Medical Xpress

Alzheimer's disease patients show improvement in trial of new drug

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A new drug has been shown to improve the brain function of people with early stage Alzheimer's disease and reduce a key protein associated with the disease in the spinal fluid, in a small study published today in the journal *Lancet Neurology* and presented at the 2008 Alzheimer's Association International Conference on Alzheimer's Disease.

The drug, known as PBT2, counteracts the production and build-up of a protein called amyloid-beta that occurs in Alzheimer's disease. This protein, which can build up into a 'plaque', is believed to be toxic to brain cells and to prevent them from functioning properly.

Seventy-eight participants with early stage Alzheimer's disease took either 50mg or 250mg doses of the drug PBT2, or a placebo, over the course of 12 weeks in a randomised, double-blind clinical trial, led by a researcher from Imperial College London working with colleagues in Australia and Sweden. Both doses of PBT2 capsules were observed to be safe and well tolerated during the course of the study.

Participants undertook a number of tests to assess their cognitive function, prior to beginning treatment and at the end of the 12-week period. In two of these tests of executive function, which involves the ability to organise information, sequence events and plan, those on a 250mg dose of PBT2 showed a significant improvement over the placebo group.

The researchers also measured how the levels of amyloid-beta in spinal

fluid changed during the course of the trial. They found that levels of amyloid-beta 42 in the cerebrospinal fluid of those on the 250mg dose of PBT2 were reduced by approximately 13 percent compared to placebo at the end of the 12-week period.

Amyloid-beta needs the metals zinc and copper in order to accumulate in the brain and these two metals become abnormally distributed in the brains of people with Alzheimer's disease. PBT2 works by interrupting the interaction between the metal ions and amyloid-beta, and returns levels of zinc and copper in the brain to normal levels.

In the cognitive tests, those on a 250mg dose of PBT2 were able to complete the task in a test known as Trail Making Part B an average of 42 seconds faster than they had at the beginning of the trial. The placebo group was an average of 6 seconds slower.

In the Category Fluency Test, which looks at a person's ability to come up with as many relevant words as possible in relation to a specified category, those in the 250mg group were able to produce an average of 2.4 more words than at the beginning of the trial. This compared with a decrease of 0.3 words in the placebo group.

Although memory loss is the problem most often associated with Alzheimer's disease, the executive cognitive functions assessed by these two tests typically begin to deteriorate in the early stages of the disease, though are sometimes less obvious than memory symptoms.

There were no significant differences in participants' scores on tests assessing their memory function in the new study, but the researchers believe this may be because the memory function deteriorates at a slower rate than the executive functions at this stage of illness, making changes harder to detect in a short study.

Dr Craig Ritchie, from the Division of Neurosciences and Mental Health at Imperial College London, who led the study, said: "Alzheimer's disease is a devastating condition and it affects hundreds of thousands of people in the UK. The results of our trial are very encouraging, although it was a relatively small study, which took place over a short period of time. Our findings certainly engender much optimism that this drug may have a significant effect on the underlying pathology of Alzheimer's, with a tangible clinical benefit for patients.

"We now need further research to see how PBT2 performs in larger, longer-term trials. Our hope is that we might be able to see treatments that can substantially improve the lives of people with early Alzheimer's disease within the next five or so years," added Dr Ritchie, who has been assisting the Australian company Prana Biotechnology with the clinical development of its new drugs for ten years.

The next step for the research is to move forward with PBT2 in further trials with a view to gaining a license for the drug.

These study results follow on from a recently published study of mice which showed that PBT2, in the space of a few days, cleared amyloid-beta, improved cognition and reduced the damage to brain cells. The parent compound to PBT2, clioquinol, was shown in a small study of 36 patients in 2003 to slow the progression of Alzheimer's disease. PBT2 was developed to be even more effective than clioquinol at attacking the core pathology of the disease.

Source: Imperial College London