

An Open-Label Trial of Donepezil (Aricept) in the Treatment of Persons With Mild Traumatic Brain Injury

SIR: We read with interest, the review by Griffin et. al.¹ on the use of cholinergic agents in the treatment of persons who sustained traumatic brain injury (TBI). As early as 1997 (Poster session at the joint meeting of the American Neuropsychiatric Association and the British Neuropsychiatry Association. Cambridge, England.), we too suspected that these medications might be beneficial in treating cognitive dysfunction, memory deficits, and emotional instability, all observed in TBI.

Our findings revealed the following:

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Methods:

In an open label trial, subjects who participated in this pilot program were the first 10 consecutive patients known to have sustained TBI and received treatment in one outpatient practice after the release of donepezil. Patients were given 5 mg daily for the first 4 weeks and 10 mg daily for the second 4 weeks. Pretreatment and posttreatment neuropsychiatric evaluations, including clinical global improvement (CGI) ratings and a symptom focused neuropsychological test battery, were used to measure responses to the medication.

Results:

Eighty percent (8/10) of the subjects completed the study. One subject withdrew due to noncompliance, and another dropped out due to intolerable GI side effects of nausea. This heterogeneous group ranged in age from 26–60 years, with a mean of 41 years. Severity of head injury included mild (6 cases), moderate (1 case), and severe (3 cases). Time since head injury ranged from 1 to 5 years, with a mean of 1.2 years.

Discussion:

Although we predicted improvement in the domain of memory, we were unable to document any such positive change. The Global Memory Scale (GMS) of the Memory Assessment Scale (MAS) does not seem to improve (MAS margin of error is ± 4 points.) However, CGI's conducted by two independent raters showed improvement. Patients also rated themselves somewhat improved in most cases, but not necessarily in the memory domain as expected. The overall impression was that they had improved focus, attention and clarity of thought while on the medication. A number of patients commented that their speed of processing appeared to be better or they were able to keep multiple ideas in mind simultaneously. Family members frequently described improved socialization.

We are encouraged by the results and believe that further study of donepezil in TBI is indicated. We would recommend assessing change by using other test instruments, such as the Categories Test, which is better suited to assess cog-

nitive flexibility, nonverbal abstract reasoning, learning from mistakes, and incidental visual memory. In addition, a larger trial should, as a minimum, control for age, severity of injury, time since injury, and intelligence quotient (IQ). A subsequent controlled trial that uses traditional blinding methods and placebo could follow if warranted.

Of note, is that at the end of the study, seven of the eight subjects who completed the study (88%) elected to remain on donepezil, as they believed it was efficacious. The only subject who completed the study and did not elect to stay on the medication reported a positive effect on memory, but experienced nausea as a side effect.

Conclusion:

Testing Donepezil—which is approved, available, and well tolerated—in a patient population that historically has limited progress should prove useful. As in Alzheimer's disease (AD), the acetylcholinesterase inhibitors may be of greater benefit in the overall functioning of the individual than the specific domain of memory.²

Dr. Kaye speaks for Pfizer Pharmaceuticals. He has never owned stock in the corporation and has never been an employee. No funding from any outside source was used in this study.

NEIL S. KAYE, M.D.

Clinical Assistant Professor of Psychiatry and Human Behavior and Clinical Assistant Professor of Family Medicine, Jefferson Medical College, Philadelphia, Pennsylvania.

JOHN B. TOWNSEND, III, M.D.

RICHARD IVINS, PH.D.

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Patient	DOB	Age	Date of TBI	Age at TBI	Severity	Imaging	MAS Pre Donepezil	MAS on Donepezil GMS	CGI on Donepezil GMS	Notes
1. S.D.	04/04/61	36	03/06/92	30	Severe LOC	CT +	98	87	4	No change
2. X.P.	03/09/47	50	01/17/94	46	Severe LOC > 20"	SPECT - PET + MRI + PET +	Bender 3 memories Digit Span 6 forward Digit Span 4 back 108	Bender 5 memories Digit Span 5 forward Digit Span 4 back 83	0	Nausea, not tolerated
3. S.E.	12/01/57	39	12/03/93	36	Mild LOC	PET + MRI + PET +	82	Not available	2	Better focus Increased speed of processing Dropped out
4. O.R.	1/10/69	28	02/22/95	26	Mild GCS 13 LOC	CT - PET +	80		0	
5. C.G.	06/29/59	37	02/26/96	36	Mild LOC < 5"	MRI - PET +	65	68	2	Better focus, memory
6. I.A.	08/17/51	45	06/29/95	43	Mild No LOC	MRI - CT -	88	63	3	Better memory but felt too nauseous to continue after study completed
7. B.M.	07/04/41	56	03/31/95	53	Mild No LOC	PET + CT -	58	66	3	Some improvement in memory
8. B.K.	06/01/56	41	12/11/95	39	Severe LOC > 45"	MRI + CT +	80	53	3	Better memory, focus Increased speed of processing Better memory
9. M.G.	12/18/51	45	01/24/96	44	Moderate LOC	CT - MRI -	89	89	2	Returned to work part time
10. H.D.	05/22/35	62	03/01/96	60	Mild No LOC	PET + MRI -	Bender 0 memories Digit Span 5 forward Digit Span 3 back	Bender 1 memory Digit Span 5 forward Digit Span 3 back	1	Returned to work part time

Neil S. Kaye, M.D., John Townsend, M.D., and Richard Ivins, Ph.D.

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2. Rogers S, et al: Donepezil improves cognition and global function in Alzheimer disease. *Arch Intern Med* 1998; 14:197-230

In Reply

SIR: Thank you for the opportunity to respond to Dr. Kaye and colleague's letter. The open-label pilot study that these authors describe adds to the data from other reports/investigations reviewed in our paper¹ that suggest some promise for acetylcholinesterase inhibitors in treating the neurobehavioral sequelae of traumatic brain injury (TBI). We agree with Dr. Kaye's conclusion that additional research into the efficacy of donepezil (and other acetylcholinesterase inhibitors) in TBI is warranted. Like many of the uncontrolled studies that we reviewed, positive findings in Dr. Kaye's report (i.e., increase in clinical global improvement ratings) are difficult to disentangle from the potential effects of placebo, spontaneous recovery, and/or concurrent treatment. Negative findings (i.e., no significant improvement on a memory measure) are similarly difficult to interpret, in the context of a short follow-up period.

Based on our review of the literature, we believe that there is now sufficient theoretical and preliminary empirical evidence to move beyond pilot studies to large-scale clinical trials. We recommend that such trials incorporate methodological considerations, including: a) randomized double-blind placebo-

controlled design; b) sample size selection based on the hypothesized degree of improvement on the primary outcome measure; c) selection of subjects based on specific cognitive inclusion criteria (e.g., demonstrable impairment at baseline in those cognitive realms that are hypothesized to be responsive to cholinesterase inhibition); and d) sufficient duration of intervention to allow for measurement of cognitive and functional improvement. Additionally, we would like to underscore recommendations made in our review article that stress the importance of selecting outcome measures that: a) are sensitive to the type of cognitive impairment observed following TBI; b) have been associated with cholinergic deficit; c) have been shown to be responsive to acetylcholinesterase inhibition; and d) address outcomes other than cognition, including affect, behavior, and functional outcome. Certainly, Dr. Kaye's call to include cognitive outcome measures targeting executive functioning (i.e., "cognitive flexibility, verbal abstract reasoning, learning from mistakes") is supported by the literature relating to the mechanisms of action of acetylcholinesterase inhibitors. In keeping with the above recommendations, we are in the process of conducting a double-blind randomized controlled trial (RCT) to study the effects of donepezil on cognitive, behavioral, functional, and quality of life outcomes during a 6-month follow-up period in 92 subjects with TBI. We look forward to reporting our data when the study is complete.

Sincerely,

STEFANIE L. GRIFFIN, PH.D.

Division of Behavioral Neurology and Cognitive Neuroscience, University of Iowa Hospitals and Clinics. Iowa City, IA

ROBERT VAN REEKUM, M.D.,
FRCPC

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Akinetic Mutism Following Unilateral Anterior Cerebral Artery Occlusion

SIR: Since the initial description of akinetic mutism in 1931, lesions in a variety of locations have been associated with this and other disorders of diminished motivation.¹ Akinetic mutism, the most severe of these disorders, is most commonly associated with bilateral hemispheric pathology,² although unilateral lesions may produce this condition as well.³ We describe a man with akinetic mutism due to an ischemic stroke in the distribution of the left anterior cerebral artery. This report may offer additional insight into the mechanism of akinetic mutism following unilateral hemispheric injury.

Case Report

Our patient is a 61-year-old right-handed man who presented to the emergency department with an acute onset of right-leg weakness. During the course of several hours, his weakness progressed to include his right arm; and he stopped speaking. On examination, he was alert but produced no spontaneous speech and had only rare, spontaneous movement of his nonparetic left arm and leg. With repeated prompting, he followed single-step commands, using only his left side.

An arteriogram demonstrated occlusion of the left anterior cerebral artery. Magnetic resonance imaging, which included diffusion-weighted sequences, was performed 6 days after the onset of symptoms

and demonstrated an infarction in the distribution of the left anterior cerebral artery, involving the cingulate gyrus and the left half of the corpus callosum.

During the course of several weeks, as the patient became more interactive, he demonstrated normal language function and some improvement in his right hemiparesis. As he became more communicative, right hemineglect became apparent. Despite these improvements, the patient remained apathetic and functionally disabled and was transferred to a rehabilitation facility for further care.

Comment

To our knowledge, this case is the first *in vivo* description of acute akinetic mutism produced by a unilateral infarction of the cingulate gyrus in combination with disconnection of the contralateral cingulate gyrus due to hemi-infarction of the corpus callosum. The syndrome of akinetic mutism is typically the result of bilateral hemispheric injury, usually involving the anterior cingulate gyri.² Other locations for lesions producing akinetic mutism include the thalami, globus pallidus, internal capsule, and frontal white matter.³ These lesions are thought to disrupt anterior frontal subcortical circuits that subservise motivation.⁴ In our patient, the syndrome of akinetic mutism appears to be the result of a lesion in the body of the cingulate gyrus in one hemisphere in combination with the extension of the stroke into the body of the corpus callosum, effectively disconnecting the functional contralateral cingulate gyrus. In effect, this unilateral lesion disrupted bilateral pathways that are necessary in order to sustain normal motivation.

The involvement of bilateral callosal fibers in the regions of the anterior cingulate may also explain

the profound hemineglect that emerged as the akinetic mutism improved. The anterior cingulate cortex is part of a bihemispheric network of cortical, subcortical, and white matter structures that are involved in attention, including spatial attention.⁵ The left cingulate lesion and callosal disconnection may have sufficiently disrupted the patient's spatial attention network such that right visual neglect and anosognosia resulted.

C. ALAN ANDERSON, M.D.

DAVID B. ARCINIEGAS, M.D.

DANIEL C. HUDDLE, M.D.

MAUREEN A. LEEHEY, M.D.

Departments of Neurology (C.A.A., D.B.A., M.A.L.), Psychiatry (C.A.A., D.B.A.), and Radiology (D.C.H.), University of Colorado Health Sciences Center, Denver, CO; (C.A.A., M.A.L., D.B.A.), Denver Veteran's Affairs Medical Center, Denver, CO

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Genetic and Environmental Interactions in Psychiatric Illnesses

Strong evidence supports a genetic basis for many psychiatric illnesses,

such as Huntington disease (HD), autism, schizophrenia, and depression. In most of these diseases, environmental factors are implicated. Interactions between environment and genome, however, are unclear.

Although HD, autism, schizophrenia, and depression are genetically determined diseases, they do not inevitably have onset at birth. In fact delayed onset is generally the case. In autism, the peak onset is before 3 years of age and between 20 and 30, 20 and 40, and 35 and 40 years of age in schizophrenia, depression, and HD, respectively. Since detecting the disease depends on the sensitivity of clinical evaluations and the degree of repercussion of the disease on the patients' ability to function in daily life, a reasonable assumption might be that the disease process precedes the clinical manifestation. In fact, the degeneration process in HD unfolds over a lengthy period prior to clinical manifestation, and appropriate screening for schizophrenia detects prodromes before the first break.⁵ Granting these factors account for the delay in clinical onset relative to gene expression (or active disease process), they are not sufficient to indicate that the underlying genes are expressed from the very beginning since birth.

In addition to the variation in the age of onset between HD, autism, schizophrenia, and depression, these illnesses vary considerably in their time course. In autism, steady qualities of deficits are present, and learning and adaptation are impaired or facilitated in specific ways. Schizophrenia and depression have episodic courses, with variable degrees of remission between episodes, while the deficits in HD progress steadily. Furthermore, genes have variable roles in these illnesses. Defective genes are sufficient for the development of HD,

however, current opinions suggest that genes are necessary but not sufficient for the development of schizophrenia or depression.

The variation in age of onset and time course and the possibility of environment-dependant gene expression leave a number of questions open for discussion: (1) What is the relationship between gene expression and clinical manifestation? (2) Are underlying genes expressed, from the outset since birth (or even before birth) or at different time points during development? (3) Are the exacerbation and remission of schizophrenia and depression associated with corresponding fluctuation in gene expression?

Jacob and Monod⁶ discovered that genes in prokaryotes could be regulated by environmental factors. They showed that only in the presence of lactose does *Escherichia coli* greatly synthesize an enzyme that breaks down lactose. Since the Jacob and Monod⁶ study, the regulation of gene expression in eukaryotes has been investigated extensively and found to take place at multiple levels, such as transcription, translation, and gene rearrangement. The widely accepted view is that genes fall into one of two basic categories: those that express themselves at a steady rate, regardless of environmental conditions (i.e., constitutive genes), and those that are subject to regulation (i.e., inducible genes).

The first category probably subserves the essential constituents of an organism. On the other hand, gene expression regulation has been implicated in a variety of processes, such as learning, memory, adaptation, and development.⁷⁻¹⁰ Thus the second category must be the site for environmental and genetic interaction.

We hypothesize that autism is determined by constitutive genes,

which would explain the possibility of onset at birth, the stable time course, and the qualities of deficits. According to this view, autism thwarts development; but the pathology itself is not developmental, and environmental factors are of no importance. We also propose that the HD gene is from the constitutive group, which explains the steady progression. The variability of the age of onset could be linked to the variability in the rate of gene expression. In addition, we believe that schizophrenia and depression are linked to genes from the second group (inducible genes). At some point during adaptive and cognitive development, defective genes are called upon, giving rise to psychotic or mood breakdown. The brain dynamic systems could restabilize to some extent, but only for awhile, which accounts for the late onset and the episodic course.

MASSOUD STEPHANE, M.D.

Department of Psychiatry, and the Domenici Research Center for Mental Illness, VA Medical Center, University of Minnesota, Minneapolis, MN 55417

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