Valproic Acid Induced Pancreatitis Presenting With Decreased Level of Consciousness in a Child With Tuberous Sclerosis Complex

Pierre-Charles Deschenes, MD; Julie Autmizguine, MD, MHS; Philippe Major, MD; and Niina Kleiber, MD, PhD

A 2-year-old Caucasian boy with tuberous sclerosis complex presented to the emergency department with lethargy and new onset myoclonias. Pancreatitis, thrombocytopenia, and coagulopathy associated to a decreased level of consciousness were diagnosed. Valproic acid had been initiated 13 months before and had been slowly increased to a dose of approximately 38 mg/kg/day. All the symptoms resolved after discontinuation of the medication. The clinical presentation of this child highlights that valproic acid-related pancreatitis can present with decreased level of consciousness without associated gastrointestinal symptoms. Adverse drug reactions associated with valproic acid can lead to damage of multiple organs and may prove fatal if not promptly recognized and managed.

ABBREVIATIONS ADR, adverse drug reaction; AED, antiepileptic drug; INR, international normalized ratio; VPA, valproic acid

KEYWORDS adverse drug effect; adverse drug reaction; pancreatitis; seizures; side effect; tuberous sclerosis complex; valproic acid

J Pediatr Pharmacol Ther 2020;25(3):256–260

DOI: 10.5863/1551-6776-25.3.256

Introduction

The rate of hospital admission attributed to adverse drug reactions (ADRs) in the pediatric population is 2%.¹ Among these admissions, nearly 40% concern potentially life-threatening reactions.¹ Pediatric patients are particularly vulnerable to ADRs given issues related to developmental pharmacokinetics across all ages. The frequent off-label prescribing of medications in this population² makes them particularly vulnerable to ADRs.^{3,4} Children with chronic neurologic conditions are particularly at risk of ADRs because of underlying conditions and the high frequency of polypharmacy.^{2,5}

The highest rate of fatalities due to antiepileptic drugs (AEDs) have been reported to occur in children.⁶ One such widely used AED, valproic acid (VPA), has regularly been incriminated in significant ADR and even fatalities.⁶

Case

A 27-month-old Caucasian male (weight: 15.7 kg; height: 96.4 cm) with tuberous sclerosis complex presented to the emergency department with lethargy. He was on multiple anticonvulsants (i.e., clobazam since he was 12 months old, levetiracetam since he was 15 months old, felbamate since he was 24 months old, and VPA since he was 14 months of age) for refractory epilepsy and was on low dose hydrocortisone for adrenal insufficiency secondary to previous treatment

with adrenocorticotrophic hormone.

Treatment with VPA had been initiated 13 months before admission and 3 weeks prior to admission had been increased from 250 mg to 300 mg twice daily (approximately 38 mg/kg/day). Previous VPA serum concentrations were all within the desired range (50–100 mg/L) except for one value of 122 mg/L that was noted 3 months prior to admission. At that time, no adverse effects were noted and a month later the serum VPA concentration was 68 mg/L.

The child was behaving normally until the morning of admission, when his mother found him drowsy and with new onset of myoclonus. No other symptoms were noted, namely no nausea or vomiting. Also, there was no history of fever, trauma, infection, or intoxication. On arrival, he was afebrile (rectal temperature: 37.1°C) with a heart rate of 145 beats/min, blood pressure of 124/88 mm Hg, and oxygen saturation of 99%. His Glasgow coma scale was 9. Physical examination was otherwise normal, except for mild abdominal tenderness.

Serum glucose, electrolytes, and liver enzymes (alanine aminotransferase 25 U/L [normal: 11–30]) were within age-related normal limits as reported by our clinical laboratory. Urea was slightly elevated (588.6 mg/L [normal: 192–455]) and creatinine value was normal (5.2 mg/L [normal: 3.8–5.5]). His complete blood count revealed leukocytosis ($18.5 \times 10^9/L$ [normal: 5.5–15.5]) and mild thrombocytopenia (see Figure). International normalized ratio (INR) was mildly increased (see Figure), partial thromboplastin time was 34.5 seconds, and

Figure. Valproic acid level (A), lipase (B), international normalized ratio (INR) (C), and platelet count (D) from admission until hospital discharge.

C-reactive protein was mildly elevated (124 nmol/L). Serum lipase was markedly increased (>1200 U/L). Serum ammonia was within normal limits for age (442.8 $\mu\text{g/L}$). Serum VPA concentration, measured 18 hours after the last dose, was 101.1 mg/L (reference range: 50–100 mg/L). No other AED serum concentration was determined. Abdominal tomodensitometry revealed moderate amount of ascites, a swollen pancreas, and normal biliary and pancreatic ways. Head computed tomography scan was unremarkable, apart from the known tubers.

The initial differential diagnosis included sepsis, adrenal insufficiency, nonconvulsive status epilepticus, postictal state, and VPA toxicity. Thus, initial treatment in the emergency room included empirical antimicrobial coverage with ceftriaxone (50 mg/kg IV), lorazepam (0.1 mg/kg IV), and stress dose of hydrocortisone (100 mg IV (150 mg/m^2) followed by 30 mg IV every 6 hours (50 mg/m^2). His level of consciousness was not associated

to the episodes of myoclonia or any other movement suggestive of seizure and was improving; therefore, no EEG was performed. Based on the clinical presentation and laboratory findings, a provisional diagnosis of VPA-associated pancreatitis was made and VPA was discontinued.

After stopping VPA, the patient's condition improved rapidly. Within a day, his level of consciousness returned to normal, he stopped having myoclonias, his pancreatic enzymes decreased and slowly returned to normal, and his coagulogram normalized (Figure). He was discharged after 10 days of hospitalization and was continued on oral clobazam (12.5 mg twice daily), levetiracetam (250 mg twice daily), and felbamate (300 mg twice daily). VPA was not restarted.

Discussion

VPA is a commonly prescribed medication for epi-

Table. Patient's Naranjo Adverse Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
Are there previous <i>conclusive</i> reports of this reaction?	1	0	0	1
Did the adverse event appear after the suspected drug was administered?	2	0	0	2
Did the adverse reaction improve when the drug was discontinued or a <i>specific antagonist</i> was administered?	1	0	0	1
Did the adverse reaction reappear when the drug was readministered?	2	-1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	2	0	2
Did the reaction reappear when a placebo was given?	-1	1	0	0
Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	1	0	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	0
Was the adverse event confirmed by any objective evidence?	1	0	0	1
Total score*				7

* A score of 7 suggest that the adverse reaction is probably due to valproic acid.

lepsy, migraine, and bipolar disorder. Although the common adverse effect associated with VPA are typically benign, less common significant and life-threatening adverse effects can occur.⁷ According to the World Health Organization Collaborating Centre for International Drug Monitoring Individual Case Safety Report database, VPA-related fatality rate in children between 1977 and 2012 was 7.4 per year.⁷ Factors associated with serious VPA reactions include young age (<6 years), use of multiple AEDs, and developmental delay.⁷ Our patient had all of these factors; hence, he was at increased risk for significant ADRs. Although hepatotoxicity was the most frequently described cause of death, a significant number (42%) of patients who died did not present with hepatic failure.⁷ Our patient's ADR, namely decreased level of consciousness, pancreatitis, and coagulopathy, were among the most frequently reported manifestations of ADRs in children with fatal VPA toxicity.⁷

Pancreatitis. Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. In fact, it carries a boxed warning from the FDA for hemorrhagic pancreatitis, which rapidly progresses from initial symptoms to death in approximately 10% of patients who develop pancreatitis.⁸ Although patients may present with abdominal pain, nausea, vomiting, and/or anorexia, our patient did not present with any of these clinical findings. Our patient did have markedly elevated serum lipase concentrations (>1200 U/L), which is consistent with a diagnosis of pancreatitis.

In our patient, pancreatitis appeared more than a year after initiating treatment. VPA-induced pancreatitis can happen many years after VPA introduction and therefore, should be considered regardless of the duration

of therapy in any symptomatic individual.⁸ In a study on 22 children with VPA-associated pancreatitis, mean duration of VPA therapy before the onset of pancreatitis was 32 months (range: 2–84 months).⁸

VPA serum concentrations were close to the therapeutic range, serum concentrations do not correlate with the occurrence of pancreatitis; hence, it should not be ruled out based on a therapeutic blood concentration.^{8,9} Our patient's symptoms quickly resolved after discontinuation of VPA. Our patient was not challenged with VPA as most patients who are given VPA again develop pancreatitis. This ADR was probably due to VPA per the Naranjo Adverse Drug Reaction Probability Scale (score = 7; Table).¹⁰ All other routine AEDs taken by the patient have not be associated with pancreatitis and were not discontinued.

Drowsiness. Our patient presented with drowsiness. We did not believe that his level of consciousness was associated to the new episodes of myoclonia or any other movement suggestive of seizure and he was improving; therefore, no EEG was performed. VPA-induced pancreatitis can present with decreased level of consciousness in the absence of frank gastrointestinal symptoms.^{11,12} Our patient's drowsiness may also have occurred independent of pancreatitis. Although his liver enzymes and ammonia concentration were normal, VPA-associated disturbed consciousness have been reported in 30% of children in the absence of hepatotoxicity.⁷ Also, hyperammonemia can occur despite normal liver enzymes.¹³

Thrombocytopenia. The most frequent clinical manifestations of thrombocytopenia are prolonged bleeding time, abnormality in laboratory platelet tests,

or petechial bleeding.¹⁴ Our patient presented with profound thrombocytopenia and mild coagulogram disturbance (INR), which place him at a significant risk of bleeding; however, he did not have petechial or active bleeding. Thrombocytopenia can occur in 5% to 50% of those given VPA.¹⁴ In the studies with a larger sample size (>150 patients), thrombocytopenia was reported in 12% to 18% of those receiving VPA.¹⁴ Coagulopathy has been described in 9% of patients with fatal ADRs.⁷ Studies note that thrombocytopenia occurs more frequently in women and elderly subjects and that a lower baseline platelet count was an additional risk factor for thrombocytopenia.¹⁴ Platelet count has been reported to inversely correlate with VPA dose and both free and total VPA serum concentrations.¹⁵ Our patient's serum concentration was within the reference range of 50 to 100 mg/L. Mild thrombocytopenia does not warrant treatment discontinuation, but our patient presented with profound thrombocytopenia and mild coagulogram disturbance (INR), which placed him at increased risk of bleeding.

Conclusions

The clinical presentation of this patient highlights the importance of considering VPA-associated pancreatitis in any child presenting with drowsiness or other signs suggestive of encephalopathy, even in the absence of gastrointestinal symptoms. Lipase, which is more sensitive than amylase for diagnosis of VPA-pancreatitis,⁸ serum ammonia, and hepatic enzymes should be measured in any patient with a decreased level of consciousness. Although the median time from start of VPA to onset of toxicity is 2 and 4 months for hepatotoxic and non-hepatotoxic reactions, respectively,⁷ either may occur after many years of therapy.^{8,13} For this reason, the clinician must suspect VPA toxicity even in patients on long-term VPA. Prompt recognition of VPA as a cause is critical as discontinuation usually leads to complete recovery.¹³ Rechallenge with VPA is dangerous and should be avoided because it triggers a second pancreatitis in the vast majority of patients;^{8,12,13} hence, patients and families should be informed that VPA should never be restarted, and the patient's medical record should note a contraindication to VPA.

ARTICLE INFORMATION

Affiliations Université de Montréal, Quebec, Canada (PCD), Division of General Pediatrics, Department of Pediatrics, Sainte-Justine Hospital, Université de Montréal, Quebec, Canada (NK), Neurology Service, CHU Ste-Justine, Department of Neurological Sciences (PM), Université de Montréal, Québec, Canada, Clinical Pharmacology Unit, Department of Pediatrics Sainte-Justine Hospital, Université de Montréal, Quebec, Canada (JA, NK), Department of Pharmacology and Physiology Université de Montréal, Quebec, Canada (JA, NK),

Division of Pediatric Infectious Disease, Department of Pediatrics, Sainte-Justine Hospital (JA), CHU Sainte-Justine Research Center, Université de Montréal, Quebec, Canada (JA, NK)

Correspondence Niina Kleiber, MD, PhD;
email: niina.kleiber@umontreal.ca

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Ethical Approval and Informed Consent Given the nature of this study, the project was exempt from institution review board/ethics committee review; however, parenteral consent was obtained.

Accepted December 19, 2019

Copyright Pediatric Pharmacy Association. All rights reserved. For permissions, email: mhelms@pediatricpharmacy.org

REFERENCES

1. Impicciatore P, Choonara I, Clarkson A, et al. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Brit J Clin Pharmacol*. 2001;52(1):77–83.
2. Hoon D, Taylor MT, Kapadia P, et al. Trends in off-label drug use in ambulatory settings: 2006–2015. *Pediatrics*. 2019;144(4). doi:10.1542/peds.2019-0896.
3. Pratico AD, Longo L, Mansueto S, et al. Off-label use of drugs and adverse drug reactions in pediatric units: a prospective, multicenter study. *Curr Drug Saf*. 2018;13(3):200–207.
4. Gore R, Chugh PK, Tripathi CD, et al. Pediatric off-label and unlicensed drug use and its implications. *Curr Clin Pharmacol*. 2017;12(1):18–25.
5. Anderson M, Egunsola O, Cherrill J, et al. A prospective study of adverse drug reactions to antiepileptic drugs in children. *BMJ Open*. 2015;5(6):e008298. doi:10.1136/bmjopen-2015-008298.
6. Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child*. 2002;87(6):462–466.
7. Star K, Edwards IR, Choonara I. Valproic acid and fatalities in children: a review of individual case safety reports in VigiBase. *PLoS One*. 2014;9(10):e108970. doi:10.1371/journal.pone.0108970.
8. Werlin SL, Fish DL. The spectrum of valproic acid-associated pancreatitis. *Pediatrics*. 2006;118(4):1660–1663.
9. Pohl JF, Uc A. Paediatric pancreatitis. *Curr Opin Gastroenterol*. 2015;31(5):380–386.
10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
11. Cofini M, Quadrozzi F, Favoriti P, et al. Valproic acid-induced acute pancreatitis in pediatric age: case series and review of literature. *G Chir*. 2015;36(4):158–160.

12. Grauso-Eby NL, Goldfarb O, Feldman-Winter LB, McAbee GN. Acute pancreatitis in children from Valproic acid: case series and review. *Pediatr Neurol.* 2003;28(2):145–148.
13. Chopra A, Kolla BP, Mansukhani MP, et al. Valproate-induced hyperammonemic encephalopathy: an update on risk factors, clinical correlates and management. *Gen Hosp Psychiatry.* 2012;34(3):290–298.
14. Buoli M, Serati M, Botturi A, Altamura AC. The risk of thrombocytopenia during valproic acid therapy: a critical summary of available clinical data. *Drugs R D.* 2018;18(1):1–5.
15. Gidal B, Spencer N, Maly M, et al. Valproate-mediated disturbances of hemostasis: relationship to dose and plasma concentration. *Neurology.* 1994;44(8):1418–1422.