Vite Progress report (May 2014)
Lay description

Using the cat model of NPC1 disease we administered 2-hydroxypropyl-beta-cyclodextrin (HPBCD) directly into the spinal fluid and showed improvements in clinical and biochemical endpoints. These data have been provided to the Therapeutics for Rare and Neglected Diseases (TRND) NPC group and have helped guide the clinical trial in patients. We showed that when NPC cats were treated with 30 mg or more HPBCD into the spinal fluid every 14 days beginning at 3 weeks of age, the neurological disease completely resolved for at least 24 weeks of age (the age when untreated NPC cats die), and all treated cats remained alive at one year of age. Specialized staining of brain tissue demonstrated survival of Purkinje cells and more normal levels of cholesterol and glycolipids in treated cats when compared to untreated cats at 24 weeks. Spinal fluid doses lower than 30 mg (and as low as 3 mg) resulted in lesser improvements in neurological disease by 24 weeks of age, and in less improvement in lifespan. Finally, cats which began treatment into the spinal fluid at 16 weeks of age, when significant clinical neurological disease was present, showed a slowing of progression of their clinical signs and an increase in lifespan compared to untreated cats. BAER data (hearing data) indicated that HPBCD raised the hearing threshold, i.e., reduced the ability of cats to hear. This effect was most profound in cats receiving greater than 30 mg HPBCD into the spinal fluid.

The use of biochemical markers to monitor response to HPBCD was examined in the NPC cat model with Dr Dan Ory. Cats receiving HPBCD into the spinal fluid showed a significant dose-dependent increase in 24(S)-HC in the CSF 3 days following the initial dose. The plasma 24(S)-HC concentration was likewise significantly increased. Consistent with the 24(S)-HC response, CSF CE species were elevated in the treated cats. Finally, the incidence of peripheral nerve disease in NPC patients is not known. We investigated peripheral nerves in the feline model of NPC disease and identified loss of myelin in NPC cats which does not appear to be treated by HPBCD therapy.

Key outcomes.

- HPBCD injected into the spinal fluid of cats affected by NPC disease, when given either before or after onset of clinical neurological deficits, improves clinical disease and overall survival.
- HPBCD treatment of cats affected by NPC disease causes an improvement in overall survival although hearing is affected negatively. Except for the hearing decrement there were no adverse effects of treatment noted in this animal model of disease.
- Following direct CNS delivery of HPBCD, we found significant increases in CSF and plasma 24(S)-HC in the feline model of NPC disease.