Lack of effect of 4-aminopyridine on choreic movements

Sir: The pathophysiology of Huntington’s disease remains unknown, but recent research has pointed out defects of several neurotransmitter systems in the corpus striatum of such patients. Both cholinergic and GABA-ergic transmission are thought to be diminished, and substance P-containing neurons may be reduced, indicating a complex pathophysiology. Dopaminergic transmission, on the other hand, is probably normal and the involuntary movements have been ascribed to the resulting dysequilibrium between cholinergic and dopaminergic transmission. Attempts to treat this disorder pharmacologically have not been successful and no curative therapy is known. Anti-dopaminergic drugs are considered to have some effect on the choreic movements, but drugs supposed to enhance cholinergic transmission have proved ineffective. Results on GABA-ergic drugs have been conflicting.

Our lack of knowledge on the pathophysiology and treatment of Huntington’s disease justifies clinical trials of new drugs. 4-Aminopyridine (4-AP) is neuropharmacologically a very active substance enhancing several types of synaptic transmission. In the peripheral nervous system activity at cholinergic, adrenergic, and glutaminergic synapses is potentiated, and in the central nervous system both excitatory and inhibitory postsynaptic potentials are augmented. The drug has an analeptic effect. The drug has been used clinically in the treatment of disorders of neuromuscular transmission and as an anticonvulsant.

We have tried 4-AP in the treatment of three cases of Huntington’s disease. All three patients (age 49, 49 and 53 yr) had during the last few years developed a typical clinical picture of this disease with generalized choreic movements and dementia. Two of them had a positive family history and in the third case heredity could not be assessed. Treatment with haloperidol and lithium carbonate did not eliminate the involuntary movements but may have had some minor effect. All drugs, except insulin in one case, were withdrawn before the trial. The patients and their relatives gave their written consent.

The clinical status of the patients was assessed before and during the different treatments by the following tests, most of them timed: tongue protrusion, alternating movements, filling a pegboard, putting a nut on a screw, and walking on a straight line. Choreic movements were recorded by exposing a still film for 90 seconds to a wall in a dark room, to which the patient pointed with a laser beam, aiming at a specific mark, and then trying to move the beam in a pre-determined pattern. Finally in one patient, moving pictures were taken during 3-10 minutes of different activities. Double-blind, cross-over technique was used, each patient receiving an iv injection of 15-20 mg of 4-AP chloride or saline (placebo) at the same hour on two consecutive days. Continuous oral treatment was given 7-14 days with 50-120 mg of 4-AP sulphate in 4-5 doses per day or sugar (placebo) in identical capsules.

Neither intravenous injection nor oral treatment eliminated the choreic movements in these patients. Critical evaluation of all the test results demonstrated that 4-AP had no discernible effect on the choreic movements although two of the patients themselves reported that their chorea improved on 4-AP. After intravenous injection of 4-AP perioral parasthesiae were reported regularly and one patient complained of sleepiness, but no other side effects occurred. The great difficulties in evaluating possible significant changes of choreic movements against a variable spontaneous background of involuntary movements became obvious during the performance of this project, and may be the explanation for the many contradictory reports on drug effects in Huntington’s disease including the positive results with 4-AP recently reported by Wesseling and Lakke.

It may be of interest that psychological tests in one of the patients showed improvement during continuous oral medication with 4-AP, but no systematic examination of effects on mental functions was performed. Considering the strong cholinergic activity of 4-AP and the low concentration of choline acetyltransferase found in dementia, we suggest that the drug should be tried in different types of dementia, perhaps in combination with the acetylcholine precursor choline. We also tried 4-AP treatment in a 52-year-old male with oromandibular dystonia (Meige’s or Brueghel’s syndrome) without effect on the involuntary movements in that disease.

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