# Alpha Methyldopahydrazine as an Adjunct to Levodopa Therapy in Parkinson's Disease

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SUMMARY: *A double-blind, double-observer study was carried out in twenty-five patients with Parkinson's disease. Alpha methyldopahydrazine in combination with L-dopa was compared to placebo with L-dopa. Combination therapy resulted in a reduction in L-dopa dosage to ⅓ of the amount required during the baseline. There were no side effects attributed directly to the alpha methyldopahydrazine. The overall incidence of side effects in the two groups was similar but the combination therapy significantly reduced the incidence of nausea and vomiting. The limiting factor in the combination therapy was the presence of L-dopa induced dyskinesias.*

RÉSUMÉ: *Une étude à double insu et par deux observateurs fut entreprise chez vingt-cinq patients atteints de la maladie de Parkinson. Nous avons comparé la thérapie combinée d'alpha-méthyldopahydrazine et de la L-dopa avec un placebo ajoutée à la L-dopa. La thérapie de combinaison a résulté en une réduction de la dose de L-dopa de ⅓ de la quantité requise pour les patients qui recevaient un placebo ajouté à la l-dopa. Aucun effet secondaire n'a été attribué directement à l'alphaméthyldopahydrazine. L'incidence globale des effets secondaires fut similaire chez les deux groupes mais la thérapie combinée a réduite de facon significative l'incidence de nausée et de vomissement. Le facteur limitant dans la thérapie combinée fut la présence de dyskinésies induites par la L-dopa.*

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The most exciting advance in neurological disease in the last twenty years has been the introduction of Levodopa. The biochemical studies of amine metabolism in the brain followed by the introduction of L-dopa in the therapy of Parkinson's disease have been a beautiful demonstration of advances in therapy based on well-worked out preliminary basic science studies (Symposium — 1972). Many patients with Parkinson's disease are now able to live a relatively normal life because of these important advances. We report, in this study, our experience with the modification of L-dopa therapy with alpha methyldopahydrazine (MK-486, Carbidopa) which may extend the therapeutic efficacy of L-dopa to a number of Parkinsonian patients who have been unable to tolerate L-dopa therapy because of nausea and vomiting. Previous studies of alpha methyldopahydrazine in the therapy of Parkinson's disease (Chase & Wantabe 1972, Mars 1973, Marsden, et al 1973) have shown a 60-75% decrease in daily L-dopa requirements and some increase in clinical response. Side effects from L-dopa therapy were considered reduced, particularly nausea and vomiting. Most of these studies have found an increase in dyskinesias secondary to the L-dopa therapy.

## METHODS

Twenty-five patients with idiopathic Parkinson's disease under the age of 72 were randomly assigned to treatment with combination alpha methyldopahydrazine and L-dopa or to placebo combined with L-dopa. These patients had all been under stable L-dopa therapy for at least six months. The study consisted of a four-week baseline followed by twelve weeks of treatment on the assigned medications. One physician (therapist) controlled the dosage of medication throughout the study for all of the patients involved. The referring neurologist from our department (evaluator) conducted "blind" serial observations of disability and other clinical manifestations at weeks 4, 8, 12 and 16 of the study. The patients gave informed consent to a double-blind protocol.

Blood and urine samples were collected at each visit, looking for possible toxic effects of the drugs. Routine determinations were complete blood count; Coombs' test, both indirect and direct; BUN; electrolytes; calcium; phosphorus; alkaline phosphatase; two hour postprandial blood sugar; and urinalysis. ECG's were also done at each visit.

Medication for the study was all from a single lot of 250 mg. tablets of L-dopa and a single lot of alpha methyldopahydrazine 25 mg. per tablet. At the beginning of the study period, the L-dopa dosage for all of the patients was reduced. Those patients receiving placebo had their L-dopa dosage cut in half. The L-dopa was then re-adjusted by the therapist back to an optimum level. The patients on alpha methyldopahydrazine had their L-dopa dosage cut to 750 mg. a day with the addition of 100 mg. of alpha methyldopahydrazine per day. These patients were also adjusted by the therapist to an optimum level of anti-Parkinsonian therapy.

TABLE I

*Age, Sex & Duration of Disease, Severity*
*Alpha Methyldopahydrazine Study*

| | Placebo | Alpha Methyldopahydrazine |
|---|---|---|
| Number of Patients: | 12 | 13 |
| Male | 8 | 9 |
| Female | 4 | 4 |
| Mean Age: (Range) | 56 (40-69) | 60 (48-71) |
| Mean Duration of Parkinson's Disease: | 7 yr. 3 mo. | 6 yr. 8 mo. |
| Clinical Stage: | | |
| I | 6 | 7 |
| II | 3 | 1 |
| III | 1 | 5 |
| IV | 2 | 0 |

## RESULTS

The experimental and placebo patient groups were found to be comparable with respect to age, sex, stage of disease, duration of disease and prior therapy (Table I). The placebo group was made up of 8 males and 4 females with the mean age of 56 years and a mean duration of disease of 7 years 3 months. The experimental group was made up of 9 males and 4 females with the mean age of 60 years and an average duration of disease of 6 years 8 months.

The mean L-dopa dosage during the baseline in the placebo group was almost 4000 mg. per day (see Figure 1). The mean L-dopa dosage during the baseline in the alpha methyldopahydrazine treated group was 3750 mg. per day. After adjustment to a clinically optimum dose, it is apparent that at weeks 8, 12 and 16, that the mean L-dopa dosage in the placebo group did not vary significantly. The mean L-dopa dosage necessary for optimum control in the alpha methyldopahydrazine group dropped to approximately one third of that required in the baseline.

Figure 2 displays the total disability over the study as determined by modified Northwestern Disability Scale. It is evident that the alpha methyldopahydrazine group began with a slightly higher mean disability score but this gradually improved over the study period. A statistical analysis at week 16 shows that there was a significant decrease in disability from the baseline in this group. The mean disability score in the placebo group remained unchanged throughout the study.

Figures 3, 4 and 5 show the determinations of rigidity, tremor and bradykinesia. Rigidity decreased in both groups but there was no change in the other parameters.

Table 2 gives an analysis of the side effects during this study. The overall incidence of adverse reactions was the same in the two groups, but there was a considerable difference in the type of reaction seen. It is evident from this table that even though six out of the twelve patients in the placebo group developed adverse side effects, the majority of these were nausea with only one patient developing dyskinesias. Comparison with the alpha methyldopahydrazine treated group, shows that while the majority of the patients with adverse side effects had dyskinesias, five out of six had reported intermittent dyskinesias during the baseline period as well. There was one death from myocardial infarction and one patient with a reversible paranoid psychosis. There were no significant laboratory abnormalities associated with this study.

TABLE II

*Major Side Effects*

| | Baseline | Study Period |
|---|---|---|
| Placebo (N-12) | | |
| Nausea | 2* | 5 |
| Dyskinesias | 1 | 1 |
| Paranoia | 0 | 0 |
| Death | 0 | 0 |
| Alpha Methyldopahydrazine (N-13) | | |
| Nausea | 6 | 2 |
| Dyskinesias | 5 | 6 |
| Paranoia | 0 | 1 |
| Death | 0 | 1 |

*Number of patients.

## DISCUSSION

The addition of alpha methyldopahydrazine to L-dopa therapy in Parkinson's disease is based on this drug's peripheral blockage of dopa decarboxylase activity (Bartholini & Pletscher, 1968). This allows more L-dopa to be available for transport across the blood brain barrier, while at the same time it decreases the circulating catecholamines that appear as a side effect of L-dopa therapy.

Our double-blind study has shown a significant decrease in the amount of L-dopa necessary for adequate Parkinsonian control. The most dramatic effect was the reduction in the incidence of nausea and vomiting as a complication of therapy. This was replaced by the appearance of L-dopa induced dyskinesias.

There seemed to be a minor increase in overall effectiveness with the combination therapy than with L-dopa alone. It was our general impression that there was also smoother control of the dosage using the combination therapy. Many patients with L-dopa induced dyskinesias were not particularly annoyed by the low levels of dyskinesias in order to benefit from what they thought was a better mobility due to the combination therapy.

There was no indication during this study of any toxicity due to the alpha methyldopahydrazine itself. All of the side effects were thought to be due to the effects of L-dopa. Postural hypotension (drop of 20 mm/hg or more from sitting to stand-



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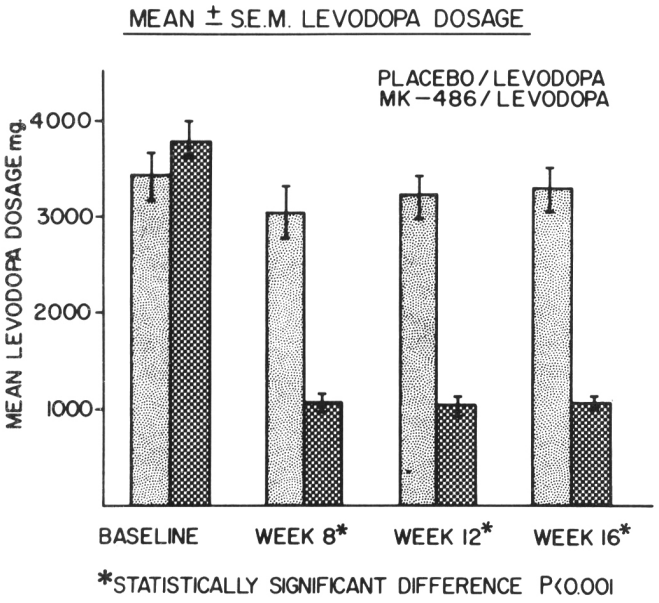



*Figure 1*

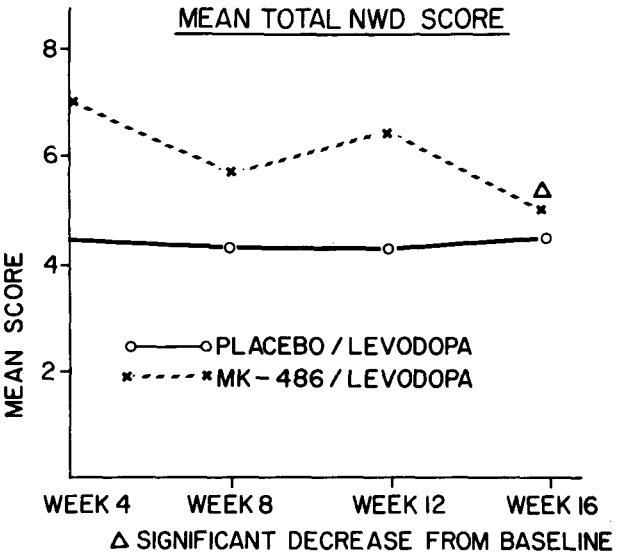



*Figure 2*

ing) was found frequently in all of the patients. The distribution of the incidence of postural hypotension was not significantly different between the two groups. Cardiac arrhythmias were not a serious problem in either group.

In conclusion: from the results of this study, we would feel that combination therapy of L-dopa along with alpha methyldopahydrazine is a significant advance in treating Parkinson's disease. There is a significant reduction in nausea and vomiting associated with this combination therapy along with a mild increase of efficacy of anti-Parkinsonian therapy. The limiting factor in therapy becomes L-dopa induced dyskinesias. The patients generally tolerate these dyskinesias very well, and minor adjustments in the L-dopa therapy can usually minimize this side effect.

*Figure 3*

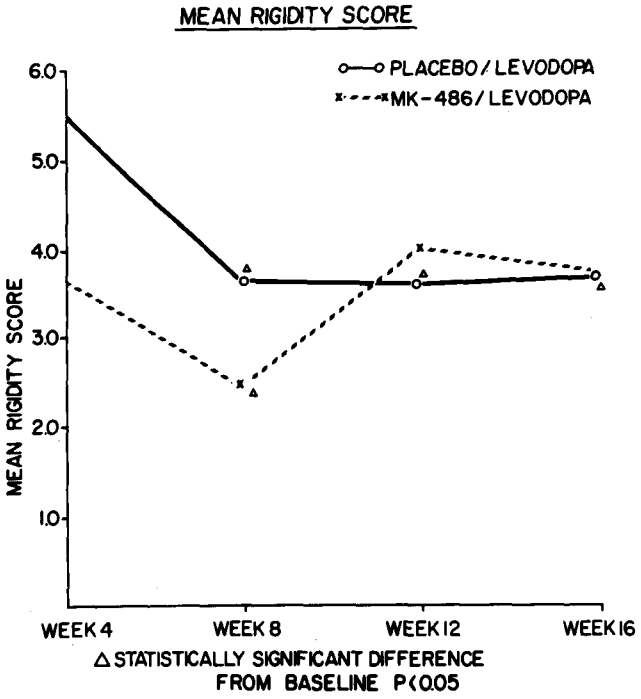
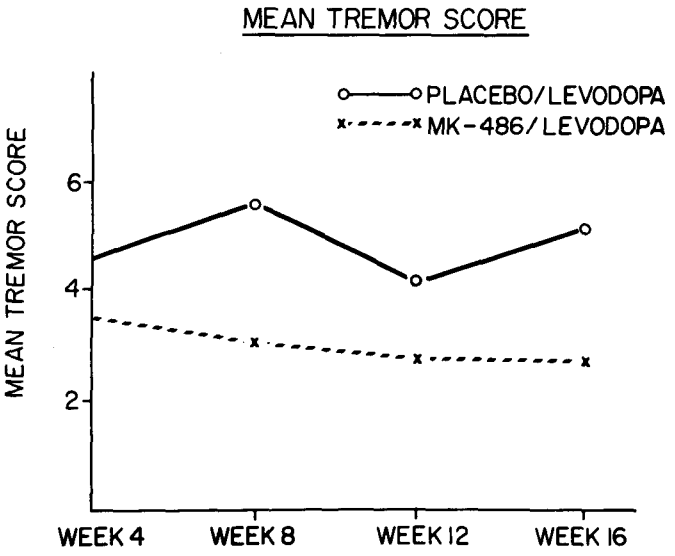



*Figure 4*



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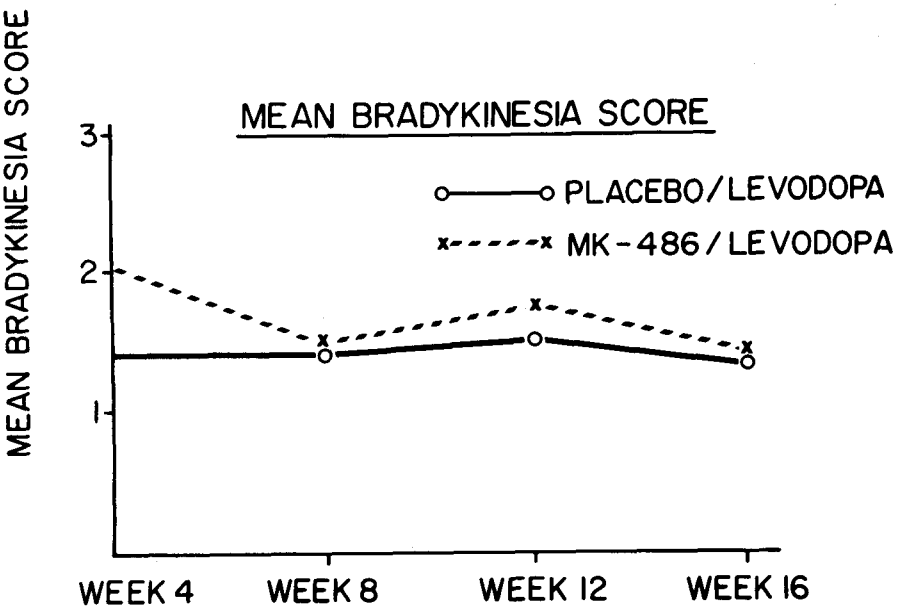


*Figure 5*