Amantadine for the Treatment of Parkinson’s Disease and its Associated Dyskinesias

Keywords: Parkinson’s disease; Amantadine; Dyskinesia; Nigrostriatal; Corticospinal; NMDA; RCT; Meta-analysis; Systematic review; Adverse events

Abstract
Disturbances of motor function characteristic of Parkinson’s Disease (PD) are commonly treated with L-Dopa. However, prolonged treatment commonly results in L-Dopa-Induced Dyskinesias (LIDs) with high negative impact on patient’s quality of life that seriously limits the use of L-Dopa. Amantadine, like L-Dopa, is effective for the replenishment of defective dopamine production in PD by mechanisms involving increased synthesis and decreased synaptic reuptake with consequent improvements of the patient’s motor symptoms. Results of RCTs and meta-analyses continue to support the claim that amantadine is effective for the treatment of early or stable PD. Preclinical and clinical studies reveal that LIDs result from inactivation and cocarboxylation (glutamatergic) and nigrostriatal (dopaminergic) connectivity resulting from the relative over-activation of NMDA receptors, a phenomenon shown to occur in patients with LIDs using Positron Emission Tomography. In addition to its beneficial actions in restoring dopaminergic function, amantadine is a potent non-competitive NMDA receptor antagonist and, as such, offers a potentially effective agent for the treatment for LIDs. Indeed, beneficial effects of amantadine for the treatment of LIDs have been described in multiple Randomized Controlled Trials (RCTs) using a range of well-established dyskinesia rating scales over the last two decades and extended-release formulations of amantadine have also been found to be effective. Confirmation of clinical efficacy of amantadine for the treatment of LIDs has been complemented by the results of systematic reviews and meta-analyses that include a Movement Disease Society (MDS)-commissioned evidence-based update of treatment options. The efficacy of amantadine for the treatment of LIDs using Positron Emission Tomography. Moreover, iv administration of the NMDA receptor antagonist MK 801 significantly attenuated the enhancement of NMDA receptor activation and the release of dopamine in striatum was demonstrated directly in experimental animals using the technique of in vivo cerebral micro-dialysis in which perfusion of amantadine (0.1-1 mM) via the micro-dialysis probe resulted in increases in Ca++ dependent release of dopamine. Moreover, iv administration of the NMDA receptor antagonist MK 801 significantly attenuated the amantadine-induced increase in striatal dopamine release [5]. These findings support the concept of an interaction between dopaminergic and glutamatergic transmission in the regulation of striatal dopamine release (Figure 1).

Mechanisms of action of amantadine in the treatment of the motor symptoms of PD

PD is an age-related neurodegenerative disease characterized by progressive degeneration of dopaminergic neurons. The neurodegenerative process in PD is characterized by a loss of dopamine-secreting cells in the substantia nigra. The most-widely employed treatment for PD is L-Dopa, the metabolic precursor for dopamine; the transformation from L-Dopa to dopamine is catalyzed by the enzyme L-Dopa Decarboxylase (DDC) located in the presynaptic nerve terminal (Figure 1). L-Dopa serves to replenish the precursor pool leading to increased dopamine synthesis.

Amantadine and the dopamine system: Amantadine, like L-Dopa, is also able to prevent the reduction of dopaminergic synaptic activity in PD and this, via multiple putative mechanisms. Studies in a range of in vitro synaptic preparations reveal that amantadine has the potential to increase dopamine synthesis, turnover and release and similar actions have been reported in vivo [2-5]. An additional proposed mechanism involves the direct inhibition of dopamine-reuptake by amantadine that has been demonstrated in both in vitro preparations [6] and in vivo [3].

Anti-Parkinson activity of amantadine: Role of glutamate (NMDA) receptors: The potential for amantadine to increase dopamine synthesis from L-Dopa has been attributed, at least in part, to the drug’s effect as an antagonist of NMDA receptors [7]. Support of the novel concept of a dynamic functional interaction between NMDA receptor activation and the release of dopamine in striatum was demonstrated directly in experimental animals using the technique of in vivo cerebral micro-dialysis in which perfusion of amantadine (0.1-1 mM) via the micro-dialysis probe resulted in increases in Ca++ dependent release of dopamine. Moreover, iv administration of the NMDA receptor antagonist MK 801 significantly attenuated the amantadine-induced increase in striatal dopamine release [5]. These findings support the concept of an interaction between dopaminergic and glutamatergic transmission in the regulation of striatal dopamine release (Figure 1).
occurs as the result of NMDA receptor antagonism by amantadine to the human condition made use of the technique of Positron Emission Tomography (PET) and the ligand 6-[18F]-Fluoro-L-Dopa [7]. The study involved the measurement of radioactivity in brains of normal human volunteers following iv administration of the 18F PET ligand under baseline conditions and again following three consecutive days of treatment with amantadine (100 mg/d po). Data from several brain regions of interest were obtained and coefficients of in situ 18F-L-Dopa decarboxylation were calculated. Amantadine treatment resulted in significant 12%, 28% and 27% increases in caudate nucleus, putamen and ventral striatum respectively. These findings are consistent with stimulation of DDC activity in striatum of healthy human brain secondary to NMDA receptor antagonism by amantadine.

Other proposed mechanisms: Serotonin (5HT) neurons express the genetic and metabolic machinery necessary for dopamine synthesis and synaptic release. Chronoamperometric studies in rodent models of PD suggest a central role for the 5HT system in L-Dopa-derived dopamine synthesis and the potential for L-Dopa-induced deterioration of 5HT function to reduce the clinical efficacy of L-Dopa to promote motor side effects [8]. Additionally, based on studies in primary cultures of dopaminergic neurons, microglia and astroglia, it has been suggested that clinically-relevant concentrations of amantadine have the potential to manifest neuroprotective properties resulting from a dual mechanism of action involving a reduction in release of proinflammatory factors from activated microglia together with increased expression of the neurotrophic factor GDNF [9].

Evidence for the efficacy of amantadine for treatment of motor symptoms of PD

Evidence from systematic reviews and meta-analyses: A Cochrane Review of RCTs [10] selected 6 trials that compared amantadine to placebo with or without L-Dopa or anticholinergic drugs. The studies included 215 patients treated for periods of from 6 to 64 weeks and amantadine doses of 100-200 mg/day. Exclusion criteria included patients with non-idiopathic forms of PD, patients who had previously undergone stereotactic surgery as well as uncontrolled or non-randomized trials. Unfortunately, methodological limitations together with potential sources of bias meant that it was not possible to draw firm conclusions regarding the efficacy or safety of amantadine for the treatment of idiopathic PD.

On the other hand, the MDS published an evidence-based report of 7 studies on amantadine monotherapy and 14 studies on the efficacy of amantadine as an adjunct therapy to anticholinergics or L-Dopa concluded that amantadine was likely to be efficacious at controlling PD symptoms [11]. The MDS subsequently commissioned a review by way of update on treatments for the motor symptoms of PD that covered the findings from trials published in the period ending 31 December 2016 [12]. They concluded that amantadine was likely efficacious and clinically useful as symptomatic monotherapy as well as symptomatic adjunct therapy in early or stable PD. However, there was insufficient evidence for the effective treatment of motor fluctuations.

More recently and as part of a systematic review with meta-analysis of the efficacy of amantadine for the treatment of the motor symptoms of PD, electronic searches of Medline, PubMed, Cochrane Library and other databases up to May 2016 were performed using appropriate keywords yielding 9 placebo-controlled RCT’s and 303 patients. Results demonstrated that amantadine was of significant benefit for improvement of PD motor symptoms as assessed by UPDRS III scores even at advanced stages of the disorder with [MD: -0.29 (95% CI: -0.53, -0.06) Z= 2.49, p=0.01]. Details relating to the efficacy of independent trials are shown in the Forest Plot [13] (Figure 2).

Amantadine for the treatment of motor fluctuations in PD: The effect of amantadine on motor fluctuations was investigated in advanced PD [14]. Amantadine significantly lessened the severity of motor fluctuations; diary scores were lower with amantadine versus placebo (n=9; mean, 1.03 ± 0.12 vs 1.62 ± 0.16, p<0.01; variance, 1.3 ± 1.62 ± 0.16, p<0.01; variance, 1.3 ± 1.62 ± 0.16, p<0.01; variance, 1.3 ± 
0.3 vs 3.3 ± 0.5, p<0.01) and the duration of daily ‘OFF’ time declined while on amantadine (n=14; UPDRS IV item 39, 1 [0-2] vs 1.5 [1-3]; p<0.001). Activities of daily living while ‘ON’ and ‘OFF’ (UPDRS II) were also improved with amantadine. The effect of amantadine on motor fluctuations in PD patients was also investigated in an open-label infusion study [15]. Based on patients’ diary notes, there was a reduction of 38% in the mean duration of ‘OFF’ times during amantadine infusion and improvement of 53% (p<0.001).

Freezing of gait (FOG) is one of the most disturbing symptoms in advanced PD as well as in some atypical PD syndromes. FOG is often refractory to dopaminergic drugs [16]. There is evidence for the therapeutic use of amantadine for FOG in two RCTs [17, 18].

Akinetic crises such as acute akinesia, neuroleptic malignant and neuroleptic malignant-like syndrome, and Parkinsonism-hyperpyrexia syndrome can be successfully treated by acute administration of amantadine [19].

Amanadine has been reported to be of benefit in patients with progressive supranuclear palsy (PSP) [20], and in 14 patients with cortico-basal degeneration [21]. Reports on the open-label use of amantadine in multiple system atrophy (MSA) suggest variable anti-parkinsonian efficacy [22].

**Amantadine for the Treatment of L-Dopa-Induced Dyskinesias (LIDs) in PD**

Dyskinesias occur in up to 90% of patients with PD treated with L-Dopa for ten years or more. Such dyskinesias manifest as increased spontaneous motricity in the form of hyperkinesias occurring at high plasma levels of L-Dopa and are also known as ‘peak-dose dyskinesias’. Amantadine has been successfully employed in the
management of this type of LID.

Mechanisms of action of amantadine in the treatment of LIDs in PD

LIDs are generally considered to result from biochemical mechanisms in striatal neurons that result from rapidly-changing exposure to dopamine [23]. More recent investigations provide convincing evidence that these changes in the dopamine system are, in large part, the result of alterations in corticostriatal connectivity through changes in functional activity of NMDA receptors. Thus, as depicted in Figure 1, the corticostriatal (glutamatergic) and nigrostriatal (dopaminergic) input stimuli converge at the striatum where they have a key modulating influence on neuronal activity and consequently on motor control. Using the technique of PET and the ligand 11C-N-methyl-3-(thiomethylphenyl)-cyamamide, a marker of activated NMDA receptor channels, glutamatergic function in patients with PD with and without LIDs were compared [24]. Patients were assessed twice; after taking L-Dopa and again after withdrawal from it. Striatal uptake of tracer was calculated. Tracer uptake measured in the ‘ON’ condition following L-Dopa was higher in dyskinetic patients compared to patients without dyskinesia. These findings were consistent with those previously observed in animal studies and suggest that increased glutamatergic synaptic activity is implicated in the pathogenesis of LIDs. Amantadine is a non-competitive antagonist of the NMDA receptor [25]. Consequently, blockade of NMDA receptors by amantadine has the potential to provide an approach to the control of LIDs in PD.

Efficacy of amantadine for the treatment of LIDs; results of systematic reviews and meta-analyses

Electronic searches of The Cochrane Controlled Trials Register issue 3 (2001), Medline (1966-2001), Embase (1974-2001), Clinicaltrials.gov (2001) and other databases as well as manual searches of reference lists from selected studies/reviews were examined in order to select RCTs comparing amantadine with placebo for the treatment of dyskinesias in patients with a clinical diagnosis of idiopathic PD. Three RCTs satisfied search criteria and were double-blind crossover trials for a total of 53 patients. Regrettably, as a result of inadequate trial quality, missing data, lack of washout interval or dystonia but decreased the duration of LIDs and its influence on motor control. Using the technique of PET and the ligand 11C-N-methyl-3-(thiomethylphenyl)-cyamamide, a marker of activated NMDA receptor channels, glutamatergic function in patients with PD with and without LIDs were compared [24]. Patients were assessed twice; after taking L-Dopa and again after withdrawal from it. Striatal uptake of tracer was calculated. Tracer uptake measured in the ‘ON’ condition following L-Dopa was higher in dyskinetic patients compared to patients without dyskinesia. These findings were consistent with those previously observed in animal studies and suggest that increased glutamatergic synaptic activity is implicated in the pathogenesis of LIDs. Amantadine is a non-competitive antagonist of the NMDA receptor [25]. Consequently, blockade of NMDA receptors by amantadine has the potential to provide an approach to the control of LIDs in PD.

Efficacy of amantadine for the treatment of LIDs; results of individual RCTs

Benefits of oral or intravenous formulations of amantadine have been evaluated in patients with PD and LIDs in 10 RCTs the key elements of which are summarized as follows:

Savada et al. [2010]: In a 27-day trial carried out in 36 patients with PD and LIDs, amantadine treatment (300 mg/d) was associated with a significant improvement of 64% in the Rush Dyskinesia Rating Scale versus 16% of placebo patients. The adjusted odds ratio for improvement by amantadine was 6.7 (95% Confidence Interval [CI], 1.4-31.5, p<0.016). UPDRS IVa, dyskinesia improved to an even greater degree following amantadine treatment [27].

Wolf et al. [2010]: The long-term anti-dyskinetic effect of amantadine was evaluated in 32 patients with PD who were receiving L-Dopa and who had been on stable amantadine therapy for at least 1 year [30]. In patients who had been switched to placebo at the 3-week follow-up, there was a significant increase in dyskinesias, as measured with UPDRS item 32-33, but there was no significant change between baseline and follow-up in patients who had continued on amantadine.

Da Silva Junior et al. [2005]: The effects of amantadine on LIDs were assessed in 18 consecutive PD patients in an RCT [31]. The primary outcomes were improvements in CDRS and UPDRS IVa scores. Secondary outcomes were improvements in UPDRS II and III scores. Amantadine did not change the CDRS score for hyperkinesia or dystonia but decreased the duration of LIDs and its influence on daily activities (p=0.04) and UPDRS II score (p=0.01) more than placebo. These findings show that amantadine reduces the duration of LIDs and improves motor disability in PD.

Thomas et al. [2004]: A trial of amantadine was conducted in 14 PD patients treated with L-Dopa for 7.5 ± 2.2 yrs with motor fluctuations and dyskinesias evaluated by UPDRS IV and blinded videotape-based ratings using DRS. After 15 days of amantadine treatment, total dyskinesia scores decreased by 45%, and there was a reduction in UPDRS IV item 32-34 scores compared with baseline and placebo (p<0.001). The mean positive duration of the effect in reducing dyskinesia was 4.9 months for amantadine versus 1.3 months for placebo (p<0.001) [32].

Del Dotto et al. [2001]: Nine patients with PD and severe peak-
dose dyskinesias received L-DOPA followed by amantadine (200 mg iv) or placebo and were assessed by UPDRS, motor exam & AIMS. Amantadine improved dyskinesias by 50% with no loss of benefit for the motor symptoms of PD [33].

**Luginer et al. [2000]:** A 5-week, crossover trial examined the effect of amantadine on LIDs. Ten of 11 patients completed the study. Dyskinesia severity, following oral L-Dopa challenges, was significantly reduced by 52% after amantadine treatment (baseline score 14.5 ± 9.4 vs post-treatment score 7.0 ± 8.2; p<0.05) but not placebo (baseline score 16.6 ± 11.4 vs post-placebo score 15.5 ± 12.1; p>0.05). Similarly, amantadine was associated with a significant reduction of 53% in the cumulative dyskinesia score in self-scoring dyskinesia diaries (post-amantadine treatment period 11.9 ± 11.4 vs post-placebo period 25.6 ± 16.7; p<0.05). Dyskinesia duration and dyskinesia disability, as measured by UPDRS IV items 32-33, were also significantly reduced by amantadine (baseline score 3.4 ± 0.3 vs post-treatment score 1.7 ± 0.5; p<0.05) [34].

**Snow et al. [2000]:** A trial examined the effect of amantadine on LIDs in 22 patients with PD. Patients were treated with amantadine (up to 200 mg/d for 3 weeks) in addition to other antiparkinsonian medications. Dyskinesias were evaluated following an oral L-Dopa challenge. Amantadine treatment significantly reduced the total dyskinesia score by 24%; this was also reflected in the subjects’ perception that dyskinesias, measured by UPDRS III and IV, were reduced [35].

**Verhagen Metman et al. [1998]:** A trial evaluated amantadine for treatment of dyskinesias in 18 patients with advanced PD. Patients, who had already been treated with L-Dopa for a mean period of 12 years, were given amantadine (up to 400 mg/day) or placebo for 3 weeks. Signs and symptoms of PD and dyskinesias were recorded at the end of the 3-week treatment period during intravenous L-Dopa infusions over 7 h under steady-state conditions. Amantadine reduced dyskinesia severity by 60% (p=0.0001) compared to placebo in completers and this was not accompanied by aggravation of the signs and symptoms of PD [36]. Beneficial effects of amantadine on motor response complications were maintained in a 1-year follow-up study in which a 56% reduction in dyskinesia was noted with amantadine versus 60% in the initial study. Motor symptoms associated with L-Dopa were still improved [14].

**Goetz et al. [2013]:** Assessment of the effects of treatment of patients with PD and dyskinesia with amantadine (up to 300mg/d for 8 weeks) versus placebo were made by comparing the sensitivity to treatment effects at 4 and 8 weeks using 8 different dyskinesia rating scales. Four of the eight scales (UDysR, Lang-Fahn, PDys-26 and CGI-C) demonstrated a significant improvement in dyskinesia after 8 weeks treatment with amantadine vs placebo [28].

**Ory-Magne et al. [2014]:** The AMANDYSK trial was a 3-month, multicenter, parallel group/wash out in single line RCT in patients with PD. Fifty-seven dyskinetic patients who had received amantadine at a dosage of 200 mg/d for ≥6 months were included in the study. Washout of oral amantadine significantly worsened LIDs where UPDRS IV item 32-33 deteriorated more in patients who switched to placebo (‘discontinuing’ group; +1.7 ± 2.0 units; 95% CI: 0.9-2.4) compared with those maintained on amantadine (‘continuing’ group; +0.2 ± 1.5 units; 95% CI: -0.4 to 0.8; p=0.003).

Amantadine treatment of PD during the COVID-19 pandemic

PD and COVID-19 share multiple common features including age-dependency of disease severity and an association with co-morbidities such as diabetes, respiratory problems and cardiovascular disorders. Concerns have been raised regarding the potential effects of COVID-19 on PD severity and, conversely, on the effects of PD on immune status that could impact disease outcome in COVID-19. Symptoms of PD are known to deteriorate during systemic infections and diagnostic features of COVID-19 such as fever, fatigue and stress are known to not only aggravate tremor, gait disturbances and dyskinesias in PD but may also compromise the efficacy of L-Dopa [40].

Concerns on the likelihood of interactions between COVID-19 and PD with the potential to result in the clinical worsening of both conditions described above may be mitigated once treatment with amantadine is initiated. Recent investigations provide convincing evidence for significant benefit of amantadine for the treatment of COVID-19 per se. Two independent mechanisms have been proposed namely 1. The down-regulation of expression of host-cell proteases leading to impaired release of the viral genome into the host-cell cytoplasm and 2. Activation of NMDA receptors has been implicated in the pathogenesis of the acute respiratory failure characteristic of COVID-19 [41]. The pertinence of these mechanisms of action of amantadine in relation to the management of COVID-19 in patients with PD is worthy of further investigations in future research.
Adverse Events (AEs) associated with amantadine treatment for LIDs in PD

AEs listed in the present review are largely taken from data provided in the reports of meta-analyses, systematic reviews and individual RCTs described in the text and relate to AEs using therapeutically-relevant concentrations of amantadine. Common AEs included visual hallucinations, confusion, blurred vision, foot edema and constipation. Behavioral symptoms characteristic of impulse control disorders including pathological gambling, hypersexuality and compulsive spending/eating have been described. Other AEs include laryngitis, nausea, dry mouth, dizziness and somnolence, peripheral edema, anxiety and depression [13,29,30,35,36]. Similar AEs for the extended-release formulations of amantadine in the treatment of LIDs in PD have been reported [37,38].

Conclusions

Amantadine is effective for the replenishment of defective synaptic DA turnover by mechanisms involving both increased synthesis and decreased release of the transmitter with consequent improvements of motor control in PD patients. LIDs in such patients, on the other hand, appear to be the consequence of modifications of both corticostriatal (glutamatergic) and nigrostriatal (dopaminergic) neurotransmitter systems leading to impaired striatal connectivity resulting from the relative over-activation of the NMDA subclass of glutamate receptors. Being an effective non-competitive NMDA antagonist, amantadine affords a potentially-effective agent for the treatment of LIDs. The functional interplay between glutamatergic and dopaminergic systems in striatum and beneficial effects of amantadine have been demonstrated using PET and the ligand 6-[F18]-Fluoro-L-Dopa in human brain.

Evidence in support of the efficacy of amantadine for the treatment of PD and its associated dyskinesias has been forthcoming in the form of numerous RCTs, systematic reviews and meta-analyses. The MDS published an updated evidence-based report of clinical trials in which amantadine monotherapy was effective for the control of the motor symptoms of PD and, more recently, a systematic review with meta-analysis confirmed that amantadine was of significant benefit for improvement of motor symptoms assessed by UPDRS even at advanced stages of the disorder. There is evidence to support the notion that amantadine may also be beneficial for the control of motor fluctuations in PD such as ON and OFF times as well as FOG including impulse control disorders such as pathological gambling, hypersexuality and compulsive spending/eating. Adverse Events (AEs) associated with amantadine are largely taken from data provided in the reports of meta-analyses, systematic reviews and individual RCTs described in the text and relate to AEs using therapeutically-relevant concentrations of amantadine. Common AEs included visual hallucinations, confusion, blurred vision, foot edema and constipation. Behavioral symptoms characteristic of impulse control disorders including pathological gambling, hypersexuality and compulsive spending/eating have been described. Other AEs include laryngitis, nausea, dry mouth, dizziness and somnolence, peripheral edema, anxiety and depression [13,29,30,35,36]. Similar AEs for the extended-release formulations of amantadine in the treatment of LIDs in PD have been reported [37,38].

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