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REPORT

Needless Brain Wasting

Many afflicted with neurological disease have a poor prognosis. A drug that has been used in Germany for more than twenty years offers hope, but is not yet available to Americans. The following report is highly technical. It has been written for the purpose of making a scientific statement so that the FDA may approve this promising therapy sooner.

Neurotransmitters in the brain oversee our mental and physiological functions. They are the chemicals that allow our nerve cells (neurons) to communicate with each other, our muscles and other cells. Neurotransmitters are essential for nearly all of our bodily functions.

The amino acid glutamate is known as an “excitatory” neurotransmitter because it induces activity or “firing” of a neuron. Under normal circumstances, glutamate helps send signals along nerve neuronal pathways. It is related to learning, memory, other cognitive functions and much more.

In certain medical conditions, however, glutamate becomes toxic to nerve cells. This damage starts with an excess of glutamate in the spaces between neurons, where it binds to— and overstimulates— NMDA (N-methyl-D-aspartate) receptors.

NMDA receptors are one of many different types of proteins that reside on cell surfaces. When NMDA receptors get overexcited, a cascade of events result in nerve cell death.

Many degenerative brain diseases may have a connection to the out-of-control glutamate-NMDA related killing of brain cells. Stroke, trauma and various forms of dementia are related to glutamate-NMDA excitotoxicity.

A drug that suppresses “excitotoxicity”

Knowing about the sinister role of glutamate with regards to NMDA receptors, scientists have been weighing the therapeutic possibilities of utilizing NMDA receptor blockers to inhibit glutamate’s capacity for neuronal damage.

In fact, over 20 different NMDA receptor blockers are currently being investigated. The trouble with many NMDA antagonists is that they are overactive, causing a complete blockage of normal glutamate activity. The trick is finding an NMDA antagonist that blocks only the excessive glutamate signaling, which is causing the damage.

One partial blocker called MK-801 (dizocilpine) could not be used because it impaired normal neuronal functioning, becoming toxic at therapeutic dosages. Another contender, however, called memantine, seems to strike a favorable balance, inhibiting NMDA enough to help prevent damage, but not so much as to be too toxic to normal neuronal function. Memantine, a derivative of the decades old anti-influenza drug Amantadine, is being explored as potentially useful for a number of neuropathological disorders.

Memantine and Alzheimer’s disease

The best known neurotransmitter, especially with regard to Alzheimer’s dementia, is acetylcholine. However, drugs aimed at increasing acetylcholine levels, especially Tacrine and Aricept (trade names), have been shown to have only moderate effect in delaying the deterioration associated with Alzheimer’s disease. Memantine is in a completely different class of drugs than what is currently approved by the FDA for the treatment of Alzheimer’s, as it targets glutamate instead of acetylcholine. A number of studies have been turning up evidence that memantine may hold promise in the treatment of Alzheimer’s.

For example, when researchers studied 151 patients with severe dementia in a placebo controlled study, they found that more than 70% responded to memantine compared to less than 50% for placebo.(1) The patients on memantine also significantly outperformed the placebo group in terms of cognitive functioning and, consequently, care dependence. The more that patients improved mentally, the better they could care for themselves. To date, the drugs used and approved in the U.S. for Alzheimer’s have only been able to slow the progression of the disease but have not, as the memantine research shows, been able to



demonstrate significant cognitive and quality of life improvements.

In another study of 531 patients from 136 different centers with various forms of dementia, including Alzheimer's disease, results showed improvement among 78% of the patients.(2) In addition, memantine seemed to have a cumulative benefit in those who responded to the drug treatment, including a notable improvement in behavior, communication skills and motor function. Only four patients had "poor" tolerance to the treatment (0.8%) and 15 patients (2.8%) had "fair" tolerability.

The two studies relayed above underline findings from earlier placebo controlled studies, which have demonstrated a role for memantine in Alzheimer's and other forms of dementia. Moreover, consider that while this so-called novel drug undergoes vigorous scrutiny in North America, it has been approved for Alzheimer's for over a decade in Germany, where it is also used to treat Parkinson's disease, dementia in the elderly and to speed the recovery of comatose patients.(3-5)

Recently, at the World Alzheimer Congress 2000, Barry Reisberg of the New York University School of Medicine, reported on the "hot topic" that memantine appeared to benefit Alzheimer's patients with moderately severe disease. Even Neil Buckholtz, manager of the Alzheimer's drug development program at the NIA (National Institute on Aging), says that the results are interesting.(6) This phase III study was the first in the US, and included 252 patients treated at 32 clinical centers. Meanwhile, the journal, Science, published a piece last year that asked for the medical benefits of memantine to be weighed against other ethical issues,(7) although it seems unclear what moral dilemmas would arise from the use of memantine.

Another illuminating report notes that, "If memantine is approved by the FDA for some of these indications by the year 2005, it can become a blockbuster drug by crossing the US \$1 billion mark in annual sales." (8) It is strange to see the year 2005 as the time of reckoning for memantine, considering that Alzheimer's research has focused on the drug since even prior to 1990.

Memantine and Parkinson's disease

Memantine is actually referred to in some literature as an anti-Parkinson's drug. This was its first application, and the initial studies pre-date 1977 and possibly the computerized searches in use today. A preliminary study on Parkinsonian patients suggested both efficacy and low toxicity. Eventually, a follow-up study on 12 patients suggested that the short-term effects of the drug could be differentiated from placebo and learning effects. These later results were published in 1977.(9) In 1984, a similar German group looked at 67 patients treated in a placebo-controlled study, and again, an overall improvement was clearly demonstrated.(10) Recently, from Argentina, a study on 12 Parkinsonian patients demonstrated a statistically significant improvement, which means the effect had to be quite impressive considering the small number of patients.(11) All of these studies showed reasonable safety and efficacy, but somehow, 24 years after the first studies, there seem to be zero studies in the U.S. on Parkinson's disease using memantine.

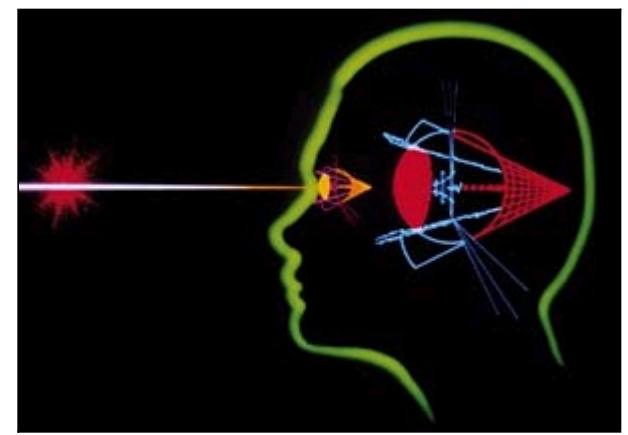
Memantine and neuropathy

In diabetes, one complication is chronic, progressive and hard-to-treat pain known as peripheral diabetic neuropathy, which afflicts 60% to 70% of diabetics according to the National Diabetes Information Clearinghouse.

Findings from a Phase IIB trial presented at the 52nd Annual Meeting of the American Academy of Neurology in San Diego, April 29 - May 6, 2000, showed memantine to be effective for relieving neuropathic pain related to diabetes. The US study involved 421 patients, which were divided into three groups: one group received daily doses of placebo, while the two other groups received either 20 mg or 40 mg of memantine. Results revealed that those on the 40 mg regimen had significantly less intense nighttime pain compared to the placebo group at the end of eight weeks of treatment. In the group taking 20 mg of memantine, positive results were not striking enough to be deemed "statistically significant." In addition, a phase II study sponsored by the National Institute of Dental and Craniofacial Research is currently underway to compare memantine, dextromethorphan and a placebo for treating pain associated with diabetic neuropathies, herpes zoster (shingles), pain and neuralgia.

Memantine and glaucoma

There are a variety of neuronal cells directly involved in sending the visual signal to the brain. The first cells to receive the light signals are the rods and cones. The second level of cells to process the information are the so-called horizontal cells, bipolar cells and amacrine cells. Finally, the ganglion cells, which make up the optic nerve leading to the visual cortex in the brain, transmit the signal.



There are a variety of neuronal cells directly involved in sending the visual signal to the brain

Going back as far as 1957, it has been known that glutamate only damaged the inner most layers of cells.(12) In addition, it has been noted that glaucoma results in the selective damage of the ganglion cells—the only cells in this network that are part of the central nervous system. While the stimulus for the excess glutamate may be related to the intraocular pressure, the damage appears connected to glutamate-NMDA receptor excitotoxicity. In fact, glaucoma patients have high levels of glutamate in the vitreous and research has shown that artificially raising glutamate to the same level in rats leads to a 50% loss of retinal ganglion cells within three months. Normalization of intraocular pressure, however, frequently fails to prevent vision loss in glaucoma patients, suggesting its indirect role in the retinal cell death.

Drawing on these considerations, several researchers have focused on the glutamate-NMDA receptor hypothesis for glaucoma, and are investigating drug therapies that block signaling within the NMDA receptor channel, such as memantine. As one study demonstrated, memantine “protects against retinal ganglion cell loss in retinal ischemia, optic nerve crush and chronic glutamate toxicity models” while having no role in the intraocular pressure.(13) As a result, combined with the prior favorable human experience in Parkinson’s (pre-dating 1980) and Alzheimer’s (since 1989), the authors conclude that memantine for glaucoma is the “most promising candidate for trial in humans.”

Memantine and HIV dementia

The root cause of HIV dementia is thought to be the same as that underlying Parkinson’s and glaucoma, namely neuronal loss through cell death. Figures suggest that AIDS dementia may affect one third of adult AIDS patients, and neuropathic pain occurs in about 40% of them. Recent research suggests that the HIV virus triggers a build-up of toxins that result in neuronal injury. In vitro studies have demonstrated that NMDA receptor blockers, such as memantine, reduce neuronal injury caused by HIV, while animal studies have indicated that memantine can also slow down AIDS-related neuronal damage.

A study sponsored by the National Institute of Allergy and Infectious Diseases combines memantine with anti-HIV drugs to treat AIDS dementia complex. The study is a phase II randomized, double-blind, placebo-controlled trial of memantine as a concurrent treatment with antiretroviral therapy for AIDS Dementia Complex (ADC). The study is no longer recruiting patients, and results are pending. Current therapy for AIDS Dementia Complex is a highly toxic drug called zidovudine, which shows decreased efficacy by the 2nd and 3rd year of therapy.

Memantine and alcohol dementia

Neuronal loss is associated with alcohol dementia too, apparently through excitotoxicity during repeated alcohol withdrawal. A brief anecdotal report suggests that memantine may have some role in treating alcohol dementia.(14) Memantine appeared to help in terms of improved mental state, verbal fluency, word recall, drawing and general intellectual capacity. In addition, PET scans demonstrated a renormalization of glucose metabolism and an increase in cerebral blood flow. Such a case report is often the first step to a clinical trial, but the isolated findings should not be generalized until a controlled trials, since alcohol dementia can spontaneously improve.

Memantine and vascular dementia

As with glaucoma and alcohol dementia, various stresses appear able to induce excitotoxicity related to the glutamate-NMDA receptors and, in fact, both are related to blood flow. Severe vascular dementia has demonstrated a response to memantine roughly equivalent to severe Alzheimer’s, with more than 70% of the patients responding, as compared to less than 50% for placebo.(1)

Will memantine be approved in time?

We have presented evidence that memantine could help alleviate the suffering of tens of millions of Americans suffering from Alzheimer’s and Parkinson’s disease, peripheral neuropathy, stroke, HIV and alcohol-induced dementia. For glaucoma patients whose disease is uncontrollable by conventional therapies, memantine could potentially save them from future blindness.

Memantine has been used in Germany for ten years, but is not scheduled to be approved in the United States until the year 2005.

Even when it is allowed to be sold in the United States, memantine may not be approved for anything except Alzheimer's disease.

In 1991, The Life Extension Foundation sued the FDA on behalf of American Alzheimer's disease patients who were being denied access to the drug Tacrine (THA). The mechanism of action of Tacrine is to inhibit the acetylcholinesterase enzyme, thus making more of a neurotransmitter called acetylcholine available to brain cells. A judge tossed out our lawsuit on the grounds that the Federal Courts were not the proper forum to determine what drugs the FDA should approve.

Six months after our lawsuit was dismissed, the FDA approved Tacrine. (A few years later, the FDA approved a safer drug called Aricept that shares some of the same mechanisms of action as Tacrine.)

Now here it is ten years after we filed our lawsuit against the FDA and American Alzheimer disease patients are again being denied a drug (memantine) that could improve their quality of life.

Side effects of memantine

A delicate point raised by research about NMDA receptor blocking drugs has been the lack of discretion they use. That is, while reducing the possibility of cell death associated with overstimulation of neurons, they also indiscriminately shut down normal signaling systems required for mental functioning.(15) In fact, both animal and human studies have indicated that NMDA antagonists can reduce learning and memory.(16) For example, one study showed that after administering memantine and a placebo to 40 healthy male volunteers, a significant reduction in the subjects' ability to recognize objects under memantine therapy was observed.(17) Clearly, drugs such as memantine are only to be used in patients where these side effects are minor in comparison to the disease process.

In addition, while memantine seems to be well tolerated in dementia cases and elderly patients (the adverse effects are comparable to placebo), a number of adverse reactions have been reported in various patient groups. In patients being treated for dementia, for instance, memantine has been reported to cause vertigo, restlessness, hyperexcitation and fatigue. Parkinsonian patients using 30 mg/day of memantine have experienced nervous energy, emotional agitation, confusion, dizziness and stomach upset. The potential for side effects with this kind of drug might be much greater in AIDS patients, and when memantine is taken concurrently with certain antidepressants. People with AIDS can have adverse reactions, such as feeling like climbing the walls, emotional agitation, headaches, stomach aches and changes in mucous secretions, sweating or any other sign of body dehydration. Some clinicians suggest, though, that a go-slow approach can help side-step nasty side effects, such as starting patients on a low dose, watching for adverse reactions and then gradually increasing the dose. Doses of memantine range from 5 mg to 60 mg a day, with 10 mg to 30 mg a day being the standard maintenance dose in patients with Parkinson's disease.

A cautionary note is in order for anyone taking any antidepressants to start on a low dose, including those on SSRIs (e.g. Prozac, Zoloft) and MAO inhibitors (e.g. phenelzine sulfate, pargyline hydrochloride and methylclothiazide, furazolidone, isocarboxazid, procarbazine and tranylcypromine), since memantine can cause hyperactive or "manic" states. Those prone to seizures should also be cautious about memantine, since data from animal studies suggests that very high doses of the drug could make seizures worse.

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