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Blockade of glutamatergic transmission as treatment for dyskinesias and motor fluctuations in Parkinson's disease

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Summary. In animal models of Parkinson's disease (PD), glutamate antagonists diminish levodopa (LD)-associated motor fluctuations and dyskinesias. We sought to investigate if these preclinical observations can be extended to the human disease, by evaluating the effects of three non-competitive NMDA antagonists (dextrorphan, dextromethorphan and amantadine) on the motor response to LD in patients with advanced PD. In four separate trials, adjuvant therapy with these drugs reduced LD-induced dyskinesias and motor fluctuations. These findings support the view that drugs acting to inhibit glutamatergic transmission at the NMDA receptor can ameliorate LD associated motor response complications.

Keywords: NMDA antagonists – Motor response complications

Parkinson's disease (PD) is a neurodegenerative disorder clinically characterized by tremor, bradykinesia and rigidity. The pathological hallmark is degeneration of dopaminergic neurons in the substantia nigra of the midbrain that project to the striatum. As a consequence, there is marked striatal dopamine deficiency (Bernheimer et al., 1973). Dopamine replacement therapy via its precursor levodopa (LD) remains, thirty years after its introduction, the backbone of antiparkinson therapy. However, almost inevitably associated with its long-term administration are the well-recognized but incompletely understood changes in motor response to this drug, that collectively are called motor response complications (Marsden, 1994). The beneficial effects of individual LD doses become increasingly briefer and more unpredictable (wearing-off and on-off phenomena), rendering patients immobile ("off") more frequently and unexpectedly, whereas their periods of mobility ("on") become shorter and are often spoiled by disabling involuntary movements (dyskinesias). The realization that long-term LD therapy eventually falls short of the high expectations raised by its nearly complete symptom reversal early in the disease, has prompted exploration of new approaches targeting non-dopaminergic systems. In recent years, the glutamatergic system has emerged

as a prime candidate for such a strategy, based on evidence that glutamate is the major excitatory neurotransmitter in the basal ganglia and that glutamatergic pathways become hyperactive following dopaminergic denervation (Albin et al., 1989). In line with this concept is the reversal of parkinsonism in parkinsonian animals following chemical or surgical inactivation of glutamatergic neurons in the subthalamic nucleus (STN) or their efferents in the internal part of globus pallidus (GPI) (Bergman et al., 1990; Brotchie et al., 1991). Similarly, increased neuronal firing rates are found in GPI of parkinsonian patients undergoing pallidotomy and lesioning of this nucleus results in immediate improvement of their symptoms (Dogali et al., 1995; Laitinen et al., 1992). More recently, the pathogenesis of LD-associated motor response complications has been hypothetically linked to hyperfunction of glutamate receptors at the level of striatal medium spiny efferent neurons (Chase et al., 1996), possibly as a result of non-physiologic, pulsatile stimulation of co-expressed dopamine receptors.

In animal models of PD, behavioral studies of the effects of glutamate antagonists have led to mixed results. Given as monotherapy, most glutamate antagonists do not improve motor behavior, but when given as adjuvant therapy, the majority of studies report enhancement of the response to LD (Starr, 1995). Furthermore, in animal models of motor fluctuations and dyskinesias, blockade of the NMDA-subtype of glutamate receptors corrects the shortened duration of the motor response to LD that occurs as a consequence of chronic LD therapy (Engber et al., 1994; Papa et al., 1995), and reduces LD-induced dyskinesias (Papa and Chase, 1996). These intriguing findings have led us to evaluate several NMDA-antagonists as adjuvant therapy in LD-treated PD patients with motor complications.

Dextrorphan

In a preliminary pilot trial the motor effects of the non-competitive NMDA-antagonist dextrorphan hydrochloride (DX) (Wong et al., 1988) were evaluated in two advanced PD patients (Blanchet et al., 1996). Intravenous DX monotherapy (10–30 mg/hr) had no antiparkinsonian effects. When DX was co-administered with a previously determined dyskinetic LD dose, the antiparkinson response to LD remained intact, but dyskinesia scores were substantially lower than with placebo (Table 1).

Table 1. Motor effects of DX alone and with LD in patient A and B

Outcome measure	Baseline		DX alone		LD alone		DX + LD	
	A	B	A	B	A	B	A	B
Parkinson	19.5	17	18	22	7.5	5	6	5.5
Dyskinesia	0	0	0	0	3.5	1	0.5	0.5

Parkinson score: modified Columbia University Rating Scale (0–64) Dyskinesia score: modified Abnormal Involuntary Movement Scale (0–20) Co-administration of intravenous LD with intravenous DX led to lower dyskinesias while preserving the antiparkinson effect of LD (Blanchet et al., 1996).

Thus, this limited study suggested that the NMDA-antagonist DX is able to differentially modify the response to LD by reducing dyskinesias without worsening parkinsonian symptoms.

Dextromethorphan (DM)

The commonly used anti-tussive DM is the parent compound of DX and also has non-competitive NMDA-antagonistic properties (Wong et al., 1988). Genetically determined metabolic polymorphism results in "extensive" and "poor" DM metabolizers. We therefore co-administered quinidine, an inhibitor of the P450 enzyme system in the liver responsible for the O-demethylation of DM, turning all participants into poor metabolizers (Zhang et al., 1992).

DM study 1

Eighteen PD patients with LD-associated motor response complications underwent open label dose-escalation screening to determine if subjective benefit could be obtained from DM adjuvant therapy. In six a DM dose (60–120 mg/day) could be established that subjectively improved their overall condition, and they subsequently entered a double-blind, placebo-controlled, cross-over study. Twelve, however, did not meet accession criteria because they either experienced side-effects before any change in PD symptoms (50%), or reported decreased LD efficacy, resulting in prolonged "off" time, or LD dose failure. The cross-over study consisted of two arms of two weeks each, separated by a one-week wash-out. On the last day of each arm, patients were admitted to the hospital, and their motor symptoms and dyskinesias were scored every 20 minutes for an 8-hour period by a neurologist unaware of the study design. Their condition was also evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) part IV (Motor Response Complications, MRC), part II (Activities of Daily Living, ADL), and patient-diaries kept half-hourly, while awake, during the three preceding days, as well as on the day of the hospitalization at which time diary notes were supervised.

With the addition of DM, physician-rated dyskinesia scores during the 8-hour observation period in the hospital were 25% lower with DM than with placebo ($p < 0.05$), whereas parkinson scores remained unchanged (Table 2). According to the UPDRS, the proportion of the day dyskinesias were present decreased by 41%, dyskinesia severity by 59% and proportion of the day spent in the "off" state by 57% ($p < 0.05$). The variance of diary scores was 70% lower with DM, indicating improved motor fluctuations. ADL scores in the "on" and "off" state improved by 37% and 27%, respectively. Particularly, ADL subscores relating to axial symptoms such as turning in bed, walking and freezing improved significantly.

Several interesting observations can be made from the foregoing results. As with DX, chorea improved when patients were taking active drug. In addition, motor fluctuations improved; the improved "off" state, a condition characterized by suboptimal dopaminergic stimulation, could be explained by a synergistic effect between LD and DM, but also by an effect of DM of its

Table 2. Effects of dextromethorphan on motor function in 6 patients with advanced Parkinson's disease

		Placebo	DM
Parkinsonism	– physician-rated "off" scores[a]	23 ± 1.9	20 ± 1.8
	– physician-rated "on" scores[a,b]	7.8 ± 2.0	7.5 ± 1.7
Dyskinesias	– physician-rated dyskinesia scores[c]	4.6 ± 1.3	3.5 ± 1.0[d]
	– UPDRS part IV-item 32[e]	1.7 ± 0.2	1.0 ± 0.0[d]
	– UPDRS part IV-item 33[f]	1.7 ± 0.6	0.7 ± 0.3[g]
Motor fluctuations	– UPDRS part IV-item 39[h]	2.3 ± 0.3	1.0 ± 0.0[d]
	– Variance of patient-kept diaries	3.2 ± 0.5	1.1 ± 0.5[d]
Activities of daily living	– UPDRS part II[i] "on"	9.8 ± 2.5	6.2 ± 1.9[d]
	– UPDRS part II "off"	24 ± 2.1	18 ± 1.3[d]

UPDRS, Unified Parkinson's Disease Rating Scale. [a] Columbia University Rating Scale modified; [b] patient were considered "on" when parkinson scores showed > 50% improvement over baseline; [c] Abnormal Involuntary Movement Scale modified; [d] $p < 0.05$; [e] item 32: duration of dyskinesias (*0* none, *4* 76–100% of the waking day); [f] item 33: disability of dyskinesias (*0* not disabling, *4* completely disabling); [g] $p = 0.06$; [h] item 39: proportion of the day that patient is "off", scale 0–4 (*0* none, *4* 76–100% of the waking day); [i] scale: 0–52 (13 items: 0–4 score; *0* normal, *4* completely disabled).

own. The improvement in freezing, in some cases dramatic, is worth noticing. Whether this represents synergism during times of insufficient dopaminergic stimulation or perhaps indicates a non-dopaminergic basis for the freezing phenomenon cannot be determined.

No obvious reason, such as concomitant medications, was found for the discrepancy between the "responders" and the patients who did not respond. One can only speculate that DM has a very narrow therapeutic window that differs among parkinsonian individuals. In some the DM dose may have been insufficient for a motor effect while already causing side-effects. Even more intriguing is the fact that in some patients the response to LD appeared to be antagonized, sometimes at relatively low doses, reminiscent of reports in primate studies (Papa and Chase, 1996). It is possible that these patients were especially sensitive and that we should have given an even lower dose. In fact, one such individual was asked to return to participate in another study (see below) combining intravenous LD to oral DM; a lower dose of DM than previously administered clearly decreased dyskinesias compared with placebo. Another possible explanation for these interindividual differences could be that, despite the administration of quinidine, polymorphism of DM metabolism persisted, leading to different ratios of DM and its metabolites.

DM study 2

Six PD patients with LD associated motor response complications received DM or placebo for two or three weeks each, in a double blind, cross-over

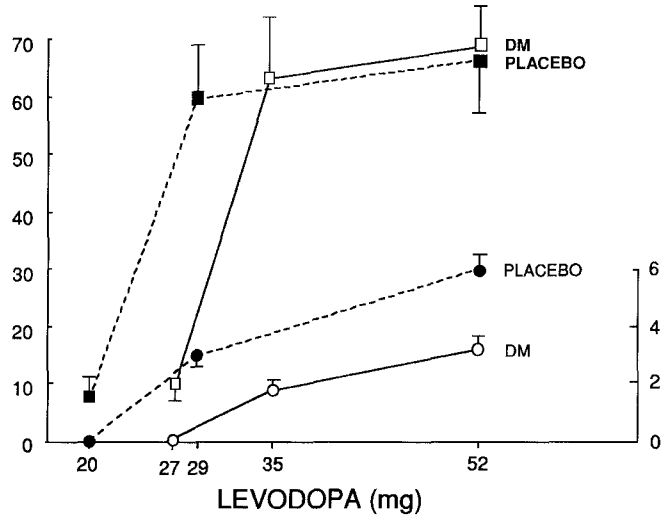

Fig. 1. Intravenous levodopa dose-response profiles with or without DM. Motor improvement (squares) was similar with DM (open symbols) and placebo (closed symbols). At the highest LD dose given, dyskinesia scores (circles) were 54% lower with DM than with placebo ($p < 0.05$). LD threshold dose (defined as the lowest LD dose inducing $\geq 25\%$ motor improvement) tended to be higher with DM but this did not reach statistical significance (Verhagen Metman et al., unpublished data)

design, in addition to their usual antiparkinson medications. At the end of each study arm patients were admitted to the hospital for intravenous levodopa dose-response studies. At the highest LD dose, maximum dyskinesia scores were 54% lower with DM than with placebo (Fig. 1). Average dyskinesia scores (mean of dyskinesia scores while patients had at least 25% motor improvement) improved by 60% with DM ($p < 0.05$). Maximum antiparkinson efficacy of LD was similar with DM or placebo.

Thus, DM ameliorated LD-induced dyskinesias without affecting the antiparkinson response.

Amantadine

This compound has traditionally been used as treatment for early PD. Recently, it was found to be a non-competitive NMDA-antagonist (Kornhuber et al., 1991). Safety and dose range are well established.

Eighteen patients with advanced PD complicated by motor fluctuations and dyskinesias received 300–400 mg amantadine or placebo for three weeks each, in a double blind, cross-over, random-access design. At the end of each study arm they received intravenous levodopa infusions at an individually determined optimal rate, defined as the lowest rate providing a maximal antiparkinson effect. After LD steady state conditions had been achieved, parkinsonian symptoms and dyskinesias were scored every 10 minutes for two hours. In addition UPDRS part II, IV, and patient-kept diaries were used to evaluate motor fluctuations.

Four subjects had to discontinue the study because of mild and transient side effects (two with confusion or hallucinations, 1 with nausea, 1 with recurrence of pre-existing palpitations). All remaining patients experienced significant benefit on subjective and objective measures. Dyskinesia rating scores were 60% lower with amantadine compared with placebo, whereas parkinson scores were similar (Fig. 2). Subjective measures of dyskinesia severity and duration, measured with UPDRS-IV, showed 65% improvement with amantadine. Motor fluctuations lessened, as indicated by 61% lower variance of diary scores, 44% decrease in daily "off" time and improved Activities of Daily Living (UPDRS-II) in "off" and "on" states. In the "off" state, axial motor activities such as walking, freezing and turning in bed, appeared to improve more so than fine motor skills.

In summary, amantadine substantially ameliorated dyskinesias without worsening parkisonian symptoms when the patients were treated with steady state, optimal rate, intravenous LD infusion. In addition, when patients were at home taking oral LD, amantadine reduced "off" states both in duration and severity. In contrast to our findings with DM, the effects of amantadine were similar in all subjects. None reported decreased LD efficacy and some were able to decrease their LD intake.

Conclusion

These pharmacological studies have, broadly, two factors in common: 1) they involve NMDA-antagonists as adjuvant therapy to LD, and 2) they show a palliative effect on LD-asssociated motor response complications. These findings support the hypothesis, based on similar results in animal models of PD, that glutamatergic hyperfunction in the basal ganglia contributes to the pathogenesis of motor response complications.

On the other hand, intriguing differences exist with respect to the homogeneity of the data. With amantadine, all patients able to tolerate the

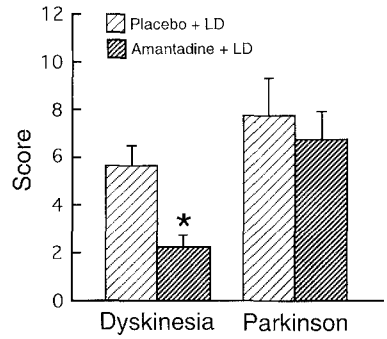

Fig. 2. The effects of amantadine on parkinsonian symptoms and dyskinesias during intravenous LD infusions at steady state. Dyskinesias were 60% lower with amantadine than with placebo, whereas parkinson scores were unaffected (Verhagen Metman et al., unpublished data)

drug experienced motor improvement, whereas with DM only one third of subjects benefitted and one third actually experienced worsening of their response to LD. In addition, the effect size was smaller with DM than with amantadine. Such differences between the two drugs may be related to their respective affinities and/or dissociation kinetics for the NMDA receptor. Although both are considered low-affinity NMDA antagonists, amantadine has the highest Ki value and is thus considered to have the lowest affinity for the NMDA receptor. Associated with low-affinity are strong voltage dependence and rapid binding kinetics. As a consequence, amantadine should exhibit the most rapid clearance from the NMDA receptor channel under physiological activation. In addition, either drug may be preferentially active at certain subtypes of NMDA receptors, or at receptor subunits with specificity for certain brain regions (Bresink et al., 1995). Alternatively, differences in efficacy profile may occur as a result of additional actions at non-NMDA binding sites. For instance, amantadine, DM and DX all bind to sigma receptors, again with varying affinities (Kornhuber et al., 1993; Tortella et al., 1988). Although little is known about their exact role in basal ganglionic function, sigma receptors have been proposed to modulate NMDA-receptors (Debonnel and de Montigny, 1996), implying an indirect effect on glutamatergic transmission. Thus, pharmacodynamic properties may explain differences in effect size and, at least in part, may have led to the contradictory findings in the DM study; if the effect size in some patients was too small to be noticed, the DM dose may have been increased to levels causing excessive NMDA receptor blockade leading to disruption of motor function and dystonia (Papa and Chase, 1996; Rupniak et al., 1992). The more evident effects of amantadine at tolerated doses prevented the need for dose escalation above 400 mg. Recent studies in MPTP-intoxicated non-human primates, however, suggest that the anti-dyskinetic effect of increasing doses of amantadine is associated with a gradual decrease in LD efficacy (Blanchet et al., submitted). Achievement of a delicate balance between LD therapy and NMDA receptor blockade is required to obtain optimal results with this promising approach against LD induced motor response complications. Development of more selective NMDA antagonists for NMDA-receptor subtypes most prevalent in the basal ganglia may improve the efficacy and therapeutic index of such agents in the treatment of advanced Parkinson's disease.

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