

The Use of Amantadine in Parkinson's Disease and other Akinetic-Rigid Disorders

Introduction

Amantadine was originally introduced as an antiviral agent to treat influenza A and was coincidentally found to ameliorate symptoms in a patient with Parkinson's Disease (PD) in 1969.¹ Since that time many clinical trials have investigated the efficacy of amantadine alone and in combination with other antiparkinsonian drugs. Most of these trials took place in the early 1970s. More recently, the use of amantadine has focused upon the treatment of levodopa-induced motor fluctuations and dyskinesias.

This article will summarise the evidence available for the use of amantadine in PD and other movement disorders.

Mechanism of action

Amantadine hydrochloride is a tricyclic amine that is well absorbed orally and is excreted largely unchanged in the urine. It has several proposed mechanisms of action.

- It acts on the pre-synaptic membrane, enhancing the release of dopamine and inhibiting its reuptake.² In vitro, however, the latter effect occurs only with high doses and is therefore thought to be unlikely to contribute to its clinical efficacy.³
- Post-synaptically, amantadine acts directly on the dopamine receptor, and up regulates D2 receptors in vivo.⁴ This may be due to amantadine-induced hypersensitivity of dopamine receptors, which has been demonstrated in rats, although the effects were only transient.⁵
- It has antimuscarinic properties.⁶
- Amantadine has antiglutamatergic properties, via non-competitive antagonism of NMDA receptors.⁷ In 6-hydroxydopamine lesioned rats, systemic and intrastriatal injection of a NMDA antagonist can reverse or prevent the changes in motor response that occur with sustained levodopa treatment.⁸ Furthermore, potent, competitive, non-subunit selective NMDA receptor antagonists reduce the severity of levodopa-induced dyskinesias in non-human pri-

mates with MPTP parkinsonism.^{9,10} These and other observations suggest that NMDA receptor sensitisation may be a key event in the genesis of levodopa-induced dyskinesias.

- Amantadine may have immunomodulatory properties. It restored the production of interleukin-2 (IL-2), which is defective in PD patients.¹¹ IL-2 levels did not correspond to clinical improvement so the significance of these findings is uncertain.
- One study has shown that amantadine was an independent predictor of improved survival in PD.¹²

Symptomatic control of Parkinson's disease

Although many trials have assessed the efficacy of amantadine versus placebo for the treatment of motor impairment in PD, the majority were undertaken in the 1970s and suffer from poor methodology or small patient numbers. A Cochrane review in 2002 described six randomised controlled trials that used amantadine as either mono- or adjunctive therapy in PD. Although all reported beneficial effects for amantadine, it was concluded that the evidence available was insufficient to draw any firm conclusions.

Monotherapy

Initial open label or unblinded studies did not show any consistent results and are difficult to analyse.^{13,14} Randomised, double-blind crossover trials are summarised in Table 1. Most trials showed mild beneficial effects of amantadine but follow up periods were too short to comment on long term effects of the drug.

Adjuvant therapy

Amantadine has been trialled in PD as adjuvant therapy to levodopa and anticholinergics. As with monotherapy, poor methodology limits the interpretation of the results, but some of the more robust trials are summarised in Table 2.



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Table 1: Monotherapy randomised, double-blind crossover trials

Author/Date	Type of trial	Number of PD patients in trial	Intervention	Outcome	Comments
Mawdsley C et al 1975 ¹⁵	Double-blind crossover (4 weeks)	42	Amantadine v placebo	Initial Improvements not maintained at 4 weeks	Some patients had non-idiopathic PD. Patients allowed to chose which drug to continue
Fahn S et al 1975 ¹⁶	Double-blind crossover (4 weeks)	23	Amantadine v placebo	70% improvement in patients on amantadine	Did not present data from placebo arm
Butzer JF et al 1975 ¹⁷	Double-blind crossover (4 weeks)	30	Amantadine v placebo	12% improvement	Some patients had non-idiopathic PD. 3 patients also on anticholinergic treatment
Cox B et al 1973 ¹⁸	Double-blind crossover (6 weeks)	27	Amantadine v levodopa	No improvement in amantadine group	Some improvement when amantadine used in second arm
Parks JD et al 1974 ¹⁹	Double-blind crossover (8 weeks)	15	Amantadine v benzhexol v amantadine + benzhexol	15% improvement in symptoms and not separated for each drug alone, 40% with combined treatment	Some non-idiopathic PD were included in analyses

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Table 2: Amantadine as adjuvant therapy. ADL – Activities of daily living

Author/Date	Type of trial	Number of patients in trial	Intervention	Outcome	Comment
Bauer RB et al, 1974 ²⁰	Randomised double-blind crossover (6 weeks)	48	Amantadine v placebo in patients taking anticholinergics	Improvement in timed tests in 10% of patients	Included some patients with non-idiopathic PD
Jorgensen PB et al, 1971 ²¹	Randomised double-blind crossover (3 weeks)	149	Amantadine v placebo in patients taking anticholinergics	Functional improvement in 56% patients. Most benefit in most severely affected patients	Included some patients with non-idiopathic PD
Rinne UK et al, 1972 ²²	Double-blind, non-randomised crossover (4 weeks)	38	Amantadine v placebo in patients taking anticholinergics	60% showed improvement in disability and parkinsonism	Included some patients with non-idiopathic PD
Barbeau A et al, 1971 ²³	Randomised double-blind crossover (8 weeks)	54	Amantadine v placebo in patients taking anticholinergics	Significant improvement in disability and impairment	Included some patients who had undergone stereotactic brain surgery
Forssman B et al, 1972 ²⁴	Randomised double-blind crossover	27	Amantadine v placebo in patients taking anticholinergics	Significant improvement in parkinsonism and functional status	Included some patients who had undergone stereotactic brain surgery
Walker JE et al, 1972 ²⁵	Randomised double-blind crossover (6 weeks)	42	Amantadine v placebo. Anticholinergics were stopped in all but 6 patients	64% v 21% improvement in ADLs, but of little statistical significance	No withdrawals
Silver DE et al, 1971 ²⁶	Randomised double-blind parallel (mean 35 weeks)	50	Amantadine v placebo in patients taking their usual medication (mostly anticholinergics)	Improvement in parkinsonism peaking at 2-3 months	Gradual tapering of effect, but maintained up to 7 months
Fehling C et al, 1973 ²⁷	Randomised double-blind crossover (2 months)	30	Amantadine v placebo in patients continuing with other therapy (levodopa and anticholinergics)	Significant improvement in PD scores, marginal improvement in functional ability	9 patients withdrew
Savery F et al, 1977 ²⁸	Randomised double-blind crossover (18 weeks)	42	Amantadine v placebo in patients taking levodopa	Improvement in all but 2 patients, in symptoms and functional activities	
Millac P et al, 1970 ²⁸	Double-blind, non-randomised parallel (3 months)	32	Amantadine v placebo in patients then started on levodopa	No significant difference in symptoms or examination and no difference in dose of levodopa needed	Included some patients with non-idiopathic PD
Callaghan N et al, 1974 ²⁹	Open label	31	Amantadine v levodopa v both	Levodopa treatment superior + no benefit when amantadine added	Included some patients with non-idiopathic PD
Muller T et al, 2003 ³⁰	Open label (4 days)	31	Intravenous amantadine in patients on pre-existing PD therapies	Improvements in motor symptoms and peg insertion but not hand tapping	No control group

The lack of high quality clinical trials limits conclusions which can be drawn as to the efficacy of amantadine in improving motor symptoms of PD. Variable results are seen when amantadine is used in addition to levodopa although there appears to be some benefits when added to anticholinergic therapies. The studies were all very short and there was some suggestion of tachyphylaxis occurring over longer treatment duration. Interestingly, in one trial those patients with most severe disease seemed to derive the greatest benefit.²¹

In our practice we rarely use amantadine as monotherapy, but occasionally find it useful as adjunct therapy to dopamine agonists to delay the need to start levodopa.

Amantadine to treat dyskinesias in Parkinson’s disease

In 1998, a double-blind placebo-controlled crossover study (3 weeks each arm) found amantadine reduced dyskinesia severity, induced by intravenous levodopa, by 60% without altering the antiparkinsonian effect of levodopa.³¹ Eighteen patients were included in the trial and four withdrew due to side effects, notably confusion and hallucinations. In a follow up study one year later the anti-dyskinetic effect of amantadine was maintained (56%),³² although this study was of an unusual design and patient numbers were small. Two further double-blind placebo controlled crossover studies included 24 and 11 patients and reported reductions in dyskinesias of 24%³³ and 50%³⁴ respectively with oral amantadine. A total of three patients withdrew from these studies. Only one of the three studies included a wash out period between treatment arms³⁴ so the potential for a carry over effect exists. An open label study of 21 PD patients with no control group found intravenous amantadine followed by oral treatment reduced dyskinesias from 2.5 to 1.3 hours per day.³⁵ In another open label study of 26 patients amantadine improved dyskinesias by approximately 70% at 3 weeks.³⁶ This beneficial effect was maintained over an average follow up period of 6.5 months. Intravenous amantadine given on two consecutive days also improved dyskinesias by 50% in nine PD patients.³⁷ A more recent double-blind placebo controlled study of oral amantadine in 40 patients demonstrated a 45% reduction in dyskinesias in the first month which was not maintained at three to eight months.³⁸ Five patients withdrew due to side effects. Eleven patients suffered rebound dyskinesias on withdrawal of the drug, two resulting in febrile reactions and confusion.

Two trials have assessed the effect of amantadine on motor fluctuations as secondary outcomes. One reported beneficial effects, with significant reduction in off times,³¹ while the other found no difference.³⁴

Although most trials have suffered from methodological problems, the overall trend suggests that amantadine is useful for the short term treatment of dyskinesias while little is known of its long term efficacy and patients may become tolerant to the drug. A Cochrane review in 2003 concluded there was insufficient evidence to determine the effectiveness of amantadine in treating levodopa-induced dyskinesias.

Our practice in patients with dyskinesias, unresponsive to conventional measures such as reduction of levodopa, is to start amantadine at 100mg in the morning and increase to 100mg twice a day thereafter. Occasionally an extra 100mg needs to be added at lunch time, but we rarely exceed 300mg per day, and would not use the drug in patients with a history of visual hallucinations or neuropsychiatric problems.

Dose of Amantadine in clinical studies

In most studies a daily dose of 200mg or 300mg of amantadine was used. One study used only 100mg²⁷ and another used up to 400mg.³¹ It is difficult to assess if higher doses produced more side effects, and there is no data on whether an increase in dose may improve the long term efficacy of amantadine.

Side effects and adverse reactions

The side effects of amantadine appear to be mild and transient, most commonly livedo reticularis, dizziness, anorexia and blurred vision. This resulted in few patient withdrawals. However, confusion and hallucinations can be problematic, particularly in the elderly PD patient.³⁹ Toxic levels of amantadine can occur in patients with renal insufficiency as the drug is excreted largely unchanged in the urine.⁴⁰

Withdrawal of amantadine can lead to an encephalopathy, acute delirium, neuroleptic malignant syndrome and motor deterioration.^{21,41,42} Three patients with a mean age of 73 years developed acute confusion, disorientation and paranoia on stopping long-term treatment of amantadine.⁴³ Reinstating the drug restored baseline status. It is noteworthy that all three had a previous history of cognitive impairment and transient hallucinations.

Patients’ characteristics

The mean age of patients in most trials was 60-66 years, but with a wide range (29 to over 80 years of age). There is little evidence to determine whether the age or gender of the patient has any overall effect on treatment response. Disease duration also varied widely between trials, being an average of seven to nine years in the motor treatment trials and over ten years in the dyskinesia trials.

Use in our clinical practice	Comment	Dose	Caution
Treatment of motor symptoms - monotherapy	Rarely used	100 – 300mg in divided daily doses	Avoid in patients with a history of hallucinations or psychiatric symptoms. Avoid sudden withdrawal
Treatment of motor symptoms – adjunct therapy	May be useful as adjunct to dopamine agonists, as levodopa delaying agent	100 – 300mg in divided daily doses	
Treatment of dyskinesias	Useful if dyskinesias problematic after reduction of dopaminergic therapies	100 – 300mg in divided daily doses	
Other akinetic-rigid syndromes	May be useful as adjunct or alternative to levodopa	100 – 300mg in divided daily doses	

Amantadine in other akinetic-rigid disorders

There is very limited data available for the efficacy of amantadine in other akinetic-rigid disorders, and well designed clinical trials are needed. Often, in the absence of response to other treatments (particularly levodopa) amantadine is used. Anecdotally, patients may improve with treatment and deteriorate on discontinuation, but whether amantadine provides true clinical benefit remains questionable.

Multiple System Atrophy (MSA)

In the only placebo controlled trial of amantadine (200mg daily) in 30 patients with MSA-C (previously known as the olivopontocerebellar type of MSA), the drug produced significant improvements in reaction and movement time over three to four months.⁴⁴ Two other studies have reported improvements in reaction and movement times with amantadine but they had either no placebo group⁴⁵ or only an "untreated" group for comparison.⁴⁶

Progressive Supranuclear Palsy (PSP)

Three retrospective reviews of treatment in PSP have considered amantadine. Marginal benefit in symptoms (parkinsonism and dystonia) in very few patients were reported in all.⁴⁷⁻⁴⁹ In the only autopsy confirmed report,

two of five patients improved with amantadine but three patients had shown deterioration.⁴⁹

Other akinetic-rigid syndromes

There is one case report of a patient with corticobasal degeneration showing improvement in praxis with amantadine, which was reproducible on retesting.⁵⁰ There are no reports of its use in vascular parkinsonism.

The use of Amantadine in our clinical practice

Due to the lack of well designed clinical trials for the benefits of amantadine in PD and other akinetic-rigid disorders, clinical practice is often based on personal experience. The use of amantadine in our own practice is summarised in Table 3.

Conclusions

Amantadine appears to improve dyskinesias in the short term in PD but it is unknown how long these beneficial effects are sustained. It probably also has a mild benefit on the motor symptoms of PD but is far less potent than levodopa. Amantadine should be used with caution in patients with a history of confusion or hallucinations. The dearth of information available for PD and other akinetic-rigid syndromes highlights the need for more robust clinical trials of this pharmacologically interesting drug.

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