References

1. Sattes H. Die Behandlung der Chorea major mit dem Manomin-Freisetzer Nitaman. Psychiatr Neurol Neurochir 1960;140:13-9.
2. Brandrup E. Tetrabenacine treatment in persisting dyskinesia caused by psychopharmaca. Am J Psychiatry 1961;118:551-2.
3. Pakkenberg H. The effect of tetrabenazine in some hyperkinetic syndromes. Acta Neurol Scand 1968;44:391-3.
4. Dalby MA: Effect of tetrabenazine on extrapyramidal movement disorders. Br Med J 1969;2:422-3.
5. Swash MA, Roberts AH, Zakko H, Heathfield KWG. Treatment of involuntary movement disorders with tetrabenazine. J Neurol Neurosurg Psychiatry 1972;35:186-91.
6. McClellan DL. The suppression of involuntary movements with tetrabenazine. Scott Med J 1972;17:367-70.
7. Godwin-Austin RB, Clark T. Persistent phenothiazine dyskinesia treated with tetrabenazine. Br Med J 1971;2:25.
8. Kingston D. Tetrabenazine for involuntary movement disorders. Med J Aust 1979;1:628-30.
9. Hawkes CH, Nourse CH. Tetrabenazine in Sydenham's chorea. Br Med J 1977;1:1391-2.
10. Sweet RD, Brunn R, Shapiro E, Shapiro A. Presynaptic catecholamine antagonists as treatment for Tourette syndrome. Arch Gen Psychiatry 1974;31:857-61.
11. Lane JD, Smith JE, Shea PA, McBride WJ. Neurochemical changes following the administration of depleters of biogenic monoamine. Life Sci 1976;19:1663-7.

Amantadine and guanidine are ineffective in ALS

Article abstract—Amantadine and guanidine were evaluated in two groups of 10 amyotrophic lateral sclerosis patients each. In a double-blind, crossover design lasting 1 year, neither drug showed therapeutic benefit as compared to placebo.

NEUROLOGY (Ny) 1981;31:1054-5

Theodore L. Munsat, M.D., Catherine Schmidt Easterday, M.S., RPT, Steven Levy, M.D., Sheldon M. Wolff, M.D., and Robert Hiatt, D. Pharm.

Amyotrophic lateral sclerosis (ALS) remains an enigma for both the research scientist and the clinician. Although many etiologic theories have been proposed, none has withstood scrutiny and none, unfortunately, has led to successful therapy. Among current hypotheses, a viral etiology is the most attractive.[1] We therefore evaluated antiviral agents of low toxicity in a double-blind, crossover study of amantadine HCl and guanidine HCl. Amantadine has been reported to be effective in Creutzfeldt-Jakob disease,[2,3] a neurologic disease of proven viral etiology. Although no longer in common use, guanidine was also reported to be effective in ALS.[4-6]

Methods. After institutional protocol approval and informed patient consent, 20 ALS patients were randomly assigned in equal numbers to either amantadine or guanidine treatment groups. Within each drug group, patients were assigned to treatment or placebo categories and "crossed" at 6 months for an additional 6 months.

All patients met the following criteria: The patient could walk and swallow and had adequate hand function. All patients were free of significant past or present medical illness. Criteria for the diagnosis of ALS included: a combination of both upper and lower motor neuron signs, evidence of disseminated lesions at two or more spinal levels, solely motor abnormality, progressive course, and no evidence of secondary forms of motor neuron disease.[1] All patients had a lumbar puncture, and most had a muscle biopsy and myelography that were consistent with the diagnosis.

Although patients' subjective responses were recorded, evaluation of drug effectiveness was based on a 68-item protocol administered by a research physical therapist to quantitate functional performance and strength. Evaluations were carried out without knowledge of treatment. Respiratory, oropharyngeal, gait, arm, and leg functions were evaluated. In a prestudy evaluation of normals and ALS patients tested repeatedly under controlled conditions by the same examiner, individual test items were found to be reliable within 5 to 15% error. Details of the testing battery can be obtained by request. Each patient was examined monthly for about 1 year. Data were computer-analyzed by standard statistical methods.

Active drugs and placebo were packaged in identical capsules and given three times a day after meals. Guanidine was started at a total daily dose of 25 mg per kilogram. Amantadine was given in a dosage of 100 mg three times daily. Routine blood studies, liver function tests, and tests for nephrotoxicity were carried out monthly.

Results. *Toxicity.* Seven of the 10 patients receiving guanidine had disturbing side effects that required lowering of the dosage. At the conclusion of the study, the mean dose tolerated for the 10

patients was 18.5 mg per kilogram. A prominent increase in weakness, shortly after an individual dose, was reported in four patients. Four patients complained of annoying oral and limb paresthesia. Anorexia in three patients and a mild delusional state in one remitted on a lower dose. No patient had evidence of significant hematologic, hepatic, or renal toxicity.

Amantadine was tolerated well, and in no case was the dosage lowered or the drug discontinued. Single patients reported dryness of the mouth or depression. One patient had mild transient hypertension, and one each had transient elevation of serum albumin, alkaline phosphatase, or sedimentation rate.

Clinical course. No significant measurable drug benefit was observed for either active agent or placebo.

Discussion. Although the etiology and pathogenesis of ALS are not understood, a continued search for therapy is justified, because of the destructive nature of the disease. In addition, therapy has resulted in significant alleviation of Wilson disease and parkinsonism, even though the etiology has not been established. Therapy in ALS directed against the putative viral agent has been unsuccessful. Therapeutic failure has been reported for isoprinosine in Guamanian and sporadic ALS,[7-10] idoxuridine,[11] tilorone,[12] and transfer factor.[13,14] In an uncontrolled trial of amantadine, there was no benefit.[15]

Guanidine enhances neurotransmitter release and has modest antiviral activity.[16,17] In 1971, Norris[4] reported "improvement sustained more than six months in each of eight (ALS) patients in a group of 17 treated with vitamins, active physical therapy and guanidine hydrochloride. In two of the eight cases, cessation of guanidine seemed to be followed by neurologic deterioration and resumption of the drug was followed by improvement." Subsequently, Norris[4] reported that 30 of 84 patients treated for 6 months "seemed to stabilize neurologically and some even improved." The complete study appeared later,[6] reporting a lower mortality at 6 months in patients receiving high-dose (25 mg per kilogram per day) guanidine, although at 10 months no difference in mortality was observed. Our study failed to confirm reports of any benefit.

From the Department of Neurology, School of Medicine, University of California, San Francisco, CA.

Presented in part at the thirty-second annual meeting of the American Academy of Neurology, New Orleans, LA, 1980.

Accepted for publication December 1, 1980.

Address correspondence and reprint requests to Dr. Munsat, Tufts-New England Medical Center, Department of Neurology, 171 Harrison Avenue, Boston, MA 02111.

References

1. Munsat TL, Bradley WG. Amyotrophic lateral sclerosis. In: Tyler RR, Dawson DD, eds. Current neurology. Boston: Houghton Mifflin, vol 2, 1979.
2. Braham J. Jacob Creutzfeldt diseases: treatment by amantadine. Br Med J 1971;4:212-3.
3. Sanders WL, Dunn TL. Creutzfeldt-Jakob disease treated with amantadine: a report of two cases. J Neurol Neurosurg Psychiatry 1973;36:581-4.
4. Norris FH. Prognosis in amyotrophic lateral sclerosis. Trans Am Neurol Assoc 1971;16:290-1.
5. Norris FH Jr. Guanidine in amyotrophic lateral sclerosis (letter to the editor). N Engl J Med 1974;288:690-1.
6. Norris FH Jr. The administration of guanidine in amyotrophic lateral sclerosis. Neurology (Minneap) 1974;24:721-8.
7. Brody JA, Chen KM, Yase Y, et al. Inosiplex and amyotrophic lateral sclerosis: therapeutic trial in patients on Guam. Arch Neurol 1974;30:322-3.
8. Fareed GC, Tyler HR. The use of isoprinosine in patients with amyotrophic lateral sclerosis. Neurology (Minneap) 1971;21:937-40.
9. Davidson MB. Failure of isoprinosine in amyotrophic lateral sclerosis (letter to the editor). N Engl J Med 1971;285:689.
10. Percy AK, David LE, Johnston D, Drachman DB. Failure of isoprinosine in ALS. N Engl J Med 1971;285:689.
11. Liversedge LA, Swinburn WR, Yuill GM. Idoxuridine and motor neurone disease. Br Med J 1970;1:755-6.
12. Olson WH, Simons JA, Halaas GW. Therapeutic trial of tilorone in ALS: lack of benefit in a double-blind placebo controlled study. Neurology (Ny) 1978;28:1293-5.
13. Jonas S, Wichter M, Spitter L. Amyotrophic lateral sclerosis: failure of transfer factor. Ann Neurol 1979;6:84.
14. Olarte M, Gersten J, Zabriske J, Rowland L. Transfer factor is ineffective in ALS. Ann Neurol 1979;5:385-8.
15. Engel WK, Hogenhuis LAH, Collis WJ, et al. Metabolic studies and therapeutic trials in amyotrophic lateral sclerosis. In: Motor neuron diseases: research on amyotrophic lateral sclerosis and related disorders. Contemp Neurol Symp, New York: Grune & Stratton, 1968:199.
16. Rightsel WA, Dice JR, McAlpine RJ, et al. Antiviral effect of guanidine. Science 1961;134:558-9.
17. Crowther D, Melnick JL. Studies of the inhibitory action of guanidine on poliovirus multiplication in cell cultures. Virology 1961;15:65-74.

Amantadine and guanidine are ineffective in ALS

Theodore L. Munsat, Catherine Schmidt Easterday, Steven Levy, et al.

Neurology 1981;31;1054
DOI 10.1212/WNL.31.8.1054