AMANTADINE HYDROCHLORIDE IN THE TREATMENT OF PARKINSONISM: A PLACEBO-CONTROLLED DOUBLE-BLIND STUDY*

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SUMMARY

This report covers a review of the literature and a description of a double-blind placebo-controlled trial, of 200 mg of amantadine hydrochloride daily in the treatment of 23 parkinsonian patients. Statistical analysis of clinical results showed a significant improvement in rigidity and tremor at rest and a fair improvement in initiating movements and alertness. Subjective mood elevation was not confirmed by statistical analysis. Gait, voice control, jaw tremor and salivation showed no statistical improvement, while eye convergence may be adversely affected. Side-effects were minimal. Amantadine hydrochloride (Symmetrel, Geigy) appears to have real value in the treatment of parkinsonism.

There is growing interest in the effects of amantadine hydrochloride (1-adamantanamine hydrochloride; Symmetrel, Geigy) in parkinsonism. This substance, an antiviral agent, was first used in the treatment of A-2 (Asian) influenza.

A patient with parkinsonism, on receiving the drug, showed unexpected improvement of her neurological disorder.[1] Since then medical interest has been directed to this aspect of the drug's effect. Amantadine hydrochloride is a stable, white, crystalline compound, freely water soluble, and is the salt of a symmetrical 10-carbonamine, with an unusual cyclic structure. In man, the drug is rapidly absorbed and there is almost complete recovery of an administered dose in unaltered form from the urine.[2] Its antiviral effect stems from its ability to alter the host-cell membrane, thus preventing the virus from entering the cell. Its effect in parkinsonism is ill understood. Parkes *et al.*[3] suggested that 'amantadine probably has a central effect but a direct or indirect effect on areas of the central nervous system, in which dopamine is a recognized transmitter, cannot be inferred at this stage'.

Another possibility is that amantadine acts in an anti-RNA manner. Stephanis and Issidorides[4] suggested that there may be a disturbance of protein synthesis in parkinsonism, as well as a disturbance of dopaminergic and cholinergic activity. They postulated that an unknown agent stimulates the production of a new messenger-RNA (mRNA). As a result, the neurone is not capable of synthesizing certain proteins needed in signal transmission. Issidorides[5] submitted that there is an increase in RNA, inversely related to melanin content in parkinsonism. He pointed out that Gonirato and Hyden[6] found an increase in aberrant mRNA in the glia of the globus pallidus early in the disease and that later there was a similar increase in RNA in the neurones of the same area.

To test their hypothesis Stephanis and Issidorides used chloramphenicol, a known inhibitor of protein synthesis resulting from too rapid a turnover of mRNA in proliferating cells.[4] They gave chloramphenicol to 18 patients suffering from parkinsonism. They claimed that 'nearly all' patients improved and they interpreted this as due to inhibition of abnormal protein synthesis in the nigral neurones.

Review of the Literature

Schwab *et al.*[1] were the first authors to publish an account of the effect of amantadine in parkinsonism. They found 66% of a group of 163 patients with parkinsonism exhibited improvement in akinesia, rigidity and tremor while receiving amantadine hydrochloride. Improvement was maintained in 58% for a period of 3 - 8 months. The maximum daily dose was 200 mg. Patients helped by amantadine were also helped by L-dopa and in one patient the combination of amantadine and L-dopa seemed beneficial. Side-effects occurred in 22% of patients and consisted of restlessness, insomnia, abdominal uneasiness, dizziness, depression, confusion and, in a few cases, hallucinations. In most cases side-effects were controlled by reducing the dose of amantadine or of concomitant medication.

Parkes *et al.*[3] carried out a double-blind cross-over trial of amantadine. Dosage was 200 mg daily, given for 2 weeks. Thirty-seven outpatients with parkinsonism were invited to take part in the trial and 35 completed it. Patients were included irrespective of age, sex, duration of symptoms or extent of disability, provided no other neurological disorder was manifest. The parkinsonism was thought to be of idiopathic origin in the majority of patients, and of postencephalitic or cerebrovascular origin in the remainder.

All 35 patients who completed the trial expressed 'a highly significant preference for amantadine'. Features of history and examination were assessed by means of a standard questionnaire and all symptoms and signs showed a significant improvement on amantadine except for the patients' own assessment of walking ability and the observers' assessment of rigidity. Parkes *et al.* found that the degree of improvement was not related to sex, age, duration or severity of disease, previous thalamolysis or concurrent medication. They found the drug to be free of side-effects and well tolerated by all patients undergoing the trial.

Millac *et al.*[7] reported the effects of amantadine given continuously for 3 months to 32 patients with idiopathic parkinsonism. The patients were assessed at 3-weekly intervals. Amantadine was added to concomitant medication, the dose being gradually increased from 100 mg to 400 mg daily if required. Unfortunately, the authors do not give the precise criteria for increasing the dosage.

Five patients withdrew because of side-effects; these consisted of insomnia, nightmares and, in one patient, confusion with hallucinations. All side-effects disappeared on discontinuing amantadine. The authors found that increasing the dose of amantadine above 200 mg daily sometimes resulted in further improvement, contrary to the experience of Schwab *et al.*[1] They concluded that the results of the trial were 'disappointing, since in no instance could improvement be described as dramatic'. The improvement noted was a reduction in akinesia in 19 out of 27 patients.

Fieschi *et al.*[8] carried out a double-blind cross-over trial of amantadine in 20 patients with parkinsonism. They concluded that amantadine has a prompt antiparkinsonian effect, with 'significant improvement' in rigidity and an absence of side-effects. They are currently comparing the effects of amantadine with those of L-dopa in the same group of patients.

MATERIAL AND METHODS

Our trial was carried out on 23 patients, 10 of whom were female, taken consecutively from the neurology outpatient department. Ages ranged from 51 to 74 years with an

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average age of 62·5 years. The duration of manifest parkinsonism ranged from 2 years to 7 years with an average of 4·6 years. The severity varied from unilateral lower-limb rigidity to a severely incapacitated non-ambulatory state. In 12 patients cerebral arteriosclerosis had been diagnosed, in one patient the parkinsonism was thought to be postencephalitic, and in 10 cases the aetiology was unknown. None of the patients had surgical treatment for parkinsonism.

All patients were on conventional antiparkinsonian medication, which included one or a combination of the following preparations: trihexiphenidyl (Artane), orphenadrine (Disipal), procyclidine (Kemadrin) and biperiden (Akineton). Five patients were on antihypertensive medication.

Each patient was given a supply of test capsules identified only by a code number, the code being kept secret by the drug company. The patients were instructed to take one capsule in the morning and one at midday, in addition to their usual medication which was not altered. The patients were informed that the medical staff did not know whether drug or placebo was used. After 2 weeks patients were given another bottle of identical-looking capsules (cross-over).

Clinical assessment of symptoms and signs was carried out by 2 clinicians at weekly intervals for 5 weeks. Care was taken to standardize test conditions and all assessments took place between 9 a.m. and 12 noon. The assessment consisted of scoring 14 symptoms on a scale of 0 - 4 (Table I). Patients were also observed and cinefilmed, while writing, stringing beads, manipulating pegs in pegboards, rising from a sitting position from a chair and sudden changes in direction while walking.

TABLE I. RESULTS OF CLINICAL TESTS

	K=Number of (0·0)	*N*	T_{OBS}	*Probability*
Initiating movements	6	9	8	0·196
Rigidity	1	14	13	0·009*
Tremor at rest	2	13	10	0·046†
Tremor action	4	11	7	0·274
Depression	9	6	5	—
Alertness	5	8	6	0·144
Gait	7	7	5	—
Blinking	0	15	8	0·518
Voice/speech	11	4	3	—
Jaw tremor	7	6	1	—
Arm swing	5	10	5	0·623
Salivation	13	2	2	—
Convergence	4	11	3	0·903
Sleep	11	4	2	—

When K>N no statistical test was applied as the majority of patients had improved equally with amantadine and placebo, therefore no probability value was obtained.
K=Number of (0·0), i.e. number of patients who showed no marked difference between amantadine and placebo.
N=15−K, i.e. there were 15 patients not solely on amantadine or placebo.
T_{OBS}=patients observed showing improvements on amantadine.
*Significant at 1% level, i.e. 1 chance out of 100 of obtaining this result by chance alone.
†Significant at 5% level, i.e. 5 chances out of 100 of obtaining this result by chance alone.
To interpret the table consider for example the symptom, 'Initiating movements'. Out of 15 patients under observation, six (K=6) improved equally with amantadine as with placebo. Out of nine patients (N=9), eight (T_{OBS}=8) showed a greater improvement on amantadine. The probability of obtaining this result by chance alone, assuming there is no difference between amantadine and placebo, is 0·196, i.e. about 1 chance out of 5.

RESULTS

Clinical

Of the 23 patients, 16 reported subjective improvement ranging from mild to marked; 4 patients reported 'less of a glued feeling' when describing their gait. Seven reported that they felt more cheerful. A 58-year-old woman reported that within 2 days of starting the capsules she was able to climb stairs completely unaided for the first time in 4 years. All patients who felt better did so within 48 hours of starting one of the test bottles.

Objectively there appeared to be improvement in rigidity, tremor at rest, initiation of movements and blinking. The elevation of mood was striking in 7 cases. Cine-films were successful in some cases of highlighting improvement in movement. Of the many handwriting specimens taken during the trial, two comparisons are shown, from two patients, taken a week apart (Fig. 1).

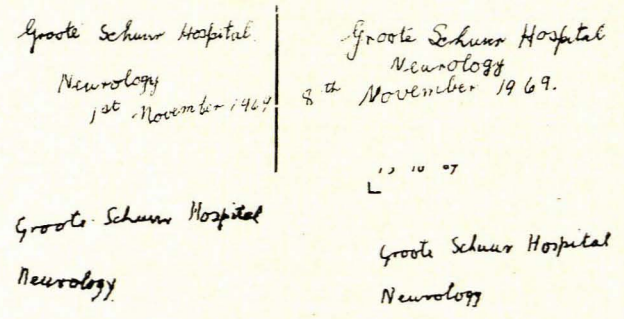

Fig. 1. Influence of amantadine on handwriting.

The neurological scores were assessed as follows: In analysing the data, 3 assumptions were made:

(*a*) The effect of the 2 drugs (i.e. amantadine and placebo) are independent. In practical terms, this means that the assumption was made that the drugs take immediate effect and are not retained in the body.

(*b*) A patient with severe parkinsonism is as likely to show the same amount of improvement (or deterioration) as a patient with a lesser degree of parkinsonism. Although this is clinically unlikely, this assumption is a necessary prerequisite of statistical analysis.

(*c*) As was obvious from the scores relating to patients only on drug or only on placebo, there is a variation within each patient which could not be estimated due to the brevity of the exposure period; hence the assumption is made that the score obtained by each patient is due to the drug or placebo and not to his own individual variation.

Side-Effects

Dizziness was reported in 8 patients, in 7 of whom cerebrovascular disease had been diagnosed. Three patients complained of headache, one of muzziness and one of increased irritability. No patient regarded these symptoms as incapacitating. Fourteen patients were free of side-effects.

DISCUSSION

The results of this trial show that, both clinically and statistically, amantadine hydrochloride appears to be of value in the treatment of parkinsonism. Improvement was noted in akinesia and rigidity and, to a lesser extent, tremor. A striking feature in our trial has been the rapidity of effect of amantadine. When it was effective it was so within 48 hours. This was noted by Schwab *et al.*,[1] Parkes *et al.*

and Fieschi *et al.*[8]

Our findings suggest that amantadine is relatively free of side-effects. Parkes *et al.*[3] found side-effects more common with placebo treatment but Fieschi *et al.*[8] found them to be absent. However, Schwab *et al.*[1] reported quite marked side-effects in some 22% of patients. Millac *et al.*[7] reported effects severe enough to compel 5 of 32 patients to withdraw from the trial. These, however, used amantadine in doses varying from 100 mg to 400 mg daily and claimed some further improvement, but did not elaborate on this. In other trials the maximum dose administered was 200 mg daily except for Schwab *et al.*[1] who increased the dose to 300 mg daily in some patients. They reported that 'it soon became apparent that there was no increase in benefits from doses greater than 200 mg per day'. The possibility of amantadine potentiating the effects of concomitant medication or vice versa has been raised[1,3,7] and it may be necessary to reduce the dosage of the 'conventional' antiparkinsonian medication to eliminate side-effects. To illustrate this, Schwab *et al.*[1] report a case of a 67-year-old man who, after 3 weeks of tested amantadine therapy, manifested hallucinations and confusion. They reported that 'reducing the procyclidine and benztropine eliminated these side-effects and the patient remained much improved'.

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