

JUL 26 2004

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 21 Jul.04	3. REPORT TYPE AND DATES COVERED MAJOR REPORT		
4. TITLE AND SUBTITLE HYPERAMMONEMIC ENCEPHALOPATHY RESULTING FROM INTRAVENOUS VALPROATE FOR STATUS EPILEPTICUS			5. FUNDING NUMBERS	
6. AUTHOR(S) MAJ RICHARDS KAREN C				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) BAYLOR COLLEGE OF MEDICINE			8. PERFORMING ORGANIZATION REPORT NUMBER CI04-504	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) THE DEPARTMENT OF THE AIR FORCE AFIT/CIA, BLDG 125 2950 P STREET WPAFB OH 45433			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION AVAILABILITY STATEMENT Unlimited distribution In Accordance With AFI 35-205/AFIT Sup 1			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words)				
<p>DISTRIBUTION STATEMENT A Approved for Public Release Distribution Unlimited</p> <p style="font-size: 2em; font-weight: bold;">20040809 071</p>				
14. SUBJECT TERMS			15. NUMBER OF PAGES 9	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT	

**HYPERAMMONEMIC ENCEPHALOPATHY RESULTING FROM
INTRAVENOUS VALPROATE FOR STATUS EPILEPTICUS**

Richards, K. C. MD; Verma, A. MD; Newmark, M. E. MD; and Hrachovy, R. A. MD

From the Department of Neurology (Dr. Richards), Wilford Hall Medical Center, Lackland AFB, TX, Department of Neurology, Peter Kellaway Section of Neurophysiology (Drs. Richards, Verma, and Hrachovy), Baylor College of Medicine, Houston, Texas; Department of Neurology (Dr. Newmark), Kelsey-Seybold Clinic, Houston, Texas, and Michael E. Debaque Veterans Affairs Medical Center (Dr. Hrachovy), Houston, Texas.

Correspondence: Dr. R.A. Hrachovy, Peter Kellaway Section of Neurophysiology, Department of Neurology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030 email:

rhrachovy@bcm.tmc.edu

No disclosures.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

The FDA approved valproate sodium injection (iv VPA) for seizure management in patients unable to receive oral VPA. Subsequent studies confirming the safety of rapid infusion of iv VPA led to investigations of its use for status epilepticus.^{1,2} Intravenous valproate has been suggested as an alternative to phenytoin and/or phenobarbital in patients with hypersensitivity to or at high risk for the sedative or vasoactive effects of these drugs, or for seizure types more likely to respond to valproate (e.g. absence).¹

Hyperammonemic encephalopathy is a well-recognized complication of oral valproate. This may be common during introduction of VPA, as one case series of 38 patients reported 8 patients acutely manifesting confusion, somnolence and elevated ammonia.³ We report 2 cases of acute encephalopathy with hyperammonemia following iv VPA for status epilepticus.

Case 1

A 35 year old man with lifelong medically-refractory epilepsy developed progressive stupor over two days. An EEG revealed nonconvulsive status epilepticus characterized by rhythmic generalized 2-2.5 Hz spike and slow wave discharges (figure 1A). He improved in response to 25 mg/kg iv VPA. The following day, VPA level was 81 mcg/mL, and an EEG confirmed resolution of status epilepticus. Oral VPA 1000 mg/day was added to his outpatient anticonvulsants (levetiracetam and phenobarbital). He received three additional doses of iv VPA. Six days later he became somnolent, raising concern for recurrent status epilepticus. A repeat EEG showed generalized slowing with

frequent frontocentral diphasic sharp waves, suggesting a metabolic encephalopathy (figure 1B). Liver function tests were normal, but serum ammonia was 222 mcg/mL (normal 25-78); VPA level was 122 mcg/mL. VPA was replaced by felbatol. He required intubation due to deepening stupor. The serum ammonia level decreased to 36 mcg/mL within 48 hours and his EEG showed an occipital rhythm of 8-9 Hz with mild diffuse slowing (figure 1C). He was extubated and his mental status normalized.

Case 2

A 51 year old man underwent resection of a right temporal glioblastoma multiforme. Prophylactic phenytoin was stopped due to a rash two days postoperatively. The next day he developed left facial twitching and decreased responsiveness. A CT scan showed temporal lobe edema with a midline shift. An EEG showed diffuse 1.5-3 Hz activity and focal electrical status epilepticus characterized by frequent seizures arising from the right anterior hemisphere. He received Decadron, lorazepam and 1500 mg iv VPA but continued to have frequent seizures. Intravenous VPA was continued at 750 mg every 6 hours. Electrographic and clinical seizures persisted for two days despite a VPA level of 63 mcg/mL. The seizure frequency decreased with elevation of iv VPA to 1000 mg every 4 hours. Four days after the onset of seizures he became lethargic and disoriented. An EEG showed diffuse 3-7 Hz activity mixed with 1-2 Hz activity and diphasic and triphasic sharp waves, but no seizures. His VPA level was 117 mcg/mL. Levetiracetam was added when seizures recurred. Two days later the ammonia level was 400 mcg/mL (normal 25-78), with normal liver function tests. Iv VPA was discontinued, and carnitine and lactulose were added. The ammonia level peaked at 509 mcg/mL, then declined to

52 mcg/mL over four days. He returned to his preoperative baseline. Seizures remained controlled on Keppra.

To our knowledge, this is the first report describing acute hyperammonemic encephalopathy induced by iv VPA in patients without a predisposition for hyperammonemia. Schwarz et al described a fatal case of hyperammonemia following iv VPA treatment of a patient with preexisting mild elevation of ammonia due to ureterosigmoidostomy.⁴

Attributing acute encephalopathy to VPA-induced hyperammonemia is complicated by the frequent occurrence of asymptomatic ammonia elevation in patients receiving VPA. Case series report that 17- 53% of patients receiving oral VPA develop elevated ammonia ranging from 40 to 140 mcmol/L without adverse symptoms.^{5,6} Most reports of encephalopathic patients demonstrate substantially higher ammonia levels, although some patients develop symptoms at levels asymptomatic in other cases.^{3,6}

In both our patients, the decline in mental status was initially attributed to seizures rather than a metabolic encephalopathy. The diffuse slowing with diphasic and triphasic waves without seizure activity on EEG prompted tests for hyperammonemia. Although Kifune et al reported the appearance of triphasic waves in one case of VPA-induced hyperammonemic encephalopathy, the EEG usually shows only diffuse or rhythmic frontal slowing.⁷

Our cases demonstrate that like oral VPA, iv VPA can acutely induce hyperammonemic encephalopathy. In the setting of recent status epilepticus, recurrent seizures may be suspected as the cause of declining mental status. An EEG will differentiate recurrent status from an acute encephalopathy.

References

- ¹Kian-Ti Y, Mills S, Thompson N, Cunanan C. Safety and efficacy of intravenous valproate in pediatric status epilepticus and acute repetitive seizures. *Epilepsia* 2003; 44(5):724-726.
- ²Ramsay RE, Cantrell D, Collins SD, Walch, JK, Naritoku DK, Cloyd JC, Sommerville K and the Depacon Rapid Infusion Study Group. Safety and tolerance of rapidly infused Depacon. A randomized trial in subjects with epilepsy. *Epilepsy Research* 2003; 52(3):189-201.
- ³Zaccara G, Paganini M, Campostrini R, Arnetoli G, Zappoli R, Moroni F. Hyperammonemia and Valproate-induced alterations of the state of consciousness. *Eur Neurolo* 1984; 23:104-112.
- ⁴Schwarz S, Georgiadis D, Schwab S, Gehlen F, Mayatepek E, Zoubaa S. Fulminant progression of hyperammonaemic encephalopathy after treatment with valproate in a patient with ureterosigmoidostomy. *J Neurol Neurosurg Psychiatry* 2002; 73:86-95.
- ⁵Murphy JV, Marquardt K. Asymptomatic hyperammonemia in patients receiving valproic acid. *Arch Neurol* 1982;39:591-592.
- ⁶Hamer HM, Knake S, Shomburg U, Rosenow F. Valproate-induced hyperammonemic encephalopathy in the presence of topiramate. *Neurology* 2000; 54(1):230-233

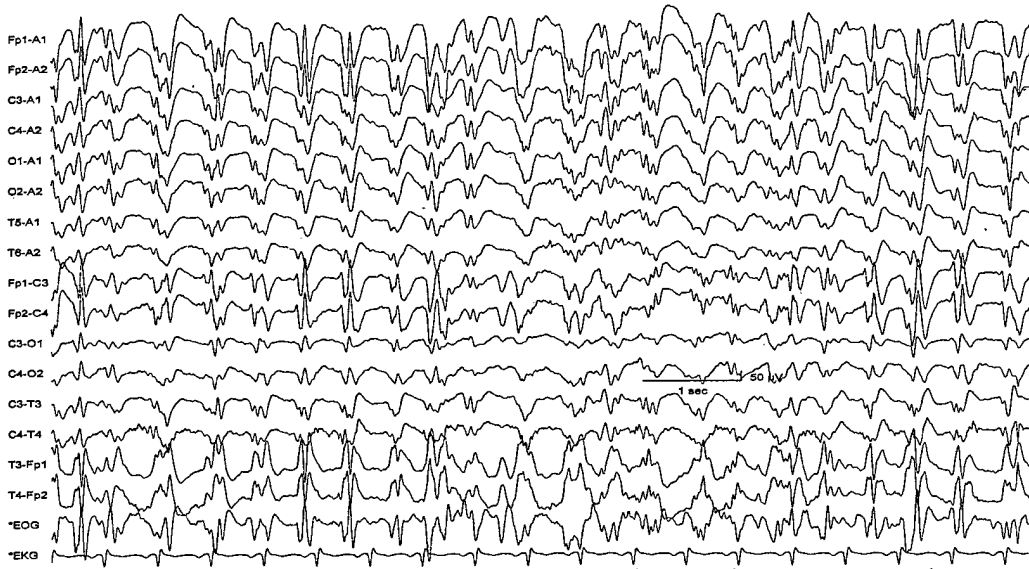
⁷Kifune A, Kubota F, Shibata N, Akata T, Kikuchi S. Valproateacid-induced hyperammonemic encephalopathy with triphasic waves. *Epilepsia* 2000; 41(7):909-912.

Title character count: 88

Word count: 746

Figure 1. (A) Digital EEG recorded on admission showing rhythmic frontal-dominant generalized spike and wave discharges consistent with status epilepticus. (B) Digital EEG recorded 6 days later after patient became lethargic. Frequent diphasic sharp waves have developed on a background of generalized slow activity. (C) Resumption of faster background activity and resolution of diphasic waves accompanied the normalization of serum ammonia levels.

A



B



C

