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Cystic Fibrosis Research News

Title:
Ebselen attenuates tobramycin-induced ototoxicity in mice

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What was your research question?
We developed a mouse model to investigate hearing loss resulting from tobramycin, a common antibiotic treatment for lung infections. We also tested if ebselen, a new anti-inflammatory drug being tested in other human trials, could reduce the hearing loss in this mouse model.

Why is this important?
Hearing loss, tinnitus and dizziness are major side effects of aminoglycoside antibiotics such as tobramycin and these side effects are called ototoxicity. Aminoglycosides also harm the kidneys and as people with CF get older, hearing loss, and kidney failure can become debilitating. Ebselen has been shown to prevent the hearing loss due to ototoxic medications in mice and rats, and to treat other human inner ear disorders such as Meniere's Disease that involve tinnitus and dizziness. Therefore, we wanted to investigate if ebselen could prevent hearing loss due to tobramycin in mice. These results support the ongoing testing of ebselen in people with CF receiving tobramycin intravenously (directly in the blood) for acute lung infections.

What did you do?
First, we tested the direct effects of tobramycin and ebselen on the hair cells which allow us to hear in a culture model of the inner ear of mice. Second, we injected the adult mice daily with tobramycin and/or ebselen for 14 days, a dose schedule that is similar to that given to people with CF. Before and after these injections, we tested hearing using the auditory brainstem response (ABR), a way of recording brain responses to sounds of different frequencies and intensities. We then followed the mice for months and analysed the auditory hair cells.

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What did you find?

In adult mice injected with tobramycin for 14 days, there was significant hearing loss with severe damage to the hair cells. However, when ebselen was also added, we saw far less damage. We modified the criteria from the American Speech-Language-Hearing Association (ASHA) involving pure tone hearing tests to include ABR. We used these modified criteria, individual mice hearing was evaluated for tobramycin-induced ototoxicity, similar to what an audiologist would do in for a person with CF.

What does this mean and reasons for caution?

This culture and live animal data confirm that tobramycin damages the inner ear and causes hearing loss when dosed over 14 days. We showed that giving ebselen at the same time as the aminoglycoside antibiotics prevents much of this hearing loss when measured using modified ASHA criteria. It should be noted that the degree of damage from tobramycin and the amount of protection from ebselen may vary between mice and humans based on route of administration, dose and dose schedule. In addition, there are at least 3 other aminoglycosides that are used to treat lung and gut infections. These should also be tested in this animal model.

What's next?

We plan to investigate if ebselen can prevent hearing loss caused by other common aminoglycoside antibiotics used to treat cystic fibrosis such as amikacin, gentamicin and streptomycin. We also want to investigate the long-lasting impact of these antibiotics on the brain, which may cause hearing problems such as tinnitus and hyperacusis (a heightened sensitivity to particular sounds).

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