Sodium Thiosulfate Prevents Cisplatin-Induced Hearing Loss in Some Children

In the study, the antioxidant made children less likely to permanently lose hearing without affecting their chemotherapy treatment.

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The drug sodium thiosulfate can protect the hearing of children with cancer undergoing treatment with the chemotherapy drug cisplatin, results from a new study show.

The clinical trial involved children with liver cancer that had not spread (localized cancer), for whom cisplatin is the standard chemotherapy. Although cisplatin is very effective, it also causes hearing loss in many children.

The participants in the trial, which was conducted primarily in Europe, were randomly assigned to receive sodium thiosulfate 6 hours after each cisplatin treatment or to receive only cisplatin. The children in the sodium thiosulfate group were half as likely to experience permanent hearing loss than children who received cisplatin alone, the researchers reported.

Importantly, sodium thiosulfate did not appear to make cisplatin less effective: there was no difference in how many children in each treatment group were alive 3 years after completing treatment. The trial findings were published June 21 in the New England Journal of Medicine.

These results mirror those from a similar trial conducted in the United States, published last year, which tested sodium thiosulfate's ability to prevent cisplatin-induced hearing loss in children with diverse types of cancer.

"It's encouraging to see two studies show that you can reduce the risk of hearing loss in these kids without reducing the effectiveness of the chemotherapy," commented Lisa Cunningham, PhD, of the National Institute on Deafness and Other Communication Disorders, who was not involved in either trial.

Hearing Loss Impacts Development

Today, more than 80% of children diagnosed with cancer are alive at least 5 years after diagnosis, and many are considered to be cured.

Researchers are now turning greater attention to reducing the long-term side effects that children

experience with many widely used cancer treatments. These can include heart or lung problems, cognitive difficulties, infertility, and hearing loss.

“Over the last decade or so, we’ve really developed a much deeper understanding of how [some of] these drugs damage the inner ear,” commented Cunningham. Earlier this year, for example, her lab published results showing that cisplatin is retained for a long time in the inner ear, which may explain why its use can lead to hearing loss.

Hearing loss can have significant long-term consequences for children treated for cancer, said Edward Neuwelt, MD, of Oregon Health & Science University, who helped lead both recent trials. “Around 60% to 80% of kids who get cisplatin have significant hearing loss,” Neuwelt explained. The impact of that hearing loss can be profound, he continued, including greatly increasing the risk of failing a grade in school.

The consequences can be even more serious for very young children, added Cunningham. “Hearing loss actually impairs their ability to develop normal speech and language skills, which … can lead to severe developmental problems for a child,” she explained.

Confirming That Sodium Thiosulfate Doesn’t Compromise Survival

Sodium thiosulfate is a type of drug called an antioxidant. It is thought to bind to harmful molecules called reactive oxygen species that are produced in cells that have taken up cisplatin. This binding may prevent free radicals from damaging the hair cells in the inner ear that play a critical role in hearing.

It’s also possible that sodium thiosulfate is working by binding to cisplatin itself, preventing any residual cisplatin from killing cells in the ear, Cunningham said.

The results from the trial published last year, which was led by the NCI-supported Children’s Oncology Group, enrolled children with a variety of cancer types who all received cisplatin as part of their initial treatment. The 104 participants were randomly assigned to receive chemotherapy alone or chemotherapy followed by sodium thiosulfate 6 hours after each dose of cisplatin.

The timing of the sodium thiosulfate infusions, Neuwelt explained, was based on several decades of laboratory and clinical work to establish how long cisplatin is active in the body. After 6 hours, cisplatin is no longer actively killing cancer cells, he continued, so giving sodium thiosulfate at that time should not interfere with cisplatin’s anticancer effects.

Hearing loss occurred in 31 (56%) of the children who received chemotherapy alone, compared with 14 (29%) who also received sodium thiosulfate. Sodium thiosulfate did not appear to cause any side effects.

Overall, no differences in overall survival were seen between the groups. However, in an analysis that was not planned before the trial started, the researchers did see a reduction in overall survival for children who received sodium thiosulfate and who had cancer that had spread beyond

the site of origin (disseminated disease).

Although such analyses are largely used to identify issues that should be explored with further research, some people became concerned about the safety of sodium thiosulfate in children with later-stage cancer, explained Neuwelt.

In the European trial, which was funded in part by NCI, the researchers enrolled only children with one type of cancer—a type of liver cancer called hepatoblastoma—and only those with localized disease. Cisplatin was the only chemotherapy drug received by participants in the trial. Of the 101 participants, hearing loss occurred in 29 (63%) of the children who received cisplatin alone, compared with 18 (33%) of those who also got sodium thiosulfate.

Three years after treatment, 98% of the children who received cisplatin and sodium thiosulfate and 92% who received cisplatin alone were alive. One child experienced a side effect (a buildup of acid in the blood) that required discontinuation of sodium thiosulfate during the trial. The researchers reported that other side effects possibly caused by sodium thiosulfate were mild, and included nausea, vomiting, and a reduction in blood cell numbers.

“These data are compelling, and the conclusions of this trial should trigger a major change in practice,” commented Eric Bouffet, MD, of the Hospital for Sick Children at the University of Toronto.

Remaining Questions About Sodium Thiosulfate

Some questions remain about protecting hearing in children undergoing cisplatin-based chemotherapy, added Bouffet. “Some children still present with hearing complications despite the use of sodium thiosulfate. The results of ongoing studies to better understand which patients may be at risk of hearing loss are needed,” he said.

Additional trials are also needed to answer lingering concerns about the drug’s use in children with disease that has spread, continued Bouffet.

Neuwelt is hoping to develop a clinical trial testing whether adding sodium thiosulfate as part of the treatment regimen can improve survival in children diagnosed with medulloblastoma. Often, parents of children with the disease opt to have them not complete their course of cisplatin because of hearing loss.

“We’re going to see if we can decrease the number of kids who need a dose reduction [of cisplatin], and see if that will improve survival,” he explained.

“There’s enthusiasm right now in basic science and in the pharmaceutical industry for developing new therapies that will reduce hearing loss, both in children and in adults,” said Cunningham. “There are a number of drugs at various stages of development in the pipeline right now that are being developed specifically for this purpose.”

For now, “sodium thiosulfate is cheap and can be incorporated [easily] into chemotherapy

protocols that contain cisplatin," Bouffet said. "The positive results from [the European] trial call for additional studies of sodium thiosulfate in other cancer types, including in adults."

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http://beta.docker.cancerhealth.com/blog/sodium-thiosulfate-prevents-cisplatininduced-hearing-loss-children