

Hearing Loss in a Woman on Aspirin: The Silent Pharmacokinetic Parameter

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Abstract: A sudden hearing loss in a woman on aspirin has uncovered a frequently neglected toxicological parameter.

Key Words: hearing loss, aspirin, systemic lupus

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Clinician

I am caring for a 25-year-old woman with systemic lupus erythematosus. She has been treated with high-dose acetylsalicylic acid (Aspirin; 80 mg kg⁻¹·d⁻¹) due to severe arthritis with good clinical response. She well tolerated her aspirin for 3 years now.

Starting 2 years ago, she has been exhibiting increased degrees of proteinuria as part of her lupus glomerulonephritis. She came to see me yesterday because she has experienced tinnitus (ear ringing) over the last week.

Can this be due to aspirin, and why now, after 3 years without such effect?

TDM Consultant

Tinnitus and hearing loss are known adverse effects of acetylsalicylic acid.^{1–3}

The toxicity is related to biochemical and electrophysiological changes in the inner ear and eighth cranial nerve. Tinnitus and hearing loss, usually reversible, can occur after both chronic use and acute intoxication.

The question is why would this happen 3 years into therapy? What were her serum concentrations of acetylsalicylic acids over the 3 years of therapy with aspirin?

Clinician

She has been on 80 mg kg⁻¹·d⁻¹ aspirin for more than 3 years, and levels were monitored every couple of months. Trough levels were quite consistent between 12 and 19 mcg/dL, within the therapeutic range.

TDM Consultant

What is her serum concentration now?

Clinician

Levels from yesterday before the morning dose was 17.2 mcg/dL, very similar to the concentration 3 months ago, which was 17.4 mcg/dL. I am not sure that it is the aspirin that causes the audiological complaints.

TDM Consultant

Typically, ototoxicity has been associated with serum concentrations above 20 mcg/dL.¹

What is the present status of the patient's proteinuria?

Clinician

She is heavily losing protein in the urine (+4 protein). Her serum albumin yesterday was 1.2 mg/dL; she is edematous and exhibits anasarca.

TDM Consultant

Acetylsalicylic acid is highly bound to serum albumin (between 80% and 90%).⁴ This means that when serum albumin decreases, more drug is unbound. It is the unbound drug that is pharmacologically and toxicologically active.⁵ It is quite possible that her unbound salicylate has dramatically increased.

Clinician

Can you measure unbound salicylate?

TDM Consultant

We conducted microdialysis and her salicylate protein binding is 50%. Assuming that her protein binding was 90% at normal albumin level of 35 g/L, she is experiencing now acute intoxication despite unchanged total drug.

Clinician

In the last 48 hours, her hearing loss has progressed, and presently, she is functionally deaf.

TDM Consultant

Although her total salicylate serum concentration did not change, her free salicylate increased.

The calculation is simple: at 90% protein binding and total serum concentration of 17 mcg/dL, her free salicylate concentration was 1.7 mcg/dL. Now with 40% free drug, her free concentration is 4-fold higher, at 6.8 mcg/L.

Clinician

In this case, the total drug level is quite confusing. I was sure it is not the aspirin that caused the problem.

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TDM Specialist

I would now certainly discontinue her aspirin. If you consider later to renew it, you should monitor carefully free drug levels and titrate her dose to ensure her that free drug level is not increased.

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