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Clinical Observations

Levetiracetam-induced Anaphylaxis in a Neonate

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ABSTRACT

BACKGROUND: Neonatal seizures are often refractory to treatment with initial antiseizure medications. Clinicians turn to agents such as levetiracetam despite the paucity of published data regarding its safety, tolerability, or efficacy in the neonatal population. **PATIENT PRESENTATION:** We describe a neonate who developed anaphylactic shock developing after receiving intravenous levetiracetam. **RESULTS:** This is the first neonate to develop anaphylactic shock due to intravenous administration of levetiracetam. **CONCLUSION:** Clinicians should be aware of this potentially fatal adverse effect occurring with intravenous levetiracetam in newborns.

Keywords: levetiracetam, newborn, anaphylaxis, seizure

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Introduction

The use of some of the newer, already-available antiepileptic drugs has become wider in clinical practice, although off-label, and their results are described in case series. The main example includes levetiracetam, which displays a favorable pharmacokinetic profile and alternative mechanisms of action that could positively affect tolerability and efficacy in the neonatal period.¹ Levetiracetam has few known serious adverse side effects, in contrast to other antiseizure medications, which may cause cardiopulmonary depression, arrhythmia, and coagulopathy. The estimated frequency of hypersensitivity to levetiracetam in children and adults is 0.6%.² These features suggest that levetiracetam could be safe and efficacious in treating neonatal seizures; however, neonatal data are needed.³ To date, anaphylaxis or other life-threatening adverse effects attributable to levetiracetam in neonatal period have not been reported.

Case Report

A male infant, 40 weeks' gestation with a birth weight of 3300 g, was delivered by Caesarean delivery because of fetal distress. At birth, he had

an Apgar score of 2 at 1st, and 6 at 5th min. He was hospitalized with a diagnosis of severe asphyxia, seizures, and pneumothorax. He was referred to Megapark Hospital because of seizures refractory to treatment with initial antiseizure medications. No allergic specification was present in his family history. No specific drug was mentioned to have been used in prenatal period. Erythematous rash and urticaria developed 2 seconds after 10 mg/kg intravenous administration of levetiracetam (Keppra 500 mg/5 mL; Patheon Italia S.p.A, Monza, Italy) that began from the infant's scalp and face and invaded the entire body in about 3 min (Fig 1A–B).

Investigations revealed a normal full blood count, normal urea and electrolytes, glucose, normal calcium, magnesium, liver functions, and C-reactive protein. Blood culture did not reveal any microbial agent. Severe metabolic acidosis was detected (pH 7.01, pCO₂: 52 mmHg, pO₂: 35 mmHg, HCO₃: 12 mmol/L and base excess: –13 mmol/L). The blood pressure was detected as hypotensive (29/12 mmHg, mean blood pressure 20 mmHg; before the administration of levetiracetam, blood pressure was 75/45 mmHg, mean 51 mmHg). The infant was given intramuscular adrenaline, and cardiopulmonary resuscitation was performed. His heart rate increased as spontaneous respirations appeared regularly. The rash began to fade in 18 hours, and his blood pressure and blood gases normalized after 60 min. The generalized rash faded away entirely at the end of the first day. The patient remains well at 1 month of age without any complaints of allergy.

Discussion

Survey data suggest that levetiracetam is commonly recommended by pediatric neurologists managing neonatal seizures, despite a paucity of data regarding safety, tolerability, and efficacy.³ The pharmacokinetic profile of

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FIGURE 1. Erythematous rash and urticaria on the scalp and face (A) and lower extremities (B).

levetiracetam suggests it could be a useful medication in critically ill neonates with seizures, but neonatal data are needed.³ We reported anaphylactic shock associated with intravenous administration of levetiracetam in a newborn. Adverse drug reactions to levetiracetam are reported in the literature. Serious dermatologic reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome are listed as potential side effects of the medication,^{4,5} but they are unlikely in this case secondary to the timing of the reaction.

Newborns are less likely to develop anaphylaxis via either immunoglobulin E (IgE)-mediated immunity or nonimmune mechanisms because their immune system is weaker than older infants and children. However, proven reports of patients and animal studies with anaphylaxis are available in limited number in the literature.⁶ Rare cases of newborns with anaphylaxis or anaphylactoid shock caused by hepatitis B immunoglobulin, cefotaxime, thiopentone, and atracurium also have been reported.^{7–9} Similar life-threatening anaphylactic reactions have been reported with the use of ceftriaxone.^{10–12} To date, the

possible mechanism of anaphylaxis formation in the newborn is still obscure. Anaphylaxis is usually triggered by an agent such as an insect sting, food, or medication, through a mechanism involving IgE and the high-affinity IgE receptor on mast cells or basophils. Less commonly, it is triggered via other immunologic mechanisms or nonimmunologic mechanisms.¹³ The causes of adverse reactions to levetiracetam are not yet thoroughly understood. Activating indirectly the complement system by levetiracetam should have given rise to the anaphylaxis in our patient.

Anaphylaxis is an acute, severe type I hypersensitivity reaction developing over the course of minutes to hours with multisystem involvement due to the systemic effects of histamine release. The newborn presented with sudden poor sensorium, flaccidity, apnea, and cyanosis, which is in sharp contrast to the classical symptoms of anaphylaxis. The most common organs affected in anaphylaxis include skin, respiratory, gastrointestinal, heart and vasculature, and central nervous system.¹⁴ Administration of adrenaline is the treatment of choice with antihistamines and steroids often used as adjuncts.¹⁴ The case described in this report could be secondary to an immune-mediated or a nonimmune-mediated drug reaction. The fact that the symptoms occurred so quickly after the medication was infused would make it more likely to be an anaphylactic (IgE-mediated degranulation of mast cells or basophils) or an anaphylactoid reaction (the medication directly causes the degranulation of mast cells). The symptoms, including rash and hypotension, which occurred after the medication infusions can be consistent with an allergic drug reaction. The timeline for the rash and its improvement could be consistent with an allergic reaction.

We could not find any report of neonatal anaphylactic shock caused by the intravenous administration of levetiracetam in the English language literature. It is important to recognize the possibility of this type of reaction in a newborn receiving levetiracetam.

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