e.g. a lower dose was given to slow acetylators. The same authors reported a limited improvement, in only 1 out

of 9 patients, in a subsequent controlled trial with INH (140). Stober et al (141) confirmed a significant effect of INH in 4 out of 10 patients with classic, hyperkinetic HD. They emphasized the importance of maintaining the trial for at least two-to-three months before evaluating its success. It is unclear why only a limited number of patients responded to the treatment with INH, but the results of these studies (139–141) are probably the most interesting for the practical management of HD. INH increases the brain GABA content by an inhibition of its degradative enzyme GABA-aminotransferase (GABA-T). Other inhibitors of GABA-T, sodium valproate, gamma-acetylenic GABA and gamma-vinyl GABA, which are also inhibitors of GABA-synthetizing enzyme GAD, failed to elicit any clinical improvement (142–145). 4,5,6,7-Tetrahydroisoxazolo-[5,4-6]pyridin-3-ol (THIP), a GABA receptor agonist, was not effective, and interestingly, during the treatment with THIP, CSF content of HVA was increased (146). This finding is in agreement with previous studies of Waddington & Cross (147). These authors predicted the failure of treatment with GABA agonists in HD because these drugs would induce a striatal dopaminergic hyperfunction by acting on the supersensitive GABA receptors in the substantia nigra. In our opinion, further studies with proper dosage and duration of treatment are required to confirm if INH is useful in a subpopulation of patients with HD.

All clinical conditions with AIM's of different types, chorea, dystonia, tics, ballismus, are relieved by neuroleptics. In HD, where there is a preponderance of dopamine, the effect of neuroleptics is particularly pronounced, at least in the first stages of the disease. An important side effect of neuroleptics in HD is mood depression, since these patients are prone to this condition that can lead to suicide. Reserpine, haloperidol, fluphenazine and tetrabenazine are among the first drugs used successfully in HD (1,120). Recently fenfluramine, an inhibitor of serotonin reuptake, has been claimed to be effective in a short-term, open trial on 7 patients with HD (148). Lithium carbonate was also reported to improve dyskinesias in HD (149). A combined treatment of lithium and haloperidol at low doses (1 mg/day) may be useful for both dyskinesias and mood stabilization (150). However, pulse rate must be regularly checked because lithium may cause severe bradycardia in patients with HD (G. Campanella et al, unpublished information). In advanced stages of HD, no drug can help the severely disabled patients.

GILLES DE LA TOURETTE'S SYNDROME

Gilles de la Tourette's syndrome (GTS) begins in childhood and is characterized by multiple tics and inapposite vocalizations. It is often accompanied by complex mannerisms and antics, echophenomena, and coprolalia. The biochemical basis of GTS is unknown, as is its anatomopathology, if any. The

pharmacological approach to the treatment of GTS has long been disappointing. In spite of its serious drawbacks, haloperidol, the all-purpose drug, was the most used neuroleptic until recent years, with a fair, but often short-lived, response in 60–90% of patients (151). Specifically, patients treated with haloperidol complain of the "zombie syndrome," i.e. difficulty in thinking adequately and intellectual dulling (152). The effect of haloperidol was supported by the theory of a DA receptor supersitivity in GTS (153). Tetrabenazine and fluphenazine are alternative treatments, with fewer side effects than haloperidol (154, 155). Gillmann & Sandyk (156) recently reported the effectiveness of nitrous oxide (N_2O), an opioid receptor agonist, in controlling tics in one patient with GTS. On the basis of this observation and other experimental data on the link between dopaminergic and opioid systems, they suggested that an opioid underactivity may cause the clinical symptoms of GTS. Further studies are required to validate this therapeutic approach.

Another interesting alternative drug for GTS is clonidine HCl, an antihypertensive agent with an α-adrenergic agonistic effect in the brain. Since 1979 (157) several studies have confirmed the efficacy of clonidine in GTS (see 158 for references). About 46–62% of patients improve with clonidine, and the initial severity of GTS can lead to a positive response (158). Even at the high dosage required in GTS, i.e. 0.125–0.3 mg per day, clonidine has relatively few side effects, mainly sedation and orthostatic hypotension. The mechanism of action of clonidine in GTS is still unknown, but it probably is not simply based on its central adrenergic effect. Treatment with methylphenidate HCl and other central stimulants is contraindicated in GTS (159).

WILSON'S DISEASE

Hepatolenticular degeneration or Wilson's disease (WD) is a rare but important illness. It was the first neurological disease to be successfully managed in the 1950s. The well-known results, treatment scheme, and side effects of therapy with D-penicillamine, (β,β-dimethylcystein) can be found in several comprehensive reviews (160–162). We summarize some points that thirty years of therapeutic experience with this drug have emphasized with increasing clarity. D-Penicillamine is a very active drug that can completely reverse the symptoms of WD and stop its progression. The sooner the diagnosis is made and the treatment started, the better are the results. It is never superfluous to repeat what Sternlieb & Scheinberg recommended, that the diagnosis of WD in the presence of signs of chronic hepatitis should always be suspected, particularly in patients under age 40. Recent reports showed that WD is still considerably underdiagnosed or that diagnosis is often dangerously delayed (164, 162). The chelating effect on

copper of D-penicillamine must be constant and life-long. In this type of long-term treatment, a patient's compliance is a very delicate problem. Many patients, after experiencing a complete remission of their symptoms for several years, abandon their medication, often with severe and irreversible damage and even a fatal outcome (165). The maintenance dose of D-penicillamine depends on the time of its administration and on the concomitant dietary restriction of copper-rich foods. The drug must be taken about half an hour before meals to avoid saturation of copper sites by copper contained in the food ingested. If a low-copper diet is observed (160–162), 600–750 mg per day are sufficient as a maintenance dose. In Walshe's and our experience, side effects of D-penicillamine are much less frequent in WD than in other diseases such as rheumatoid arthritis.

Although D-penicillamine is the most effective and specific drug for WD, other medications have been introduced in recent years that are valuable alternatives, particularly when D-penicillamine is not well tolerated. The drugs are trientine dihydrochloride (trien) and zinc salts. Trien is as effective as D-penicillamine, and its only side effect is iron deficiency that can be overcome by iron supplements (166). Zinc sulfate or acetate induce a negative copper balance, increasing fecal copper excretion (167, 168). Zinc salts are also useful in addition to D-penicillamine to counteract the hypogeusia caused by the latter drug (164). Finally, if treatment with D-pencillamine is started late and does not alleviate the neurological symptoms, L-DOPA (169) and anticholinergic drugs (164) may help in decreasing akinesia, rigidity, and dystonia.

CONCLUSION

In 1974 Barbeau (1) concluded his review on drugs affecting movement disorders with an important statement that could not have been made several years before: chronic neurological movement disorders *can* be treated. After 13 years we can conclude by emphasizing two outstanding aspects: (*a*) we have much better knowledge of the mechanism of action, indications, and long-term effects of drugs that had already been discovered in 1974, such as L-DOPA, anticholinergics, and penicillamine; (*b*) many new drugs have subsequently been introduced that represent important pharmacologic approaches for treating these disorders. The growing therapeutic arsenal requires a thorough knowledge of the properties of these drugs and thus increases the physician's responsibility.

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