Valproic Acid-induced Hearing Loss and Tinnitus

Key words: valproic acid, ototoxicity, auditory dysfunction, hearing loss

Valproic acid (VPA) is a widely used anticonvulsant. There has been only one report that valproic acid caused ototoxicity in an elderly person (1). We report two patients with hearing loss and tinnitus induced by valproic acid.

Patient 1
A 9-year-old girl had suffered from severe hearing loss from birth. Hard of hearing (HOH) was found at the age of three months. She was able to communicate with a loud voice to others. Although she showed absence seizures occasionally, she had not been taking medication.

She stumbled and fell on her head, and visited us in 1999. Physical and neurological examination demonstrated no abnormality except for hearing and speech problems. Routine blood examination was normal. Wechsler intelligence scale for children-revised (WISC-R) testing showed 97 in Total Intelligence Quotient (TIQ) (VIQ 85, PIQ 112), and MRI was negative. Audiogram on the left side revealed severe HOH with low frequency predominance average of 76.25 dB at 500, 1,000, and 2,000 Hz on the air conduction (Fig. 1A). The same findings had been documented on audiogram every year from three years previously. Bone conduction threshold was not available because of her unstable response to vibratory stimulation. She showed complete hearing loss on the right side. Interictal EEG was normal. Ictal EEG demonstrated 3 Hz spike and wave complex bursts occasionally. She showed unresponsiveness clinically during these EEG changes. VPA at a dose of 100 mg/day was started for her seizures. Four weeks after starting VPA, she complained of tinnitus on the left side, and difficulty of hearing and verbal communication worsened. The findings on otoscopic examination were normal. There was no evidence of exudative otitis media. Plasma concentration of VPA was 21.0 µg/dl at this time. Six weeks after On-VPA, audiogram revealed increased threshold about 20 dB in 4,000 Hz (average 83.75) (Fig. 1B), and VPA was discontinued. However, her hearing loss worsened and complete deafness developed on day three after discontinuing VPA. Audiogram demonstrated worsened hearing level with high frequency predominance (average 116.25 dB) on the left side (Fig. 1C). Three times re-examination of audiogram demonstrated the same result in two weeks. No evidence of low frequency hearing loss was documented. She was administered steroid without an improvement. Two months after Off-VPA, her tinnitus improved and her hearing level was mildly recovered to average 102.5 dB (Fig. 1D). Unfortunately, no further improvement was noticed in the two years of follow-up (average 108.75) (Fig. 1E).

Patient 2
A 20-year-old woman developed generalized tonic convolution. She had a past history of otitis media 5 weeks before visiting, which was completely recovered. Neurological examination and brain MRI were normal. EEG demonstrated irregular spike and wave complex bursts with diffuse fashion. She was then administered 400 mg of VPA. Two months after on VPA, 800 mg/day (plasma concentration was 59.4 µg/dl), she complained of tinnitus. Audiogram was within the normal limit (average of 8.8 dB on the right side and 7.5 dB on the left side). VPA was continued. Her tinnitus disappeared without medication. Follow-up audiogram showed no significant changes.

Patient 1 had a preexisting problem in auditory function by birth. Armon et al reported two patients over the age of 70 manifesting VPA-induced sensorineuronal hearing loss. They suggested that preexisting presbycusis was a contributing factor to this side effect (1). VPA might produce irre-

![Figure 1. Audiogram before and after valproic acid (VPA) administration: A. Pre-VPA. B. Six weeks after On-VPA. C. Three days after Off-VPA. D. Two months after Off VPA. E. Two years after Off-VPA.](image-url)
versible auditory dysfunction in patients with preexisting illness in auditory system. Patient 2 had no preexisting hearing problem except for a history of otitis media, which was completely recovered, and showed transient tinnitus only after VPA administration. VPA might have induced tinnitus related to a previous inflammatory problem in the auditory system in patient 2. Transient and benign medical history in the auditory system could be the only cause for the transient auditory effect due to VPA.

In basic studies, VPA reduces sustained, repetitive, high frequency firing of neurons by blocking voltage-sensitive sodium channels or by activating calcium-dependent potassium conductance. This action might interfere with the vulnerable auditory system in patients with auditory problems (2, 3).

Since VPA-induced ototoxicity could depend on preexisting illness in auditory system, VPA should be discontinued when continuous HOH occurs or worsens during administration of VPA. In patients without a preexisting auditory problem, VPA might be continued with careful observation by audiogram.

There have been no reports on VPA-induced hearing loss in patients without hearing problems. VPA may be used cautiously in patients with auditory dysfunction.

References