Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

PRELIMINARY EVALUATION OF THE THERAPEUTIC POTENTIAL OF LITHIUM IN MILD COGNITIVE IMPAIRMENT

Researchers
Dr Calum Sutherland, University of Dundee
Dr Ashleigh Duthie, NHS Tayside
Professor Simon Lovestone, University of Oxford
Professor John Geddes, University of Oxford.

Aim

Almost 2% of the UK population has a diagnosis of dementia, and this is expected to rise to more than 2 million by 2051 (150% increase in 40 years). Alzheimer's disease (AD) is the most common form of Dementia (more than half), but there are no effective treatments, while clinical trials into AD are failing at an alarming rate. This could be because we do not fully understand the disease and are trying to develop treatments against the wrong targets. We believe it is worthwhile looking at the amount of Dementia in people currently taking drugs for other diseases. If Dementia rates are lower in people taking such drugs it could mean the drugs have benefits against the development of Dementia. Lithium is taken all over the world as a treatment for Bipolar disorder (a form of depression). A recent study looking at thousands of people taking Lithium for Bipolar disorder in the USA suggested there was significantly less incidence of Dementia compared to people taking different drugs for Bipolar disorder. This was exciting, if not conclusive, evidence that Lithium may reduce the development of Dementia. Meanwhile, laboratory-based work has identified an enzyme called GSK3 as a direct target for Lithium, GSK3 activity is blocked by Lithium. We, and others, have lots of evidence suggesting high GSK3 activity could contribute to some of the problems in the brain associated with AD. It is therefore mechanistically plausible that inhibitors of GSK3, such as Lithium, could reduce the development of AD. Only a clinical trial investigating whether Lithium could prevent Dementia progressing in people with early AD, would really answer this question. However, there are many safety concerns around taking Lithium (such as kidney and behavior problems). It was also not clear how much Lithium would be needed to treat AD, and for how long, since we didn't know whether it would be the same as for Bipolar disorder.

Therefore, our pilot study was funded by CSO to work out whether these issues could be overcome and thus allow us to move to a full clinical trial. The main Aims of our study were:

1) Establish how much Lithium is required to inhibit GSK3 in people with early AD (using biomarkers of GSK3 activity in blood cells),
2) Establish how easy it is to recruit people with early AD to a trial with Lithium and how safe it is for them to take.

This information would then allow us to design a full clinical trial, safely and efficiently, using the right dose of Lithium.

Project Outline/Methodology

The project had three related parts;
Part 1) *We isolated blood cells from rats given an injection of Lithium (across a range of Lithium doses), and investigated if there were potential biomarkers of GSK3 activity in the blood cells, especially if there were any biomarkers that responded to Lithium. We also measured the same biomarkers in the brain of the rats to investigate whether any response to Lithium in the blood cells was mirrored in the brain (as we think we would need to inhibit GSK3 in the brain for it to affect Dementia, but we would only be able to look at GSK3 in the blood cells of volunteers).*

Part 2) We then measured these GSK3 biomarkers in blood cells isolated from volunteers with high risk of developing AD and compared their levels in age-matched healthy volunteers. Two blood samples were taken from every volunteer twelve weeks apart. This part aimed to check that biomarker levels were consistent between two different samples from the same volunteer, and to see if volunteers with early AD had any differences in the biomarkers compared to controls.

Part 3) We administered Lithium to volunteers with a diagnosis of early AD, and monitored tolerance to Lithium, and measured the GSK3 biomarkers in their blood cells at baseline and after 3 increasing doses of lithium as well as after a wash-out period. This aimed to establish the safety of the 3 lithium doses, and whether any of the biomarkers of GSK3 activity were changed by Lithium, and if so at what dose.

Key Results

There are three main findings:

1) Recruitment- The interest in getting involved in research in the early-AD patients was much greater than anticipated with almost half of those approached giving a positive response. Even with some exclusions due to weight (we had limited the study to body mass index <30) we had no problems recruiting to the study in Tayside.

2) Safety- A fairly large number of volunteers withdrew from the study after starting Lithium. There were many reasons given but there was no correlation to the amount of Lithium being given, or to the blood Lithium levels. None of the withdrawals were due to kidney problems, most were related to feelings of fatigue, or difficulty sleeping. Interestingly, these are actually common symptoms of early AD, and are often reasons given by the early AD patients for withdrawing from many drug trials. Basically, the Lithium appeared very safe, and so we don't believe there will be any issues with safety at these Lithium doses.

3) Biomarkers- We investigated 18 biomarkers of the GSK3 pathway in blood cells and brain of the rats. Eight of these were detectable in the blood cells as well as the brain, but only 4 were robustly and consistently detected. Two of these biomarkers responded to Lithium, and are thus potential readouts of the efficacy of Lithium in blood. Unfortunately, we did not detect a change in these biomarkers in the brain in response to Lithium. This may mean that the biomarkers in the blood cells are not a good surrogate measure of brain GSK3 activity.

We measured all 8 of the biomarkers that we detected in rat blood cells in the blood cells from the human volunteers. As with the rat study only 4 of these were robustly detected. However, we found that there was much greater variation in these biomarkers when measured in the human blood cells, even between the two samples from the same individuals. This appears to be related to technical issues around how and where blood is collected, meaning there was some variation in how long blood samples were stored before isolation of blood cells. This made it difficult to accurately quantification the biomarkers across the volunteers (control vs early AD, or with increasing dose of Lithium), which was a fundamental aspect of the project.

Conclusions

The study has provided sufficient information on recruitment and safety to inform the design of a clinical trial using lithium as a novel intervention for the prevention of dementia in high risk groups. The study identified serious technical limitations to the accurate and robust measurement of biomarkers of GSK3 activity in blood cells. This suggests it would not be possible to use these biomarkers for assessing the appropriate dose of lithium to use in order to target GSK3.

What does this study add to the field?

This is a pilot study that lays the foundation for improving the design of a clinical trial for the repurposing of lithium for use in prevention of dementia.

Implications for Practice or Policy

The pilot study was not aimed at an immediate change in practice or policy, rather to improve the quality of the data generated from a clinical trial using lithium in order to increase the chances that it would inform future treatment options for dementia.

Where to next?

The study aimed to generate information to guide the design of lithium use in a clinical trial on prevention of dementia. The work will be published this summer and we are in discussions to provide the recruitment and safety data to current clinical trials that are comparing different interventions on the development of dementia, with a view to have lithium included into these ongoing trials.

Further details from:

Dr Calum Sutherland
c.d.sutherland@dundee.ac.uk