Update on Dopamine Agonists in Parkinson's Disease: "Beyond Bromocriptine"

Anthony E. Lang

ABSTRACT: Since the initiation of bromocriptine therapy for Parkinson's disease several newer dopamine agonists have been developed. Pergolide has reached the stage of Phase 3 clinical trials and will probably be available for general use sometime in the foreseeable future. Lisuride shows most promise in its parenteral form for infusion therapy of patients with severe fluctuations. Mesulergine, another ergot-derivative and ciladopa, a new non-ergot agonist, have been withdrawn from further clinical use due to tumorogenesis in rats. It is questionable how applicable these findings are to the use of the drugs in elderly humans with parkinsonism. Recently a small number of drugs have been found to have postsynaptic dopamine agonist properties only in the setting of denervated supersensitive dopamine receptors. These agents may be particularly effective in the early treatment of patients with Parkinson's disease. This paper will review a number of the dopamine agonists which have been developed since the introduction of bromocriptine therapy. Several of these have shown beneficial effects in early clinical trials while others show promise in preclinical studies of animal models of parkinsonism.

RÉSUMÉ: Mise à jour sur les agonistes dopaminergiques dans le traitement de la maladie de Parkinson. Depuis l'avènement de la thérapie par la bromocriptine dans la maladie de Parkinson, plusieurs agonistes dopaminergiques plus récents ont été développés. Les études sur le pergolide en sont rendues au stage 3 des essais cliniques et il est probable que ce médicament sera disponible sous peu pour utilisation courante. La forme parentérale du lisuride pour infusion chez les patients qui ont des fluctuations sévères, semble donner des résultats prometteurs. La mésulergine, un autre dérivé de l'ergot, et la ciladopa, un nouvel agoniste non dérivé de l'ergot, ne sont plus utilisés en clinique parce qu'ils se sont avérés être tumorigènes chez le rat. On peut se demander s'il est justifié d'appliquer cette observation à l'utilisation de ces médicaments chez des vieillards parkinsoniens. Récemment, on a constaté qu'un petit nombre de médicaments avaient des propriétés d'agoniste dopaminergique postsynaptique seulement dans un contexte de dénervation et d'hypersensibilité des récepteurs dopaminergiques. Ces agents peuvent être particulièrement efficaces en début de traitement chez les patients atteints de la maladie de Parkinson. Cet article fait une revue de quelques uns des agonistes dopaminergiques qui ont été développés depuis l'introduction du traitement par la bromocriptine. Plusieurs d'entre eux se sont avérés efficaces dès les premiers essais thérapeutiques alors que d'autres semblent prometteurs dans les études précliniques chez des animaux de laboratoire rendus parkinsoniens.

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In 1951, before the importance of dopamine deficiency in Parkinson's disease was understood, Schwab and his colleagues described an improvement in parkinsonism with the first postsynaptic dopamine agonist, apomorphine.[1] Subsequent studies[2] confirmed the efficacy of this drug, however, for optimal effects it had to be given parenterally, it had a high incidence of short-term side effects such as nausea, vomiting and postural hypotension and long-term oral treatment caused dose-dependent azotemia.[3] An early derivative of apomorphine, N-n-propyl norapomorphine was found to have antiparkinsonian effects without nephrotoxicity, however, tachyphylaxis developed rapidly.[3] The piperidin derivative piribedil was found to have prolonged motoric dopaminergic properties in animals[4] probably on the basis of both presynaptic dopamine-releasing and postsynaptic dopamine receptor agonist effects. However, in man the clinical antiparkinsonian effects of piribedil were somewhat disappointing. Much greater strides were made with the development of the next class of postsynaptic dopamine agonists, the ergot derivatives, led by bromocriptine.

In this paper I propose to review briefly the generation of dopamine agonists which has come since the development of bromocriptine. The majority of these agents have been ergot derivatives of one type or another (lysergic acid amides, clavines or 8-alpha-amino-ergolines). Numerous clinical trials have been carried out with two of these drugs, pergolide and lisuride while a third, mesulergine, has undergone less extensive testing. I do not intend to review all clinical trials with these agents. Patient characteristics, treatment regimes, rating scales and methodologies have varied so extensively that it serves no purpose to compare percentage improvements in terms of the different major features of parkinsonism. Instead I will attempt to present an update on these agents emphasizing any controversial

From the Movement Disorders Clinic, Toronto Western Hospital, Toronto
Reprint requests to: Dr. A.E. Lang, 25 Leonard Avenue, Suite 301, Toronto, Ontario, Canada M5T 2R2

questions which may exist. Other ergot derivatives, such as CF 25-397[5] and CM 29-712,[6] have failed to show sufficient promise for use in Parkinson's disease and these will not be considered further. Recently several newer classes of non-ergot dopamine agonist have been developed. A small number of these have undergone preliminary trials in Parkinson's disease (eg ciladopa, PHNO) and others show some promise for this purpose. Only selected examples from this rapidly expanding field will be mentioned. Several selective Dl (eg SKF 38393[7]) and D2 agonists (eg LY 141865, RU 24926[8,9]) will not be discussed. Although these have provided important insights into the categorization of dopamine receptors[10] their utility in the treatment of Parkinson's disease remains to be investigated.

I will discuss these drugs roughly in the order in which they were introduced for the treatment of Parkinson's disease beginning with the ergots developed after bromocriptine and ending with some of the newer non-ergots which may be of some clinical use in the future.

Pergolide

Pergolide mesylate is a synthetic ergoline of the clavine subclass. It lacks the halogen in the second position and the cyano-group in the eighth position of its forerunner lergotrile. These structural features are thought to account for the occurrence of the hepatotoxicity which eventually resulted in lergotrile being withdrawn from further clinical trials. It has been approximately 6 years since publication of the first trials of pergolide in Parkinson's disease.[11-13] In contrast to other ergot dopamine agonists used in PD to that time (eg. bromocriptine, lergotrile, and lisuride), which are D2 agonists, some with D1 antagonist properties, pergolide stimulates both D1 and D2 receptors.

Early open-label clinical studies clearly established that pergolide was a potent, long-acting dopamine agonist which could improve all of the primary manifestations of Parkinson's disease as well as the clinical fluctuations which develop with long-term L-dopa therapy. Placebo substitution for pergolide tended to confirm the observed response in most patients.[14] More recently, randomized double-blind placebo controlled trials of adjunctive therapy with pergolide combined with levodopa have been reported.[15,16] Although Sage and Duvoisin[15] reported significant improvement in total disability and gait as well as wearing-off and on-off, Diamond and her colleagues[16] found no significant difference between the pergolide and placebo groups. In the latter study both groups improved significantly in terms of severity of parkinsonian disability and fluctuations. The dosage of Sinemet was lowered in the pergolide group while the dosage in the placebo group remained unchanged. The authors suggested that the lack of difference between the two groups may have been related to the psychological support the patients obtained as a cohort attending the clinic to participate in a research study. Preliminary reports from two additional randomized double-blind controlled studies comparing pergolide to placebo as an adjuct to Sinemet showed significant differences between the two treatments with the pergolide groups obtaining significant improvement in parkinsonian parameters and severity of fluctuations.[17,18]

The chronic efficacy of pergolide has been assessed in a small number of studies published recently with conflicting results. Kurlan and his colleagues,[19] using a mean dose of 2.2 mg found that the initial benefit obtained in their 9 late stage patients virtually disappeared by 18 months of therapy. In 7 there was a partial but only temporary restoration of response when the drug was given in an alternate day schedule. These authors suggested that the development of pergolide-induced down regulation of dopamine receptors accounted for the loss of clinical efficacy. Using similar doses, Lieberman and his colleagues[20] also found that parkinsonian disability and number of "on" hours deteriorated over the 2 years of therapy to levels similar to those seen in the pretreatment state. They felt that this change probably indicated disease progression rather than receptor desensitization by the drug. Although Sage and Duvoisin[21] found that disease parameters were no longer significantly improved after 2 years of therapy none were worse and 6 of 8 patients who had discontinued the drug believing it was no longer effective had a marked deterioration in their symptoms. This experience and the lack of progression over a two year period was interpreted as evidence that the drug was still effective in these patients after two years of therapy. In support of this, Jankovic[22] reported continuing improvement in motor disability and fluctuations after 28 months of therapy, although the benefit had decreased from levels seen at the 10-week point. Sudden transient freezing had become the most disabling problem in 9 of the 18 patients. Finally, Goetz and his colleagues[23] compared the long-term effects of pergolide to those of bromocriptine in the same patients. These 10 individuals had initially responded to bromocriptine but had lost initial benefit after a mean of 29 months of therapy (mean 50 mg). Subsequent pergolide treatment resulted in a significant improvement and this benefit was maintained for most disease parameters after a mean of 29 months of therapy (mean 3.8 mg). Interestingly, scores for total disease severity, tremor and postural stability were significantly better than those pre-bromocriptine recorded 62 months earlier. These results support the earlier impression of Lieberman et al[24] that pergolide is more potent than bromocriptine but contrast with the results of LeWitt et al's short term cross-over study which found that the two drugs were equally effective.[25] Recently, Tanner and her colleagues have reported preliminary evidence for the prolonged efficacy of pergolide over a period of four years experience.[26] Although disease severity and disability were no longer improved by 36 and 48 months of therapy, they did not deteriorate to levels worse than pre-treatment. Importantly, the mean number of hours "on" per day remained significantly greater than before the drug was introduced. Side effects, particularly dyskinesias and hallucinations, became increasingly frequent over the course of the trial.

Another concern regarding pergolide has been its potential cardiotoxicity. In the earliest stages of clinical trials with pergolide Lieberman's group found that 7 of 13 patients assessed by Holter monitor developed repetitive ventricular rhythms.[27] The dose at which changes occurred were a function of underlying heart disease. Below 3 mg/day changes occurred in patients with heart disease and above 3 mg/day in those without. These findings contributed to the FDA suspension of clinical trials with pergolide which was later lifted in mid-1983. Subsequently, Tanner and her colleagues[28] found no worsening of cardiac status in 6 patients with stable heart disease given 2 to 3.6 mg. In a randomized double blind study, Kurlan et al[29] found only a mild and transient bradycardic effect in patients without evidence for underlying heart disease; however doses of less than 2 mg were used. Although these studies fail to support the concern regarding serious cardiac toxicity with pergolide, it

seems advisable to exercise appropriate caution especially in patients with underlying heart disease requiring higher doses of the drug.

To date most studies have not tried to replace L-dopa by pergolide, although the doses of L-dopa have often been reduced as pergolide was introduced. Maer et al[30] reported the use of pergolide monotherapy in 16 patients who had all existing antiparkinsonian therapy discontinued before pergolide was started. A mean daily dose of 6.3 mg (quite a bit higher than previous studies which combined pergolide with L-dopa) introduced relatively rapidly, resulted in a 73% improvement in parkinsonian disability. Although it was stated that the effects on parkinsonism were the same as obtained with levodopa, the data provided do not allow comparison of the pre-pergolide treated state (in terms of parkinsonism, time "off", severity of dyskinesias etc) with that on pergolide alone (three patients required additional L-dopa for "persistent on-off phenomena"). The time to onset of benefit after a dose of pergolide and the duration of action were significantly longer than for L-dopa given with a peripheral decarboxylase inhibitor (82 vs 49 min and 329 vs 138 min respectively).

Although several studies contain small numbers of previously untreated cases, careful double-blind controlled studies in de novo patients have not been published. Results of bromocriptine monotherapy have been disappointing. Recently, Goldstein and his colleagues[31] have suggested that the reason bromocriptine seems to be more effective when given with levodopa in many patients is because synaptic dopamine is required to convert the D2 receptor from a low to high-affinity state. Bromocriptine might then replace dopamine from the ternary complex and, by virtue of its higher affinity, enhance the duration of dopaminergic activity. However, in response to this hypothesis others[32,33] have suggested that the lower potency of bromocriptine and the apparent synergism it demonstrates with L-dopa is due to the simple fact that bromocriptine lacks the D1 agonist effects of dopamine which are necessary to restore normal motor behaviour. If this is so, then pergolide, which stimulates both D1 and D2 receptors, may have less need for concomitant L-dopa therapy. The simple fact that pergolide is a more potent and longer acting agonist must also be taken into account when comparing results of monotherapy. This issue takes on considerable practical importance if longterm L-dopa truly has toxic effects on remaining nigral neurons.

Lisuride (Dopargine)

Lisuride is a semi-synthetic ergot derivative of the isolysergic acid type. It was the first 8-alpha-amino-ergoline in clinical use with initial reports beginning to appear in 1981. In addition to potent D2 agonist effects, which are not dependent on presynaptic dopamine stores, lisuride has additional high affinity for serotonin receptors.[34] Two other distinctive features of lisuride are its short mean plasma elimination half-life of 1.7 hours[35] and its water solubility. Side effects of lisuride are similar to those of other ergot-derived dopamine agonists, particularly gastrointestinal intolerance, hypotension and psychiatric disturbances. One possible distinction is the occurrence of more frequent drowsiness or sedation which may relate to lisuride's serotonin agonist effects.

Greater than four hundred patients have been treated with oral lisuride.[36] Experience with lisuride in previously untreated patients is limited.[37-40] These patients have usually obtained a mild to moderate significant improvement which has been maintained in a small number for greater than two years.[38] All features of parkinsonism have improved although some investigators have found that tremor is most affected[39] while others report that tremor is minimally altered.[37]

As with all other dopamine agonists, most patients receiving lisuride were experiencing late-stage complications of levodopa treatment. In these patients, just as with bromocriptine and pergolide, all features of parkinsonism may improve and the dosage of levodopa may be reduced. A small number of studies have compared the efficacy of lisuride to bromocriptine. Lieberman[41] found that baseline disability scores in the "on" and "off" states were the same, however, patients treated with lisuride experienced more "on" hours. Other open comparisons[40,42] have found lisuride to be slightly more effective than bromocriptine. However, in a double-blind crossover study, LeWitt and his colleagues[43] found that the two drugs were equally effective with an optimal dosage ratio of bromocriptine (mean dose 56.6 mg) to lisuride (mean dose 4.5 mg) of 13:1. Schacter and his colleagues had previously estimated the bromocriptine to lisuride ratio as 15:1.[44] The dosage of lisuride required by individual patients varies markedly. It has been suggested that this relates to a variable first-pass hepatic metabolism. However, finding a higher steady state in a patient taking 10 mg compared to one requiring less than 1 mg, LeWitt and his colleagues[45] concluded that those requiring higher doses were not "high metabolizers" of the drug but that the variations in optimal daily dosage related to individual differences in response to the drug at the level of the CNS. LeWitt and his colleagues[45] have also found that lisuride and pergolide are roughly equivalent in their antiparkinsonian effects with an optimal dosage ratio of 1.2:1. Lieberman et al[46] found that similar doses (lisuride 2.6 mg per day and pergolide 2.5 mg per day) caused a similar reduction of disability in the "on" and "off" periods. However, pergolide resulted in significantly more "on" hours. They suggested that this difference related to the much shorter half-life of lisuride. In one of the earliest trials of lisuride, Schacter and colleagues[44] had also found the short duration of action of lisuride to be a major limiting factor in its use. Few trials combining lisuride with levodopa have reported on the long-term efficacy of this treatment. Although some patients seem to demonstrate loss of efficacy over time[47,48] others continue to maintain benefit from one to three years after initiation of therapy.[35,49]

The potency and water solubility of lisuride has encouraged its intravenous use, both for experimental and therapeutic purposes.[36] Early on, it was suggested that this approach could be of considerable value in treating patients with severe akinesia and in the emergency management of patients in the perioperative period.[44] More recently, intravenous and subcutaneous infusions of lisuride have been used successfully in the management of patients with disabling fluctuations (see *Obeso* in this issue).

In addition to the treatment of Parkinson's disease, lisuride has been used in a variety of other movement disorders. Although initial studies in cranial dystonia claimed a marked response[50] further trials failed to demonstrate a significant benefit.[51,52] Occasional patients with other forms of dystonia obtain benefit but there does not seem to be any useful way of predicting these

individuals in advance.[52] Intravenous lisuride has improved cortical reflex myoclonus[53] but it is not clear that this is of practical use to the long-term management with oral medication.

Mesulergine

Mesulergine (CU 32-085) is another 8-alpha-amino-ergoline. This drug has been shown to have initial antagonistic properties for both D1 and D2 receptors, however, later it has potent D2 agonist properties only. This biphasic effect probably relates to its metabolism to the bimethylated derivative.[54] However, the occurrence, nature and clinical relevance of this biphasic effect remain controversial.[55,56]

Clinical trials of mesulergine reported over the past four years have consistently shown significant antiparkinsonian effects. Mean doses have ranged between 6.7 mg[57] and 27.4 mg.[58] There has been a variable effect on all features of Parkinson's disease with the significance of changes seen often related to the dosage used. Both de novo[59-65] and levodopa-treated patients suffering late-stage complications have responded. Some investigators[57,59,65] have found that the drug was particularly effective against tremor. Interestingly, in addition to the D2 agonist effects, the drug has additional weak anticholinergic properties.[65,66] However, tremor has not consistently responded and Teravainen et al[61] found that this was the only feature which did not improve. Two patients in Jellinger's study experienced an increase in tremor and one had to discontinue the drug because of this.[65] Pfeiffer and his colleagues[67] found that postural stability, a notoriously difficult management problem in later stages of Parkinson's disease, responded in patients given higher (20 mg) doses. Although additional antidepressant properties have been noted[57,62] some patients have had to be withdrawn from the drug because of depression.[58]

The few long-term studies lasting between 12 and 18 months [65,68-70] found no reduction in the response over this time. However, Schneider et al's[71] recent 3 year follow-up showed a decline in efficacy which began after 18 months of therapy. De novo patients often required the addition of L-dopa while those already treated required increasing doses of levodopa to maintain the initial improvement obtained with mesulergine.

In previously untreated patients, Dupont et al[60] found that mesulergine was 2/3 as effective as levodopa. Although some authors are of the opinion that mesulergine is more effective and better tolerated than bromocriptine,[64,65] in double-blind crossover[58] and parallel[70] studies the two have resulted in approximately the same degree of benefit. The equipotent dosage ratio of mesulergine to bromocriptine has varied between 50%[64] and 70%.[58] Baas et al[70] found that the initial response to mesulergine was maintained while that to bromocriptine had begun to wane after one year of therapy. Lieberman and his colleagues[72] found that the disability scores of patients no longer responding to pergolide improved to the same extent on mesulergine as they had when pergolide was first used. However, pergolide was more effective in reducing the amount of time in the "off" state.

Many investigators have commented on the excellent patient tolerance of mesulergine. Several have noted that the frequency of side effects was less than that of other dopamine agonists.[57,64,65,69,70] However, in a double-blind crossover comparison with bromocriptine, Burton and his colleagues found that the nature and frequency of adverse effects were similar with the two drugs.[58] Although gastrointestinal side effects are not uncommon, Pfeiffer and his colleagues commented that levodopa-induced nausea and GI discomfort consistently improved.[67] They postulated that this might relate to the early dopamine receptor antagonist effects of mesulergine.

In 1984, further clinical development of mesulergine was halted because of toxicological observations in animal experiments. High dose, long-term treatment in rats resulted in interstitial cell tumours in the testes. The causative doses were several-fold higher than those required to treat Parkinson's disease and the tumours became apparent only in the last third of life-long (2½ years) treatment. The applicability of these studies to parkinsonian patients must be questioned (see below).

Ciladopa

Ciladopa (AY-27,110) was one of the first non-ergot dopamine agonists to be developed for clinical use in Parkinson's disease since the earlier disappointing results with apomorphine and its derivatives. This is a troponylpiperazine derivative which has low binding affinity for normosensitive postsynaptic dopamine receptors but which in low doses stimulates presynaptic and supersensitive postsynaptic striatal D2 receptors. These effects qualify the drug as a "partial agonist" similar to transdihydrolisuride (see below), LY141865 and EMD23448. In addition to its effects as a partial agonist, ciladopa fails to cause behavioural supersensitivity in animals.[73] This phenomenon, which occurs with levodopa[74] bromocriptine[75] and d-amphetamine,[76] may be a predictor of the development of dyskinesias and psychiatric side effects in parkinsonian patients, suggesting that ciladopa may be less likely to cause these complications.

There have been three reports dealing with the open-label extension component of double blind trials with ciladopa. Snider[77] and Lieberman et al[78] reported significant improvements in the majority of patients with respect to most disease parameters. Weiner and Berger[79] found significant improvement in total disability but no change in the major manifestations of parkinsonism. However, analysis of the double-blind trial[80] revealed significant improvement in total disability and gait and a trend towards improvement in bradykinesia and rigidity in patients treated with 15 mg b.i.d. There was no change in tremor and patients in the low dose group (5 b.i.d.) showed no significant benefit. Snider[77] reported a side effect profile similar to other dopamine agonists while Weiner et al's patients experienced no adverse effects. Behavioural and biochemical studies with ciladopa indicated a relatively short duration of action and the need for doses between 20 and 50 mg for clinical efficacy (based on a comparison with bromocriptine in animals). It is likely that greater antiparkinsonian efficacy would have been seen had the drug been used in higher doses given more frequently.

As with mesulergine, during the early phase of clinical trials, parallel animal toxicology studies revealed the development of testicular tumours in chronically treated rodents. Again, this effect occurred in rats given 10 to 100 times the dosages used in patients over a period of 20 to 24 months which represents the first half to two thirds of their life span. It is not clear that D2 agonist tumorogenesis in rat toxicology trials is of any relevance to the use of these drugs in the treatment of parkinsonian patients in whom lower doses are given for a much shorter portion of their life span. Weiner and his colleagues[80] have suggested that a "risk versus benefit" approach should be taken into consideration before discontinuing further clinical trials of such agents or we will continue to see additional

withdrawals of newer, potentially useful, antiparkinsonian agents in the future.

Terguride

Terguride, or transdihydrolisuride is the 9,10-dihydrogenated analogue of lisuride. Like ciladopa, this drug is thought to be a "partial" dopamine agonist. It lowers prolactin more potently and for a longer period of time than does lisuride without the usual side effects of the parent compound, such as nausea, vomiting and postural hypotension.[81] In animal models, it has dopamine antagonistic effects in the nigrostriatal and mesolimbic systems. However, in the presence of super-sensitive postsynaptic dopamine receptors (e.g. with 6-hydroxy-dopamine-induced nigrostriatal lesions) it shows dopamine agonist properties. Based on this pharmacological profile, it has been suggested that terguride may be effective in treating states of excessive dopamine activity such as the chorea of Huntington's disease, tardive dyskinesia and levodopa-induced dyskinesias as well as in treating patients with Parkinson's disease in whom nigral dopamine deficiency has resulted in supersensitivity of postsynaptic striatal dopamine receptors. Preliminary studies show that this drug may improve chorea in Huntington's disease[82] and may even improve psychotic symptomatology in schizophrenia.[83]

Three preliminary trials in Parkinson's disease have shown promising results. Corsini and his colleagues[83] used doses of up to 1.2 mg in eight patients on no other antiparkinsonian therapy (7 previously treated with levodopa and one untreated). There was an average improvement of 50.6% on the Webster Scale and five Stage IV patients improved by 64%. All features of parkinsonism benefited, however tremor improved less markedly than other signs. Aside from transient nocturnal polyuria and hot flushes, there were no side effects experienced. In three patients, single-blind placebo replacement resulted in a clinical deterioration. The authors commented on preliminary results which indicated that both levodopa-induced dyskinesias as well as "wearing off" were improved.

Brücke[84] used doses of up to 1.5 mg per day for three months in fifteen patients with advanced disease. Fifty percent of patients obtained mild improvement in bradykinesia and rigidity and one patient with prominent tremor was markedly improved. In contrast to previous suggestions, dyskinesias were seen in two patients on doses of 0.37 and 0.75 mg. One patient required a reduction in dosage, due to orthostatic hypotension. Suchy et al[85] used terguride in ten patients with mild, previously untreated disease. A slow dosage increment transiently increased parkinsonian symptoms in some patients while a more rapid increase in dosage resulted in no initial dopamine antagonist effect. A large proportion of patients obtained additional mood elevation which the authors questioned may have been due to the central alpha-2-receptor blocking effects of the drug.

Further trials of this agent are clearly indicated. The theoretical advantages in patients with levodopa-induced dyskinesias or psychiatric disturbances must be explored. However, a preliminary trial of terguride by Calne and his colleagues (personal communication) was abandoned because of a high incidence of side effects (lightheadedness, emesis, skin rash) in doses which resulted in little clinical benefit.

Critchley and Parkes[85a] have just recently published results of a single dose (0.25 - 1 mg) and short-term (0.25 tid) studies. 0.5 mg resulted in clinical effects roughly equivalent to those obtained with 1 - 2 mg of lisuride in previous studies. Side effects were similar to other dopamine agonists. L-dopa-induced dyskinesias increased while pre-existing levodopa-induced psychosis did not change after five to ten days of terguride therapy.

PHNO

(+)-4-propyl-9-hydroxynaphthoxazine (PHNO) is a unique selective D2 agonist with a molecular structure unrelated to the morphine and ergot derivatives previously used to treat Parkinson's disease. Preliminary trials in a small number of patients have shown that this naphthoxazine compound has the ability to improve all features of parkinsonism. In a double-blind dose-ranging study in eight patients, Stoessl et al[86] documented significant improvement in tremor and mechanical measurements of rigidity, however, in this short study, the effects on rigidity, bradykinesia, speed of movement and postural sway were not significant. The effects lasted up to six hours. Side effects similar to other dopamine agonists, particularly gastrointestinal upset, fatigue, postural hypotension, and shivering were present in all patients, however, these were "successfully blocked" by pretreatment with domperidone.

Weiner and his colleagues[87] obtained improvement in all parkinsonian features in ten patients using doses of 0.25 mg tid to 1 mg tid. Half of the patients were withdrawn due to side effects at the higher doses, however, domperidone pretreatment was not used. Coleman and his colleagues in Marsden's group (personal communication) have carried out single dose oral trials as well as nasogastric and intravenous infusions using PHNO. Oral doses of 4 mg have been roughly equivalent to Sinemet 250/25 mg in terms of clinical effect and duration of action. Muenter (personal communication) has also obtained similar very promising results with this agent.

Some pharmaceutical workers handling PHNO developed nausea and emesis, suggesting dopaminomimetic side effects. This suggests that the drug may be effective when given transdermally or intracutaneously. "Patch" therapy has been effective in improving MPTP-induced parkinsonism in the marmoset (R. Coleman, personal communication). This is an interesting prospect which may be usefully applied to Parkinson's disease in the future.

Newer Drugs

Abeorphines

As mentioned in the introduction, the earliest dopamine agonists to be used in Parkinson's disease were apomorphine and its derivative N-n-propyl-Norapomorphine. However, despite potent dopaminergic properties, these drugs did not find broader clinical application because of emetic side effects, nephrotoxicity and tachyphylaxis. Recently, Jaton et al[88] have explored rigid analogues of apomorphine with emphasis on a series of derivatives possessing a novel tetrahydro-dibenz [cd,f] indol-skeleton termed abeorphines. One such compound, abeorphine 201-678, has been found to be a potent agonist for both D1 and D2 receptors. It is orally active and demonstrates a long duration of action. The drug possesses a higher affinity for 3H-dopamine binding sites than bromocriptine and, in contrast to this latter agent, its effects are only minimally reduced by decreasing presynaptic dopamine stores (with alpha-methylparatyrosine). 201-678 has considerably more affinity for 3H-clonidine binding sites in vitro than ergot-derived dopamine agonists, how-

ever, Jaton et al found no significant effect on the levels of noradrenaline or its metabolite MHPG in the pons/medulla.

Preliminary clinical study of abeorphine 201-678 has revealed definite antiparkinsonian effects.[89] Birbamer et al reported that 6 of 13 patients obtained a marked improvement in disability while 3 of 13 obtained no benefit. Two patients whose doses were rapidly increased had to be withdrawn due to tactile hallucinations in one and a cardiac arrhythmia in the other. Unlike apomorphine, emesis was a problem in only one of their patients. Further studies of 201-678 and other members of this class of potent dopamine agonists are awaited with interest.

2-Aminotetralins

Another newer class of drug which has been found to have potent D2 agonist effects is the di-substituted 5-hydroxy-2-aminotetralin group exemplified by the compound 2-(N-propyl-N-phenylethylamino)-5-hydroxytetralin (N-0434).[90] Recently, Van der Weide and his colleagues have prepared bioisosters of N-0434 by the replacement of the phenyl ring by an thienyl group.[91] Both possible isomers (N-0437 and N-0734) were prepared and evaluated with the parent compound in a variety of test systems used to study pre- and postsynaptic dopamine agonist properties. All three compounds proved to have potent D2 receptor agonist effects. 2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin (N-0437) had the greatest activity when given per os. This factor and its long duration of action suggests that N-0437 may be useful in the treatment of Parkinson's disease. The drug was effective in causing stereotyped behaviour in alphamethylparatyrosine-pretreated animals, however, the behaviour lasted a much shorter period of time. In addition, the 2-aminotetralins were less active than apomorphine in reversing reserpine-induced hypomotility in mice. Van der Weide and his colleagues[91] suggest that this relates to the absence of D1 agonist activity of this group of drugs in contrast to the mixed D1/D2 agonist effects of apomorphine.

B-HT 920

B-HT 920 or 6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]azepine is a potent alpha-2-adrenoceptor agonist which was found to have dopamine autoreceptor agonist effects.[92] Recently, Hinzen and his collegues[93] have published evidence that this chemically novel compound has potent agonist effects for "denervated" supersensitive postsynaptic dopamine receptors. These effects were seen in reserpine-pretreated mice (after a delay of 12 or more hours), 6-OH-dopamine lesioned rats and rhesus monkeys with severe MPTP-induced parkinsonism. In these latter animals B-HT 920 reversed severe akinesia more completely and with fewer side effects than L-dopa combined with benserazide. In naive rats B-HT 920 reduced exploratory activity and did not cause the stereotyped behaviour induced by apomorphine. This profile indicates that B-HT 920 is another agent with considerable potential for clinical application in the treatment of Parkinson's disease.

3-PPP

It was initially thought that 3-(3-hydroxyphenyl)-N,n-propylpiperidine (3-PPP) selectively stimulated dopamine autoreceptors in striatal and limbic regions.[94] Subsequent work[95-97] has revealed that the two enantiomers of 3-PPP interact with central dopamine receptors in different ways. (-)-3-PPP is an agonist at dopamine autoreceptors but acts as an antagonist at postsynaptic receptors. In low doses it decreases spontaneous activity while in high doses it also antagonizes the increase in locomotor activity which occurs after the administration of apomorphine. The (+) isomer is an agonist at the dopamine autoreceptor but also possesses agonist effects at normosensitive postsynaptic receptors. In low doses (+)-3-PPP causes suppression of locomotor activity while in high doses behavioural activation occurs. Interestingly, in the unilateral 6-hydroxydopamine-lesioned rat, a model commonly used to assess possible anti-parkinsonian effects of drugs, both enantiomeric forms cause contralateral rotation suggesting activation of denervated postsynaptic dopamine receptors.[98]

Recently, Nomoto, Jenner and Marsden[99] have investigated the potential antiparkinsonian effects of both (+)-3-PPP and (-)-3-PPP in the MPTP-treated marmoset. In both controls and MPTP-treated animals (-)-3-PPP caused a dose-dependent suppression of motor activity. In normal animals (+)-3-PPP resulted in suppression of motor activity at low doses but stimulation at higher doses (i.e. a biphasic effect). However, in the MPTP-treated animals (+)-3-PPP caused only a dose-dependent increase in locomotor activity which was greater than that seen in controls, suggesting a loss of the presynaptic agonist effects, possibly due to a loss of presynaptic receptors, or the development of postsynaptic receptor supersensitivity. These results suggest that (+)-3-PPP may be a useful agent in Parkinson's disease. However, it remains to be shown that oral administration is effective and the duration of action (locomotor activity was increased only for 60-90 minutes in MPTP-treated animals) may be too short to be of practical value in patients.

Conclusions

By no means has this been an exhaustive review of all new dopamine agonists which could be used in the treatment of Parkinson's disease in the next few years. The field continues to expand rapidly. I have chosen to highlight a number of compounds which have shown promising effects in preclinical or early clinical development. We are just beginning to see the application of the MPTP model of parkinsonism to early testing of dopamine agonists. It is hoped that this model will provide more accurate prediction of the effectiveness and side-effect profile of new drugs when used in the human disease.

In addition to the ongoing development of newer ergot derivatives there are now a number of novel non-ergot compounds with potent postsynaptic dopamine agonist properties. Some of these stimulate presynaptic dopamine autoreceptors and only have postsynaptic agonist properties when these receptors have become supersensitive secondary to denervation. Although this is probably the situation early in untreated Parkinson's disease, it is not necessarily so for the later L-dopa treated stages.[100] For this reason it is possible that these agents may be less effective in patients already taking L-dopa or another agonist. Early trials might better emphasize de novo patients to a greater extent than has been the case in the early development of previous agonists.

Longterm study of the clinical effects of L-dopa reveals an uneven decline in the response of various features of parkinsonism. Klawans[101] has reported recently that the progression of disability in patients over a period of 12.9 years did not involve all pretreatment parkinsonian features equally. While postural

reflexes, speech and gait deteriorated and showed poor response to L-dopa after 10 or more years of therapy, rigidity, tremor, handwriting and finger dexterity continued to respond in the majority of patients. This suggests a differential involvement of dopamine deficiency to the causation of the symptoms seen in late-stage L-dopa-treated patients. Although it is of great importance to know if newer dopamine agonists could improve some of these resistent late-stage problems, it must be considered that such patients, especially those without clear diurnal fluctuations, are probably not the best test-bed for the antiparkinsonian efficacy of newer medications.

We are entering a new era in the management of Parkinson's disease which will emphasize attempts to slow or halt the progression of the ongoing nigral cell loss.[102] Until this goal is achieved, further development of effective symptomatic therapies must be encouraged. It is the common experience of many investigators that patients may benefit from the addition of a new agonist having lost previous response to another or having failed to respond altogether. This applies both to ergot derivatives with slightly different chemical structures as well as to the newer non-ergot compounds with less basic structural similarities. Whether this phenomenon relates to some form of down-regulation or selective desensitization of the dopamine receptors to individual agonists remains to be determined. Whatever the mechanism, in practice this experience supports the need for the availability of several different dopamine agonists in the ongoing management of Parkinson's disease until more definitive therapy becomes possible.

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