2-Hydroxypropyl-β-Cyclodextrin Raises Hearing Threshold in Normal Cats and in Cats With Niemann-Pick Type C Disease

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ABSTRACT: 2-hydroxypropyl-β-cyclodextrin (HPβCD) is a promising experimental therapy for Niemann-Pick type C disease that improved intracellular cholesterol transport, substantially reduced neurodegeneration and hepatic disease, and increased lifespan innpc1<sup>−/−</sup> mice. On the basis of favorable treatment outcome in mice, HPβCD is being evaluated as a therapy in children with Niemann-Pick type C (NPC) disease. We evaluated the efficacy of HPβCD in the feline model of NPC disease and recognized a dose-dependent increase in hearing threshold associated with therapy as determined by brain stem auditory evoked response (BAER) testing. To further assess the effect of HPβCD on hearing threshold, normal cats were administered the drug s.c. at either 4000 mg/kg or 8000 mg/kg body weight, or intrathecally at a dose of 4000 mg/kg brain weight. HPβCD caused a significant increase in hearing threshold following one dose of 8000 mg/kg s.c. or 120 mg intrathecally, and the effect was maintained for at least 12 weeks. Repeated weekly s.c. administration of 4000 mg/kg HPβCD resulted in a similar increase in hearing threshold. These studies are the first to describe a specific negative effect of HPβCD on the auditory system and suggest the need for auditory testing in patients receiving similar doses of HPβCD.

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Cyclodextrins are cyclic oligosaccharides with hydrophobic interiors used as formulation vehicles to increase the amount of drug, including hormones and vitamins, which can be solubilized in aqueous vehicles (1). 2-hydroxypropyl-β-cyclodextrin (HPβCD) was extensively studied in rodents, dogs, and monkeys where it was generally well tolerated at low doses (1,2). Daily i.v. administration of greater than 200 mg/kg caused reduced body weight, foamy macrophage infiltration of the lungs, elevations in hepatic enzymes, increased Kupffer cells in the liver, and renal cortical tubular vacuolization in rodents (1,3,4). All of these changes were reversible following cessation of HPβCD administration (1).

Niemann-Pick type C (NPC) disease is an incurable lysosomal storage disorder characterized by the intralysosomal accumulation of unesterified cholesterol, hepatosplenomegaly, progressive neurologic dysfunction, and early death (5,6). Weekly intraperitoneal administration of 1500 mg/kg of HPβCD to npc<sup>−/−</sup> mice resulted in improvement in hepatic disease with no effect on neurologic disease or lifespan (7). In contrast, the administration of a single s.c. dose of 4000 mg/kg of a 20% solution of HPβCD to 7-d-old npc<sup>−/−</sup> mice reversed the defect in the lysosomal transport of cholesterol and significantly improved hepatic dysfunction, decreased neurodegeneration, and prolonged lifespan (8). Every other day s.c. administration of 4000 mg/kg of a 20% solution of HPβCD to npc<sup>−/−</sup> mice was the most effective treatment regimen at ameliorating clinical disease and increasing lifespan, and also significantly decreased neuronal cholesterol, ganglioside, and sphingosine accumulation, and decreased neuroinflammation (9). It was hypothesized that high doses of HPβCD were needed to ameliorate neurologic dysfunction because higher blood levels allowed more drug to cross the blood-brain barrier. An alternative hypothesis was that increased serum levels of HPβCD could bind enough circulating sterols to result in enhanced cholesterol egress from the CNS by an undefined mechanism (9). In each of these animal studies, no significant toxicity was observed after the administration of HPβCD except for increased macrophage infiltration of the lungs found at post-mortem examination (9). On the basis of these data from the murine model, HPβCD has been approved for use in a group of children with NPC disease by the Food and Drug Administration (FDA).

Naturally occurring NPC disease occurs in cats which have a missense mutation inNPC1 (2864G-C) with clinical, neuropathological, and biochemical abnormalities similar to those present in juvenile-onset patients making this model homologous to the most common form of the disease seen in human patients (10,11). Brain stem auditory evoked response testing (BAER) of cats with NPC disease showed a prolongation in central conduction time with no significant alteration in hearing threshold compared with wild type cats (11). While evaluating the efficacy of HPβCD to treat NPC disease in cats, we noted a significant elevation of hearing threshold in animals receiving repeated s.c. doses of 4000 mg/kg. To our knowledge, a negative effect of HPβCD on auditory function has not been evaluated in any species. This study investigated the effects of the s.c. and intrathecal administration of HPβCD treatment on the BAER of both normal cats and cats with NPC disease.

METHODS

Animals. Cats were raised in the animal colony of the School of Veterinary Medicine, University of Pennsylvania, under National Institutes of Health and USDA guidelines for the care and use of animals in research. The experi-

Abbreviations: BAER, brain stem auditory evoked response; HPβCD, hydroxypropyl-beta-cyclodextrin; NPC, Niemann-Pick type C
mental protocol was approved by the University of Pennsylvania Institutional Animal Care and Use Committee.

All animals examined were produced from the same line bred to produce cats with a familial recessively inherited Niemann-Pick type C (NPC) disease. All cats were housed at 21°C with ad libitum food and water, 12-h light cycles, with 12–15 air changes per hour. Peripheral blood leukocytes from all cats were tested at 1 day of age for the NPC1 mis-sense mutation using a PCR-based DNA test (10). Cats with two copies of the mis-sense mutation were classified as affected with NPC disease while cats with one or no copies of the mutation were classified as normal. Heterozygote to heterozygote breeding resulted in ~25% affected and ~75% normal offspring.

**Study groups.** Normal cats were placed in one of five study groups (Table 1). Group 1 (n = 7) were 6 months old and received no drug. Group 2 (n = 3) received one dose of 4000 mg/kg body weight HPβCD sc. at 6 months of age. Group 3 (n = 3) received one dose of 8000 mg/kg body weight HPβCD sc. at 6 months of age. Group 4 (n = 3) received one dose of 4000 mg/kg brain weight (120 mg for a 30-g brain weight) HPβCD intrathecally at 6 months of age. Intrathecal administration was achieved by anesthetizing cats with i.v. propofol (up to 6 mg/kg; Abbott Laboratories, Chicago, IL). A 20-gauge spinal needle was placed into the cerebellomedullary cistern and 1.0 mL of saline was removed. 0.6 mL of 20% HPβCD in saline was injected intrathecal over a 2-minute time period into the cerebellomedullary cistern. Group 5 (n = 3) received weekly 4000 mg/kg body weight HPβCD sc. beginning at 8 weeks of age for a total of seven doses.

Cats affected with NPC disease were also involved in a clinical study evaluating the efficacy of HPβCD to treat disease. All cats were first administered the drug at 3 weeks of age, before the onset of clinical signs of disease, and continued to receive the drug weekly thereafter. Cats were placed into one of five groups (Table 2). Group 6 (n = 8) received no HPβCD and served as the control group for cats with NPC disease. Groups 7 (n = 5), 8 (n = 2), and 9 (n = 5) received a weekly dose of 1000 mg/kg HPβCD body weight sc. 4000 mg/kg body weight HPβCD s.c., and 8000 mg/kg body weight HPβCD s.c., respectively. Group 10 (n = 2) received 4000 mg/kg brain weight (120 mg for a 30-g brain weight) HPβCD intrathecally every 2 wk (intrathecal administration methods described earlier).

**HPβCD formulations.** All HPβCD was administered in a 20% (wt/vol) solution dissolved in 0.9% sodium chloride. HPβCD was received from Sigma Chemical Co. and the powdered form (HPβCD-H107; Sigma Chemical Co. Aldrich, St. Louis, MO) was used in all s.c. administrations and the cell culture tested form (HPβCD-H9252; Sigma Chemical Co. Aldrich) was used for all intrathecal administrations. As a control for the saline injection, addition normal cats were injected one time sc. (n = 2) and intrathecally (n = 2) with similar volumes of saline.

To control for possible differences between HPβCD available from Sigma Chemical Co. and the product used in published mouse studies (8,9) and the FDA-approved formulation for use in patients (Trappsol–Pharm grade. Cyclodextrin Technologies Development, Inc, High Springs, FL), Trappsol was administered to four cats: one dose of 8000 mg/kg body weight s.c. (n = 2) and one dose of 4000 mg/kg brain weight intrathecally (120 mg for a 30-g brain weight; n = 2).

**Brain stem auditory evoked response testing.** All measurements of the BAER studies were performed at 16 weeks of age. BAER studies were performed every week in group 5 for a total of 12 wk. In cats with NPC disease, BAER studies were performed at 16 weeks of age.

**Statistical methods.** The mean and SD of the threshold, central conduction time, and wave V/I ratio estimates in each group were calculated to determine the data and an unpaired 2-tailed t test was used to compare data between various groups. Since values of p < 0.05 (*) are given. Threshold differences between groups were considered statistically reliable if the probability of chance occurrence was 0.05 or less.

**RESULTS**

**Normal cats.** None of the normal animals that received either sc. or intrathecal HPβCD injections showed evidence of loss of balance or ataxia at any point during the study. No clinical signs were attributable to HPβCD administration aside from pain at the sc. injection site which was common in cats receiving weekly doses. Subjective evaluation of hearing was difficult to perform because normal, untreated colony-bred animals frequently do not respond repeatedly to sound. Detailed behavioral testing was not performed.

A single s.c. dose of 4000 mg/kg HPβCD evoked waveforms the same as in cats which received no HPβCD (Fig. 1, groups 1 and 2). In contrast, a single s.c. dose of 8000 mg/kg HPβCD resulted in diminished wave form amplitude with changes severe enough to make specific waveforms difficult to identify (Fig. 1, group 3). Similarly, a single intrathecal dose of 120 mg HPβCD resulted in altered evoked responses characterized by reduced amplitude (Fig. 1, group 4). A single injection of intrathecal saline left the BAER unchanged in two cats (data not shown).

Hearing threshold, wave V/I amplitude, and central conduction time were measured for groups 1–5 (Table 3). Cats in groups 3 and 4 showed a significant increase in hearing threshold 2 weeks after injection compared with un.injected cats (group 1). The average click BAER threshold in control cats was 66 dB, whereas in groups 3 and 4 that were treated with 4000 mg/kg and 8000 mg/kg HPβCD, respectively, the

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cats</th>
<th>Dose and method of administration of HPβCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4000 mg/kg body weight subcutaneously once</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>8000 mg/kg body weight subcutaneously once</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>4000 mg/kg brain weight intrathecally once</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>4000 mg/kg body weight subcutaneously weekly for 7 doses</td>
</tr>
</tbody>
</table>

NA, not applicable.

Table 2. Summary of groups of cats with NPC disease treated with HPβCD

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cats</th>
<th>Dose and method of administration of HPβCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>8</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>1000 mg/kg body weight subcutaneously weekly</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>4000 mg/kg body weight subcutaneously weekly</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>8000 mg/kg body weight subcutaneously weekly</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>4000 mg/kg brain weight intrathecally every two weeks</td>
</tr>
</tbody>
</table>

NA, not applicable.

sPL, click to the recorded ear and delivered an 85 dB SPL, white noise to the contralateral ear. The high pass filter on the amplifier was 20 Hz and the low pass cutoff was 3 kHz. A sensitivity of 1 uV/cm was used to record the responses and the averaging epoch was 10 ms with a sampling resolution of 0.01 ms. One thousand evoked responses were averaged for each BAER response obtained. Central conduction time was defined as the time between the first and the fifth peak. Wave V/I amplitude was determined by dividing the amplitude of the fifth wave by the amplitude of the first wave and multiplying by 100; amplitude was measured from peak to trough and expressed as microvolts. A modified method of limit procedure was used to estimate threshold. When a clearly defined BAER was identified at the reference stimulus of 125 dB, the attenuator was then increased in 3 dB steps and a signal averaged response was sought at each step. If an evoked response was observed, the attenuator was then increased by another 3 dB and the BAER response again observed. This continued until a sound level was reached at which an averaged evoked response could not be identified.

In normal cats, BAER studies were performed every other week following the administration of HPβCD in groups 2, 3, and 4 for a total of 12 wk, and were performed every week in group 5 for a total of 12 wk. In cats with NPC disease, BAER studies were performed at 16 weeks of age.

**RESULTS**

**Normal cats.** None of the normal animals that received either s.c. or intrathecal HPβCD injections showed evidence of loss of balance or ataxia at any point during the study. No clinical signs were attributable to HPβCD administration aside from pain at the s.c. injection site which was common in cats receiving weekly doses. Subjective evaluation of hearing was difficult to perform because normal, untreated colony-bred animals frequently do not respond repeatedly to sound. Detailed behavioral testing was not performed.

A single s.c. dose of 4000 mg/kg HPβCD evoked waveform the same as in cats which received no HPβCD (Fig. 1, groups 1 and 2). In contrast, a single s.c. dose of 8000 mg/kg HPβCD resulted in diminished wave form amplitude with changes severe enough to make specific waveform difficult to identify (Fig. 1, group 3). Similarly, a single intrathecal dose of 120 mg HPβCD resulted in altered evoked responses characterized by reduced amplitude (Fig. 1, group 4). A single injection of intrathecal saline left the BAER unchanged in two cats (data not shown).

Hearing threshold, wave V/I amplitude, and central conduction time were measured for groups 1–5 (Table 3). Cats in groups 3 and 4 showed a significant increase in hearing threshold 2 weeks after injection compared with un.injected cats (group 1). The average click BAER threshold in control cats was 66 dB, whereas in groups 3 and 4 that were treated with 4000 mg/kg and 8000 mg/kg HPβCD, respectively, the
were statistically the same in normal cats (group 1, 66.4 dB rate disease progression. At 16 wk of age, hearing thresholds therapy with HP significantly greater than the hearing threshold observed the same dose resulted in a progressive elevation of hearing threshold 2 weeks after the first injection (data not shown), repeated weekly injections of significant elevation in hearing threshold 2 weeks after the administration of HPßCD (65 dB; group 3). The first dose was administered immediately after Week 0 threshold testing. Repeated HPßCD administration resulted in progressive elevation of the hearing threshold with a statistically significant (p < 0.05) increase from weeks 4 to 7 when compared with week 0.

### Table 3. Hearing threshold, wave V/I amplitude, and central conduction time 2 weeks after administering a single dose of HPβCD to normal cats (groups 2–4) and 1 wk after the sixth dose (group 5)

<table>
<thead>
<tr>
<th>Group</th>
<th>Hearing threshold (dB SPL)</th>
<th>Wave V/I amplitude</th>
<th>Central conduction time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>66.4 ± 3.2</td>
<td>181 ± 16.7</td>
<td>2.41 ± 0.09</td>
</tr>
<tr>
<td>Group 2</td>
<td>63.0 ± 5.2</td>
<td>212 ± 24.0</td>
<td>2.43 ± 0.02</td>
</tr>
<tr>
<td>Group 3</td>
<td>79.0 ± 4.6*</td>
<td>545 ± 402</td>
<td>2.36 ± 0.02</td>
</tr>
<tr>
<td>Group 4</td>
<td>81.0 ± 3.0*</td>
<td>525 ± 127</td>
<td>2.37 ± 0.05</td>
</tr>
<tr>
<td>Group 5</td>
<td>80.0 ± 1.7*</td>
<td>469 ± 423</td>
<td>2.38 ± 0.09</td>
</tr>
</tbody>
</table>

*p < 0.05.

Cats with NPC disease. Affected cats began weekly s.c. therapy with HPβCD at 3 weeks of age in an attempt to ameliorate disease progression. At 16 wk of age, hearing thresholds were statistically the same in normal cats (group 1, 66.4 dB ± 3/2 dB) and cats with NPC disease (group 6, 71.9 dB ± 7.9 dB). Interestingly, significant differences were absent between cats treated s.c. with 1000 mg/kg HPβCD (65 dB ± 7.5 dB; group 7) and untreated affected cats (group 6; n = 8). Both cats treated with weekly 4000 mg/kg (group 8; n = 2) showed an increase in hearing threshold and cats treated with weekly 8000 mg/kg (group 9; n = 5) had a statistically significant (p < 0.05) increase in threshold. No waveforms were evoked at the maximum stimulus intensity of 125 dB from two cats treated with every other week intrathecal HPßCD (group 10).
vestibular dysfunction occurred in affected cats beginning with
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neurologic dysfunction (16), and for evaluating efficacy of ex-
dritogenesis (19), for correlating neuroaxonal dystrophy with
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gangliosides (GM2 and GM3) (18), for evaluating the association
somal/lysosomal accumulation of unesterified cholesterol and
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logical, and biochemical abnormalities similar to those present in
mutation in
model of NPC disease has a spontaneously occurring mis-sense
mutation represents
heterozygosity of disease in human patients. One particular mis-sense
disorder because of the relatively low incidence and the hetero-
ary studies and therapy trials are difficult to perform on this

Figure 4. Normal cats treated with either intrathecal or s.c. Trappsol showed
abnormal waveforms 1 week after administration. A, shows BAER tracing
immediately before intrathecal injection of 120 mg Trappsol; B, shows BAER in
same cat 1 week later. C, shows BAER tracing immediately before s.c.
injection of 8000 mg/kg Trappsol; D, shows BAER in same cat 1 week later.
administered. BAER recordings were first made within 15 min
of s.c. and intrathecal administration and no changes in the
waveforms were noted (data not shown). Figure 4A and C
show the BAER recordings before Trappsol administration in
two cats. Figure 4B shows the BAER recording 1 week after
the administration of HPβCD intrathecally, and Figure 4D
shows the tracing obtained 1 week after the administration of
s.c. HPβCD. The administration of Trappsol to normal cats
resulted in changes to the BAER similar to that seen with the
Sigma Chemical Co. product. Hearing threshold in two cats
were treated intrathecally increased from 69 dB to 72 dB before
drug administration to 87 dB and 90 dB following adminis-
tration. Hearing threshold in two cats treated s.c. increased
from 69 dB and 72 dB before drug administration, to 87 dB in
both cats following drug administration.

**DISCUSSION**

Niemann-Pick type C disease has an incidence of 1:150,000,
with >250 disease-causing mutations identified (5). Natural his-
tory studies and therapy trials are difficult to perform on this
disorder because of the relatively low incidence and the hetero-
genesis of disease in human patients. One particular mis-sense
mutation represents >20% of mutant alleles and >50% of
patients have a juvenile onset of neurologic disease. The feline
model of NPC disease has a spontaneously occurring mis-sense
mutation in NPC1 (2864G-C) and exhibits clinical, neuropatho-
logical, and biochemical abnormalities similar to those present in
juvenile-onset patients. Thus the cat model is homologous to the
most common form of disease seen in human patients (10,12–17).
The feline model has been useful for identifying the late endo-
osomal/lysosomal accumulation of unesterified cholesterol and
gangliosides (GM2 and GM3) (18), for evaluating the association
of GM2 storage with meganeurite formation and abnormal den-
dritogenesis (19), for correlating neuroaxonal dystrophy with
neurologic dysfunction (16), and for evaluating efficacy of ex-
perimental therapies (10,13). The onset and progression of neu-
rologic dysfunction in the feline model has been well character-
ized (11,15). A regular onset of progressive cerebellar and
vestibular dysfunction occurred in affected cats beginning with
intention tremors and ataxia at 6 weeks of age. This dysfunction
progressed until cats could no longer maintain sternal recum-
bency at ~24 wk of age. Changes in hearing threshold were not
found although a delay in central conduction time and a decrease
in wave VI amplitude ratio was observed in 16- and 24-wk old
affected cats compared with wild type cats (11).

HPβCDs are cyclic oligosaccharides consisting of seven β-
(1–4) glucopyranose units (7). HPβCDs have a hydrophilic
exterior and a hydrophilic interior making them useful for
increasing the aqueous solubility of hydrophobic molecules
such as cholesterol, steroids, and vitamins (20). *In vitro*
studies using β-cyclodextrins have shown a marked removal
of cholesterol from cultured neuronal (21,22) and nonneuronal
cell lines (23–25). HPβCDs were shown to cross the blood
brain barrier in *in vitro* (25) and in *in vivo* with difficulty
(7,26). However, β-cyclodextrins were safely administered
intrathecally in rodent studies and used to improve the delivery
to the brain of drugs including anesthetic agents, galanin-
like peptide, and estradiol (27–29).

Recently, HPβCD was shown to release cholesterol from
NPC-deficient lysosomes and allowed unesterified cholesterol to
be available to the NPC cell. This resulted in the amelioration
of disease and the prolongation of life in the murine model (8,9,30).
However, high doses of HPβCD (at least 4000 mg/kg) however
appeared necessary to retard the progression of neurologic
disease. Studies in npc1<−/−> mice showed that 1500 mg/kg HPβCD
administered weekly caused a decrease in hepatic unesterified
cholesterol concentrations without substantial effect on neuro-
logic signs (7). Increasing the dose to either 4000 mg/kg weekly
or every other day delayed clinical disease onset, increased
survival time, corrected cholesterol metabolism, and improved
biochemical and histologic disease (8,9). Because β-cyclodextrins
do not easily penetrate the blood brain barrier (7,25), these
studies suggested that parenteral administration of high doses of
HPβCD are necessary to get sufficient amounts of HPβCD to
cross the blood brain barrier and to have an effect on neurologic
disease. Unfortunately, the pharmacokinetics of HPβCD are not
well understood particularly in the nervous system. A plasma
elimination half-life in rats was 0.4 h and in dogs was 0.8 h,
although the concentration in cerebrospinal fluid after systemic
administration was not described (1). Serum and cerebrospinal
measurements of unlabeled HPβCD are technically difficult to
perform, and these concentrations were not determined in the
recent murine articles (8,9,30). Clearly, the kinetics of HPβCD in
serum and spinal fluid will be necessary to clarify how HPβCDs
effect neurologic dysfunction in NPC disease and to determine
what dose is most efficacious while also limiting toxicity.

As a result of the dramatic improvement in clinical signs seen
in the mouse model of NPC disease, HPβCD was given recent
FDA approval for use in a small number of patients with NPC
disease. This has increased the urgency to more fully characterize
any dose-related potential toxic effects of the drug. In humans,
i.v. administration of up to 3 g in healthy volunteers was well
tolerated and doses of 16 g per day given with itraconazole did
not result in hearing abnormalities (4). The authors could not find
examples of doses of 1000 mg/kg and higher being used in
human patients, although these are being proposed to treat pa-
tients with NPC disease. The authors are aware of no previous
study examining the effect of HPβCD on auditory function and yet we were able to determine an effect on hearing using a small number of normal cats and cats with NPC disease. Our data show that 1000 mg/kg had no effect on the BAER response when given weekly for 14 doses between the ages of 3 and 16 wk of age. Doses of 4000 mg/kg body weight resulted in an increase in hearing threshold only after repeated dosing and doses of 8000 mg/kg body weight resulted in significant increases in hearing threshold in both normal cats and cats with NPC disease following the administration of a single dose. Interestingly, the doses needed to negatively impact the BAER response were the same dose necessary to retard nervous system dysfunction in mice. Our preliminary data in cats affected with NPC disease suggest a similar requirement for doses equal to or >4000 mg/kg to positively affect neurologic disease (data not shown). One conclusion that suggested itself is that doses of 4000 mg/kg positively affect neurologic disease (data not shown). One conclusion that suggested itself is that doses of 4000 mg/kg positively affect neurologic disease (data not shown).

The increased hearing threshold with no change in central conduction time suggested that the damage from HPβCD occurred in the peripheral auditory pathway (cochlea or eighth nerve) and that potential mechanisms of action for the hearing loss observed include a direct effect on the stria vascularis and its role in maintaining the ionic environment of the inner ear fluid space, the transduction and motility mechanisms of inner and outer hair cells, and/or the excitation patterns in the auditory nerve discharges. Identifying the site of action of HPβCD within the peripheral auditory system will likely be the first step in overcoming toxicity of HPβCD applications. Otoacoustic emission testing would be a useful method for evaluating outer hair cell function in cats but was unavailable for these studies. Histopathology of the cochlea should be performed in the future to identify any pathologic changes.

In summary, hearing impairment following HPβCD administration appeared to be both dose dependent and long lasting and may be a limiting factor in the use of this drug at high doses to treat Niemann-Pick type C disease. Auditory testing is recommended for patients receiving doses of 4000 mg/kg HPβCD or greater to evaluate the effect on hearing threshold in these patients.

Acknowledgments. We acknowledge the critical review of the manuscript by Drs. Shel Steinberg and James Saunders. Trapposl was provided by Dr. Rick Stratton.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES