Case: Pediatric Valproic Acid Overdose
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Target Audience: Emergency Medicine Residents, Medical Students

Primary Learning Objectives:

1. Generate a broad differential for a suspected intoxication
2. Identify the need to secure the airway of a pediatric patient
3. Treat valproic acid overdose with L-carnitine

Secondary Learning Objectives: Detailed technical/behavioral goals, didactic points

1. Describe the pathophysiology of valproic acid
2. Discuss management priorities in CNS compromise associated with valproic acid toxicity
3. Describe the antidote and how it inhibits or reverses toxicity

Critical Actions Checklist:

1. Obtain appropriate history and workup to identify possible causative agents
2. Measure total serum valproate levels
3. Measure serum ammonia levels
4. Treat valproic acid overdose correctly with L-carnitine
5. Consider hemodialysis, especially if L-carnitine is unavailable
6. Intubation
7. Verbalize common alternative diagnoses such as non accidental trauma, toxicity from other home medications, meningitis, TBI, intracranial hemorrhage, hypoglycemia, hepatic encephalopathy
8. Consult poison control/toxicology
9. Admit to PICU

Environment:

1. Room Set Up - ED Pediatric Area
    a. Manikin Set Up: 3 year old, small for age, wearing helmet, wearing medical bracelet with parents number, ecchymosis/healing scabs on bilateral knees due to frequent falls, abrasion on tongue indicating trauma from previous seizure
    b. Props - Standard ED Equipment

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CASE SUMMARY

Synopsis of Case

This is a 3-year-old male with a past medical history significant for Lennox-Gastaut Syndrome who presents with his mother for concerns of increasing drowsiness and lethargy over the preceding week. When he presents, the patient is sleepy but continues to decompensate to the point of requiring intubation for airway protection. Upon review of his medications, the patient is found to be on a variety of anti-epileptic medications at higher than usual doses. These medications include levetiracetam (200mg BID), lamotrigine (30mg BID) and valproate 500mg (TID). Laboratory analysis is performed, and the patient is found to be hyponatremic, hypoglycemic, and has an elevated ammonia level. Valproic acid is the most likely cause of the patient's findings so further dosing is held and the patient is provided L-Carnitine for treatment The valproic acid level does return elevated later in the case, though the lamotrigine and levetiracetam levels return in therapeutic range. The patient is admitted to the PICU for further care.

Setting is a busy community emergency department

Synopsis of Physical

3-year-old male laying in mother's arms. Somnolent. Difficult to arouse.

Repeat physical shows decompensation requiring intubation.

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Critical Actions

1. Recognize the need for intubation in a pediatric patient.
    a. Cue: The SpO2 continues to decline and patient becomes obtunded.
2. Consult Poison control/toxicology
    a. Cue: The nursing staff asks if any consultation is needed.
3. Obtain workup to allow for narrowing of causative agents.
    a. CBC, CMP, UA, UDS, Total valproate, Salicylate, Acetaminophen, POC glucose, Lactate, ammonia, VBG, EKG, CXR
    b. Cueing guideline: The nurse asks if you would like to send off any blood work.
4. Verbalize a broad differential diagnosis including some of the following as examples:
    a. Non-accidental trauma
    b. Poisoning or ingestion including home medications
    c. Meningitis, TBI, intracranial hemorrhage
    d. Hypoglycemia, hepatic encephalopathy
    e. Cueing guideline: The nurse can ask if the doctor has gotten a list of all medications in the home.
5. Recognize the need for L-carnitine treatment or hemodialysis once valproate levels return from the lab.
    a. 100 mg/kg IV loading dose over 30 min (max 6g), follow with 15 mg/kg q4hrs
    b. Serum ammonia levels should be simultaneously measured, and when serum ammonia levels start decreasing, L-carnitine therapy can be discontinued
    c. Hemodialysis is indicated for serum valproate concentrations > 3,500 mg/L and in patients experiencing shock, cerebral edema, or coma
6. Admit to PICU
    a. For serial labs, L-Carnitine treatment, vent management, possible hemodialysis and activated charcoal depending on ingested dose
    b. Cueing guideline: If the learner attempts to place the patient on a general medical floor, the pediatrician firmly refuses stating that the patient is inappropriate for the floor.

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Critical Actions Checklist

Resident Name								
Case Description								
Skills measured **Core Competencies**: **PC** Patient Care, **MK** Medical Knowledge, **P** Professionalism, **SB** System-based Practice, **PB** Practice-based learning and improvement, **IC** Interpersonal and communication skills	**Very Unacceptable**		**Unacceptable**		**Acceptable**		**Very Acceptable**	
Data Acquisition (DA) PC, MK, IC	1	2	3	4	5	6	7	8
Problem Solving (PS) PC, MK, PB	1	2	3	4	5	6	7	8
Patient Management (PM) PC, MK, IC, P, PB, SB	1	2	3	4	5	6	7	8
Resource Utilization (RU) PC, PB, SB	1	2	3	4	5	6	7	8
Health Care Provided (HCP) PC, SB	1	2	3	4	5	6	7	8
Interpersonal Relations and Communication Skills (IRCS) IC, P	1	2	3	4	5	6	7	8
Comprehension of Pathophysiology (CP) MK, PB	1	2	3	4	5	6	7	8
Clinical Competence (CC) PC, MK, IC, P, PB, SB	1	2	3	4	5	6	7	8

Modified ABEM oral certification examination checklist and scoresheet
Modified checklist and scoresheet from the previous publication

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Yes	No	Critical Actions
		Consult Toxicology or Call the poison center

Comments:

Yes	No	Dangerous Actions

Comments:

Modified checklist and scoresheet from the previous publication

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History

Age: 3 years old

Sex: Male

Name: Charles Wilson

Method of Transportation: Personal Vehicle

The person giving information: Mother

Chief Complaint: Sleepiness, Decreased Activity

HPI: The patient's mother is concerned that he has been increasingly sleepy with decreased activity levels. He is not acting like his normal self. She denies any recent trauma or new medications.

Allergies: No known drug allergies

Medications:
levetiracetam (200mg BID), lamotrigine (30mg BID) and valproate 500mg (TID).

Past Medical History:
- Lennox-Gastaut Syndrome
- Developmental delay (cognitive and physical)
- Seizure Disorder

Past Surgical History:
- none

Allergies:
- None

Family History:
- None

Social History:
- Lives at home with both parents and is an only child. Parents do not use tobacco or marijuana.

Family Medication History:
- Multivitamins, ibuprofen, and acetaminophen are in the home. No plants are in the home.

Play of Case Guidelines

This is a case of a 3-year-old male with a past medical history of developmental delay and seizures secondary to Lennox-Gastaut Syndrome who presents with sleepiness due to intoxication from prescription valproic acid.

1. The patient will present with vitals normal for age.
2. Sleepiness turns into lethargy and difficulty to arouse requiring intubation
3. The learner should appropriately consider non-accidental trauma as part of their differential.
4. Valproic acid is the primary toxicant in this case.
5. L-Carnitine should be given in this case as indicated.
6. The learner must obtain a thorough history, physical, and workup to uncover the causative agent.
7. The patient requires PICU admission for continued observation and serial reassessments

Physical Exam

Vitals: BP 115/73, HR 115, T 37.4*C Resp Rate 10, SpO2 92%
Wt 9.07 kg, Glucose (if asked for) 67 mg/dL GCS 12

General Appearance: Underdeveloped for stated age and appears drowsy sitting in mother's lap

HEENT: Wearing old helmet, no obvious trauma

Lungs: Bradypnea. Clear to auscultation bilaterally without rales, rhonchi, or wheezes.

CV: Normal rate and rhythm without murmurs, gallops, or rubs

Abdomen: Non-tender, non-distended, with normal bowel sounds

Extremities: Scattered bruises over the knees and elbows b/l

GU: Normal male genitalia. The testes are undescended.

Back: No midline tenderness

Neurological: Drowsy, underdeveloped physically and cognitively for age

Skin: Various bruises and cuts on knees/elbows in different stages of healing

Required Actions within the first two minutes:

- Obtain history from the patient's mother
- Obtain vital signs, IV access, point of care glucose level, and provide oxygen

Branch Points

- Nursing staff call you back into the room as the patient's pulse oximetry is in the 80s.
- Repeat vitals show: **BP 99/71, HR 115, T 37.4*C Resp Rate 8, SpO2 84% Wt 9.07 kg, Glucose (if asked for) 67 mg/dL GCS 8**

Required Actions over the next four minutes

- Perform primary survey
    - Patient is not protecting his airway
- Perform intubation
- Order confirmatory CXR
- Order VBG, supplementary labs, and imaging to help differentiate the patient's altered mental status/respiratory compromise

Branch Point

- The labs return showing hyponatremia, hypoglycemia, and elevated LFTs.
- The CT of the head is unremarkable. The remainder of the imaging is unremarkable.
- The patient's mother reports a recent increase in dosing of valproic acid a week ago.

Required Actions over the next two minutes:

- Call poison control
    - Valproic acid intoxication leads to:
        - Hyponatremia, hypoglycemia, and lactic acidosis
        - Hyperammonemia and hepatotoxicity
        - Lethargy, coma
    - Management of toxicity (valproate level >100 mg/L):
        - Antidote L-carnitine 100 mg/kg IV over 30 minutes (max 6g) followed by 15 mg/kg q4h if valproate levels >450 mg/L
        - Repeat levels every 4-6 hours until <100 mg/L
- Order EKG, total Valproic acid level, ammonia level, UA, UDS, Salicylate, Acetaminophen, POC glucose, Lactate, ammonia, VBG

Branch Point

- The learner should call nephrology for consideration of hemodialysis given the patient's decompensation requiring intubation.
- If the learner does not contact nephrology, the PICU attending will identify the need for consult at the time of admission request.

Required Actions Over the Next Several Minutes

- Give L-carnitine 100 mg/kg IV over 30 minutes followed by 15 mg/kg q4h.
- Consult nephrology for initiation of hemodialysis
- Admission to PICU

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STIMULUS INVENTORY

1. VBG + electrolytes
2. CBC
3. BMP+LFTs
4. UA
5. Co-ingestions: Acetaminophen, EtOH, UDS
6. Ammonia
7. Valproic Acid Level
8. 12-lead EKG
9. CXR following intubation

Labs and imaging results

Stimulus #1:

Complete Blood Count (CBC)	
WBC	8.000/mm3
Hg	9.4 g/dL
Hct	40%
Plts	249,000/mm
Differential	
PMNs	55%
Lymph	27%
Mono	12%
Eosin	4.5%
Baso	1.5%

Stimulus # 2:

BMP with LFTs	
Sodium	131
Potassium	3.6
Chloride	110
Bicarb	16
Glucose	67
BUN	17
Creatinine	1.2
AST	61
ALT	50
ALP	156
T. Bili	1
D. Bili	< 0.3
Albumin	4.3

Stimulus #3:

Urinalysis	
Color	Yellow
Specific gravity	1.017
glucose	Negative
protein	Negative
ketones	Trace
LE/Nitrites	Negative
Blood	Negative
WBC	0
RBC	Many
Crystals/Bacteria	Negative

Stimulus #4:

Urine Drug Screen	
Benzodiazepines	Negative
THC	Negative
Cocaine	Negative
Opiates	Negative
TCAs	Negative
THC	Negative
Amphetamines	Negative

Co-ingestions	
ETOH	<0.05
Acetaminophen	Undetected

Stimulus #5:

Ammonia Level		reference range
Serum NH_3	125 µmol/L	< 50 µmol/L

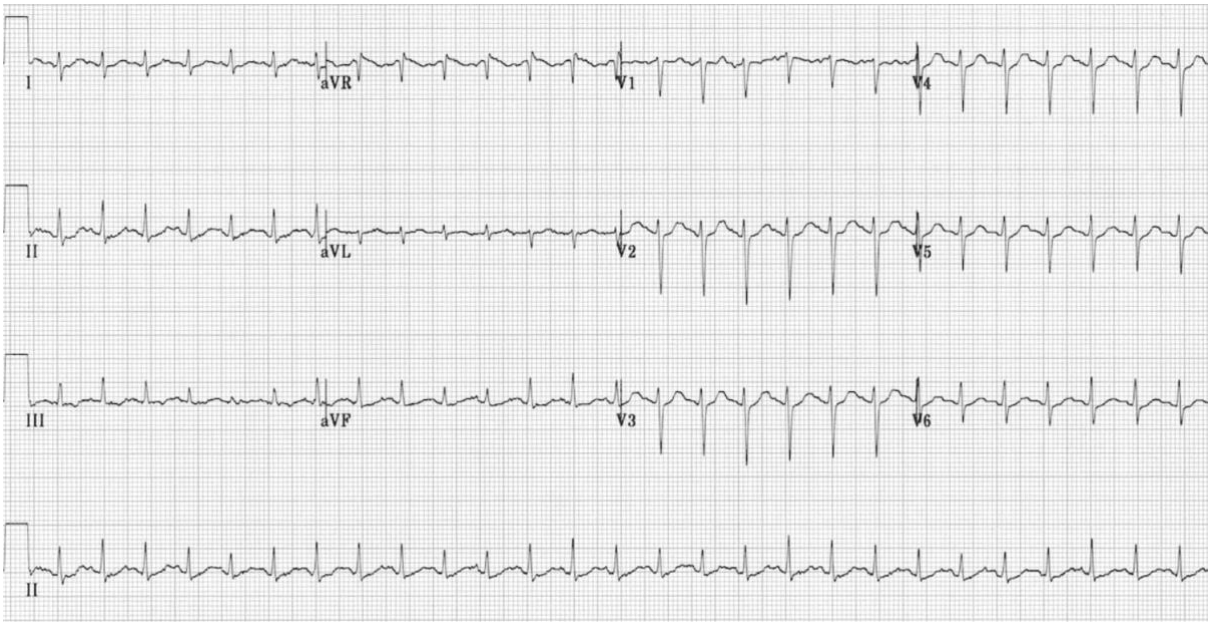
Stimulus #6:

Valproic Acid Levels		reference range (therapeutic)
Serum valproate	507 mg/L	50-100 mg/L

Lamotrigine Level		reference range (therapeutic)
Serum lamotrigine	10 mcg/mL	3 – 15 mcg/mL

Levetiracetam Levels		reference range (therapeutic)
Serum levetiracetam	30 mcg/mL	10 – 30 mcg/mL

Stimulus 7:
EKG



Stimulus #8:

CXR after intubation shows appropriate tube placement. Negative for acute infiltrate or pneumothorax.

Debriefing Notes: Valproic Acid Toxicity

Educational Objectives:

- To create a broad differential for lethargy in the pediatric population
- To understand the importance of repeat evaluations in identifying any need for further intervention or testing

Learning Points:

- Pathophysiology:
    - Anticonvulsant mechanism: It increases levels of GABA by inhibiting GABA transaminase, thereby inhibiting its degradation. Additionally functions as a sodium channel blocker, T-type calcium channel blocker, and modulated NMDA modulator of glutaminergic transmission.
    - Overdose: Interferes with fatty acid and mitochondrial metabolic pathways, via disruption of beta-oxidation. Downstream effects of this disruption include decreased ATP production and mitochondrial membrane potential, as well as increased production of reactive oxygen species.
- Understand the utilization of L-carnitine in the treatment of valproic acid toxicity
- Learn the transition point of when to initiate hemodialysis to further augment elimination.
    - Hemodialysis is indicated for serum valproate concentrations > 1,300 mg/L and in patients experiencing shock, cerebral edema, or coma.[3]
    - Hemodialysis treatment can be discontinued once the serum valproate concentration < 100 mg/L and the patient shows signs of clinical improvement, including normotension, improved mental status, pH normalization, and resolution of electrolyte abnormalities.[3]

  *NB: the mu-opioid receptor antagonist naloxone may reverse the central nervous system depression in some cases of valproate poisoning.[1,5] Although naloxone is not widely considered as first line therapy, it may function as a possible adjunct.

  Utilization of poison control is essential. The phone number is 1-800-222-1222.

Clinical Presentation:

- Lethargy, Coma, Multi-Organ Failure
- Hypernatremia, Hypoglycemia, Lactic Acidosis, Hyperammonemia, Elevated LFTs.

Toxic Dose:

- Ingestion of <200 mg/kg asymptomatic or mild drowsiness/ataxia
- Ingestion of >200 mg/kg variable CNS depression
- Doses >1g are potentially lethal

Diagnosis:

- Elevated total valproic acid level
- Suspicion if hyponatremia, hypoglycemia, lactic acidosis in coma patient
- Elevated ammonia and transaminases.

Emergency and Supportive Care:

- Supportive care, which may include intubation.

- L-Carnitine treatment 100 mg/kg IV over 30 minutes (maximum of 6 grams) followed by maintenance doses of 15 mg/kg every 4 hours.

- Serum ammonia levels should be simultaneously measured, and when valproic acid level <100 mg/L, L-carnitine therapy can be discontinued.

- Hemodialysis is indicated for serum valproate concentrations > 1,300 mg/L and in patients experiencing shock, cerebral edema, or coma.

Decontamination:

- GI decontamination with lavage or activated charcoal 1g/kg NG could be considered if ingestion occurred within 1 to 2 hours of presentation and valproate doses > 400 mg/kg as it may limit absorption.
- If GI decontamination is utilized, prior stabilization and airway protection should be completed to minimize risk of aspiration.

Specific Drugs and Antidotes:

- L-Carnitine: 100 mg/kg IV over 30 minutes (maximum of 6 grams) followed by maintenance doses of 15 mg/kg q4h

Prognosis:

- Dependent on dose, associated complications (i.e. hepato-toxicity), and early medical intervention
- Severe ingestions may resolve without any sequelae after aggressive decontamination, enhanced elimination, and adequate supportive care
- Prognosis of patients with acute valproate toxicity may be sufficient with supportive care alone
- Coma during initial presentation has been associated with a poor prognosis.[6]

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