รายงานผู้ป่วย
Case Report

ภาวะชักกระตุกต่อเนื่องจากพิษยาชาเฉพาะที่และฟีนิโตอินกับอาการยึกยือ: รายงานผู้ป่วย 1 ราย

*ศิริพร ปิ่นเจริญ พ.บ.**

บทคัดย่อ

ยาฟีนิโตอินเป็นยากันชักที่มีประสิทธิภาพในการรักษาอาการชักและใช้บ่อยในทางเวชปฏิบัติ อาการเคลื่อนไหวผิดปกติที่เกิดตามหลังการใช้ยาฟีนิโตอิน เช่น อาการสั่น (tremor), การสั่นกระพือของมือ (asterixis), กล้ามเนื้อกระตุกเร็ว (myoclonus), การเคลื่อนไหวกล้ามเนื้อที่ไม่สามารถควบคุมอาการได้ หรือกลุ่มอาการยึกยือ (tardive dyskinesia) เป็นกลุ่มอาการผิดปกติบริเวณกล้ามเนื้อใบหน้า ลิ้น ริมฝีปาก ขากรรไกร (orofacial dyskinesia) และแขนขา (limbs dyskinesia) ลำตัวเป็นผลตามหลังจากการใช้ยากันชักฟีนิโตอินที่พบไม่บ่อย รายงานผู้ป่วยเด็กเพศชายอายุ 6 ปี ถูกส่งตัวมาจากโรงพยาบาลเอกชน ด้วยประวัติอุบัติเหตุลื่นล้มถูกหินบาดเป็นแผลฉีกขาดบริเวณที่แขนสองข้าง ไม่มีอาการบาดเจ็บที่ศีรษะผู้ป่วยรู้สึกตัวดีได้ไปตรวจที่ห้องฉุกเฉินและได้รับการเย็บแผลขณะถูกเย็บแผลผู้ป่วยมีอาการชักกระตุกต่อเนื่อง (status epilepticus) ผู้ป่วยได้รับยากันชัก diazepam 5 มิลลิกรัมฉีดทางเส้นเลือดดำ 2 ครั้ง (0.3 มิลลิกรัมต่อกิโลกรัม) และ Phenytoin ขนาด 400 มิลลิกรัม (21.6 มิลลิกรัมต่อกิโลกรัม) ทางเส้นเลือดดำจนหยุดชัก หลังชักไม่รู้สึกตัว จึงได้รับการใส่ท่อช่วยหายใจ และส่งตัวมาโรงพยาบาลชลบุรี โดยได้รับยา Phenytoin รักษาต่อในขนาด 5 มิลลิกรัมต่อกิโลกรัมต่อวัน วันที่สองของการนอนโรงพยาบาลผู้ป่วยมีอาการเคลื่อนไหวกล้ามเนื้อลักษณะเข้าได้กับกลุ่มอาการยึกยือ Tardive dyskinesia โดยผู้ป่วยมีอาการเกร็งบิดบริเวณใบหน้า แลบลิ้น แสยะปาก ยักคิ้ว แขนขาขยุกขยิก ขณะที่เป็นผู้ป่วยรู้ตัวดี ทำตามสั่งได้แต่ไม่สามารถควบคุมอาการที่เกิดขึ้นเองได้ ตรวจร่างกายทั่วไปและระบบประสาทปกติ ผลตรวจเลือดและตรวจน้ำไขสันหลังปกติหลังจากทบทวนประวัติการรักษาและยาที่ผู้ป่วยได้รับ พบว่าขณะทำการเย็บแผลผู้ป่วยได้ถูกฉีดยาชา 2% Lidocaine ทั้งหมด 10 ซีซี เทียบเท่าปริมาณ 200 มิลลิกรัม เมื่อเทียบกับน้ำหนักตัวผู้ป่วย 18.5 กิโลกรัม เท่ากับ 10.8 มิลลิกรัมต่อกิโลกรัม ซึ่งเกินขนาดของยาชา Lidocaine ที่เป็นพิษมีขนาดเท่ากับ 4.5 มิลลิกรัมต่อกิโลกรัม ซึ่งเป็นสาเหตุที่ทำให้ชักได้ หลังหยุดยาฟีนิโตอินพบว่าอาการเคลื่อนไหว Tardive dyskinesia หายไป ผู้ป่วยกลับมาเป็นปกติในวันที่ 3 ของการนอนโรงพยาบาล

คำสำคัญ : พิษยาชาเฉพาะที่, ชักกระตุกต่อเนื่อง, ฟีนิโตอิน-ยากันชัก, อาการเคลื่อนไหวผิดปกติ-อาการยึกยือ

Status Epilepticus following Local Anesthetic Toxicity and Phenytoin induced Dyskinesia: A Case Report

Siriporn Pinjaroen M.D.*

Abstract

Phenytoin is effective antiseizure medication which frequently prescribed in clinical practice. Involuntary movements are a less familiar complication of treatment with phenytoin and include tremor, asterixis, myoclonus and tardive dyskinesia. A case report of 6-year-old boy was refered from private hospital with history of accidental falling and he had lacerated wound at both forearm from stone cuts and during stitched suture at emergency room he had developed symptoms of convulsive status epilepticus. He received diazepam 5 mg intravenous 2 doses (0.3 mg/kg) and loading dose of phenytoin 400 mg (21.6 mg/kg) intravenous and stop seizure. He was unconscious and need intubated. He was refered to Chonburi hospital and was given maintenance dose 5 mg/kg/day intravenous of phenytoin. The second day of admission he was noted to have abnormal movement as tardive dyskinesia

* กลุ่มงานกุมารเวชกรรม โรงพยาบาลชลบุรี

* Department of Pediatrics, Chonburi Hospital

Received : Mar 30, 2024 Revised : Dec 7, 2024 Accepted : Dec 25, 2024

consisting of facial grimacing, tongue protrusion, eyebrow elevation and limbs dyskinesia. General and neurological examination were normal. Blood test and cerebrospinal fluid exam were normal. We reviewed history of patient's treatment and all drugs usage and found that he was injected 2% lidocaine amount of 10 cc or 200 mg (10.8 mg/kg) for local anesthesia during stitched wounds, his body weight 18.5 kg which over than toxic dose of Lidocain is 4.5 mg/kg. Conclusion that lidocaine toxicity caused convulsive statue epilepticus and phenytoin was immediately discontinued.The tardive dyskinesia resolved after withdrawal of phenytoin. The patient returned to normal in the third day of admission.

Keywords : Local anesthetic toxicity, status epilepticus, Phenytoin-Anticonvulsants, Tardive dyskinesia

Introduction

Phenytoin is frequently used for primary and secondary generalized tonic-clonic seizures, partial seizures, and status epilepticus in most clinical practice. The reported neurological toxicity includes both acute and chronic effect. Phenytoin is a narrow therapeutic index drug with and therapeutic range from 10 to 20 μg/ml. Elimination of phenytoin follows mixed-order kinetics; it follows first- order kinetics until ≤ 10 μg/ml, and above 10 μg/ml, it follows zero-order kinetics. Adverse event when phenytoin level > 20 μg/ml has nystagmus and phenytoin level > 30 μg/ml has ataxia, phenytoin level > 40 μg/ml has drowsiness. Thus, the elimination profile of phenytoin predisposes the patient to develop adverse drug reactions, and increased half-life due to zero-order pharmacokinetics results in prolonged duration of toxic symptoms[1-2]. The spectrum of abnormal movements related to Phenytoin included chorea[3] choreoathetosis[4], ballism[5], athetosis[6] and orofacial dyskinesia[7] However, phenytoin-induced dyskinesia has rarely been reported in both adults and children in the literature[8-12]. In 1963, Hoaken and Kane probably described the first case of phenytoin -induced dyskinesia in the American Journal of Psychiatry[13]. Some authors believe that the first study was done by Peters et al., but he only published his first work in 1966 in the Diseases of the Nervous System Journal[14]. Hoaken and Kane reported a young adult female showing writhing motor movements of the extremities associated with stiffening after a single dose of phenytoin[15]. Phenytoin may cause different movement disorders, including orofacial and limb dyskinesias, trembling, asterixis, hemiballismus, dystonia, and myoclonias[15]. Of these disorders, orofacial dyskinesia is the most commonly described. Lidocaine is a local anesthetic drug that blocks pain signals, it can have toxic effects throughout the body if too much is used. In some cases, lidocaine overdose can be a life-threatening medical emergency. Local lidocaine toxicity is determine by the total dose 4.5 mg/kg. The CNS is the site of premonitory signs of overdose in awake patients. Early symptoms are circumoral numbness, tongue paresthesia and dizziness. Sensory complaints may include tinnitus and blurred vision. Excitatory signs, such as restlessness, agitation, nervousness, or paranoid may progress to muscle twitches and seizure. The diagnosis is made clinically. The timing, dose, and site of the lidocaine injection are the main factors in considering systemic manifestations[16]. We present the case of a child who developed convulsive status epilepticus after injection with overdose of 2% lidocaine and then presented with orofacial dyskinesia secondary to treatment with phenytoin.

Presentation of case

A 6-year-old Thai boy was refered to Chonburi hospital with history of convulsive status epilepticus. Patient's Medical record from referral hospital noted that the patient had visited to emergency room due to slip and falling and had lacerated wound from stone cuts both forearms. No history of head injury and he was alert. He need to suture many stitches and 2% lidocaine 10 cc was injected for local anesthesia, at Left forearm 27 stitches, at right forearm 6 stitches as he was stitching the wound right arm, he developed generalized tonic-clonic seizures and given 2 doses of Valium 5 mg IV (0.3 mg/kg) and followed by phenytoin

400 mg (21.6 mg/kg) to stop seizures. He was unconscious and was intubated After his intubated, computed tomography of the brain was done and resulting in normal study. No history of previous medication and no history of drug use or drug allergy.

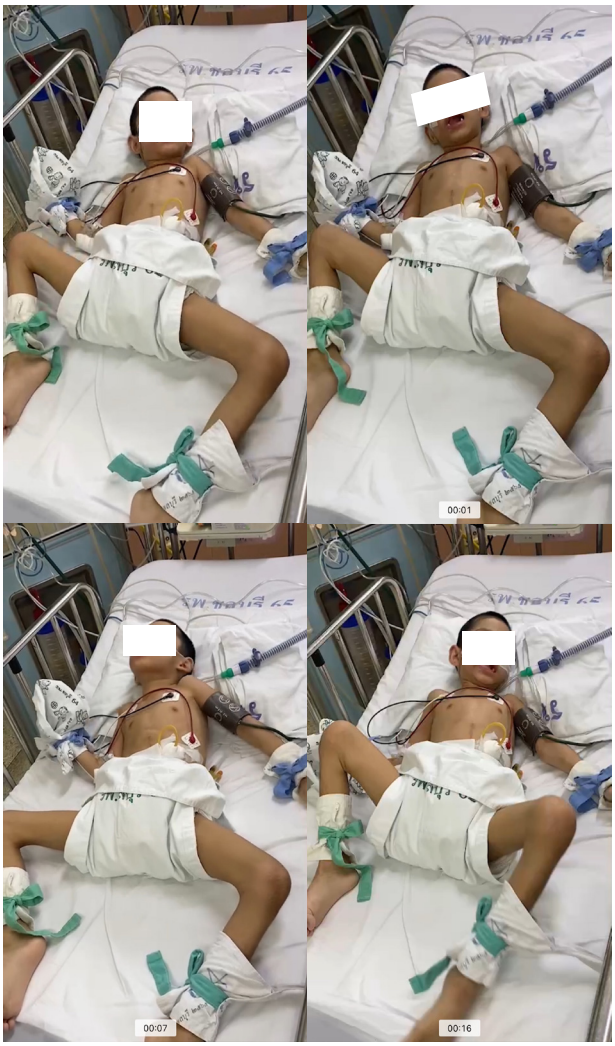
At Pediatric intensive care unit, Chonburi hospital

Physical examination: the temperature was 37°C, respiratory rate of 20/minute, pulse rate of 98/minute, and blood pressure of 137/88 mm Hg. His weight of 18.5 kg and height of 120 cm, Oxygen Saturation of 99%.

General examination: A Thai boy was on Endotracheal tube NO 5.5 dept 17 cm, Drowsiness, Glasglow coma score E2M3VT, multiple sutured wounds both forearms. HEENT : not pale conjunctivaes, no icteric sclera. Heart and lung normal. Abdomen : no hepato-splenomegaly. Extremities : no edema, no rash. Neurological examination : Mental status:Drowsiness, pupil 3mm RTL BE, CN III, IV, VI : normal Extraocular movement. CN VII : no facial palsy, Motor : he moves all extremities against gravity. Sensory cannot evaluate, reflex2+ all, stiff neck negative, BBK plantar flexor response, clonus-negative.

Investigation: blood glucose 140 mg/dL, Complete blood count : Hb 12.6 g/dL, Hct 38%, WBC 21,730 (PMN 58%, Lymp 34%, Mono 3%, Eo 3%, band 2%) Plt 430,000 cell/uL, urine exam –clear, SpGr 1020, pH 6.5, WBC 0-1/HPF, RBC 0-1 /HPF, serum electrolytes -Na 147 mmol/L, K 4.9 mmol/L, Cl 109 mmol/L, Co2 19 mmol/L, calcium 9.16 mg/dL, magnesium 2.0 mg/dL, liver function tests-Total Protein 7.4 g/dL, Albumin 4.34 g/dL, Globulin 3.06 g/dL, SGOT(AST) 40 U/L, SGPT (ALT) 25 U/L Alk Phosphatase 196 U/L, Total bilirubin 0.3 mg/dL, Direct bilirubin 0.04 mg/dL, lactate, C-reactive protein level were normal. Cerebrospinal examination : no cell, Protein 30 mg/dl, glucose 80 mg/dl, CSF C/S : no growth ESR 62 mm(0-20 mm/hr) and creatinine phosphokinase 1,459 (15-220 U/L). Specific lab investigation work up for autoimmmune encephalitis/encephalopathy (anti-NMDAR) : negatine, ASO titer : negative

The patient was extubation after he regained consciousness 2 hours after admission. On the second day of admission he was noted to have involuntary movement as tardive dyskinesia by clinical of facial grimacing, tongue protrusion, eyebrows elevation and also have both axial and limb dyskinesia with frequent side-to-side head movement and truncal rocking, and cause of abnormal findings were carefully reevaluated, he had no history of other drug ingestion especially. antipsychotic drug and no history of abnormal movement disorder in family. Assumed dyskinesia was attributable to phenytoin. Phenytoin was immediately discontinued and his abnormal movements markedly decreased, and disappear completely in a day. Serum phenytoin level was 10 micrograms /mL (normal 10–20 micrograms /mL) at one day after off phenytoin. He was treated with ceftriazone for wound infection. The third day of admission he was transferred to general ward and then discharge with fully recovery after a week of admission.



Discussion

Dyskinesia induced by phenytoin represent an uncommon but recognized complication of phenytoin therapy. There were cases report both children and adult. The symptoms were not related to blood level and resolved completely after withdrawal of phenytoin[17]. The demographic distribution of patients suffering dyskinesia owing to phenytoin found that 50% was less than 20 years old[18] and found that children have a 5-6 times greater risk of phenytoin-induced dyskinesia than adults[19]. The time that has been reportedly while taking phenytoin and developed dyskinesia varies in day and over 20 years[20]. The pathophysiology of phenytoin-induced dyskinesia is not well understood. Possible because of phenytoin's differential influence on dopaminergic activity[18]. The most commonly recognized theory is that underlying brain lesions or gliosis enhance dopaminergic and serotonergic activity in the striatum[21]. Movement disorders such as asterixis, tremor, dyskinesia, dystonia, and chorea have been described after administration of many antiepilepsy agents, such as phenytoin, barbiturates, carbamazepine, valproate, and primidone[23-24]. Phenytoin-induced dyskinesia can occur during either chronic or initial treatment and with normal serum phenytoin levels. However, it occurs most often in patients on polytherapy, usually after increasing dosage and with toxic serum levels. Other signs of phenytoin intoxication can be present in these patients, but often dyskinesia is the only side effect, which could delay diagnosis and treatment. The clinical characteristics of the involuntary movements vary and can be focal or generalized, most often characterized by choreoathetosis and dyskinesias. These can last for hours, days, or even years but frequently disappear completely after phenytoin withdrawal[19]. In our patient, the serum phenytoin level was within the normal range, and he was using only phenytoin. He had, prominent lingual-facial-buccal dyskinesia and dyskinesia of limp. Yoshida and colleagues reported an adult case of a small glioblastoma multiforme with orofacial dyskinesia and a slight writhing movement of his hands, developed during treatment with phenytoin and phenobarbital. The serum concentration of phenytoin was within the therapeutic range. The involuntary movements subsided following withdrawal of the drug[17]. Micheli and colleagues reported a 13-year-old girl who developed left partial motor status epilepticus with severe postictal hemiparesis. MRI showed a right frontoparietal hyperintense T2-weighted signal. Seizures subsided after treatment with phenytoin, carbamazepine, and phenobarbital but left choreic-like flinging movements, consistent with hemiballism, developed 2 days later. After phenytoin withdrawal, symptoms gradually remitted, with mild residual dystonia at 14 months follow-up. In this case, it is speculated that the lesion might have rendered the cortex more susceptible to phenytoin, inducing unilateral toxicity[20]. In our patient, CT of the brain was normal, and his abnormal movements markedly decreased and almost completely disappeared in one day after off phenytoin. Some hypothesis is that phenytoin induces dyskinesias by increasing dopaminergic and serotonergic activity in the striatum[18], and that patients with underlying brain lesions[21] or subclinical functional changes may be especially likely to suffer this adverse effect. Phenytoin may also have multiple mechanisms that cause different abnormal movements, but available data does not allow us to distinguish between different mechanisms.

In this patient the interesting issue that caused of status epilepticus assumed from Lidocaine toxicity. We had consulted Ramathibodi Poison Center in this case and reviewed history and clinical course of all drug dosage which given to our patient. He received 2% Lidocaine injection for suture amout of 10 cc, of concentration 20 mg/cc x 10 cc equal to 200 mg, (patient'weight 18.5 kg) calculate in mg/kg (200/18.5) equal to 10.8 mg/kg which dose was over than toxic dose of Lidocaine which is 4.5 mg/kg. We did not collect of plasma level of lidocaine at time of the presentation of convulsive status epilepticus. The reason was described by Lidocaine has elimination half life 1.5-2 hours, after 3-5 times of half life that about 10 hours, the drug was already elimination all. In our patient the time was late to confirm plasma level for lidocaine toxicity. It has been reported that seizures happen when the dose of

lidocaine administered exceeds 3 mg/kg[22] However, some cases of seizure following administration of recommended doses of lidocaine have also been reported[23]. Most of these seizures are self-resolving or resolve with conventional anticonvulsants. They may be dangerous because of the acidosis and hypoxia due to a prolonged duration and resulted in hypoxic-ischemic encephalopathy.

Conclusion

In conclusion, phenytoin-induced dyskinesia is a very unusual adverse effect that usually occurs at normal plasma levels of phenytoin and is not correlated with treatment duration. This type of dyskinesia may occur with no underlying striatal lesion and resolve when phenytoin is discontinued; its pathophysiological mechanism is unknown. We would like to emphasize that severe dyskinesia can be observed during phenytoin therapy in children and immediately stop phenytoin can be successfully completely resolved of dyskinesia. Lessons for this case in local lidocaine administration is essential to keep records of the total dose given to avoid its systemic toxicity.

Disclosure

The patient provided consent allowing us to publish this case report.

Conflicts of interest

All of the author have no conflicts to declare.

Funding

None.

References

1. Patocka J, Wu Q, Nepovimova E, Kuca KJF, Toxicology C. Phenytoin and antiseizure drug: overview of its chemistry, pharmacology and toxicology. FoodChem Toxicol. 2020;142:111-393.
2. Rissardo JP, Caprara ALF. Phenytoin-associated movement disorder: a literature review. Tzu Chi Medical Journal. 2022;34(4):409-17.
3. Rosenblum E, Rodichom L, Hanson PA. Movement disorder as a manifestation of diphenylhydantoin toxicity. Pediatrics. 1974;24:68-71.
4. Jan JE, Kliman MR. Extrapyramidal disturbance and vascular changes during diphenylhydantoin intoxication. Can Med Assoc J. 1974;111:636-41.
5. Opida CL, Kothals JK, Somasundaram M. Bilateral ballismus in phenytoin intoxication. Ann Neurol. 1978;3:186.
6. Buchanan N, Rosen E, Rabinowitz L. Athetosis and phenytoin toxicity. Am J Dis Child. 1977;131:105.
7. DeVeaugh-Geiss J. Aggravation of tardive dyskinesia by phenytoin. N Engl J Med. 1978;298:457-8.
8. Corey A, Koller W. Phenytoin-induced dystonia. Ann Neurol. 1983;14:92–3.
9. Choonara IA, Rosenbloom L. Focal dystonic reaction to phenytoin. Dev Med Child Neurol. 1984;26:677–8.
10. Chaudhary N, Ravat SH, Shah PU. Phenytoin induced dyskinesia. Indian Pediatr. 1998;35:274–6.
11. Reynolds EH, Trimble MR. Adverse neuropsychiatric effects of anti- convulsant drugs. Drugs. 1985;29:570–81.
12. Yamamoto K, Noda S, Itou H, Umezaki H, Morimatsu M. A case of involuntary movements probably produced by low doses of phenytoin intoxication. Rinsho Shinkeigaku. 1990;30:571–3.
13. Hoaken PC, Kane FJ. Unusual brain syndrome seen with diphenylhydantoin and pentobarbital. Am J Psychiatry. 1963;120:282-3.
14. Peters HA, Eichman PL, Price JM, Kozelka FL, Reese HH. Abnormal copper and tryptophan metabolism and chelation therapy in anticonvulsant drug intolerance. Dis Nerv Syst. 1966;27:97-107.
15. Shulman L, Singer C, Weiner W. Phenytoin-induced focal chorea. Mov Disord. 1996;11:111-4.
16. Sekimoto K, Tobe M, Saito S. Local anesthetic toxicity: acute and chronic management. Acute Med Surg. 2017 Apr;4(2):152-60.
17. Yoshida M, Yamada S, Ozaki Y, Nakanishi T. Phenytoin-induced orofacial dyskinesia: a case report. J Neurol. 1985;231:340–2.
18. Harrison M, Lyons G, Landow E. Phenytoin and dyskinesias: a report of two cases and review of the literature. Mov Disord. 1993;8(1):19–27.
19. Montenegro MA, Scotoni AE, Cendes F. Dyskinesia induced by phenytoin. Arq Neuropsiquiatr. 1999;57:356-60.

20. Micheli F, Lehkuniec E, Gatto M, Pelli M, Asconape J. Hemiballimus in a patient with partial motor status epilepticus treated with phenytoin. Funct Neurol. 1993;8:103-7.
21. Garcia-Ramos R, Ramos TM, Galende AV, Etessam JPJN. Phenytoin-induced acute orofacial dyskinesia. Neurologia. 2013;28(3):193-4.
22. Donald MJ, Derbyshire S. Lignocaine toxicity; a complication of local anaesthesia administered in the community. Emerg Med J. 2004;21:249-50.
23. Moran LR, Hossain T, Insoft RM. Neonatal seizures following lidocaine administration for elective circumcision. J Perinatol. 2004;24:395-6.