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Prevention of gentamicin induced ototoxicity by trimetazidine in animal model

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Summary

Objective: To show the efficacy of intra-peritoneally administered trimetazidine to prevent gentamicin ototoxicity, which is still an important cause of profound deafness among children in different parts of the world.
Methods: Two groups of Swiss albino mice received daily intra-muscular injections of gentamicin for 30 days. One of the groups received trimetazidine intra peritoneally in addition to the gentamicin. Auditory thresholds of the animals were measured by evoked brain stem response at the beginning and the end of the study. Results were compared to the results of the control group, which received intra peritoneal saline injections.
Results: Both groups receiving gentamicin injections had significant auditory threshold shifts, but in the group receiving additional trimetazidine, the threshold shift was not statistically significant when compared to control group. Threshold shift in gentamicin group significantly differed from that of the control group ($p = 0.0001$) and gentamicin + trimetazidine group ($p = 0.0001$), on the other hand there was no statistically significant difference between control group and trimetazidine + gentamicin group ($p = 0.102$).
Conclusion: Gentamicin ototoxicity can be prevented by intra peritoneal trimetazidine injections in animal model. This treatment modality may be a mode of protection from gentamicin ototoxicity in children.

1. Introduction

Fifty years after their discovery, aminoglycosides remain invaluable clinical tools. Even with their well known toxic effects on renal and auditory

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function, and the developing resistance for their anti bacterial efficacy, the low cost and ready availability of aminoglycosides still make them the antibiotic of choice in many countries [1]. The associated risks of such widespread use can be staggering. In investigations of profound hearing loss in China, it was estimated that 66% of all profound deafness is caused by use of aminoglycoside antibiotics in children [2]. Nevertheless, the rising rates of multi-drug resistant infections in general and the world-wide resurgence of tuberculosis seem to assure that aminoglycosides will still be used widely in the near future.

Gentamicin-induced ototoxicity is usually bilateral, symmetrical, irreversible and typically affects the higher frequencies first. With continued exposure other frequencies are also affected. The reported hearing loss varies from 2 to 25%, but may even be higher because of initial high frequency loss, which may not be evident clinically [2,3]. The most consistent histological finding of gentamicin ototoxicity is degeneration of outer hair cells with a predilection for the basal turn of the cochlea. But with the higher doses, inner hair cells, stria vascularis, supporting cells, nerve fibers and ganglion cells also degenerate. Aminoglycoside ototoxicity is initially reversible by calcium co-administration at the neuro-muscular blockage stage [3]. But the later intracellular effects of aminoglycosides are irreversible and result in cell death [3]. There are several suggested mechanisms of gentimicin ototoxicity; forming complexes with iron resulting in free oxygen radicals; binding to polyphosphoinositides resulting in blockage of several intracellular reactions; or inhibition of enzyme ornithine decarboxylase which is essential for compensatory cellular responses to injury [1,3,4].

Several studies have been carried out to protect the inner ear from potential toxic effects of gentamicin. Numerous experimental studies have been carried on in animals and some in groups of patients receiving ototoxic therapies. The use of iron chelators in combination with gentamicin in animal experiments showed some promising results for avoiding gentamicin ototoxicity [4]. Also antioxidants (*n*-acetyl cysteine, alpha tocopherol) tested on guinea pigs, gluthathione, salicylates, neurotrophic substances (glial cell line derived neurotrophic factor, vinpocetine) have all been tested and found of possible use for prevention of gentamicin ototoxicity [5—8].

Trimetazidine is a clinically available drug (in 20 mg oral form) used for ischemic heart disease since 1970 [9]. It was also reported that trimetazidine is affective in hepatic ischemia and neurotoxicity caused by cyclosprorine [10]. In general,

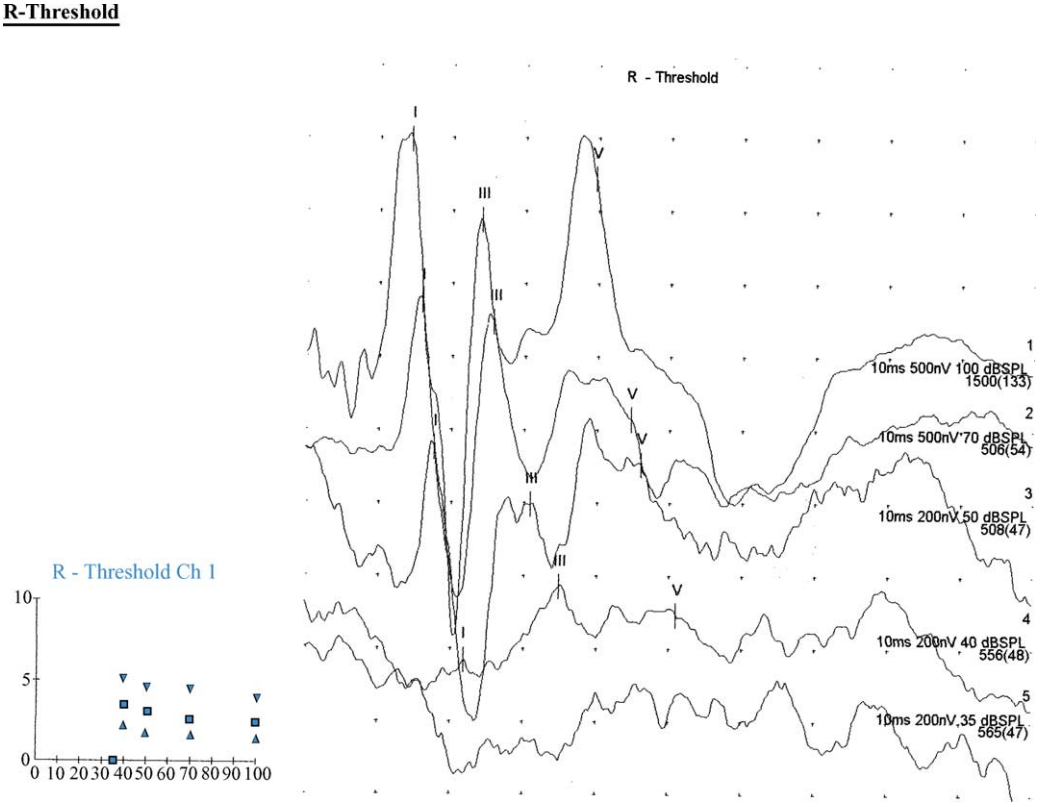

Fig. 1 An example of an ABR output of one of the mice.