BRIEF REPORT

Anticonvulsant Hypersensitivity: An Unfortunate Case of Triple Exposure to Phenytoin

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Anticonvulsant hypersensitivity manifests 2 to 12 weeks after patients start taking phenytoin, phenobarbital, or carbemazepine. The syndrome begins with fever followed by a rash that can progress to erythema multiforme, toxic epidermal necrolysis, and multi-organ system involvement. Other common manifestations include lymphadenopathy, facial edema, eosinophilia, and elevated transaminase levels. Anticonvulsant hypersensitivity can be fatal in 5% to 50% of patients if hepatic involvement or toxic epidermal necrolysis occurs. Most evidence regarding the etiology points to a genetically related defect in the detoxification enzyme. Early recognition is important in order to discontinue drug therapy. Continuity of care assists in prevention of re-exposure. Treatment includes supportive measures and steroids. All patients with anticonvulsant hypersensitivity should wear a medical identification bracelet.

KEY WORDS. Anticonvulsants; drug hypersensitivity; phenytoin; continuity of patient care; family practice. *(J Fam Pract 1997; 45:434-437)*

Anticonvulsant hypersensitivity usually manifests 2 to 4 weeks after initiating treatment with phenytoin, phenobarbital, or carbemazepine, but can begin as late as 3 months. This reaction occurs in 1 in 1000 to 1 in 10,000 patients exposed to these drugs, and is more common in African Americans.[1] The syndrome usually involves fever, rash, lymphadenopathy, leukocytosis with eosinophilia, and elevation of transaminase levels.

Case Report

A 62-year-old African American woman arrived unaccompanied at the emergency department (ED) in status epilepticus. After receiving diazepam to stop her seizure activity, she was given a loading dose of phenytoin. The patient could not communicate her medical history or drug allergy to the ED physician even after the seizure abated because she has profound dementia resulting from a cerebrovascular accident. When her medical chart arrived in the ED, the physician noted that she was being treated with carbemazepine. He therefore checked her carbemazepine level and found it to be subtherapeutic at 2.8 μg/mL.

Within 6 hours, her temperature was 101.2°F (39°C). By the next morning, a diffuse, warm erythema appeared on the skin of her ventral arms, axillas, and face. Therapy with prednisone was initiated for suspected anticonvulsant hypersensitivity, and phenytoin was discontinued. The fever resolved. By hospital day 3, the erythema spread to her shoulders, chest, and extensor surfaces of her legs. On day 5, approximately 12 target lesions appeared mostly on her legs, ranging in size from 3 to 10 centimeters, accompanied by two bullous lesions with epidermal desquamation and Nikolsky's sign (Figure 1). Her lips became dry, crusted, and fissured. No lymphadenopathy was appreciated. Maximal white blood count (WBC) was 10,100/mm^3 without eosinophilia. Seventeen days after administration of the phenytoin, the skin lesions were resolving.

Throughout her lengthy chart (the "old" chart that the ED physician received), "no known drug allergies" were noted, except on the first history and physical examination when a "skin rash to unknown anti-convulsant" had been reported by her family. On review of her previous hospital records, toxic epidermal necrolysis that began developing with 24 hours of a phenytoin bolus was confirmed; there-

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fore, it is likely that she had been exposed at least one more time previously.

During the past 1½ years this patient received continuity of care in our family practice residency's internal medicine clinic. Four months after the hospitalization detailed above, the patient came for her monthly checkup and was found to have been discharged from another hospital for status epilepticus. Again, she was given a loading dose of phenytoin in the ED and continued to receive phenytoin during the 2-day admission. In our clinic that day, she displayed target lesions and areas of epidermal sloughing that were more extensive than previously noted (Figure 2). The phenytoin level was 2.5 µg/mL; liver function tests, blood urea nitrogen, and WBC count with differential were within normal limits. Fortunately, her discharge phenytoin prescription from that hospital was not filled.

Unfortunately, her family rarely accompanies her to the ED and neglects to direct the ambulance service to our hospital for continuity of care. In addition, despite multiple reminders, her family fails to remember her drug allergy, and despite repetitive counseling regarding the importance of regularly giving the patient her anticonvulsant administration, the patient continues to have break-through seizures related to subtherapeutic levels. At this point, it became sadly clear that we could not rely on her family to convey her life-threatening drug allergy or that her family would strive to keep her care within the same group of physicians who knew her allergy. Therefore, as her advocates, we obtained a MedicAlert identification bracelet for her protection. In addition, our social services helped us to honor her wishes to remain with her family by placing her in a daytime activity center, where she could receive her anticonvulsant medication regularly.

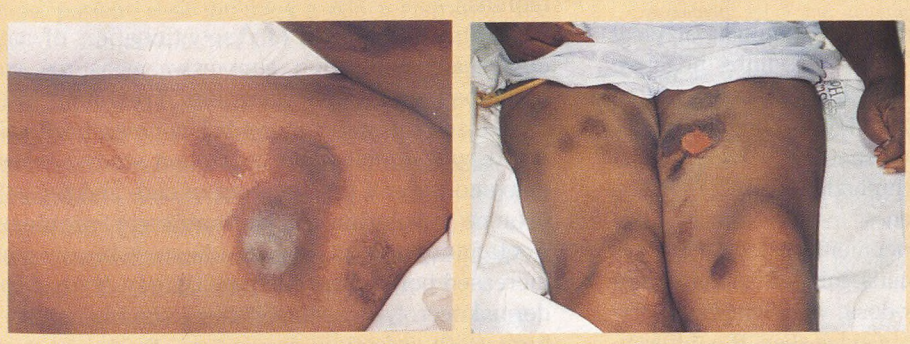
Discussion

Anticonvulsant sensitivity initially manifests as a fever of 100.4°F to 105°F (38°C to 40°C) followed closely by cutaneous signs.[2] The rash is usually diffuse, confluent, erythematous, macular, and pruritic. Often preceded by prodromal symptoms of malaise, arthralgias, myalgias, and headache, the erythroderma usually appears on the chest, face, and arms, and can progress to erythema multiforme or toxic epidermal necrolysis, or both.[3] This hypersensitivity rash is different from the mild morbilliform eruption occurring in one-fifth of patients taking phenytoin that resolves when the drug is removed and does not recur.[4,5]

The mechanism of phenytoin hypersensitivity remains uncertain but appears to be genetically related and likely autosomal codominant.[6] Phenytoin, phenobarbital, and carbemazepine are aromatic ring compounds oxidized by cytochrome p450 to arene oxides, which are then detoxified by epoxide hydrolase. If not detoxified, they bind to macromolecules producing a hypersensitivity reaction by either cell death or neoantigen formation; therefore, patients with hypersensitivity appear to have a defect in epoxide hydrolase.[7] Cross-sensitivity between phenytoin, phenobarbital, and carbemazepine appears to occur in 80% of patients, suggesting that patients who have had a reaction to phenytoin, phenobarbital, or carbemazepine should not be treated with these or any other arene-oxide-producing drugs.[5] In vitro, both parents of hypersensitive individuals have demonstrated intermediate cell death, which suggests an autosomal codominance inheritance pattern. This inheritance patterns would infer that siblings have a 25% hypersensitivity risk, and thus, should

FIGURE 1

After patient's second documented exposure to phenytoin, approximately 12 target lesions appeared mostly on her legs, ranging in size from 1 to 10 cm.

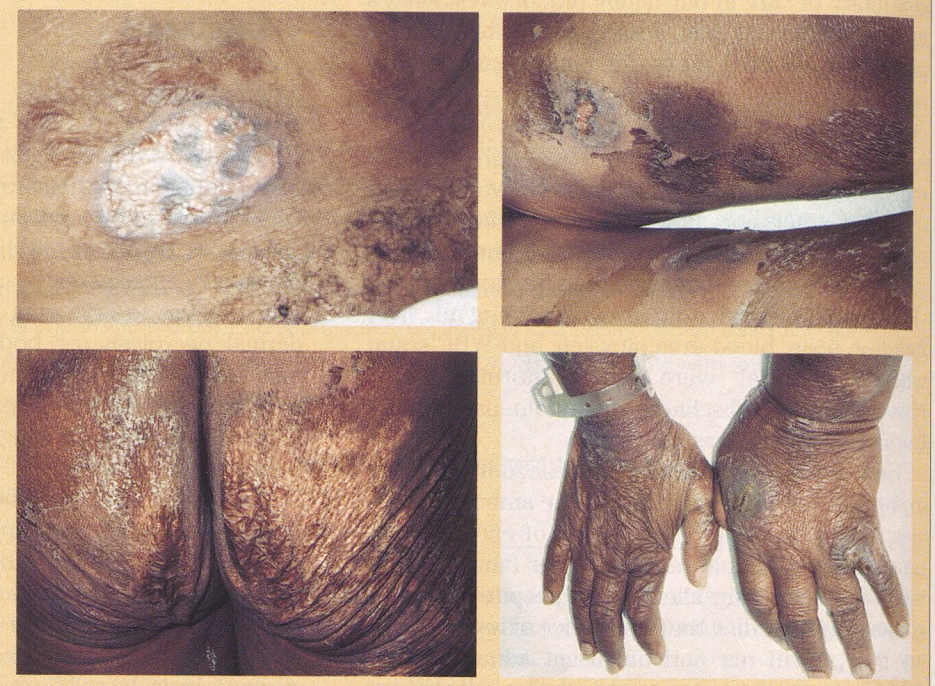


not be given any arene-oxide-producing drugs.[5,6]

Erythema multiforme is characterized by distinctive "target" or "bull's-eye" lesions containing a central vesicle or erosion surrounded by concentric rings found in a symmetric distribution over the extremities, yet usually sparing the trunk. If patients present with the mucous membrane manifestations, then the dermatologic manifestation can be defined as Steven-Johnson's syndrome. In toxic epidermal necrolysis, the patient develops bullae that enlarge, become confluent, and desquamate. The skin appearance in toxic epidermal necrolysis is similar to staphylococcal scalded skin syndrome.[8] Toxic epidermal necrolysis resembles a widespread scalding burn, but with less vascular injury. Other dermatologic manifestations include fissures of the lips, corneal ulcerations, and erosions of mucous membranes.

FIGURE 2

After the third exposure substantiated by documentation, the patient had more extensive lesions on her thighs, as well as additional lesions on her buttocks and the back of her hands.



In addition to fever and rash, various constellations of the following signs may occur:

1. Facial edema, particularly in the periorbital region but may also include the oropharynx and tongue
2. Blood dyscrasias such as eosinophilia, atypical lymphocytes, and mild Coombs'-negative hemolytic anemia
3. Elevated transaminase levels, hepatosplenomegaly, and anicteric hepatitis
4. Tender generalized lymphadenopathy
5. Elevated urea nitrogen.[1,2,9]

Less common findings documented include myopathy, eosinophilic pneumonitis, joint effusions, serum sickness, polyarteritis nodosa, and lymphoma.[4,10,11] Depending on the cluster of signs seen, the differential diagnosis often includes collagen vascular diseases, malignancies (eg, lymphoma), and infections (eg, mononucleosis, rubella, and staphylococcal scalded skin syndrome.)[7,9,11]

Reported mortality rates have been quite high if hepatitis (5% to 50%) or toxic epidermal necrolysis (15% to 25%) develops.[12,13] Death from toxic epidermal necrolysis usually occurs because of fluid and electrolyte imbalances or sepsis. Most often, full dermatologic resolution occurs within 2 to 4 weeks, but normalization of the liver function tests may take 3 months.[6]

Treatment consists of discontinuation of anticonvulsant medication, supportive measures, and high-dose oral corticosteroids. Treatment with high-dose oral corticosteroids has never been validated by a double-blind controlled study because many consider it the standard of care and report a prompt resolution of dermatologic problems. Acetaminophen is contraindicated because of increased possibility of hepatotoxicity. If toxic epidermal necrolysis occurs, it should be treated like a burn with infection prevention, fluid and elec-

trolyte support, and admission to a burn unit depending on the extent of desquamation.

Challenge doses of even 1 mg have caused recurrent anticonvulsant hypersensitivity; and since the risk of mortality is high, do not give to a challenge dose or any arene-oxide-producing drug; If a challenge dose is readministrated unknowingly, a reoccurrence of anticonvulsant hypersensitivity happens within 24 hours and toxic epidermal necrolysis is more likely.[9] In earlier trials of diagnostic rechallenge, severe reactions developed even with a 1-mg dose of phenytoin. Our patient's case reaffirms that severe reactions occur with repeat drug exposure; the amount of surface area and the number of sites increased dramatically between our patient's second and third exposure. No other case of more than two exposures has been reported. Documentation of three exposures has been found, and since the first documented reaction occurred within 24 hours of exposure, our patient must have been exposed previously at least once more, making a minimum of four total exposures.

Our patient now wears a MedicAlert bracelet indicating her drug allergy. Wearing this bracelet should be recommended, especially to all patients with anticonvulsant hypersensitivity because these patients may present post-ictal or in status epilepticus. Unlike imitations available at some drug stores, MedicAlert supplies the only identification jewelry that provides instant identification and a lifelong medical file that may be updated. These files are available in emergent situation to physicians and other emergency medical responders by a 24-hour worldwide collect-call phone system. Identification emblems are also widely used by patients with chronic conditions such as diabetes mellitus, Alzheimer's, hemophilia, and hearing impairments. Except for a few sponsored memberships, patient cost includes a $35 registration fee and $15 annual renewal fee. Physicians can receive a display with brochures free of charge from 1-800-ID-ALERT (1-800-825-3785.) As a nonprofit 3.8-million-member organization endorsed by the American Academy of Family Physicians, the MedicAlert Foundation claims that 80,000 American lives have been saved since 1956; this claim is based on a membership survey in which 5% reported that MedicAlert "saved my life."[13, 14]

This case exemplifies the importance of remaining the patient's advocate in spite of difficult psychosocial situations, especially when life-threatening conditions exist. Her circumstances demonstrate several psychosocial barriers to identification of important medical conditions including: (1) the patient's inability to comprehend and communicate adequately; (2) the family's failure to comprehend and communicate adequately; (3) lack of continuity of care. Common patient populations with barriers to condition identification include children, demented patients, mentally retarded patients, post-ictal individuals, comatose patients, patient's in status epilepticus, family neglect or absence, and patients on vacation, moving, or traveling.

With our case study patient, we have thus far been able to honor the patient's request to live with her daughter by finding other mechanisms to deliver her medication and to communicate her allergy. Recently, her carbemazepine level was reported in the normal range. Our hopes are that her seizure disorder will remain controlled and that she will never again be subjected to the lethal risk of phenytoin administration.

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