

CASE REPORT

Levetiracetam-Induced Acute Generalized Exanthematous Pustulosis

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Antiepileptic drugs have been associated with many adverse effects, including different types of rashes; however, the frequency of rash varies among the drugs. The most common adverse effects associated with levetiracetam include somnolence, asthenia, headache, dizziness, and behavioral abnormalities. Until recently, rash had not been reported as an adverse effect of levetiracetam in adults. We describe a 45-year-old, African-American woman who developed a desquamating rash after starting levetiracetam for a witnessed seizure. The rash improved after the drug was discontinued, but on rechallenge, the desquamating rash reappeared. The patient was hospitalized, levetiracetam was discontinued, and supportive care and treatment with triamcinolone 0.1% cream and oral prednisone were started. Her rash was biopsied, and she was diagnosed with drug-induced acute generalized exanthematous pustulosis (AGEP). With topical and oral steroid treatment the patient's rash improved, and she was discharged on hospital day 4. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6) between the patient's development of AGEP and levetiracetam exposure. To our knowledge, this is the first case report of levetiracetam-induced AGEP. Although levetiracetam is usually well tolerated, clinicians should be aware of this potential adverse drug reaction in patients who develop severe skin reactions while receiving this drug.

Key Words: Keppra, levetiracetam, rash, desquamating, acute generalized exanthematous pustulosis, AGEP, adverse drug reaction.
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A common adverse effect associated with antiepileptic drugs is the development of rash, which can range from a mild, diffuse, erythematous, pruritic rash to a severe skin reaction as part of Stevens-Johnson syndrome or toxic epidermal necrolysis.¹ The frequency and severity of rash vary among antiepileptic drugs. A retrospective analysis comparing 15 antiepileptic drugs in adults found that agents such as phenytoin,

lamotrigine, zonisamide, and carbamazepine were associated with higher frequencies of rash compared with agents such as levetiracetam and valproic acid.¹

Levetiracetam is an antiepileptic drug indicated for the treatment of multiple seizure disorders in children and adults. The drug's chemical structure is unrelated to other antiepileptic agents, and the exact mechanism of action for its antiepileptic effects is unknown.² Studies have shown that the action of levetiracetam may be attributed to its binding to the synaptic vesicle protein 2A to regulate vesicle exocytosis and mediate neurotransmitter release.^{3–6} Levetiracetam does not affect neuronal voltage-gated sodium channels, T-type calcium currents, or γ -aminobutyric acid-mediated neurotransmission,

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as is seen with other antiepileptic drugs.⁷ In three multicenter, randomized, double-blind, placebo-controlled studies that included 904 patients with epilepsy, the frequency of adverse effects was 15% in the levetiracetam group versus 11.6% in the placebo group.⁸ The most common adverse effects were somnolence, asthenia, headache, dizziness, and behavioral abnormalities. Behavioral abnormalities that were reported included agitation, anger, anxiety, depression, hostility, and suicidal ideation.

Rash is not a common adverse effect of levetiracetam. We found only one case report⁹ and one pediatric study¹⁰ that reported levetiracetam-associated rash. The case report described a patient receiving levetiracetam who developed a reticulated, erythematous, macular eruption on the back, chest, abdomen, and anterior lower extremities that showed slight spongiotic dermatitis on biopsy, consistent with a drug eruption.⁹ Levetiracetam was discontinued, and the rash resolved. Seven months later, the patient was rechallenged with the drug, which was titrated to a goal dose of 750 mg twice/day; once the goal dose was reached, the rash reappeared. In a study of 101 pediatric patients treated with levetiracetam, vesiculobullous rash was reported in 2%.¹⁰

We describe an adult who was receiving levetiracetam for a witnessed seizure and developed a desquamating rash that was determined to be biopsy-proven acute generalized exanthematous pustulosis (AGEP).

Case Report

A 45-year-old, African-American woman was admitted to the hospital for a “measle-like” rash that had developed on her back 2 days earlier and had spread to her neck, abdomen, and bilateral upper and lower extremities. The rash was edematous and desquamating in some areas. The patient also complained of severe pain in the areas that correlated with the rash and denied symptoms of fever and malaise.

During a previous hospitalization 3 weeks before this admission, levetiracetam 500 mg twice/day and methimazole 10 mg twice/day had been started for a witnessed partial seizure and new diagnosis of hyperthyroidism, respectively. Her hospital course was complicated by an episode of respiratory failure and septic shock that led to intubation. Within 1 week after hospital discharge, the patient developed a rash that continued to worsen. She visited her

physician and consulted with a dermatologist who recommended treatment with triamcinolone 0.1% cream once/day applied to the rash, a prednisone taper from 60 mg/day to 10 mg/day (maintenance dose) over 1 week, and discontinuation of the levetiracetam because of concern for a possible drug-related etiology. The patient reported that the rash resolved within a couple of days after discontinuing levetiracetam. After she completed the 7-day prednisone taper to 10 mg/day, she restarted the levetiracetam 500 mg twice/day without discussing it with her physician. One week later, the patient again developed a rash on her back.

The patient's other significant medical history included rheumatoid arthritis, interstitial lung disease, type 2 diabetes mellitus, hypertension, osteoporosis, gastroesophageal reflux disease, and seasonal allergies. In addition to levetiracetam and methimazole, her drug therapy consisted of propoxyphene 100 mg–acetaminophen 650 mg every 6–8 hours as needed for pain, alendronate 70 mg once/week, pantoprazole 40 mg/day, sliding-scale dosed regular insulin, fexofenadine 60 mg twice/day, atenolol 25 mg/day, ipratropium-albuterol 2 inhalations every 6 hours as needed, and oxygen at 2 L/minute. She had no known drug allergies. None of the drugs she was receiving have been reported to cause edematous and desquamating rash.

On this hospital admission, the patient's body temperature was 35.8°C, heart rate 96 beats/minute, blood pressure 96/70 mm Hg, respiratory rate 18 breaths/minute, and oxygen saturation 97% on 2 L/minute of oxygen. Significant findings on physical examination included no involvement of oral mucosa, ocular erosions, or other membranes. Diffuse erythema and edema were observed on the patient's trunk and bilateral upper and lower extremities, and desquamation of skin was noted on her back and bilateral upper and lower extremities. No evidence of skin breakdown was seen on the external genitalia. Significant laboratory results included a white blood cell count of $16.5 \times 10^3/\text{mm}^3$ (normal range $4\text{--}10 \times 10^3/\text{mm}^3$), with a neutrophil count of $13.4 \times 10^3/\text{mm}^3$ (normal range $1.5\text{--}6.0 \times 10^3/\text{mm}^3$).

Levetiracetam and methimazole were discontinued, as both could be implicated as potential causative agents of the rash. The patient received supportive care with fluids and silver sulfadiazine, and the burn and dermatology services were consulted. Epidermal necrosis, erythema multiforme, and Stevens-Johnson syndrome were

ruled out as diagnoses.

On hospital day 1, the patient underwent a 0.4 x 0.3-cm skin punch biopsy on the right arm. On day 2, results of the biopsy showed spongiotic dermatitis with early intraepidermal pustule formation that was suspicious for AGEP. Dermatopathology of the biopsy sample ruled out drug rash with eosinophilia and systemic symptoms syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, and dermatomyositis. The patient's prednisone dose was increased to 60 mg/day with a 7-day taper to 10 mg/day, triamcinolone 0.1% cream was applied to the rash twice/day, and methimazole was restarted.

On hospital day 3, the patient's rash improved, with decreased erythema, healing of the erosions from the desquamation, and decreased pruritis. She was discharged on hospital day 4, without any antiepileptic drugs, and instructed to follow-up with her primary care physician within 1 week.

Discussion

Acute generalized exanthematous pustulosis is a rare, severe, pustular eruption caused by certain infections or drugs. The pustulosis is characterized by edematous erythema, with numerous small, nonfollicular subcorneal and intraepidermal pustules, with marked spongiosis and necrotic keratinocytes. Histologic and immunochemistry studies suggest that drug-specific T cells produce large amounts of interleukin-8 (also known as CXCL8), which activate and recruit neutrophils, resulting in an inflammatory reaction of the skin.¹¹ Acute generalized exanthematous pustulosis is often associated with fever (> 38°C), and leukocytosis (neutrophil count > 7000 cells/mm³). A typical episode of AGEP lasts up to 15 days. Patients with drug-induced AGEP develop pustules of the skin within 2 days of drug exposure along with a desquamating rash that will usually resolve 9–10 days after discontinuation of the causative agent.¹² Our patient presented to the hospital with all of the major symptoms of AGEP except for fever.

Drug-induced AGEP tends to be a self-limited disease that completely resolves with supportive care along with the discontinuation of the offending drug. Antibiotics are not indicated unless there is clear evidence of infection. Systemic corticosteroids can be administered but are not required. Some experts recommend the use of systemic corticosteroids in patients with severe cases of AGEP that do not resolve within

the expected window of 15 days.¹¹ To our knowledge, no comparative studies have evaluated the effects of corticosteroid use on AGEP outcomes.

A search of the MEDLINE database was performed to identify drugs associated with AGEP. More than 90% of AGEP cases are induced by drugs, with a wide range of suspected causative agents.¹² Antinfectives (aminopenicillins and macrolides¹³), antiepileptics (carbamazepine⁸), calcium channel blockers (diltiazem^{14, 15}) and acetaminophen^{8, 16} are the most frequently reported triggers. A multinational case-control study, the European Severe Cutaneous Adverse Reactions (EuroSCAR) study, evaluated the risk of developing AGEP from various drugs.¹⁷ Between April 1997 and December 2001, 97 cases of AGEP were reported in select hospitals. The multivariate analysis categorized the drugs into one of three categories according to their association with AGEP: high association, less strong association, and no significant association. Lamotrigine, carbamazepine, phenobarbital, and phenytoin had less strong associations, and levetiracetam was not associated with any cases of AGEP. We also did not find any reported cases of levetiracetam-induced AGEP during our literature search.

A recently published case report, however, supports that levetiracetam is associated with rash.⁹ The patient developed a rash on the trunk and extremities after exposure to levetiracetam, similar to our patient. Our patient, however, had desquamation with her rash. The biopsy results of the rashes from both this patient as well as our patient showed spongiotic dermatitis, consistent with inflammatory cutaneous processes. In addition, after rechallenge, both patients developed rashes that were similar to their previous eruptions.

Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6) between our patient's development of AGEP and levetiracetam exposure.¹⁸ This assessment was based on the appearance of the rash after initiation of the drug, improvement after discontinuation of the drug, and reappearance of the rash after rechallenge with the drug.

Methimazole has been associated with a 4–6% frequency of rash compared with placebo.¹⁹ Although methimazole was started concurrently with levetiracetam, rashes associated with methimazole use are generally macular appearing and characterized by urticaria.¹⁹ Because the appearance of our patient's rash was different, and her rash improved after she restarted

methimazole therapy, this supports our conclusion that methimazole was not the causative agent.

Conclusion

Rash is a common adverse effect reported with the use of many antiepileptic drugs; however, until recently, rash associated with levetiracetam had not been reported in adults. To our knowledge, our patient represents the first case of levetiracetam-induced AGEP to be reported. Although levetiracetam is usually well tolerated, clinicians should be aware of this potential adverse drug reaction in patients who develop severe skin reactions while receiving this drug.

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