Is Valproic Acid Ototoxic?

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Valproic acid (VPA), or valproate, was first discovered in 1882 by Burton, but its anticonvulsant properties were not discovered until 1963 (Carraz, Farr, Chateau, & Bonnin, 1964). VPA was released for clinical treatment of epilepsy in 1978 (Fariello & Smith, 1989).

Although thousands of patients have been treated with VPA, only recently has the question of VPA ototoxicity been raised. The first reports described possible changes in auditory brainstem response (ABR) peak latencies (Medaglini et al., 1988; Mervaala, Keranen, Tiihonen, & Riekkinen, 1987). However, actual hearing thresholds were not measured in either study.

Armon, Brown, Carwile, Miller, and Shin (1990) reported hearing loss for two patients attaining very high blood levels of VPA (200 and 300 µg/ml). (The usual “therapeutic range in our laboratory is 50–120 µg/ml although it may be lower for add-on therapy.) Although baseline audiometrics were not obtained in the Armon et al. 1990 study, the patients’ auditory thresholds appeared to improve after termination of VPA therapy. However, several problems existed in the study methods. First, audiologic procedures, equipment, and qualifications of the individuals performing the tests were not specified. Second, only air-conduction thresholds were obtained; therefore, any change in hearing threshold could have been either conductive or sensorineural. Generally, only sensorineural changes are considered to be the result of ototoxicity. Third, the initial audiologic testing was performed while the patients were experiencing severe atypical adverse reactions to VPA including severe action tremor, weight loss exceeding ten pounds, memory and cognition problems, nausea, insomnia, irritability, and unpredictable behavior, among other difficulties. Audiometric thresholds reportedly improved after discontinuation of VPA and the other symptoms subsided. The authors did not discuss the possibility that very ill or disoriented patients may yield unreliable audiometric threshold data. When a patient’s physical and mental states improve, frequently more reliable data may be obtained.

Another consideration is that neither the study patients nor the reactions to VPA were typical. Both patients received very high dosages of VPA and had neurologic problems other than epilepsy including stroke, meningitis, resection of arteriovenous malformation (AVM), and the Janetta procedure for hemifacial spasm. Additionally, both patients were elderly (68 and 72 years) and had Parkinson’s disease. Although a postscript in the paper mentioned a third patient, specifics were not provided. It should be emphasized that the VPA levels in these patients (200–300 µg/ml) are far above the usual therapeutic range and any changes in these patients may have reflected those toxic levels.

Based on a telephone survey, Armon et al. (1991) reported that 16 of 38 VPA patients (42%) reported that their hearing had worsened recently. However, telephone surveys are not a valid method of hearing measurement because patients may suspect a change in hearing when a change in alertness or general health occurs. Armon et al. also reported that VPA had been discontinued in 36 patients because of cognitive and motor dysfunction. Specific dosage levels were not reported in their abstract, but we have not observed this level or degree of complication in our patient population nor have similar problems been reported elsewhere.

No prospective study of patients’ hearing, using standard audiologic procedures before and after receiving VPA, has been published. The purpose of this investigation was to provide...
such a study for a typical group of patients receiving valproic acid.

**Methods**

Five females and seven males (mean age 36 years, range 14–66 years) received VPA and were tested before starting VPA. Eleven of them returned for short-term follow-up testing (the mean interval for retesting was 62 ± 41 (SD) days). One patient returned for follow-up testing only after an interval of one year, and four of the eleven patients who were tested shortly after VPA treatment were tested one year later also.

Before starting VPA, three patients were receiving phenytoin, five were receiving carbamazepine, two patients were taking both phenytoin and carbamazepine, and two patients were free of antiepileptic drugs. None of these patients had used VPA previously. After taking VPA, two patients continued taking phenytoin and five patients continued taking carbamazepine, and five patients received only VPA.

All audiologic testing was completed at our audiology clinic with a Grason-Stadler Instruments diagnostic audiometer (either GSI 16 or GSI 10) in a double-walled Industrial Acoustics Company sound suite (model 1403 ACT). Pure-tone air- and bone-conduction thresholds were obtained at octave band intervals from 250 to 8000 Hz using a modified Hughson-Westlake procedure (Carhart & Jerger, 1959). Word recognition was tested using W-22 50-word lists at 40 dB sensation level (SL). When the degree of hearing loss precluded testing at 40 dB SL, word recognition was tested at the most comfortable listening level (MCL). All audiologic testing followed guidelines of the American Speech-Language-Hearing Association (ASHA, 1993).

Mean VPA dose was 18.1 ± 7.3 (SD) mg/kg (range: 9.7 to 33.0 mg/kg). VPA levels were tested on the same day as audiologic assessment. The mean VPA level on retesting was 62.3 ± 50.5 (SD) µg/ml (range 16.2–115). However, the patient with the 16.2-µg/ml level was on other medications, and the additional VPA dosing provided excellent seizure control, which was a dramatic improvement.

ANOVA for repeated measures was used for statistical analysis of auditory threshold and word recognition data for the short-term follow-up data. Because only 5 patients were retested at approximately one year, statistical analysis was not considered appropriate for that small sample; consequently, the results for this epoch are described at the end of the results section.

**Results**

Statistical analysis across patients revealed no significant change in auditory threshold before and after VPA administration for any of the test frequencies. Even for the patient with the highest VPA level in our study (115 µg/ml), no significant change occurred. Further, no significant change in word recognition occurred.

Several criteria for ototoxic-induced changes in hearing status have appeared in the literature. For audiometric threshold, test-retest variability is generally no greater than ±5 dB. In early ototoxicity literature, criterion values of threshold changes exceeding 15 dB at one or more frequencies (Redell et al., 1982; Thompson & Northern, 1981) or 20 dB at one frequency (OSHA, 1979) were suggested. However, later studies (Brummett & Morison, 1990; Meyerhoff, Maale, Yellin, & Roland, 1989) indicated that these criteria could be exceeded by random variability, yielding a high false-positive rate. Recent recommendations include a criterion level of 10 dB or greater change for either mid-frequency or high-frequency averages of multiple frequencies (Dobie, 1983; Simpson, Schwan, & Rintelmann, 1992). For this study, we considered any changes exceeding 10 dB in the threshold average of 500 Hz, 1000 Hz, and 2000 Hz (mid-frequency average) and/or in the threshold average of 2000 Hz, 4000 Hz, and 8000 Hz (high-frequency average). We also applied the ASHA, 1994 criteria of >15 dB at any one frequency, ≥10 dB at any two consecutive test frequencies, or loss of responses at three consecutive frequencies where responses were obtained previously.

Only one patient exceeded any of the above criteria for ototoxic change. Specifically, this patient’s results exceeded the criteria for both the ASHA guidelines and the mid-frequency average criterion in one ear. This patient had a history of more than 10 years of progressive sensorineural hearing loss in the affected ear before VPA administration. Because the hearing shift did not affect the contralateral ear, but only the ear with known progressive hearing loss, the shift was probably not due to ototoxicity. No significant shift for the high-frequency average, which is generally most sensitive to early ototoxic effects, occurred for any patient.

Further, no significant change occurred on an individual case basis in any ear for word-recognition scores based on critical difference criteria developed by Thornton and Raffin (1977) for repeated presentations of 50-word lists of monosyllables.

We have now examined one year retest data (range = 11 to 23 months, mean = 14 months) for five patients. Four of the five patients revealed no change in hearing threshold or word recognition in either ear, including the patient with the highest level of VPA in our study (115 µg/ml). The fifth patient did reveal a unilateral decrease in thresholds in one ear at 23 months, but the shift was primarily conductive in nature and later resolved, a pattern inconsistent with ototoxic-induced changes.

**Discussion**

A number of adverse effects of valproate have been described, including hyperammonemia, hepatic failure, thrombocytopenia, pancreatitis, hair loss, tremor, weight gain, encephalopathy, and teratogenesis (Dreifuss & Langer, 1988). Our study was designed to test prospectively for effects of valproic acid on hearing. To detect even small changes in hearing, audiometric testing was completed before and at intervals after the initiation of valproic acid. Some of our patients had side effects secondary to valproate, primarily tremor and weight gain,
but none had hearing changes attributable to valproate.

The known or suspected mechanisms of action of valproate do not offer strong support for a possible ototoxic mechanism. Two actions of valproate thought likely to be important in its antiepileptic actions are reduction in the maximal rate of sustained neuronal repetitive firing (McLean & Macdonald, 1986), and enhancement of cerebral gamma-aminobutyric acid (GABA) levels. Reduced maximal neuronal firing was suggested by Armon et al. (1990) as a possible source of reversible hearing loss with valproate. This effect is plausible because auditory nerve fibers fire at high rates. However, several other antiepileptic drugs, such as phenytoin, carbamazepine, benzodiazepines, and phenobarbital, also reduce maximal firing rates, but hearing loss has not been described with these agents.

Increased brain GABA levels is an established effect of valproate (Fariello & Smith, 1989), but the net effect of this increase on neuronal function is unclear. Alteration in hearing could occur because several GABA-containing synaptic pathways exist in the central auditory system (Faingold, Gelbach, & Caspary, 1991; Wenthold, 1991). However, these auditory pathways appear to be involved primarily in auditory processing and may have little, if any, effect on auditory sensitivity.

Studies relating VPA to ABR latency also fail to clearly document VPA ototoxicity. Mervaala et al. (1987) reported that VPA did not increase somatosensory evoked potentials latencies but did slightly increase auditory brainstem response (ABR) interpeak latencies. However, their post-treatment ABR latencies were well within normal limits and they did not consider normal inter- and intrasubject ABR variability in their analysis. In 1988, Medaglini et al. reported prolonged ABR interpeak latencies in VPA-treated epileptic patients relative to a normal control group. Unfortunately, the possible prolongation of ABR latencies attributable to the neurologic disorder itself was not discussed by Medaglini et al. Only statistical analysis of ABR data for pre- and post-VPA use can resolve this issue. Even if ABR latency shifts in response to VPA are confirmed, these shifts do not necessarily indicate hearing threshold changes. Hearing thresholds were not tested in either the Mervaala et al. (1987) or Medaglini et al. (1988) study. (The various methods for effective audiologic monitoring for ototoxicity and associated considerations are reviewed by Campbell and Durrant (1993).)

Our results suggest that valproic acid is not commonly ototoxic in a clinical patient population receiving dosage levels in the usual therapeutic range. Certainly we cannot rule out the possibility of VPA ototoxicity in some patients on the basis of our findings in 12 patients. Valproic acid may be ototoxic for certain patients such as those reported by Armon et al. (1990) who had complicated neurologic histories, Parkinson’s disease, and were elderly. Perhaps valproic acid is ototoxic or even neurotoxic at extremely high dosage levels such as the 200 and 300 µg/ml level.

Further, we cannot rule out the possibility that VPA could cause ototoxic changes above 8000 Hz. Some ototoxic agents do cause changes in this high frequency range before the conventional audiometric range is affected (Fausti et al., 1979; Fausti, Frey, Henry, Robertson, & Hertert, 1992; Fausti, Rappaport et al., 1984; Fausti, Schechter, Rappaport, Frey, & Mass, 1984; Feghali & Bernstein, 1991; Frank, 1990; Jacobson, Downs, & Fletcher, 1969; Tange, Dreschler, & van der Hurst, 1985; van der Hulst, Dreschler, & Urbanus, 1988). Our data indicate that VPA is not routinely ototoxic, as defined by conventional audiologic criteria, with therapeutic dosing levels in a typical population.

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**References**


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