CLINICAL REVIEW

L-Dopa and amantadine hydrochloride in extra-pyramidal disorders

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Summary

L-Dopa and amantadine hydrochloride were separately given to patients with diverse extra-pyramidal disorders including progressive supranuclear palsy; porto-systemic encephalopathy; oculogyric crises; drug-induced Parkinsonism; Huntington's chorea, hemiballismus; spasmodic torticollis, familial tremor; and athetosis. Akinesia and rigidity were improved in the first two conditions and simultaneously there was improvement in disordered eye movement. Amantadine provoked an exacerbation in spasmodic torticollis and familial tremor. No other condition was influenced. Both amantadine and L-dopa will facilitate eye movement mechanisms: it seems probable that both drugs act on dopamine-sensitive areas within the CNS. Neither drug will give significant benefit in the above disorders.

Introduction

In addition to improvement in Parkinsonism, L-dopa will correct akinesia and dystonia in manganese intoxication (Mena *et al.*, 1970), akinesia, rigidity and abnormal eye movements in progressive supranuclear palsy (Mendell, Chase & Engel, 1970), akinesia and rigidity in juvenile Huntington's chorea (Barbeau, 1969), and motor performance, tremor and akinesia in Wilson's disease (Barbeau & Friesen, 1970).

These disorders have little in common except for disease of the extra-pyramidal system, but it seems probable that L-dopa is active in all by increasing the cerebral dopamine concentration. Amantadine, although having no close chemical relationship with dopamine or other neuro-transmitters, causes improvement in Parkinson's disease. Amantadine produces atropine-like side effects but resembles dopa-

mine rather than drugs such as benzhexol in its therapeutic spectrum (Parkes *et al.*, 1970). Amantadine causes monoamine release from neuronal storage sites (Grelak *et al.*, 1970). Thus increased dopamine (or serotonin) may be available for neurotransmission. These facts led us to compare the action of L-dopa and amantadine in patients suffering from diverse extra-pyramidal disorders, the majority of which degenerative changes are present in brain areas with high monoamine concentration. It was hoped to define the clinical value of amantadine in such disorders and at the same time gain further knowledge as to its mode of action.

Case reports

Progressive supranuclear palsy

1. A 61-year-old man complained of unsteadiness and impairment of memory of 1 year's duration. WAIS assessment gave a performance IQ of 78 and a verbal IQ of 85. There was a slight nominal dysphasia, speech being of low volume and dysarthric. He was most unsteady whilst walking, although the posture was erect. There was considerable impairment of facial expression, great difficulty in commencing movements and increased resistance to passive movements of the neck and limb muscles. No tremor was present. Volitional and pursuit conjugate eye movements were absent both on vertical and lateral gaze, apart from limited voluntary movement of the eyes to the left. Full vertical eye movement accompanied neck flexion and extension.

2. A 62-year-old man was seen with a 3 year history of slurred speech, slowness and clumsiness of movement. This patient had a verbal IQ of 88 and

FIG. 1. The eye movements in the first patient with supranuclear palsy. On each occasion the patient is attempting voluntary right lateral gaze with the head held stationary. The upper figure shows the paralysis of gaze prior to treatment and the lower figure the voluntary gaze possible following 1 week's treatment with amantadine 300 mg/day.

FIG. 2. The eye movements of the patient with porto-systemic encephalopathy. The upper figure shows the convergence spasm accompanying right lateral gaze before treatment and the lower figure shows the reduction in this following amantadine treatment.

performance IQ of 93, showing some learning difficulty. Speech was a little dysarthric but not difficult to understand. Posture was erect with no trunk or limb flexion; however gait was considerably impaired with frequent stumbles and great difficulty in turning. No tremor was seen. There was considerable increase in resistance to passive movements of the limb muscles. Voluntary and pursuit conjugate vertical eye movements were lost but lateral gaze was present although restricted in range. Full vertical eye movement accompanied neck flexion and extension.

Both these patients were given L-dopa (4 g/day and 6 g/day respectively). The responses to L-dopa were comparable in both patients with a moderate but not dramatic improvement in akinesia and rigidity. There was a slight increase in range of voluntary lateral, but not vertical conjugate eye movements in both cases. IQ assessment remained unchanged. L-dopa treatment was stopped in both patients after 2 weeks, being replaced by amantadine 300 mg/day. This also resulted in an improvement in speed of movement with less rigidity of limb muscles and an increased range of voluntary lateral eye movements. Further tests of memory showed no change in mental function in either patient, in both of whom amantadine and L-dopa did not produce sufficient improvement to warrant long term treatment.

Porto-systemic encephalopathy

A 52-year-old-man with advanced hepatic cirrhosis developed variable confusion with impairment of concentration. He had loss of facial expression, impairment of rapid finger movements, and a slow

gait with great unsteadiness on turning. These features were attributed to porto-systemic encephalopathy, and showed some variation with treatment. In addition, he developed postural vertigo and a profound impairment of eye movements. Volitional or pursuit gaze in a vertical or horizontal direction was prevented by involuntary over-convergence of the eyes. These latter features were attributed to a brain stem vascular lesion. Posture was normal, no tremor was present and muscle tone was unremarkable.

This patient was given amantadine 300 mg/day with improvement in gait, facial expression and finger dexterity. There was also considerable recovery of eye movement, although ocular convergence still occurred after prolonged upward gaze. The patient felt better in himself but no change in postural vertigo or mental function occurred. He was able to detect amantadine substitution by placebo (although not told of this) and returned to his former condition, eye movements deteriorating. The liver disorder was progressive and we were unable to give L-dopa under conditions comparable with amantadine.

Oculogyric crises

A 56-year-old man with post-encephalitic Parkinsonism suffered frequent oculogyric crises, with upward deviation of the eyes accompanied by forced eye closure. Following amantadine 500 mg/day, these spasms became much more frequent although of shorter duration. L-Dopa (3 g/day) gave considerable relief in akinesia and rigidity, but did not change either the frequency or duration of involuntary eye movements.

Phenothiazine-induced Parkinsonism

A 62-year-old lady was referred with Parkinsonism

of 5 years duration. She denied any drug intake. Examination showed considerable akinesia and rigidity but no tremor. This patient was not helped by L-dopa 4 g/day for 2 weeks, following which she was given amantadine 300 mg/day, again with no improvement. She later admitted to taking trifluoroperazine regularly during the preceding 5 years. This drug was stopped and all Parkinsonian features disappeared in the following 2 months.

Huntington's chorea

Four female patients with this disorder, all with profound mental deterioration and very disabling chorea were given amantadine hydrochloride 300 mg/day. No change in mental state or movement disorder was seen. These patients were then given L-dopa, individual doses varying from 2 g/day to 6 g/day, but no improvement was found after a 1 month period, choreiform movements being unaltered.

Hemiballismus

A 78-year-old lady suddenly developed abrupt rapid and extensive movements of the right arm and leg. She showed uncontrollable hemiballismus, being unable to walk unaided. There was a slight improvement in this patient's involuntary movements when given amantadine 300 mg/day, but this improvement continued on stopping treatment and the patient was not given L-dopa.

Spasmodic torticollis

A 48-year-old man developed involuntary movements of the head and neck which with considerable effort he could momentarily control. This varied in severity over a 5 year period. After 2 days of amantadine treatment (300 mg/day) there was a very considerable exaggeration of both the frequency and degree of head movement and he became distressed. On stopping amantadine within 24 hr he recovered his former state. L-Dopa 4 g/day had no effect on neck movement after a 1 month period.

Familial tremor

Two female patients, aged 53 and 56, with a slight tremor of the arms and head, both with a family history of tremor, were given amantadine 300 mg/day. Both showed a marked exacerbation of tremor which subsided on stopping amantadine. In neither case did L-dopa (3 g/day:1.5 g/day) affect the tremor.

Athetosis

A man of 40 with cerebral diplegia was seen with considerable spasticity of all limbs and movements of a predominantly athetoid nature. There was a profound mental retardation and speech was

extremely dysarthric. He made no response to either L-dopa 4 g/day or amantadine 300 mg/day, both drugs being given for a 2 week period.

Abnormal movements produced by L-dopa and amantadine

In thirty-nine patients treated with L-dopa, choreiform movements have been seen in four and abnormal movements of the neck or jaw seen in two respiratory tics in a further two. Similar movements have not been seen in eighty-nine patients given amantadine up to 500 mg/day, although one such patient reported uncontrollable jerking movements of the legs on waking in the morning.

Discussion

The considerable variation from day to day in the clinical features of the conditions we describe makes the response assessment difficult. However, there seemed no doubt of improvement of eye movement and akinesia in the patients with progressive supranuclear palsy and liver disease and this was confirmed by ciné films. The increased tremor in the patients with familial tremor, exacerbation of movement in spasmodic torticollis, and increase in frequency of oculogyric crises exceeded normal variation.

There was a striking similarity between the action of L-dopa and amantadine in porto-systemic cephalopathy and progressive supranuclear palsy. Pathological changes are widespread in both (Victor, Adams & Cole, 1965; Behrman *et al.*, 1969) but akinesia is probably secondary to involvement of the substantia nigra and its connections. Neither drug affected the mental disorder over a short period.

Dopamine is the predominant catecholamine in the substantia nigra and the pallidum (Hornykiewicz, 1966) and these areas are amongst those most severely involved in progressive supranuclear palsy (Behrman *et al.*, 1969). The return of eye movement produced by L-dopa in this condition suggests that these reduced eye movements may be associated with disordered function of the substantia nigra or pallidum, this gaze palsy being thus of extrapyramidal rather than pyramidal origin. Amantadine acted like L-dopa, a finding in keeping with the concept that amantadine acts by releasing dopamine at nerve terminals.

The pathogenesis of oculogyric crises is not known but this involuntary spasm stands in contrast to the paralysis of voluntary gaze of progressive supranuclear palsy. Oculogyric crises were aggravated by amantadine and it is noteworthy that L-dopa may also provoke oculogyric spasm as in Case 1 of Cotzias, Papavasiliou & Gellene (1969), and also caused oculogyric crises in a case of Wilson's disease (Barbeau & Friesen, 1970). These facts suggest a common site and mode of action of both L-dopa and amantadine.

in the facilitation of conjugate eye movement mechanisms, probably at extrapyramidal level.

Phenothiazine-induced Parkinsonism has been attributed to a receptor blocking action of phenothiazines on CNS catecholamine transmission (Brodie, Spector & Shore, 1959). Dopa does not improve phenothiazine-induced Parkinsonism (McGeer *et al.*, 1961) and it is not surprising that L-dopa and amantadine also had no effect. Neither drug was of value in the treatment of chorea or athetosis and hemiballismus was probably not improved by amantadine. This suggests that these movement disorders are not primarily provoked by failure of dopaminergic transmission and this view is supported by the provocation of these movements by L-dopa. These movements have not been seen with amantadine and this may be secondary to an exhaustion of dopamine from synaptosomes produced by amantadine, whilst L-dopa may lead to an excess saturation of synaptic regions with dopamine.

The increased movement in spasmodic torticollis and familial tremor seen with amantadine, but not L-dopa, could be related to the hyperactive state sometimes caused by amantadine when given in high dosage (Vernier *et al.*, 1969).

These clinical findings suggest that L-dopa and amantadine are only of value in extra-pyramidal disease primarily affecting the substantia nigra and striatum. Other conditions characterized by involuntary movement are not helped by either drug.

The effects of both drugs on eye movements needs to be further explored. The similarity of therapeutic spectra of the two drugs is in favour of the suggestion that amantadine causes dopamine release at nerve terminals, although the possibility remains that amantadine may influence serotonin rather than dopamine, or act as a 'false transmitter' within the CNS.

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