Interactions of L-dopa and amantadine in patients with Parkinsonism

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SUMMARY Twenty-seven patients with Parkinson's disease participated in a double-blind crossover trial of L-dopa and amantadine. Each drug was given for six weeks, and six weeks were allowed to elapse between the two periods of treatment. Marked improvement occurred in patients given L-dopa first, whereas no clinical effect was observed in those patients treated first with amantadine. L-dopa was less beneficial to patients who had previously received amantadine, whereas amantadine became effective in patients who had previously taken L-dopa. The effect of pre-treatment with one drug on the therapeutic effectiveness of the other drug is reflected in changes of homovanillic acid levels in the cerebrospinal fluid.

A number of authors have reported improvement of symptoms in patients with Parkinson's disease who were taking L-dopa (Calne, Spiers, Stern, Laurence, and Armitage, 1969; Calne, Stern, Laurence, Sharkey, and Armitage, 1969; Godwin-Austen, Tomlinson, Frears, and Kok, 1969; Mawdsley, 1970) or amantadine (Parkes, Zilka, Calver, and Knill-Jones, 1970; Hunter, Stern, Laurence, and Armitage, 1970a). Benefit has been claimed in some patients who were taking both drugs together (Weeth, Shealy, and Mercier, 1969; Godwin-Austen, Frears, Bergmann, Parkes, and Knill-Jones, 1970; Green, 1970; Gomirato and Perfetti, 1970; Hunter, Stern, Laurence, and Armitage, 1970b). However, a comparison study showed that amantadine is less effective than L-dopa in the treatment of Parkinsonism (Fieschi, Nardini, Casacchia, Tedone, Reitano, and Robotti, 1970). The present study examines the interactions of the two drugs; in particular, the influence of pre-treatment with amantadine or with L-dopa on the therapeutic response to the other drug.

METHODS

Of 29 patients with Parkinson's disease who entered the trial, 27 completed it (15 male, 12 female). Two patients developed an unrelated disease and withdrew from the trial. Their mean age was 60.1 years (SE 1.77), and the mean duration of symptoms was 4.75 years (SE 0.654). No patient had symptoms or signs suggestive of a post-encephalitic aetiology. Three patients had undergone a unilateral thalamotomy. Although some patients had other chronic ailments, none of these contributed significantly to their physical disability.

Each patient had two six-week courses of treatment, separated by a period of six weeks without treatment. The drug in one course was L-dopa, and in the other amantadine. Patients were randomly allocated to two groups. Thirteen patients received L-dopa first and amantadine second ('L-dopa starters'), and 14 patients received the drugs in the reverse order ('amantadine starters'). During each

TABLE 1

<table>
<thead>
<tr>
<th>Schedules</th>
<th>L-dopa (g)</th>
<th>Amantadine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>200</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>200</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>300</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>300</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>400</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>400</td>
</tr>
</tbody>
</table>

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course of treatment the patients were given two preparations: an active drug and a placebo, the latter being identical in appearance with the corresponding drug. L-dopa was supplied in white tablets containing 0.5 g, amantadine in red capsules containing 100 mg. Eight dosage schedules were prepared and the daily dose of each drug is shown in Table 1. Patients were instructed to advance to the next higher schedule every four days until undesirable side-effects appeared, and then to continue treatment at an acceptable schedule for the remaining period of the course. Adjustment to the maintenance level of treatment was made three weeks after the beginning of treatment, but advice to modify the dose was often given earlier. Patients were instructed to continue throughout the trial those anticholinergic drugs they were taking on entering the study. No patient had previously received L-dopa or amantadine.

Drugs were supplied in envelopes, each containing a single day’s dose. Once the patient reached a maintenance schedule, he took the drugs from canisters. Cards were provided for patients to record the number of tablets taken each day. The current dose at each attendance was checked from the cards and unused tablets.

Patients attended at three-weekly intervals and were examined by two observers. They were seen 10 times, twice during each of the following periods: before treatment, during the first course, between the two courses, during the second course, and after the second course of treatment (Table 2). This routine was varied at times to allow for gradual withdrawal rather than sudden cessation of treatment when this was thought indicated, and for premature discontinuation of treatment when an adverse reaction was suspected. Provision was made for patients to seek advice at any time during the course of the trial.

At each attendance a standard pro-forma was completed, and no reference was made to previous notes or records. Bradykinesia of hands, rigidity, posture, upper extremity swing, gait, tremor, facies, seborrhoea, speech, and self-care were rated clinically 0, 1, 2, or 3, according to whether there was no involvement or whether there was evidence of early, moderate, or severe disease. The criteria for this rating were those described by Webster (1968). The sum of the ratings gave the total clinical score. Body

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**TABLE 2**

<table>
<thead>
<tr>
<th>Weekly attendances</th>
<th>L-dopa (g)</th>
<th>Amantadine (mg)</th>
<th>L-dopa (g)</th>
<th>Amantadine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2</td>
<td>2.92 ± 0.277</td>
<td>—</td>
<td>—</td>
<td>264 ± 32.6</td>
</tr>
<tr>
<td>3</td>
<td>3.31 ± 0.406</td>
<td>—</td>
<td>—</td>
<td>350 ± 41.7</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>323 ± 22.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5 and 6</td>
<td>—</td>
<td>300 ± 32.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>—</td>
<td>3.50 ± 0.606</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>—</td>
<td>2.96 ± 0.578</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9 and 10</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**FIG. 1. Schematic diagram of tremor recording apparatus.**

temperature, respiratory rate, supine and erect pulse rate, and lying and standing systolic and diastolic blood pressure, measured to the nearest 5 mm of mercury, were recorded. The following standardized tasks were timed with a stop-watch: specimen of writing, lighting a match, getting up from a chair, and walking 5 yards.

Some patients volunteered to have their cerebrospinal fluid (CSF) examined on two occasions and they were hospitalized for the lumbar punctures. The samples of CSF were analysed for homovanillic acid (HVA) content by a method based on that of Anden, Roos, and Werdinjus (1963). Control CSF samples were obtained from patients without Parkinsonism.

Tremor was recorded using a Grass accelerometer SPA1 attached to the middle finger of the affected hand. The accelerometer output was fed through a Devices DC2D amplifier into a Devices AC1 amplifier, and thence into a Devices DC5 driver amplifier, which in turn drove a pen that produced a record of the tremor on a Devices M2 recorder. The output from the AC1 amplifier was also passed through a limit switch into a Devices 3020 integrator, and thence into another driver amplifier which drove a pen producing an integral of the tremor (tremor score) on the Devices M2 recorder (Fig. 1).

Passive resistance to movement was measured using the apparatus described by Schnediens (1969). This consisted of an arm board supported on air bearings and capable of rotation about a fixed point over a ball bearing. The subject placed his arm on the board so that his elbow rested above the point of rotation. By pulling on a wire attached to a strain gauge mounted beneath the board, the forearm was moved through an arc of 7° at a speed of 14-8° per minute. The output from the gauge was recorded and represented a measure of the force required to overcome passive resistance at the elbow and move the board. The procedure was repeated five times and the mean force was calculated in arbitrary units (Fig. 2).

Results in the ‘L-dopa starters’ and the ‘amantadine starters’ were analysed separately. The signs that were quantitated at each attendance were averaged and, since each patient was evaluated 10 times, there were 10 means for each sign, two pre-treatment ones and eight subsequent ones.

**Statistical Analysis** Homogeneity of the two groups was tested using the $\chi^2$-test for sex and the clinical scores, and Student’s $t$ test for age, weight, height, total clinical score, timed tasks, pulse, and blood pressure.

The effect of treatment was investigated by comparing the scores at any particular attendance with the scores recorded for the second pre-treatment assessment. The Sign Test or the Wilcoxon Signed Rank Test was used for the 10 clinical signs. In the case of the total clinical score, the pulse and blood pressures, the $t$ test was used as follows. The variation within each patient—that is, the variation between the two pre-treatment scores—was pooled to give a within-patient variation. Only if changes from the second pre-treatment scores at any given period during the trial exceeded this within-patient variation, were they considered significant.

A significance level of 5% was accepted.

The product-moment correlation coefficient was computed between the clinical and mechanical assessments of tremor and rigidity using the 10 corresponding readings per patient for all patients.

**Results**

The mean daily dose of each drug taken by patients at the time of each clinical assessment is given in Table 2. The ‘L-dopa starters’ and the ‘amantadine starters’ were found comparable with respect to age, sex, weight, height, and
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AMANTADINE STARTERS

L - DOPA

\[ \begin{align*}
&\text{AMANTADINE} \\
&\text{L - DOPA} \\
&95\% \text{ CONFIDENCE} \\
&\text{LIMITS}
\end{align*} \]

\[ \begin{align*}
&3 \ 6 \ 9 \ 12 \ 15 \ 18 \ 21 \ 24 \ 27 \ 30 \\
&\text{TOTAL CLINICAL SCORE}
\end{align*} \]

L - DOPA STARTERS

AMANTADINE

\[ \begin{align*}
&\text{L - DOPA} \\
&\text{AMANTADINE} \\
&95\% \text{ CONFIDENCE} \\
&\text{LIMITS}
\end{align*} \]

\[ \begin{align*}
&3 \ 6 \ 9 \ 12 \ 15 \ 18 \ 21 \ 24 \ 27 \ 30 \\
&\text{TOTAL CLINICAL SCORE}
\end{align*} \]

Fig. 3. Mean total clinical score in 'amantadine starters' and 'L-dopa starters' during the course of the trial. Periods of treatment with either drug are shown.

severity of signs. However, the mean pre-treatment score for mechanically assessed tremor was higher in the 'L-dopa starters' than in the 'amantadine starters' (P < 0.001). Those signs and measurements not mentioned in this section were not significantly affected by treatment.

EFFECT OF L-DOPA TREATMENT Patients who received L-dopa first improved significantly at both attendances during treatment in the total clinical score (P < 0.01) (Fig. 3), and in four of its 10 components—namely, bradykinesia of hands, rigidity, arm swing, and facies (Table 3). There was significant shortening of the time taken to write the standard sentence and to light a match. They also improved when assessed quantitatively for tremor, but not for rigidity (Fig. 4).

After L-dopa was discontinued there was a

TABLE 3

<table>
<thead>
<tr>
<th>VARIABLES IMPROVING SIGNIFICANTLY DURING TREATMENT (P &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect of L-dopa</strong></td>
</tr>
<tr>
<td>Given first</td>
</tr>
<tr>
<td>Total clinical score (3, 6)*</td>
</tr>
<tr>
<td>Bradykinesia of hands (3, 6)</td>
</tr>
<tr>
<td>Rigidity (clinical) (3, 6)</td>
</tr>
<tr>
<td>Arm swing (6)</td>
</tr>
<tr>
<td>Facies (6)</td>
</tr>
<tr>
<td>Writing speed (6)*</td>
</tr>
<tr>
<td>Lighting match (6)</td>
</tr>
<tr>
<td>Tremor (quantitative) (3, 6)</td>
</tr>
<tr>
<td>Decrease in erect (3, 6) and supine (6)* systolic blood pressure</td>
</tr>
<tr>
<td>Decrease in erect diastolic blood pressure (3, 6)*</td>
</tr>
</tbody>
</table>

*P < 0.01. Numbers in parentheses indicate improvement at three or six weeks of treatment.
significant worsening of the total clinical score compared with the pre-treatment level both three and six weeks after stopping treatment (P < 0.01) (Fig. 3). There was also significant deterioration in the time it took patients to walk 5 yards at three weeks (P < 0.01) but not at six weeks after treatment with l-dopa was stopped. No significant deterioration in other parameters was found.

Patients who received l-dopa after being treated with amantadine improved only with respect to arm swing, tremor, facies, and the speed of lighting a match. The quantitative measurements of tremor and rigidity did not change significantly.

In both groups there was during treatment a significant fall in supine and erect systolic blood pressures, but no change in pulse rate. The fall in blood pressure was less in those patients who received l-dopa after amantadine (Table 3).

**EFFECT OF AMANTADINE TREATMENT** No improvements occurred in patients receiving amantadine during their first treatment course. In those patients who received amantadine after l-dopa, improvement was found in bradykinesia of hands, arm swing, and speed of writing at three weeks, but not at six weeks of treatment (Table 3). A significant worsening in the total clinical score was observed six weeks after treatment was stopped (P < 0.05) (Fig. 3). There was also deterioration in walking time both at three weeks (P < 0.05) and at six weeks (P < 0.01) after amantadine was discontinued. No significant deterioration in other parameters was found.

Treatment with amantadine did not affect the pulse rate but, when given after l-dopa, both supine systolic and supine and erect diastolic blood pressure fell significantly (Table 3). Only the erect systolic blood pressure fell in those patients receiving amantadine first.

**TABLE 4**

<table>
<thead>
<tr>
<th>Group</th>
<th>HVA (ng/ml)</th>
<th>Samples (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls without Parkinsonism</td>
<td>59 ± 9</td>
<td>32</td>
</tr>
<tr>
<td>L-dopa given first</td>
<td>233</td>
<td>5</td>
</tr>
<tr>
<td>L-dopa given after amantadine</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Amantadine given first</td>
<td>71</td>
<td>5</td>
</tr>
<tr>
<td>Amantadine given after l-dopa</td>
<td>250</td>
<td>6</td>
</tr>
</tbody>
</table>

**MECHANICAL AND CLINICAL ASSESSMENT OF TREMOR AND RIGIDITY** There was no significant correlation between the quantitative and clinical methods of assessing rigidity (r = −0.052, P > 0.05). However, the corresponding comparison of the two methods for assessing tremor showed that there was a good correlation (r = +0.478, P < 0.01).
HVA concentration in CSF

The minimum HVA concentration which could be detected in the CSF was 35 ng/ml. Therefore samples which fell below this limit were assigned zero concentration. The mean HVA concentration in samples from patients without Parkinsonism was 59 ng/ml. (SE 9). Mean HVA concentrations in the CSF of patients with Parkinsonism during therapy with either L-dopa or amantadine are shown in Table 4. Five patients who were taking L-dopa before amantadine had mean HVA concentrations higher than the controls, and in only one of the samples was the HVA below the limit of detection. Five patients receiving amantadine before L-dopa had a mean HVA concentration similar to that in control subjects. However, in three of the samples no HVA was detected, but in one sample a high concentration (300 ng/ml.) was recorded. After crossover, the mean HVA concentration in the CSF from patients previously on L-dopa but currently receiving amantadine remained high with only one zero value. The mean HVA concentration in samples from six patients changing from amantadine to L-dopa failed to rise in response to the L-dopa therapy, no HVA being detectable in three samples.

Discussion

The results show clearly that, when used as the first drug, L-dopa is much more beneficial to patients with Parkinsonism than is amantadine. L-dopa particularly improves function of the hands and hypokinesia, but there is some evidence that it also reduces rigidity and tremor. This accords with findings in previous trials.

The interaction of the two drugs is particularly interesting. Combinations of amantadine and L-dopa therapy have been used clinically. Of 10 patients on L-dopa therapy treated for two months with amantadine, seven improved (Gomirato and Perfetti, 1970). Green (1970) has reported improvement with amantadine in only two of 16 patients on L-dopa. Weeth et al. (1969) noted that when amantadine was added to L-dopa therapy, improvement occurred in only one of 15 patients. Godwin-Austen et al. (1970) found that when amantadine was added to L-dopa there was an improvement in rigidity and limb dexterity after two weeks, but this was no longer apparent after four weeks of treatment. Improvement in tremor, however, was found at four weeks but not at two weeks of combined therapy.

Although in our study amantadine had no demonstrable effect in those patients who received the drug first, it had some beneficial effect in patients pretreated with L-dopa. Pre-treatment with L-dopa also potentiated the effect of amantadine on the fall in blood pressure (Table 3). In those patients pretreated with amantadine, on the other hand, L-dopa had a less beneficial effect than in those patients not pre-treated with amantadine. The fall in blood pressure during treatment with L-dopa was also less in patients who had received amantadine than in those who had not been treated with it. The effect of pre-treatment with one drug on the clinical benefit and on the fall in blood pressure of the other drug is thus similar and suggests that similar mechanisms underlie the hypotensive and the therapeutic actions of the two drugs.

The method of analysing our results, particularly the use of the second pre-treatment assessment for comparing subsequent changes in the trial, is open to criticism. The total clinical score and walking time worsened significantly after the first course of treatment in each patient group. This was not the case, however, with the individual clinical parameters, the blood pressures, other timed tasks, and the tremor and rigidity recordings. Obviously six weeks off treatment was not long enough for the clinical condition to return to the pre-treatment state. This backlash effect would be expected to dampen the therapeutic effect during the second course of treatment in each patient group. It could account for L-dopa being less effective when given second, but could not explain the beneficial effect of amantadine on arm swing, bradykinesia of hands, and speed of writing. It is interesting that this improvement on amantadine was present at three weeks of treatment, but had disappeared at six weeks on the drug.

We felt it unjustified to use the inter-treatment assessments to define changes during the second course of treatment. One reason was the backlash effect and the other that the trial was open at this stage, thus possibly exaggerating the backlash effect. If, however, the mean total clinical score in the second inter-treatment period is used to compare the effect of the second course
of treatment, then there was significant improvement both during amantadine (P < 0.01 at three and six weeks) and L-dopa (P < 0.05 at three weeks and P < 0.01 at six weeks) treatment.

It should be pointed out that the first clinical evaluation of patients during treatment with the second drug was nine weeks after stopping the first one, while the second evaluation was 12 weeks after discontinuation of therapy with the first drug. Thus the effect of pre-treatment with one drug on the action of the other remains demonstrable even three months after the first drug is discontinued.

The biological half life of amantadine in man is between nine and 15 hours. Moreover, it has been shown that approximately 93% of a dose of 190 mg amantadine hydrochloride was excreted in the urine of a male volunteer within five days (Bleidner, Harmon, Hewes, Lynes, and Hermann, 1965). It is therefore unlikely that the carry-over effect of amantadine pre-treatment is due to retention of significant quantities of the drug in the body. It is more likely that the drug affects some enzyme system responsible for the metabolism or uptake of L-dopa.

Amantadine was originally used as an antiviral agent and it is believed to inhibit penetration of viruses into cells (Galegov, Pushkerskaya, and Lavrov, 1967). It is possible that pre-treatment with amantadine inhibits the uptake of L-dopa into sites important for its action or metabolism, thus accounting for the failure of L-dopa to be fully effective after amantadine treatment. The failure of HVA levels to rise in the CSF when L-dopa is given after amantadine pre-treatment would strongly support either or both of the above possibilities. While the actions of amantadine are still not fully understood, there is some evidence that the drug can modify the uptake of dopamine into brain homogenates (Fletcher and Redfern, 1970). Strömberg, Svensson, and Waldeck (1970) have produced evidence favouring an indirect amphetamine-like action for the drug. Release of dopamine from 'loaded stores' may explain why higher HVA levels were found when amantadine therapy followed L-dopa treatment than when amantadine was given before L-dopa therapy.

The lack of correlation between the clinical assessment of rigidity and the results obtained from the measurement of passive resistance to movement is of interest. Boshes (1966) who also used strain gauges for measuring rigidity mentions that speed of movement of the instrument may be of importance. His instrument moved the arm at a speed of 2.5° per minute and the limb was flexed through an arc of 27.5°. Webster (1966) standardized his instrument so that the limb moved through a 100° arc of passive movement at 20° per second. It is noteworthy that he showed that when a patient was alerted by being given a task, rigidity measurements profoundly increased. Our instrument measured limb movement through an arc of 7° at a speed of 14.8° per minute.

Agate, Doshay, and Curtis (1956) measured the effect of treatment with ethopropazine or placebo on the passive resistance to movement of the forelimb which was moved through 3°, 75°, and 90°. A calculation from the data presented in their paper shows that a significant difference occurred as a result of treatment (P < 0.01, Wilcoxon two-tail test) when the limb moved through 3°. Therefore, differences in responses to treatment might have been expected to become apparent also during the 7° movement allowed in the present trial.

The poor correlation found between the clinical assessment of rigidity and the results obtained from the measurement of passive resistance to movement may thus be due to differences in the range and speed of joint movement, and in the alertness of the patients during the clinical and the mechanical assessments of rigidity.

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