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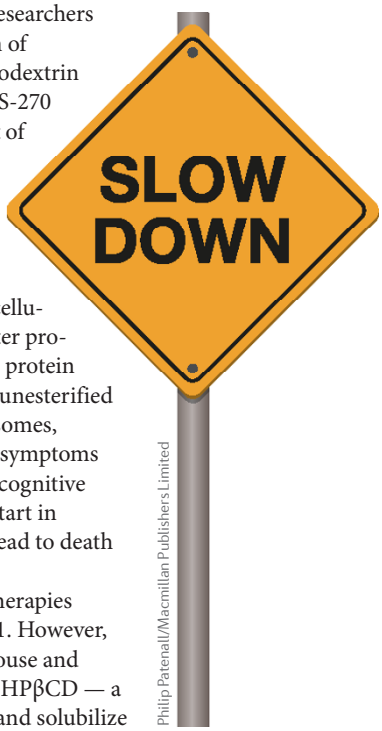
NEUROMETABOLIC DISEASE

New drug slows Niemann–Pick disease

A clinical trial has highlighted a promising new treatment for Niemann–Pick disease, type C (NPC1), a life-threatening lysosomal storage disorder that often commences in childhood. Researchers found that a preparation of 2-hydroxypropyl-β-cyclodextrin (HPβCD) known as VTS-270 slowed the development of neurological symptoms in patients with this disorder.



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NPC1 is caused by mutations in *NPC1*, which encodes an intracellular cholesterol transporter protein. Impairment of this protein causes accumulation of unesterified cholesterol in endolysosomes, resulting in progressive symptoms of cerebellar ataxia and cognitive impairment that often start in childhood and usually lead to death within 10–15 years.

No FDA-approved therapies currently exist for NPC1. However, preclinical studies in mouse and cat models showed that HPβCD — a molecule that can bind and solubilize hydrophobic molecules such as cholesterol — slowed disease progression and prolonged lifespan.

The new randomized, open-label, dose-escalation phase I–II trial of HPβCD investigated the safety and efficacy of this agent in humans with NPC1, for the first time. 14 patients with NPC1 were given monthly intrathecal injections of HPβCD at a range of doses (50–1200 mg), and three additional patients were given treatment every 2 weeks.

The team found that plasma levels of 24(S)-hydroxycholesterol, a biomarker reflecting healthy neuronal cholesterol homeostasis, increased in patients treated with high doses (>900 mg) of HPβCD. In addition, cerebrospinal fluid levels of calbindin D and FABP3 — biomarkers for neuronal damage — decreased in most participants after treatment compared with baseline levels.

Furthermore, HPβCD-treated patients had a lower rate of degeneration than did untreated patients with NPC1 from a historical cohort, as measured by NPC neurological severity score, suggesting that HPβCD treatment slows disease progression. Importantly, HPβCD was also found to have a reasonable safety profile — the drug caused some expected ototoxicity, but no severe drug-related adverse effects were observed.

"The study by Ory and colleagues is a major advance in the treatment of this devastating disease and is to be applauded," remark Robert Erikson and Maria Teresa Fiorenza in an accompanying comment piece published in *The Lancet*.

Forbes D. Porter, corresponding author for the trial, says that the group are now moving to the next phase of testing with HPβCD. "VTS-270 has been given Breakthrough Status by the FDA and is currently being studied in a phase III multinational trial," he explains.

Charlotte Ridler

ORIGINAL ARTICLE Ory, D. S. *et al.* Intrathecal 2-hydroxypropyl-β-cyclodextrin decreases neurological disease progression in Niemann-Pick disease, type C1: a non-randomised, open-label, phase 1–2 trial. *Lancet* http://dx.doi.org/10.1016/S0140-6736(17)31465-4 (2017)