Phenytoin Induced Anaphylaxis: a Case Report

Fenitoin İlişkili Anaflaksi: Olgu Sunumu

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Abstract:

Introduction: Phenytoin is an aromatic ring antiepileptic drug (AED) commonly used in epilepsy. As well as the side effects such as phenytoin-induced Steven-Johnson syndrome, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and cerebellar toxicity, a rarely life-threatening anaphylaxis requiring urgent treatment can be seen.

Case:

A 4.5-year-old girl who was followed up in our pediatric neurology outpatient clinic with the diagnosis of right hemiparetic cerebral palsy, epilepsy and autism spectrum disorder presented with a frequent and prolonged generalized tonic-clonic seizure complaint for the last 10 days. In the background; she was born mature weighing 4220 grams with cesarean section and she was followed-up in the neonatal intensive care unit for 38 days with respiratory distress due to formula aspiration and hypoglycemiaon the first day of her life. Her developmental steps were lower for her age. There was no abnormality in the family history. In physical examination; her muscle strength was 3-4/5 in the right upper and right lower extremities, 5/5 in the left upper and lower extremities. Deep tendon reflexes and muscle tonewere increased in the right extremities, there was cortical fisting on the right hand, babinski was positive on the rightand she could sit without support but could not walk. She had been receiving multiple AEDs for epilepsy for the last 1.5 years. Phenytoin loading (20 mg/kg/dose) was given as her seizures increased despite the current AEDs treatment. In the 45th minute of phenytoin loading treatment, the patient complained of sudden flushing on her face, respiratory distress and vomiting. Redness of cheeks, tongue swelling and stridor were found in her examination. Phenytoin induced anaphylactic reaction was considered in the case. Phenytoin infusion was discontinued and airway, respiration and circulation stabilization was achieved. The blood pressure was 110/60 mm/Hg, SpO2 was 93% and pulse rate was 155/min. Intramuscular adrenaline was administered and the complaints regressed during follow-up. After 24 hours monitoring for biphasic reaction, the patient was discharged without any complication.

Conclusion:

Phenytoin is a commonly used AED in the treatment of epilepsy and cardiovascular collapse, hypotension and arrhythmia may develop during the intravenous rapid administration. Anaphylaxis, which is one of the rare side effects of phenytoin, requires urgent treatment and death can also occur if the necessary intervention is not performed on time. We present our case to increase awareness of phenytoin-induced anaphylaxis.

Keywords: *Phenytoin, anaphylaxis, epilepsy*

Giriş:
Fenitoin epilepside yaygın kullanılan aromatik halkalı bir antiepileptik ilaçtır (AEİ). Fenitoine bağlı Steven-Johnson sendromu, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) ve serebellar toksisite gibi yan etkiler görülebileceği gibi nadiren yaşamı tehdit edebilen ve acil tedavi gerektiren anaflaksi de görülebilmektedir.
Olgu: Sağ hemiparetik serebral palsi, epilepsi ve otizm tanılarıyla çocuk nöroloji polikliniğimizde takip edilen 4,5 yaşında kız olgu, son 10 gündür sık ve uzamış jeneralize tonik-klonik tarzda nöbet şikayeti ile başvurdu. Özgeçmişinde; miadında, 4220 gram ve sezeryan ile doğmuş, yaşamının birinci gününde mama aspirasyonuna bağlı solunum sıkıntısı ve hipoglisemi ile 38 gün yenidoğan yoğun bakımda takip edilmişti. Gelişim basamakları yaşına göre geriydi. Soygeçmişinde özellik yoktu. Fizik muayenesinde; kas gücü sağ üst ve sağ alt ekstremitede 3-4/5, sol üst ve alt ekstremitede 5/5, sağ ekstremitelerde derin tendon refleksleri ve kas tonusu artmış, sağda kortikal fisting mevcuttu, sağda babinski pozitifti, desteksiz oturabiliyor ancak yürüyemiyordu. Epilepsi için son 1,5 yıldır çoklu AEİ tedavisi almaktaydı. Mevcut AEİ tedavisine rağmen nöbetleri sıklaştığı için fenitoin yüklemesi (20 mg/kg/doz) yapıldı. Fenitoin yükleme tedavisinin 45. dakikasında aniden yüzde kızarma, solunum sıkıntısı ve kusma şikayeti olan olgunun muayenesinde yanaklarda kızarıklık, dilde şişlik ve stridoru vardı. Olguda fenitoine bağlı anaflaktik reaksiyon düşünüldü. Fenitoin infüzyonu kesildi, havayolu, solunum, dolaşım stabilizasyonu sağlandı. Tansiyon arteriyal: 110/60 mm/Hg, SpO2: %93, nabız: 155/dk idi. İntramuskuler adrenalin yapıldı ve takipte şikâyetleri geriledi. Bifazik reaksiyon açısından 24 saat takip sonrası komplikasyon gelişmeyen hasta taburcu edildi.
Sonuç: Fenitoin, epilepsi tedavisinde sık kullanılan bir AEİ'tır ve intravenöz hızlı uygulanmasında kardiyovasküler kollaps, hipotansiyon ve aritmi gelişebilir. Fenitoinin nadir yan etkileri içinde yer alan anaflaksi acil tedavi gerektirir ve zamanında gerekli müdahele edilmezse ölüm de görülebilir. Fenitoine bağlı anaflaksi hakkındaki farkındalığı arttırmak için olgumuzu sunuyoruz.
Anahtar Kelimeler: Fenitoin, anafilaksi, epilepsi

Introduction
Epilepsy is a common, chronic neurological disease characterized by recurrent seizures (1). Phenytoin is an aromatic ring antiepileptic drug (AED), commonly used in epilepsy. It is used for focal and generalized seizures, status epilepticus, myoclonic and tonic-clonic seizures (2). As well as the side effects such as phenytoin-induced Steven-Johnson syndrome, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), and cerebellar toxicity, a rarely life-threatening anaphylaxis requiring immediate treatment can be seen.

Case Report
A 4.5-year-old girl who was followed in our pediatric neurology outpatient clinic with the diagnosis of right hemiparetic cerebral palsy, epilepsy and autism spectrum disorder presented with a frequent and prolonged generalized tonic-clonic seizure complaint for the last 10 days. In the background; she was born mature weighing 4220 grams with cesarean section and she was followed-up in the intensive care unit for 38 days with respiratory distress due to formula aspiration and hypoglycemia on the first day of her life. Her developmental steps were lower for her age. There was no abnormality in the family history. In physical examination; body weight was 18 kg (50-75p), height was110 cm (97p) and head circumference was 47 cm (<3p). Her muscle strength was 3-4/5 in the right upper and right lower extremities, 5/5 in the left upper and lower extremities. Deep tendon reflexes and muscle tone were increased in the right extremities, there was cortical fisting on the right hand, babinski was positiveon the right and she could sit without support but could not walk. She had been receiving multiple AEDs for epilepsy for the last 1.5 years. Phenytoin loading (20 mg/kg/dose) was given as her

seizuresincreased despite the current AEDs treatment. In the 45th minute of phenytoin loading treatment, the patient complained of sudden flushing on her face, respiratory distress and vomiting. Redness of cheeks, tongue swelling and stridor were found in her examination. Phenytoin induced anaphylactic reaction was considered in the case. Phenytoin infusion was discontinued and airway, respiration and circulation stabilization was achieved. The blood pressure was 110/60 mm/Hg, SpO2 was 93% and pulse rate was 155/min. Intramuscular adrenaline was administered. High flow oxygen support was provided with the mask. After 2 minutes of adrenaline, redness of the cheeks, swelling of the tongue and stridor were relieved. Vomiting continued for 2-3 times. An antihistaminic treatment and methylprednisolone were started. After 24 hours monitoring for biphasic reaction, the patient was discharged without any complication.

Discussion

Anaphylaxis is a sudden onset, life-threatening systemic hypersensitivity reaction. The most common causes of anaphylaxis are food, drug and venom allergies (3). In a retrospective anaphylaxis study, Grabenhenrich et al. reported a 5% drug anaphylaxis in 1970 patients younger than 18 years of age (4).As well as mild drowsiness, gastointestinal and skin symptoms associated with AEDs, even life-threatening side effects may be seen. For example, the mortality rate of Stevens-Johnson syndrome, which is a serious side effect associated with AEDs, is 5-10%. Phenytoin, commonly used in the treatment of epilepsy, is also a common cause of hypersensitivity syndrome (1). Phenytoin-induced anaphylaxis and anaphylactoid reaction is rare (5). It has been reported that rapid infusion of phenytoin (>50 mg/min) may cause anaphylaxis, but anaphylaxis may develop even at normal infusion rates (5,6). Although phenytoin infusion was administered at the appropriate dose (20 mg/kg/dose) and rate (6 mg/min), anaphylaxis developed in our patient.

The diagnosis of anaphylaxis is made by skin and mucosal involvement and the sudden onset of these symptoms (e.g. generalized urticaria, itching or redness, edema of lips-tongue-uvula); and respiratory failure (e.g. dyspnea, wheezing/bronchospasm, stridor, low peak expiratory flow, hypoxemia) or low blood pressure or one of the symptoms associated with it (7). In our case, in the 45th minute of phenytoin loading treatment, a sudden flushing on the face, respiratory distress and vomiting occurred. Redness of cheeks, tongue swelling and stridor were found in her examination. We considered phenytoin induced anaphylactic reaction, as the occurrence ofsudden skin, respiratory and gastrointestinal involvements.

Early recognition ofanaphylaxis is life-saving (5). The first line treatment for anaphylaxis is accepted to be the administration of intramuscular adrenaline. Intramuscular administration of adrenaline at a dose of 0.01 mg/kg in the middle of the vastus lateralis muscle is the optimal treatment. In addition, late or incorrect administration of adrenaline may increase the risk of death due to anaphylaxis (8). Immediately after the diagnosis of anaphylaxis, our case was administered 0.01 mg/kg/dose of adrenaline intramuscularly in the middle of the vastus lateralis muscle. In addition to adrenaline treatment, volume expanders, nebulized bronchodilators, antihistamines or corticosteroids may be given (9). Our patient followed-up for biphasic reactions, was given high flow oxygen with mask, intravenous fluid support, antihistaminic and corticosteroid treatment. After a 24-hour follow-up, the patient was discharged without complications.

Conclusion

Phenytoin is a commonly used AED in the treatment of epilepsy andcardiovascular collapse, hypotension and arrhythmia may develop in the intravenous rapid administration (5). Anaphylaxis, which is one of the rare side effects of phenytoin, requires urgent treatment and

death can also occur if the necessary intervention is not performed on time. We present our case to increase awareness of phenytoin-induced anaphylaxis.

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