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Valproate-induced reversible sensorineural hearing loss: a case report with serial audiometry and pharmacokinetic modelling during a valproate rechallenge

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ABSTRACT – Hearing loss has been reported with valproic acid (VPA) use. However, this is the first case of VPA-induced hearing loss that was tested and confirmed with a VPA rechallenge, supported by serial audiometry and pharmacokinetic modelling. A 39-year-old truck driver with temporal lobe epilepsy was treated with VPA at 400 mg, twice daily, and developed hearing loss after each dose, but recovered within three hours. Hearing loss fully resolved after VPA discontinuation. Audiometry performed five hours after VPA rechallenge showed significant improvement in hearing thresholds. Pharmacokinetic modelling during the VPA rechallenge showed that hearing loss occurred at a level below the therapeutic range. Brainstem auditory evoked potential at three months after VPA discontinuation showed bilateral conduction defect between the cochlear and superior olivary nucleus, supporting a pre-existing auditory deficit. VPA may cause temporary hearing threshold shift. Pre-existing auditory defect may be a risk factor for VPA-induced hearing loss. Caution should be taken while prescribing VPA to patients with pre-existing auditory deficit.

Key words: hearing loss, ototoxicity, valproic acid, epilepsy, pharmacokinetics, AED, side effects

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Hearing loss, either reversible or irreversible, has been reported with valproic acid (VPA) use (Armon *et al*., 1990; Hori *et al*., 2003). Armon *et al*. (1990) discussed two elderly patients with presbycusis who suffered reversible sensorineural hearing loss one month after VPA initiation. The audiometry tests revealed hearing

loss at both low and high frequencies in the patients and their symptoms disappeared after VPA discontinuation. Similarly, a nine-year-old and a 20-year-old patient with epilepsy and pre-existing auditory deficit experienced hearing loss within two months after being started on VPA (Hori *et al*., 2003). Their sensorineural hearing loss occurred at 500-4,000-Hz frequencies and audiological signs improved after the offending drug was discontinued. Contradictory observations, however, were found in a study comparing patients who were exposed or not to VPA (Incecik *et al*., 2007). There was no significant difference in hearing thresholds between 125 and 16,000-Hz frequencies in the two study groups. A relationship between auditory signs and the duration of VPA therapy, the administered dose of VPA, the blood level of drug, age, or sex of the patients could not be established. However, it is worth noting that all the study subjects did not have pre-existing auditory deficit.

Here, we report a case of reversible sensorineural hearing loss secondary to valproate with pre-existing bilateral auditory defect, with supportive evidence from a serial audiometry and pharmacokinetic study during a valproate rechallenge.

Case study

A 39-year-old Chinese former truck driver was diagnosed with temporal lobe epilepsy since 34 years old. His seizures presented with blank staring, head deviation to the left, slight uprolling of the eyeball, lip smacking, mouth chewing, hand gripping and right-leg dystonia, and dysphasia, which lasted for two to three minutes. His EEG showed left anterior temporal slowing, sharp waves, and TIRDA. Brain MRI showed right temporal atrophy and possible left amygdala lesion. He was treated with carbamazepine but developed drowsiness at a dose of 800 mg per day. He was treated with levetiracetam which was titrated up to 3 g/day without significant improvement in seizure control.

Sodium valproate was added to his drug regimen in January 2013. The dose was titrated up to 800 mg/day in two divided doses when he complained of hearing loss. He described the hearing loss as being most profound immediately after each valproate dose, but his hearing returned to normal three hours later. Hearing loss recovered after valproate discontinuation. The patient claimed to have no previous hearing difficulties while he was only on levetiracetam.

Clinical assessment

Clinically, there was no evidence of external and middle ear problems. Both tympanic membranes were intact. Tympanometry was normal.

Audiometry

A valproate rechallenge was considered and accepted by the patient because of the importance to determine the causal relationship between valproate and hearing loss. Rechallenge was performed after valproate discontinuation for one day with total resolution of symptom, in which the patient was given sodium valproate at 400 mg stat dose orally. Hearing loss recurred at time 0:12 after the stat dose, and resolved at 2:37. Audiometry performed at one hour, five hours, three weeks, and three months after valproate rechallenge, showed obvious improvement of hearing in the left ear (ranging from 10%-42%), as shown in *(table 1)*. There was no improvement of hearing in the right ear.

Audiometry at three-month post-valproate rechallenge showed moderate-to-severe hearing impairment at mid and high frequency with significant notch at 4 kHz bilaterally, which was worse on the left, possibly related to noise-induced hearing loss. The air-bone gap of the baseline audiometry was about 5-10 dB suggesting that the hearing loss was unlikely to be conductive in origin.

Brainstem auditory evoked potential (BAEP)

Brainstem auditory evoked potential (BAEP), using rarefaction clicks, was performed three months after valproate discontinuation *(table 2)*. The left wave I was delayed compared to the right, with insignificant difference in hearing threshold on both sides (10 db for the left *vs* 5 db for the right). The latency of wave I-III of this subject was above the normal controls, *i.e*. 2.4 msec (mean+2.5 SD) bilaterally. This was supportive of a conduction defect between the cochlear and superior olivary nucleus. Cortical evoked response audiometry would allow comparison between audiometric and electrophysiological data.

Pharmacokinetic modelling

To further investigate the relationship between valproate administration and hearing loss, serial serum VPA concentrations were measured using the ARCHITECT *i*Valproic Acid, a chemiluminescent microparticle immunoassay with a measurable range between 2 and 150 mg/L, during valproate rechallenge (*figure 1*), and the pharmacokinetic parameters of VPA were estimated using a non-linear mixed effect model (NONMEM®) *(table 3)*. Hearing loss occurred at time 0:12 after a stat dose of valproate when the serum VPA concentration was at a level, below the therapeutic range (50-100 mg/L). Hearing loss recovered at time 2:37, despite the level being above 50 mg/L.

Table 1. Hearing level of both ears one hour after valproate rechallenge when the subject developed hearing loss, and five hours, three weeks and three months after valproate rechallenge, when hearing loss resolved.

Hearing level (dB)	Hz	250	500	1,000	2,000	4,000	8,000	9,000	10,000	11,200	12,500	14,000	16,000
1 hour after valproate rechallenge (with hearing loss)	Right	10	10	10	10	40	15	20	30	55		45	
	Left	20	20	20	20	65	45	55	55	55	70	60	50
5 hours after valproate rechallenge (without hearing loss)	Right	10	10	10	10	45	15	25	35	55	70	60	50
	Left	15	15	15	15	55	45	40	50	55	65	60	50
3 weeks post-valproate rechallenge	Right	10	10	15	15	45	15	10	15	50	60	60	50
	Left	10	10	15	15	60	35	35	40	45	50	60	50
3 months post-valproate rechallenge	Right	10	10	15	10	45	30	20	25	45	75	60	50
	Left	10	10	10	10	60	45	40	45	45	55	60	50
Average level of the 5-hour, 3-week and 3-month results	Right	10	10	13	12	45	20	18	25	50	68	60	50
	Left	12	12	13	13	58	42	38	45	48	57	60	50
Difference (dB)	Right	0	0	-3	-2	-5	-5	2	5	5			
	Left	8	8	7	7	7	3	17	10	7	13	0	0
Percentage (%)	Right	0.00	0.00	-0.33	-0.17	-0.13	-0.33	0.08	0.17	0.09			
	Left	41.67	41.67	33.33	33.33	10.26	7.41	30.30	18.18	12.12	19.05	0.00	0.00

Discussion

This is the first case of valproate-induced hearing loss that was tested and confirmed with a valproate rechallenge, supported by the results of serial audiometry and pharmacokinetic modelling. Our report is consistent with some published reports of VPA-induced hearing loss (Armon *et al*., 1990; Hori *et al*., 2003). However, hearing loss in our subject recovered within three hours after VPA discontinuation, as opposed to a case in which recovery took two months (Hori *et al*., 2003).

Although the exact mechanism of VPA-induced hearing loss is not known, it is speculated that defects in the electromagnetic conductance of sound at the hairy cells of the cochlea or conductance of nerve impulses may be responsible for this adverse effect (Incecik *et al*., 2007). By blocking the voltage-sensitive sodium channels or by activating calcium-dependence potassium conductance, VPA reduces sustained, repetitive, high frequency firing of neurons and thus may interfere with the auditory system in patients with pre-existing auditory problems (Hori *et al*., 2003).

Pharmacokinetic modelling during the valproate rechallenge in this subject showed that hearing loss occurred at a threshold below the therapeutic level. Recovery in hearing occurred within three hours from the last dose, before the level dropped below the threshold, as shown in *figure 1*. Early recovery is possibly mediated by a compensatory mechanism reversing the inhibitory sensorineural effect of sodium valproate (Hori *et al*., 2003). The compensation may be

Table 2. BAEP of both ears, three months after valproate discontinuation.

Protocol/Run	Hearing threshold dB	I ms	III ms	V ms	I-III ms	III-IV ms	I-V ms	I μV	V μV	Ratio
L- BAEP	10	1.78	4.50	6.04	2.72	1.54	4.26	0.16	0.27	1.63
R -BAEP	5	1.38	4.24	6.04	2.86	1.80	4.66	0.21	0.37	1.77

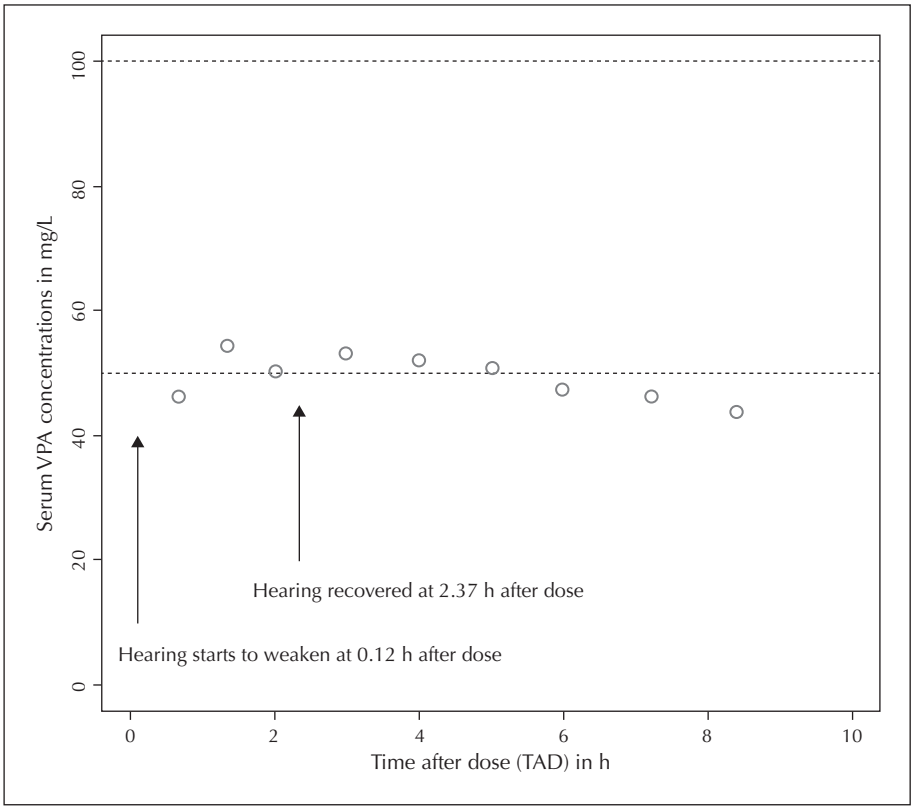

Figure 1. Observed serum VPA concentrations *versus* time after dose administration.
Sodium valproate at 400 mg was administered at time=0. Between the two dotted lines are the boundaries of the reference therapeutic range of VPA for the treatment of epilepsy..

Table 3. Estimated values of pharmacokinetic parameters of VPA.

Parameters	Literature values	Case values
Absorption rate constant (h^{-1})	0.78-4.1 (Bondareva *et al.*, 2004; Puentes *et al.*, 1999; Williams *et al.*, 2012)	1.01
Lag time (h)	2 (Williams *et al.*, 2012)	1
Clearance (L h^{-1})	0.28-0.85 (Gidal *et al.*, 2005; Vucicevic *et al.*, 2009; Jankovic *et al.*, 2010; Jankovic and Milovanovic, 2007; Park *et al.*, 2002; Puentes *et al.*, 1999; Yukawa *et al.*, 1997; Yukawa, 1995)	0.61
Volume of distribution (L)	7-35 (Gidal *et al.*, 2005; Jankovic *et al.*, 2010; Vucicevic *et al.*, 2009)	15.1
Area under the concentration vs. time curve (mg*h L^{-1})	1,408±403 and 1,536±392 (after 600 mg sustained release tablets given) (Bondareva *et al.*, 2004; Fujii *et al.*, 2009; Park *et al.*, 2002; Puentes *et al.*, 1999)	1,146 (after 400 mg BD of enteric coated sodium valproate was given)

mediated by other channels but the exact mechanism is not known.

The pre-existing auditory deficits were evidenced by, firstly, an abnormal three-month post-rechallenge audiometry which likely reflected the baseline hearing function, and secondly, bilateral prolonged wave I-III latencies in the BAEP, three months after VPA discontinuation. VPA-induced hearing loss was reported in those with pre-existing high frequency hearing loss (*i.e.* presbyacusis, congenital sensorineural hearing loss) (Armon *et al*., 1990; Hori *et al*., 2003), whereas, a case-control study recruiting those without pre-existing auditory deficit failed to show a change in hearing thresholds among the VPA group (Incecik *et al*., 2007).

The auditory deficit of this case is worse on the left side, as supported by a more prolonged left wave I latency in the BAEP and audiometry results at three months post-valproate rechallenge. The impact of VPA-induced hearing loss was worse on the left, which is likely related to the pre-existing deficit that was also worse on the left.

This report raises some questions about widespread effects of VPA on hearing, and caution should be taken while prescribing sodium valproate to patients with pre-existing auditory deficit. In addition, this may have implication on other AEDs that may work in similar ways, and future studies are needed to resolve this concern.

Conclusion

Valproate may cause temporary hearing threshold shift. Pre-existing auditory defect may be a risk factor for VPA-induced hearing loss. Caution should be taken while prescribing sodium valproate to patients with pre-existing auditory deficit. □

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