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CASE REPORT

Probable Anticonvulsant Hypersensitivity Syndrome Due to Fosphenytoin in a Pediatric Patient with *Streptococcus pneumoniae* Meningitis

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An 8-year-old previously healthy girl with *Streptococcus pneumoniae* meningitis developed probable anticonvulsant hypersensitivity syndrome (AHS) within 5 days of starting fosphenytoin. She experienced fever, rash, periorbital edema, profound hepatotoxicity and coagulopathy. Her sudden and dramatic rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to greater than 80 times the upper limit of normal in combination with an elevated INR were very concerning. Mortality from AHS has been correlated with the degree of hepatic involvement. Fosphenytoin was immediately discontinued and, within 48 hours, AST, ALT and INR began to decrease and were within normal limits by hospital day 23. Prompt recognition of probable AHS and immediate discontinuation of fosphenytoin resulted in an abrupt reversal of clinical signs and laboratory values associated with potential hepatic failure in a pediatric patient.

KEYWORDS adverse drug effect, anticonvulsant hypersensitivity syndrome, fosphenytoin, hepatotoxicity, pediatric

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INTRODUCTION

Anticonvulsant hypersensitivity syndrome (AHS) is thought to occur in 1 out of every 1,000 to 10,000 new exposures to aromatic anticonvulsants.[1] Although AHS was first described in 1950, confusion still exists regarding this syndrome.[2] It is an unpredictable, idiosyncratic reaction that can result in severe multiorgan dysfunction and death.[1] A triad of fever, skin eruption and internal organ involvement is the defining presentation of the syndrome; however, variable presentations encompassing a spectrum of clinical features often result in a delay in diagnosis.[2] Fever, rash and hepatotoxicity should serve as strong evidence for AHS, which requires immediate discontinuation of the offending anticonvulsant.[1] The purpose of this case report is to present a pediatric patient who developed fever, rash and profound hepatotoxicity that began resolving shortly after discontinuation of fosphenytoin.

ABBREVIATIONS AHS, anticonvulsant hypersensitivity syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; mgPE, mg phenytoin equivalents

CASE REPORT

An 8-year-old previously healthy Caucasian girl was transferred from a community hospital with tonic seizures, respiratory distress and presumed *Streptococcus pneumoniae* meningitis. Three days prior to admission, the patient complained of earaches and had elevated

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temperatures reaching 39°C. Two days prior to admission she began vomiting and was unable to retain sufficient oral intake; the next day she remained in bed all day, was somewhat unresponsive and had episodes of clenched teeth. Prior to admission, the patient's mother provided acetaminophen as needed for fevers and earaches. No other medications were given prior to her community hospital admission. Her immunizations were up to date.

On the day of admission to the community hospital, the patient experienced 1- to 2-minute seizures about 10 to 20 minutes apart for 1 to 2 hours and was treated with loading doses of phenobarbital and fosphenytoin. Vancomycin and ceftriaxone were initiated, and she was then transferred to our hospital. Her weight upon admission was 32 kg, temperature 38.4°C, heart rate 111 beats/minute, respiratory rate 22 breaths/minute, blood pressure 101/75 mm Hg, white blood cell count 26,000/mm^3 (differential included 66% neutrophils, 15% bands, 14% lymphocytes, 5% monocytes and 0% eosinophils), hemoglobin 13.6 g/dL, hematocrit 37.4%, platelets 455,000/mm^3, glucose 130 mg/dl, sodium 130 mEq/L, potassium 5.2 mEq/L, chloride 97 mEq/L, bicarbonate 18 mEq/L, blood urea nitrogen 7 mg/dL, serum creatinine 0.4 mg/dL and her intracranial pressure was elevated to a range of 15-27 mmHg. The patient was mechanically ventilated until hospital day 9. Her medications on hospital day 1 included a dopamine continuous infusion at 3-5 μg/kg/min, fentanyl continuous infusion at 0.5 μg/kg/hour, midazolam continuous infusion at 50 μg/kg/hr, 3% sodium chloride continuous infusion at 60-75 mL/hr, vancomycin 500 mg intravenously (IV) 4 times/day (63 mg/kg/day) , ceftriaxone 2 grams IV twice daily (125 mg/kg/day) and fosphenytoin 75 mg phenytoin equivalents (mgPE) IV twice daily (5 mgPE/kg/day) and acetaminophen 450 mg (14 mg/kg/dose) as needed every 4 hours for fever or pain.

On hospital day 2, acetaminophen was increased to 600 mg (19 mg/kg/dose) orally or rectally every 4 hours for 24 hours then decreased to 450 mg (14 mg/kg/dose) rectally every 4 hours for 12 hours and then administered as needed for fever. She was afebrile on hospital days 2 and 3. On hospital day 3, the cerebrospinal fluid culture obtained at the community hospital reported *Streptococcus pneumoniae* sensitive to ceftriaxone. Vancomycin was discontinued. On hospital day 4, five days after starting fosphenytoin, the patient's temperature rose to 39.4°C. Physical examination revealed periorbital edema, a swollen tongue, a diffuse, erythematous blanching rash that resolved with diphenhydramine but returned with subsequent fosphenytoin doses, and no lymphadenopathy. Her drug therapy on hospital day 4 consisted of fosphenytoin 75 mgPE IV twice daily (5 mgPE/kg/day), ceftriaxone 1.5 grams IV twice daily (94 mg/kg/day), ranitidine 30 mg IV 3 times a day (3 mg/kg/day), fentanyl continuous infusion 0.5 μg/kg/hour, midazolam continuous infusion 50 μg/kg/hr, 3% sodium chloride infusion, diphenhydramine 30 mg (1 mg/kg/dose) IV every 6 hours as needed for rash, as well as acetaminophen 480 mg (15 mg/kg/dose) rectally every 4 hours as needed for temperatures greater than 38.5°C.

On hospital day 5, laboratory results showed significantly elevated transaminases (aspartate aminotransferase [AST] 3,276 U/L and alanine aminotransferase [ALT] 2,100 U/L) with no eosinophilia. Coagulopathy was also evident (INR 1.93) prompting treatment with phytonadione 5 mg orally once daily plus fresh frozen plasma. An abdominal ultrasound ruled out an abdominal abscess or intrahepatic clot. At this time the differential diagnosis included acetaminophen or phenytoin toxicity; both were discontinued, and serum concentrations were obtained. The acetaminophen concentration was less than 10 μg/mL (60.6 μmol/L). The total phenytoin concentration of 17.3 μg/mL (68.6 μmol/L) was within the reference range of 10 to 20 μg/mL (40-80 μmol/L) and the albumin concentration was 2.5 g/dL (25 g/L). At this point, AHS was highly suspected. Consulting neurologists recommended lorazepam 0.1 mg/kg two to three times daily as needed for seizures. Hepatitis (A, B and C), Epstein-Barr virus, cytomegalovirus, HIV and metabolic abnormalities were ruled out on the basis of appropriate laboratory tests.

On hospital day 6, AST and ALT increased to 4,137 U/L and 3,978 U/L, respectively; however, approximately 10 hours later transaminases significantly decreased to 2,012 U/L and 2,798 U/L, respectively. The Figure shows the consistent decrease in transaminases over the next 17 days. Also on hospital day 6, the patient's ceftriaxone was changed to cefotaxime 2.4

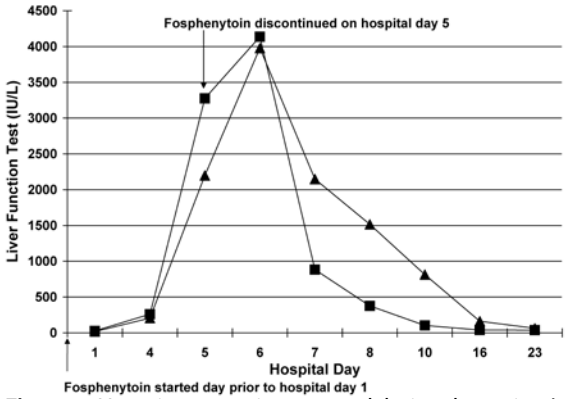

Figure 1. Hepatic transaminases trend during the patient's hospital course.
■ AST; ▲ ALT

grams IV 4 times/day (300 mg/kg/day) due to fewer potential hepatobiliary side effects, and lorazepam 3 mg (0.1 mg/kg/dose) IV 2 to 3 times/day was administered as needed to control seizures (the patient required 2 doses only on hospital day 7). Although the consulting neurologist recommended checking a free phenytoin concentration, it was not obtained because transaminases began to decline significantly. On hospital day 7, dexamethasone 8 mg (0.25 mg/kg/dose) 4 times/day was initiated due to a failed extubation attempt, and INR decreased to 1.15 following phytonadione and fresh frozen plasma. The patient became afebrile again on hospital day 10. Nutrition was provided solely by the enteral route throughout the patient's intensive care stay.

DISCUSSION

Applying the Naranjo Adverse Drug Reaction Probability scale for causality assessment, a "probable" association between the patient's untoward reaction and phenytoin was confirmed. Since the first description of the systemic complications of anticonvulsant medications in the 1950's, numerous adult patients and a smaller number of pediatric patients with AHS have been reported.[3] Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine, and primidone) are most frequently involved, and there is a high percentage of cross-reactivity (70% to 80%) among these medications.[2,3] The aromatic anticonvulsants are metabolized to a common arene oxide metabolite that is normally detoxified by epoxide hydrolase. A defect in this enzyme has been observed in patients with AHS and results in an inability to detoxify arene oxide metabolites. These metabolites may be directly cytotoxic or act as haptens, leading to a secondary immune or hypersensitivity reaction.[4]

Lamotrigine, although chemically unrelated to the aromatic anticonvulsants, recently has been reported to cause AHS.[5] Newer anticonvulsant drugs such as gabapentin, topiramate and levetiracetam are nonaromatic anticonvulsants and have not been linked to AHS. The neurologist suggested levetiracetam as an alternative anticonvulsant because it is renally excreted and should not adversely impact hepatic enzymes or function. Hypersensitivity to levetiracetam is rare, and it is not suspected to cross-react with phenytoin or other aromatic anticonvulsants.

The duration of exposure before onset of AHS symptoms is generally one to eight weeks. Symptoms occurred in this patient was after 4 to 5 days of therapy. Acetaminophen toxicity was discounted due to the lack of enhancement of acetaminophen toxicity by phenytoin and, in fact, there is a potential for reduction of acetaminophen toxicity due to enzyme induction by phenytoin. A thorough review of the literature makes it clear that therapeutic doses of acetaminophen either alone or in the presence of enzyme inducers do not produce toxicity.[6]

The manifestations of AHS, listed in order of frequency, from a case series of 14 pediatric patients can be found in the Table.[1] The patient described in our report had the following clinical features of AHS: fever, rash, periorbital edema, profound hepatotoxicity and coagulopathy. No other features of AHS such as lymphocytosis, lymphadenopathy or eosinophilia were present. The rapid rise in AST and ALT greater than 80 times the upper limit of normal was very concerning because mortality from AHS may be as high as 21% and has been correlated with the degree of hepatic involvement.[1] The prompt recognition of possible AHS in this patient and immediate discontinuation of fosphenytoin likely prevented further clinical progression and resulted in the abrupt reversal of increasing transaminases.

Another consideration was potential additive toxicity due to fosphenytoin's phosphate ester moiety. Fosphenytoin is a parenteral phosphate ester prodrug of phenytoin developed to over-

Table. Manifestations of AHS in Order of Frequency[1]

Manifestation	Number of Patients (%)
Rash	14 (100)
Fever	14 (100)
Lymphocytosis	10 (71.4)
Elevation of liver enzymes	9 (64.3)
Elevated ESR	9 (64.3)
Lymphadenopathy	8 (57.1)
Atypical lymphocytes	7 (50)
Eosinophilia	6 (42.8)
Coagulopathy (INR >1.3)	6 (42.8)
Hyperbilirubinemia	5 (35.7)
Leukocytosis	5 (35.7)
Leukopenia	5 (35.7)
Nephritis	1 (7.1)

AHS, anticonvulsant hypersensitivity syndrome; ESR, erythrocyte sedimentation rate; INR, international normalized ratio
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come the limitations associated with parenteral phenytoin administration.[7] Following IV or intramuscular administration, fosphenytoin is rapidly converted by endogenous phosphatases to its parent compound phenytoin, 1 mole of phosphate and 1 mole of formate.[7] The major advantage of fosphenytoin's phosphate ester moiety is improved water solubility and fewer infusion site reactions compared to phenytoin. Although fosphenytoin can be administered at 3 times the maximum IV infusion rate of phenytoin, therapeutic total phenytoin plasma concentrations are not attained more quickly with fosphenytoin due to a conversion half-life of approximately 15 minutes. Benefits of fosphenytoin include achieving therapeutic unbound phenytoin plasma concentrations more rapidly, less infusion-related pain and decreased risk for "purple glove syndrome." The only adverse events more commonly observed with fosphenytoin are infusion-related, non-allergic, transient paresthesias and pruritis.[7]

Management of AHS in this patient involved discontinuing fosphenytoin and acetaminophen as well as treating her coagulopathy with phytonadione and fresh frozen plasma. Although medical care is primarily supportive, other treatment modalities include the controversial use of corticosteroids and anecdotal reports of plasmapheresis, cyclophosphamide, cyclosporine and IV immunoglobulin.[8,9] The dermatologic sequelae of AHS vary widely from patchy erythema to toxic epidermal necrolysis and Stevens-Johnson syndrome.[10] This patient experienced a mild, diffuse erythematous blanching rash that resolved with diphenhydramine. Intravenous immunoglobulin was considered but not given due to limited data and possible greater benefit primarily for patients with severe cutaneous reactions. Corticosteroids were not used initially because the patient had documented *Streptococcus pneumoniae* meningitis, however, dexamethasone was initiated on hospital day 7 in response to a failed extubation attempt. Charcoal hemofiltration was suggested to remove toxins; however, this treatment modality was not available at our institution, and the patient began to show signs of improvement within days of exhibiting symptoms of AHS.

The patient was successfully extubated from mechanical ventilation on hospital day 9 and transferred to the general pediatrics unit on hospital day 13. The midazolam and fentanyl continuous infusions were discontinued on hospital day 9. Lorazepam 2 mg 4 times/day (0.25 mg/kg/day) and methadone 1.5 mg 3 times/day (0.15mg/kg/day) were started on hospital day 8 in anticipation of extubation and stopping midazolam and fentanyl infusions. The patient did not require any further anticonvulsants; lorazepam was used to prevent benzodiazepine withdrawal. She was discharged 23 days after admission with hepatic and other laboratory values within normal limits.

Confirmation of AHS by in vitro lymphocyte toxicity assay could help offer individualized risk assessment.[11] Epoxide hydrolase deficiency is transmitted as an autosomal dominant trait. It has been suggested that parents and siblings of an affected individual should consider a diagnostic assay.[11]

CONCLUSION

Prompt recognition of probable fosphenytoin AHS and immediate discontinuation of fosphenytoin resulted in an abrupt reversal of clinical signs and laboratory values associated with potential hepatic failure in this patient.

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