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Parkinson's Disease, Amantadine Hydrochloride Therapy and Dopa Metabolites

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SYNOPSIS: In an attempt to clarify the effect of amantadine hydrochloride therapy in Parkinson's disease, dopa metabolites were measured in the urine of 15 patients who were taking this medication. The results indicated that patients on amantadine therapy had lower urinary levels of epinephrine plus norepinephrine than either normal individuals or parkinsonian patients not receiving amantadine. Patients who developed livedo reticularis during amantadine therapy showed a small but significant increase in urinary dopamine levels and a similar decrease in dopac levels, when compared to other patients on amantadine who did not develop livedo reticularis.

Since Schwab and colleagues (1969) have reported on the use of amantadine hydrochloride in the treatment of Parkinson's disease the drug has been investigated by many others, most of whom have found it useful. Unlike the many biochemical studies done on parkinsonian patients on levodopa therapy, little has been reported on biochemical changes in the serum, spinal fluid and urine of patients treated with amantadine hydrochloride. The action of this drug is not well understood at present but there are several theories as to its possible mode of action. Grelak and associates (1970) suggested that the mechanism of action of amantadine may be by the release of catecholamines from storage sites. Parkes *et al.* (1971) indicated that the mode of action of amantadine remains undetermined but they demonstrated that it does not increase the low cerebrospinal fluid homovanillic acid concentrations of patients with Parkinson's disease. Amantadine hydrochloride has little or no anticholinergic action, but will release catecholamines from storage sites in peripheral nerves and myocardium (1969). Scatton *et al.* (1970) demonstrated that amantadine increased the synthesis of dopamine in the striatum of the rat, also increased the release of dopamine from the striatal dopaminergic terminals in this animal. Livedo reticularis is a well-known side effect associated with amantadine therapy in parkinsonian patients. This condition probably results from peripheral arterial constriction; there is some evidence that amantadine may release dopamine or some other dopa metabolite (1971). In an attempt to clarify the effect of amantadine hydrochloride in Parkinson's disease, dopa metabolites were measured in the urine of patients who were taking this medication. Particular attention was paid to those who developed livedo reticularis.

MATERIALS AND METHODS

Ten patients with Parkinson's disease were evaluated in a double-blind double-crossover study in which the patients alternately received either placebo or amantadine hydrochloride. At the end of the two week period of administration of placebo or amantadine hydrochloride a 24-hour urine specimen was collected. Twenty-four-hour specimens were also collected from seven patients who developed livedo reticularis in their extremities while undergoing amantadine therapy; these specimens were collected both during the height of symptoms and later after amantadine had been discontinued for at least two weeks and the symptoms of livedo reticularis had been absent for at least one week. For both groups of patients at least one urine determination was made while the patient was on amantadine and one urine determination while either on no medication or on placebo. The urine was evaluated for epinephrine, norepinephrine, dopamine, dopa, dopac, and homovanillic acid. These compounds were separated from the urine and from each other by passing an aliquot of each specimen through a series of three different ion-exchange columns. Catecholamines (epinephrine, norepinephrine and dopamine) were retained on a cation exchange column. These compounds were eluted with a boric acid solution and quantitatively measured by a fluorimetric analysis. Catechol acids (dopac and homovanillic acid) present in the effluent from the cation exchange column were retained on an anion exchange column. An aliquot of 0.1M NaCl eluate of the anion exchange column was used for a colorimetric determination of dopac. The colorimetric determination of dopa was carried out on an aliquot of the effluent from the anion exchange column. A second aliquot of the 0.1M NaCl eluate from this column was passed over an alumina column which retained all of the acidic metabolites except homovanillic acid. The homovanillic acid in the effluent of the alumina column was then subjected to fluorimetric analysis. The ion-exchange column separation scheme and the detailed quantitative methodology is being reported in a separate communication (1971).

Normal values have been established in this laboratory as follows: epinephrine plus norepinephrine: 0.04 to 0.08 μg/ml; dopac: 2-5 μg/ml; dopamine: 0.2 to 0.3 μg/ml; and dopa: less than 2.0 μg/ml.

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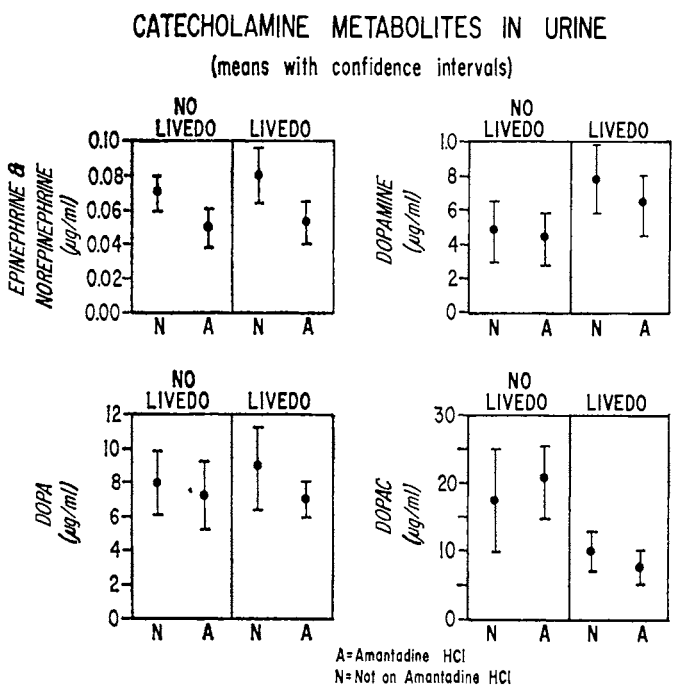
RESULTS

A total of 15 patients were evaluated for urine dopa metabolites. All 15 were grouped together; these data were evaluated and compared with respect to the patients being on and off medication and as to whether they did or did not develop livedo reticularis.

It was found that the range of values of the metabolites in normal individuals was too broad to detect meaningful increases or decreases in these substances in the urine specimens from patients. In general, patients with Parkinson's disease exhibited elevated levels of dopac, dopamine, and dopa in their urine. Patients on amantadine therapy excreted lower levels of epinephrine plus norepinephrine than normal individuals. When patients who developed livedo reticularis were compared with those who did not develop symptoms, no changes in the excretion of the metabolites were observed. Homovanillic acid excretion was similar in patients and normal individuals.



In a further attempt to assess the data, the values of the excreted metabolites from the fifteen patients were subjected to statistical analysis. The mean value of each metabolite was calculated and compared for patients on placebo as well as for patients on amantadine hydrochloride therapy. Means or averages are plotted with confidence intervals on graphs in Figure 1, for four of the measured urine catecholamines and separated into non-livedo and livedo patients. The norepinephrine plus epinephrine values differed significantly between the placebo and the amantadine data, indicating less norepinephrine plus epinephrine in the urine of patients while *on amanta*dine HCl (using a "p" value less than 0.01). This can be seen in the graph for norepinephrine plus epinephrine. The patients were also grouped into those who did and who did not develop livedo reticularis while on amantadine. From the graph no significant difference is noted for the epinephrine plus norepinephrine or dopa in these comparisons. The most significant difference is noted in the means for dopac, where patients who developed livedo reticularis while on amantadine had a significant decrease in the level of dopac in the urine ("p" value = 0.05). Also, there was a decrease of dopac in the urine of all livedo reticularis patients whether they were on or off amantadine; this also is significant at the 5 percent level. Patients with livedo reticularis on or off amantadine had higher levels of dopamine ("p" value = 0.05).

CONCLUSIONS

The results indicate that patients receiving amantadine hydrochloride excreted less norepinephrine plus epinephrine in the urine than when they were not taking the drug. The livedo reticularis patients either on or off the medication excreted less dopac and more dopamine as compared to the non-livedo reticularis patients.

From the above data there is no direct evidence of the release of catecholamines by amantadine hydrochloride as measured in the urine. On the other hand, there is less norepinephrine and epinephrine in the urine during amantadine administration. The significance of the decreased dopac and the increased dopamine levels in the urine in patients who develop livedo reticularis is unknown. Patients who did develop livedo reticularis had a lower creatinine clearance than patients who did not develop the skin disorder. In the parkinsonian patient one might postulate amantadine hydrochloride increases the physiological availability of dopamine by increasing the synthesis of and/or release of dopamine in or from the dopaminergic neurons and thus enhances its effectiveness as a neurotransmitter. This would be consistent with the finding of decreased levels of end metabolites such as norepinephrine and epinephrine. This increased synthesis and/or increased release of dopamine by amantadine hydrochloride has been demonstrated by Scatton and *associates* (1970). One hypothesis for the increased synthesis of dopamine would be some physiological enhancement or increased synthesis of tyrosine hydroxylase (1971). From our data there is little or no support for the concept that amantadine hydrochloride acts to block a metabolic pathway especially from dopamine to dopac or dopamine to norepinephrine, since no elevated levels of dopamine were detectable in the urine when the patient was receiving amantadine. Amantadine hydrochloride also probably does not act as a false neurotransmitter, since we have some data to support the concept that there is a change in the metabolic pathways because of decreased epinephrine and norepinephrine in the urines of patients receiving amantadine. This theory would also explain the development of livedo reticularis since dopamine is a vasoconstrictor, acts on alpha receptors and could produce vasoconstriction in the arteriole of the anatomical cone in the skin to result in a central ischemic area with the peripheral vasodilation. This is the typical fishnet-like appearance of livedo reticularis. Further studies need to be carried out on dopa metabolites in the urine, spinal fluid and serum

in patients receiving amantadine, using proper controls, especially in patients who do not develop livedo reticularis.

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