Trial Questioned

Methylene Blue *from page 1*

tibacterial effect sometimes used to treat urinary tract infections and methemoglobinemia. It blocks the formation of tau oligomers, converts them to paired helical filaments, and dissolves existing tau tangles.

The phase II dose-finding study included 321 patients with mild to moderate Alzheimer's. Patients were randomized to placebo or one of three drug doses: 30 mg three times daily, 60 mg three times daily, or 100 mg three times daily. The compound was contained in a gelatin capsule.

The study was conducted in two parts: an initial 24-week blinded placebo-controlled study, followed by 60 weeks of blinded active treatment. At baseline and throughout the trial, subjects received cognitive testing; functional brain imaging was performed on some at both baseline and 25 weeks. Although none of the patients were taking cholinesterase inhibitors, Dr. Wischik's presentation did not include data on any other baseline characteristics of the group, how many were randomized to each treatment arm, or the dropout rate.

At no time were the results of the 100-mg dose discussed. Dr. Wischik said the gelatin capsule containing this dose was defective, delaying release of the drug until it was in the intestine. So Dr. Wischik folded all those data into the placebo arm analysis. Dr. Schneider observed, "If they thought the 100-mg dose was badly put together, they should have eliminated it."

Describing the study's primary end point—cognitive decline at 24 weeks—Dr. Wischik said the drug did not show any cognitive benefit among the patients with mild AD at 24 weeks; neither the placebo group nor the active groups declined significantly from baseline. However, among the moderate patients, Rember appeared to have a positive effect. The moderate controls declined about 5.5 points on the ADAS-cog, while the 30- and 60-mg groups declined about 1.5 points.

At 50 weeks, Dr. Wischik pooled the mild and moderate groups. The placebo group had continued to decline, and was now almost 7 points below its baseline measurement. The 30-mg group had lost 3 points from baseline, but the 60-mg group was still not significantly different from its baseline measurement, having stabilized at a loss of about 1.5 points.

At this point, all placebo patients were offered the chance to begin taking Rember in a dose-blinded fashion. By 84 weeks, those taking the 60-mg dose still had not experienced significant cognitive decline. Since there was now no placebo group, Dr. Wischik compared the effect size to historical controls, who would have continued a sharp, linear decline during that period.

Some patients also underwent imaging studies at baseline and at 25 weeks. Positron emission tomography of 18 patients showed improved glucose metabolism bilaterally in the medial-temporal lobes of those taking the study drug; there was no change in those taking placebo. A second imaging study of 138 patients showed that those taking Rember had significantly greater regional cerebral blood flow than those taking placebo.

Dr. Schneider said: "Lots of things light up the brain and increase cerebral blood flow. And we should remember that almost as a rule of thumb, these biological effects are much, much larger than any associated clinical effects." In addition, he said, Dr. Wischik did not perform any biomarker studies to determine if Rember affected tau levels in serum or cerebrospinal fluid.

Diarrhea was the most common side effect, in 12% of the 30-mg group, 31% of the 60-mg group, and 20% of the 100-mg group. Others were dysuria, urinary urgency, dizziness, and falls—all documented in the 100-mg group as well as in the other active arms. The fact that the side effects occurred in the group taking what Dr. Wischik called "a completely ineffective dose" concerned Dr. Schneider. "What are we supposed to make of that?" Dr. Wischik answered that that the drug's delayed release into the small intestine rather than the stomach exacerbated its local effects, causing the increase in diarrhea.

First identified in 1891, methylene blue predates the FDA. Dr. Wischik predicted Rember would be available within 4 years, if its grandfathered status can help to speed the approval process. ■

Methylene Blue Boosts Mitochondria, Delays Cellular Aging, Study Says

Another researcher also believes that methylene blue holds the key to fighting Alzheimer's. But Hani Atamna, Ph.D., said that rather than directly affecting tau tangles, the drug improves mitochondrial function and thus averts the early cellular changes that lead to cognitive decline and Alzheimer's, Dr. Atamna, an assistant scientist with Children's Hospital and Research Center Oakland, Calif., said.

His most recent study examined the drug's effect in cultured human fibroblasts (FASEB 2008;22:703-12). Even at the extremely low concentration of 100 nanomolars, methylene blue significantly extended the life of the cultured fibroblasts, increasing it by more than 20 population doublings relative to control cells. These cells also exhibited an increased oxygen consumption of up to 70%, a finding the researchers said was probably due to their improved growth when exposed to methylene blue.

The fibroblasts exposed to methylene blue produced up to 70% more heme, which research suggests is important in blocking β-amyloid aggregation. This increased heme in turn helped boost the production of complex IV; several studies have shown that this enzyme, found within the mitochondria, declines in Alzheimer's patients.

"This decline is related to the hypometabolism we see in the brains of patients who have the very earliest signs of cognitive impairment," Dr. Atamna said. "It is several years after this occurs that we begin to see the lesions and other signs of dementia."

Methylene blue also appeared to protect cells against oxidative injury when they were exposed to either cadmium or hydrogen peroxide. This may be due to the drug's ability to cycle within the mitochondria from an oxidized to nonoxidized form. When the drug gives up its oxygen early in the cycle, it blocks the production of free radicals, and thus decreases oxidative damage to the cell, he theorized. Clinically, methylene blue could forestall the earliest cognitive decline of Alzheimer's by improving overall mitochondrial function, he said. "By increasing complex IV and enhancing the function of mitochondria, we give the brain more reserve to stave off decline."

Although his in vitro studies show a proof of concept, Dr. Atamna has not yet published any in vivo studies linking methylene blue with cognition. However, he said he has performed such studies, showing that normal aged rats treated with the drug showed improved mental function.

Image of the Month

Cerebral amyloid angiopathy is associated with a high prevalence of markers of small-vessel disease, including white matter hyperintensities and cerebral microbleeds and is a major cause of lobar intracerebral hemorrhage and cognitive impairment in the elderly.

"Because CAA is a relatively homogeneous small-vessel disease of the brain, we wondered whether other markers, such as mean diffusivity, as measured by diffusion tensor imaging would be predictive of either the severity of CAA or cognitive impairment prior to large hemorrhages associated with CAA," said Dr. Anand Viswanathan of the hemorrhagic stroke research program and the stroke service at Massachusetts General Hospital in Boston.

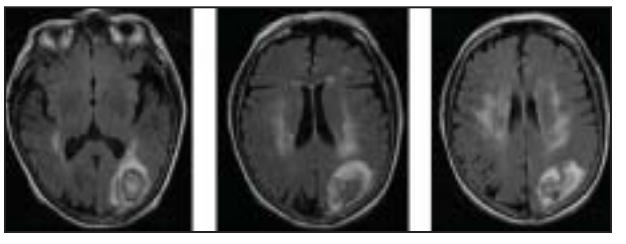
Diffusion tensor imaging (DTI) has already been used in a number of other small-vessel diseases to detect microstructural changes in cerebral tissue—even in areas that appear normal on conventional MRI. Dr. Viswanathan and his colleagues had previously studied patients with another small-vessel disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and had found a strong correlation between the apparent diffusion coefficient (ADC)—an average measure of water diffusion in all directions in brain tissue—and functional changes (see images). In fact, ADC changes were much more predictive of functional impairment than were white matter changes on fluid-attentuated inversion recovery (FLAIR) imaging, which are typically seen quite early in this disease process (Stroke 2007;38:1786-90).

For the current study, the researchers recruited subjects from an ongoing single-center, prospective longitudinal cohort study of CAA. The patients had to be at least 55 years of age at the time of presentation and have a symptomatic lobar intracerebral hemorrhage (ICH). They had MRI with diffusion-weighted sequences within 90 days of the index event. Those with other potential causes of ICH were excluded (Stroke 2008;39:1988-92).

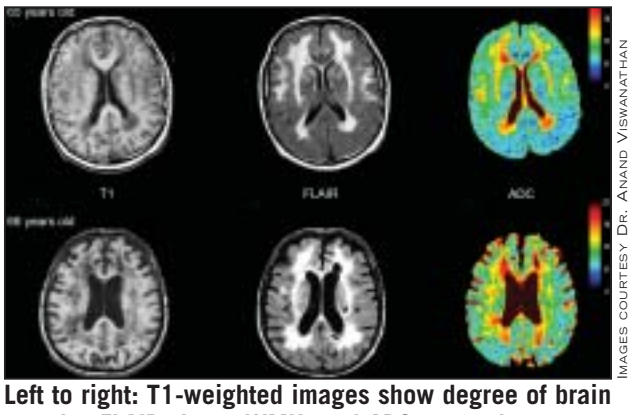
Under the Boston Criteria, 5 of the patients had definite CAA with tissue diagnosis, 19 had probable, and 25 had possible. Pre-ICH cognitive function was assessed after an interview with patients and informants and review of medical records and results of a standardized questionnaire. Pre-ICH cognitive impairment was defined as the presence of deficits in memory or other cognitive areas sufficient to interfere with tasks of daily living before ICH.

Images were acquired with a 1.5T-scanner and included diffusion-weighted, FLAIR, and gradient echo. Mean ADC was determined for the hemisphere contralateral to the hematoma. Seven of 10 patients (70%) with pre-ICH cognitive impairment had a diagnosis of probable CAA, compared with 11 of 38 (29%) without pre-ICH cognitive impairment. Patients with pre-ICH cognitive impairment had greater mean ADC values, compared with those without pre-ICH cognitive impairment.

After adjustment for age and amount of visible cerebral atrophy, only the mean ADC was independently associated with pre-ICH cognitive impairment. The effect of visible cerebral atrophy on pre-ICH cognitive impairment wasn't significant. "ADC changes [seem to] occur even in normal-appearing white matter, as [shown] by conventional FLAIR imaging, suggesting DTI may be more sensitive [for detecting] tissue changes in CAA and other small-vessel diseases in the brain," Dr. Viswanathan said.



FLAIR imaging reveals areas of white matter hyperintensities in this patient with CAA.



Images courtesy Dr. Anand Viswanathan

Left to right: T1-weighted images show degree of brain atrophy, FLAIR shows WMH, and ADC maps show tissue microstructural changes.

—Kerri Wachter