Tacrine improves Huntington’s chorea

Martin Sommer¹, Astrid Scheschonka², Wolfgang Beuche²,³

¹Department of Clinical Neurophysiology
²Department of Neurology, University of Goettingen, Germany
³Department of Neurology, St. Georg Hospital, Leipzig, Germany

Summary

Since hyperkinesia in Huntington’s disease (HD) is at least in part due to a degeneration of the cholinergic system, we undertook an open pilot trial testing the effect of the cholinesterase inhibitor Tacrine in patients with genetically proven Huntington’s disease. The extent of hyperkinesia was assessed while the patient was (i) off medication, (ii) on Tacrine alone and, in 3 patients, (II) on Tacrine and Perphenacine. Tacrine significantly reduced hyperkinesias, with only a slight additional benefit for the combined therapy. We conclude that there is a potential benefit of cholinesterase inhibitors in HD that should be evaluated in randomised, double-blind clinical trials.

Introduction

Huntington’s chorea is an autosomal dominant disorder that leads to progressive choreatic hyperkinetic movements, personality changes, and mental deterioration [2]. Although the basic genetic defect has been elucidated and resides in an increased number of glutamine coding CAG triplets over 36 copies within the reading frame of the huntingtin gene [2], the basic mechanisms of this neurodegenerative disorder is not understood. Hitherto only symptomatic treatment is possible together with genetic counselling to the patients family. Several drugs have been applied mainly for suppression of involuntary movements to give some relieve to the patients. As hyperkinesia is thought to be the consequence of damage of the acetylcholinergic system within the basal ganglia, neuroleptic drugs are able to suppress these movements by reducing the action of the dopaminergic system, thus setting both systems to an artificial balance. Several alternative drugs have been tested, from which piracetam [9], proglumide [13], milacemide [7] and cannabidiol [5] were ineffective, while bromocriptin [16], apomorphin [1], remacemide [8] and dexamethasone [12] showed positive effects. Clozapine in some studies was also beneficial [4], while in others it was ineffective at least in patients already taking neuroleptics [17]. Since hyperkinesia follows degeneration of the acetylcholinergic striatal system, we tested the pharmacological effect of the central acting cholinesterase inhibitor Tacrine in five patients with Huntington’s chorea in vivo as an open pilot study using semi-automated movement quantification. Tacrine is able to reduce mental deficits in Alzheimer’s disease patients, where degeneration of cholinergic neurons plays a central role in the development of dementia.

Methods

1) Subjects and medication
We studied 5 patients with genetically confirmed Huntington’s disease who had given informed consent to the study. Details on their history, genetic testing, family
Clinical characteristics of 5 patients with genetically proven Huntington's disease. NA = not available; Liver enzymes comprise AST, ALT, total bilirubin, alkaline phosphatase, and gamma-glutamyltransferase; * refers to delay between Baseline and measurement Post 2. In this patient recording could not be performed during Tacrine monotherapy; **= after dyspepsia had disappeared.

For quantification of hypokinesia we used a 3-dimensional motion analysis system (Optotrak 3010, Northern Digital, Ontario, Canada) placed in an ambient, silent room. This system is a well-established tool for high-precision 3D-localisation and has been used for a variety of clinical and research applications [3, 10, 11, 15]. We recorded hypokinesias three times, at baseline without Tracrine or Neuroleptics, a first time after introduction of Tacrine (Post 1), and finally after addition of a neuroleptic drug (Perphenazine or Tiaprid, Post 2). Patient 3 could not be scheduled for Post 1, so that only the combined effect of Tacrine and Tiaprid could be assessed at Post 2; patient 5 could not be scheduled for a third appointment (see table). During each recording session five special light-emitting diodes were fixed with adhesive tape on the subject who was standing in front of the recording cameras (one diode at each knee, one at each shoulder and one at the front). Recording frequency was 100 Hz, and samples of 100 seconds duration were recorded. Before starting each sample the subject was asked not to speak and not to move voluntarily. During recording, the investigator did not talk to the subject. We took particular care to reject and immediately repeat samples in which the subject had spoken or made voluntary movements.

In addition, we asked the patients and their family, if available, whether any effect of medication was observed, and we monitored liver enzymes during each visit.

2) Data analysis
Movement amplitudes were analysed for each diode separately by calculating the length of vectors between every two consecutive samples, using the square root of the sum of the squares of differences in each axis. Data was entered in a purpose-written Matlab-program for Fourier transformation, depiction of the frequency spectrum, and calculation of the sum of distance travelled per diode per recording session [14]. Frequency power was maximal below 1 Hz in all patients, above ~1.5 Hz the spectrum was flat in all patients. Frequency peaks were not always discernible, which is why used unfiltered data for statistics. The reliability of measurement was assessed in two patients in whom two samples of 100 seconds each were recorded at Post 2 and correlated using Fishers r to z test (Statview 5.0, SAS Institute, Cary, NC, USA).

To assess the effect of Tacrine and the additional effect of the neuroleptics on movement amplitude we entered the total way travelled per diode and per subject in two repeated-measures ANOVAs, one with 'time' (Baseline, Post 1) as within-subjects factor and 'limb' as between-subjects factor to assess the Tacrine effect in subjects 1, 2, 4, and 5, the other with 'time' (Post 1, Post 2) as within-subjects factor and 'limb' as between-subjects factor to assess the additional neuroleptic effect in subjects 1, 2 and 4.

Results
Tacrine was well tolerated except an initial phase of dyspepsia in two patients, which disappeared later on in patient 4 and after transient reduction of dosage and prolonged time for re-increase of daily dose in patient 1. No increase of liver enzymes occurred.

Sample-to-sample movement measurement reliability was high (r >0.9, p<0.0013 in either patient).

Across patients the total distance travelled declined from baseline to Post 1, similarly for all limbs (repeated-
Concerning clinical effects, patient 1 reported not to have fallen any more at Post 1 and Post 2 measurement, no family report was available. Patient 2 did not notice any change, her spouse indicated at Post 1 that the patient appeared more concentrated, and that she had been breaking less dishes, this effect was said to persist at Post 2. Patient 3 reported his walking to be improved and the hands less shaky, so that eating with fork and knife had become easier, no family report was available. At Post 1, patient 4 reported decreased involuntary movements, the daughter indicated a better memory of phone numbers, and the nurses from the ward a better spatial orientation of the patient (she was finding her room on the ward by herself, which she had not been able to at Baseline). Patient 5 reported no effect at Post 1, no family report was available.

Discussion

To our knowledge an application of the central acting acetylcholinergic drug Tacrine has not been reported in Huntington’s disease so far. The method applied gives the opportunity for objective quantification of movements in cooperative individuals even for single extremities. A clear antihyperkinetic effect is demonstrated by Tacrine 60 - 180 mg per day. The positive effect of Tacrine was not significantly ameliorated by addition of Perphenacine or Tiaprid.

An earlier open label study on donepezil indicated some improvement of cognitive and motor function in patients with HD, but with a marked range of side effects [6]. Apart from a more exact movement analysis, in our study the concomitant medication was limited to a minimum, and the addition of neuroleptics performed in a controlled fashion, which could have contributed to the low incidence of side effects. Limitations of our study are the lack of a placebo control and the lack of neuropsychological testing evaluating possible cognitive effects of Tacrine. Another limitation is the use of an acetylcholinergic drug with potentially important side effects.

In summary, this open-label pilot study suggests that the central acetylcholinergic drug Tacrine may be of palliative use in the fatal disorder of Huntington’s disease. Hence, we propose drugs of this class to be evaluated in double-blind, placebo-controlled studies. These studies should probably rely on newer cholinesterase inhibitors with less side effects.

Acknowledgements:

We are grateful to Arno Ickler, Third Department of Physics, University of Göttingen, for writing the analysis software.
References


Tacrine improves Huntington's chorea

Martin Sommer¹, Astrid Scheschonka², Wolfgang Beuche²,³

¹Department of Clinical Neurophysiology
²Department of Neurology, University of Goettingen, Germany
³Department of Neurology, St. Georg Hospital, Leipzig, Germany