Intracisternal cyclodextrin ameliorates neurological dysfunction, increases survival time, and stops Purkinje cell death in feline Niemann–Pick type C1 disease.

Abstract: We studied the feline model of Niemann–Pick disease type C (NPC) disease in which we could repeatedly administer 2-hydroxypropylbeta-cyclodextrin (HPßCD) either subcutaneously or intrathecally and repeatedly sample cerebrospinal fluid (CSF) and blood to evaluate mechanistic, pharmacologic, and toxicity issues. Feline NPC disease results from a single missense mutation in the NPC1 gene (p.C955S) that is evolutionarily conserved and in a cysteine-rich region commonly mutated in patients. Disease progression in this model recapitulates both the neuropathological and biochemical abnormalities observed in human patients, with the closest parallels to the juvenile form of NPC disease. In the present study, we showed that administration of HPßCD into the subarachnoid space of affected cats completely resolved the clinical neurological signs of disease and Purkinje cell loss up to at least 24 wks of age (the median age when untreated cats die). Studies in the feline animal model have provided critical data on efficacy and safety of drug administration which were central to advancing HPßCD into the current clinical trial for NPC patients. NPC cats were treated with 120 mg ICHPßCD beginning at 3 wks of age and repeated every 14 days thereafter. Remarkably, these cats were neurologically normal at 24 wks of age and showed only mild ataxia at 76 wks of age. However, no improvement in serum albumin and only small significant decreases, but still abnormal concentrations, of ALT and cholesterol were found when compared to untreated NPC cats. Liver histology and lipid biochemistry were similar to those found in untreated NPC cats. In the brain, these cats showed a marked reduction in storage of filipinstained unesterified cholesterol, of GM2 ganglioside immunostaining as well as no evidence of Purkinje cell loss. Biochemical study of the ganglioside patterns demonstrated drastically reduced levels of gangliosides GM2 and GM3, with unchanged concentrations of the major brain gangliosides. The above studies illustrate the ability of 120 mg IC HPßCD to ameliorate neurological disease, brain biochemical abnormalities, and Purkinje cell loss when treatment is initiated prior to the onset of neurological deficits. To determine the effects of instituting therapy when neurological dysfunction is already present, a cohort of NPC cats was administered 120 mg HPßCD IC every 14 days beginning at 16 wks of age, an age at which moderate ataxia and tremor exist. Eight NPC cats treated in this manner showed either no progression or slowed progression of clinical signs when evaluated at 24 wks of age. Histological and biochemical evaluation of these cats showed an accumulation of cholesterol, gangliosides, lactosylceramide, and sphingosine which was greater than that seen in NPC cats that began treatment at this dose at 3 wks of age, but less than that seen in untreated NPC cats at end-stage disease. The level of GM2 ganglioside was clearly less than at the age when treatment began, and not much higher than in 4-week old untreated cats. Subjective evaluation of Purkinje cell numbers also strongly suggested that loss of these cells was not a pronounced as that found in untreated cats.