Test quickly assesses whether Alzheimer's drugs are hitting their target

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A test developed by physician-scientists at Washington University School of Medicine in St. Louis may help assess more quickly the ability of Alzheimer's drugs to affect one of the possible underlying causes of Alzheimer's disease in humans, accelerating the development of new treatments.

Scientists used the test to show that an Alzheimer's drug given to healthy volunteers reduced production of a substance known as amyloid beta (A-beta), a normal byproduct of human metabolism that builds to unhealthy levels forming brain plaques in Alzheimer's patients. The drug candidate, LY450139, which is also known as semagacestat, is being studied in clinical trials by Eli Lilly and Company.

Ongoing clinical trials are studying the effect that semagacestat may have on cognitive function and biochemical and brain imaging biomarkers in patients with Alzheimer's disease. Washington University researchers wanted to see whether the new measurement technique, stable isotope-linked kinetics (SILK), could detect the study drug's impact on A-beta synthesis in healthy volunteers.

"Bringing an Alzheimer's disease drug into clinical trials from tests in animal models has always been challenging," says study director Randall Bateman, M.D., a Washington University neurologist who treats patients at Barnes-Jewish Hospital. "We haven't had a way to quickly and accurately assess a drug's effects, and that meant there always had to be some degree of educated guesswork when it came to setting the optimal

dosage for humans. SILK may help to eliminate much of that guesswork."

The results appear online in *Annals of Neurology* on April 10.

Scientists are unsure whether increased A-beta production, reduced clearance or a combination of the two lead to the A-beta buildup in the brain, a process that many believe triggers Alzheimer's disease. Bateman and his colleagues are currently using SILK to try to answer this question.

Until SILK, there has not been a way to directly measure the production or clearance of A-beta. The efficacy of potential new Alzheimer's drug candidates has been assessed by monitoring the cognitive functions of patients with the disease for extended periods of time, which require large, lengthy and expensive studies.

In their double-blind study, scientists gave 20 healthy volunteers varying doses of either a study drug or a placebo. At the start of the SILK test, volunteers were connected to an intravenous drip that gave them a slightly altered form of the amino acid leucine, which is a component of A-beta.

Over the course of several hours, cells in the brain picked up the labeled leucine and incorporated it into the new copies made of A-beta and other proteins. The scientists took periodic samples of the subjects' cerebrospinal fluid to determine how much of the A-beta included altered leucine.

Tracking the rise of the percentage of labeled A-beta over time reveals the A-beta production rate. Scientists then stop the leucine labeling but continue analyzing spinal fluid samples. As the body removed old A-beta and made new A-beta, the percentage of A-beta containing altered

leucine dropped, revealing the A-beta clearance rate.

The results suggest a dose-dependent drop in A-beta production, with an 84 percent reduction in A-beta production being measured with the highest study drug dose.

The SILK procedure takes 36 hours, but provides scientists a more detailed assessment of amyloid beta production and clearance levels than they can obtain through conventional methods.

"You could use a spinal tap to look directly at the amount of A-beta present in the cerebrospinal fluid, but we've shown that natural processes cause A-beta levels to change dynamically," says Bateman. "Such changes make it more difficult to assess the effects of a drug in that fashion."

Source: Washington University in St. Louis (news : web)