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17/12/09 Please note, two of the three human trials have been concluded early as they have shown no benefits to users and have in fact suggested Lithium might be detrimental at the doses taken.

Early in 2008 a report from Italy by Francesco Fornai and colleagues revealed how a study of the effects of the metal lithium on mice with MND appeared so successful that it was very quickly followed up by a small clinical trial involving patients. The results reported in their February 2008 report were based on data obtained in only the first fifteen months of the trial. As yet it is not known if these results are consistent across the whole two years of the study.

Preliminary Human Trial

44 patients (20 male and 24 female) were recruited for the clinical trial and divided into two groups. One group of 16 people received lithium carbonate in addition to Riluzole while the other group of 28 people received Riluzole only. In order that the researchers did not inadvertently influence the patients they did not know who was receiving lithium as well as Riluzole and who was receiving only Riluzole. None of the groups contained people who had familial MND and ¼ of each group were patients who had bulbar onset MND. (Seven of the 28 and four of the control group of 16.)

A number of different measures were used to objectively assess the disease progression in the patients recruited to the clinical trial. Amongst these were “functional rating scales,” i.e. ways of

assessing the effect the disease is having by measuring how someone can function; and a measure of “Forced Vital Capacity,” i.e. how much air someone’s lungs can hold and breathe out.

Preliminary Human Results

On the face of things the results from the trial were impressive. Fifteen months after the start of the trial all of the patients from the group receiving lithium were still alive and all showed much less disease progression than their counterparts who received Riluzole only. For example, the patients receiving lithium had on average more than 80% of the breath-size they had at the start of the study, while the patients receiving only Riluzole (the control group) had on average just slightly more than 60% of the breath size. On each of the different scales to measure functionality the comparison patients scored markedly worse at the end of the fifteen months than the group receiving lithium. On completion of the preliminary study almost one third of the comparison group had died whereas none of the patients receiving lithium had died, despite a statistical probability that some from each group should have died during the study.

Important Reservations

However, other researchers have serious reservations about the quality of the information obtained from this clinical trial. For example the MND Association for England Wales and Northern Ireland made the following comments;

- “The participants in the trial knew whether they were taking the trial

MND Scotland is the working name of the Scottish Motor Neurone Disease Association, the only charity funding research and providing care and information for those affected by MND in Scotland.

treatment or whether they were in the control group. This can produce bias in the way participants report how they feel and also means that the placebo effect can have an influence.

- The participants were not put into the treatment and comparison groups at random - they were chosen for each group by the researchers. Random selection is usually performed by a computer and prevents bias in choosing which patients go into each group.
- A larger proportion of the participants given lithium had disease characteristics (e.g. age and site of disease onset) that tend to be associated with slower disease progression.”

These criticisms are not trivial nit-picking by others for the sake of it. They seriously undermine the reliability that can be placed on the results from the human trial as it is easy to obtain the results you want if you grade and select the people who get the treatment to choose those with slower-progressing disease types and put those with faster-progressing disease types into the group that don't get the treatment. Because normal randomisation processes were not followed and because participants knew whether or not they were taking lithium we can have no certainty that there was not some degree of bias in the findings arising from the selection process.

Lithium

Lithium carbonate is a compound used as a mood stabiliser in psychiatric disorders, which has been noted to have nerve-protecting properties in a variety of disease models such as brain ischemia (lack of oxygen) and poisoning by a chemical called kainate, which is a potent stimulator of the central nervous system. Lithium can also promote a cellular

process called autophagy, in which cells dismantle parts of themselves to provide materials they can re-use. Autophagy can sometimes be protective against further damage in diseases that cause degeneration in the brain and nervous system. These facts together prompted the team to test the protective effects of lithium in a strain of mice which suffers from MND.

Caution in Interpreting Data

Care should normally be taken not to read too much into the results obtained from trials involving particular strains of mice as the MND they suffer from is usually caused by interfering with one of their SOD1 genes. Only 2 to 3% of human cases of MND are due to inherited mutations of this gene and not all mutations to the gene have the same degree of disease promoting effects. The other 97% of human cases are thought to be due to other inherited genes (about 7% of all cases) or unknown in origin (about 90% of all cases and described as sporadic MND.)

Laboratory mice and rats are very highly in-bred to create extremely similar individuals which should give experimental results that can be reproduced over and over again.

How “MND Mice” are “made”

To create a mouse model for MND a known mutation is introduced into a SOD1 gene and copies of this mutated gene are, in turn, introduced into some mouse embryos. One of the most commonly used mouse models is the so-called “G93A mouse.” What this name means is that at position 93 on the SOD1 protein a mutation has been created by replacing one of the chemicals that makes up the protein by another. In this case the chemical represented by “G” (Glycine) has been replaced by the chemical represented by “A” (Alanine).

This replacement was brought about by manipulating the SOD1 gene before it was introduced into the embryos, thus allowing the mutated gene to make the faulty protein and to be passed on to future generations.

The mice that are bred from these mutated strains all develop symptoms similar to those experienced by MND patients with a distinctive and predictable pattern to their disease because of the in-bred similarities of the mice and the uniformity of the cause of their MND.

Typically the first signs will appear in the G93A mouse at about 80 days of age with a weakening of the hind-limbs. Normally by 140 days the disease has run its course and all of the mice are dead. For the untreated (control) mice used in the trial their life-span was an average of 111 days and the average duration of their MND symptoms just 9 days.

Effects of Lithium on MND Mice

When Fornai and colleagues carried out their investigation they started dosing male mice with lithium at 75 days of age, five days before the first MND symptoms normally appear in this strain. They discovered that this treatment extended the duration of the disease to an average of 36 days and life-span to an average of 148 days, quite clearly slowing down the progression of the disease and extending life expectancy.

The lithium treatment also delayed the

onset of limb paralysis and significantly improved grip strength when compared to the control mice, which were given salt-water injections to make sure they all got exactly the same treatment, apart from the lithium.

The team were so impressed by the results they discovered in the mice that they rapidly moved to the clinical trial involving humans.

Mouse Post-Mortem Results

The analysis in the G93A mice showed that lithium delayed cell death amongst motor neurones within parts of the spinal cord and brain while in some parts of the spinal cord it actually increased motor neurone survival. In addition, lithium treatment helped to remove the build up of proteins, such as the SOD1 protein, and other substances that are known to accumulate when motor neurones are damaged in MND. This latter finding suggests that an increased removal of the mutated SOD1 may contribute to the improvement observed in G93A mice. The investigators concluded lithium affects multiple targets, all of which are likely to contribute to the improvement of MND.

Further Developments

The results of this preliminary trial so interested the medical research community that several trials were started in different countries around the world, 2/3rds of these trials have been closed early.

Further Information

Fornai and colleagues' paper <http://www.pnas.org/content/105/6/2052.full.pdf+html>
MND Association's Comments on the above paper
http://www.mndassociation.org/research/research_explained/news_in_research/mnd_association.html

Factsheet 22 Riluzole