Cardiac arrest after intravenous infusion of fosphenytoin

Kanae Inoue, Tetsuya Yumoto, Hiromichi Naito, Atsunori Nakao

ABSTRACT

Introduction: Fosphenytoin, a water-soluble phenytoin prodrug, is given intravenously to administer phenytoin possibly more safely than intravenous administration of phenytoin.

Case Report: A 71-year-old female was admitted to our hospital's emergency department with head trauma. She had a history of seizures that were incompletely controlled with carbamazepine. She suffered a tonic-clonic epileptic seizure in the intensive care unit and fosphenytoin was intravenously administered. After approximately three minutes of the intravenous drip-infusion, she developed sudden bradycardia followed by cardiac arrest. The patient required cardiopulmonary resuscitation and intratracheal intubation for five minutes before becoming hemodynamically stable. Mechanisms of electrocardiogram alteration by fosphenytoin were discussed.

Conclusion: Clinicians should be more aware of the association of fosphenytoin with adverse cardiac events. Baseline electrogram should be obtained for all patients receiving fosphenytoin to identify underlying cardiac problems.

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CASE REPORT

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Introduction: Fosphenytoin, a water-soluble phenytoin prodrug, is given intravenously to administer phenytoin possibly more safely than intravenous administration of phenytoin. **Case Report:** A 71-year-old female was admitted to our hospital's emergency department with head trauma. She had a history of seizures that were incompletely controlled with carbamazepine. She suffered a tonic-clonic epileptic seizure in the intensive care unit and fosphenytoin was intravenously administered. After approximately three minutes of the intravenous drip-infusion, she developed sudden bradycardia

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Keywords: Adverse effect, Cardiac arrest, Fosphenytoin

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INTRODUCTION

Phenytoin, used to treat status epilepticus, is associated with cardiovascular toxicity including arrhythmia and hypotension. Recently, the phenytoin prodrug fosphenytoin was introduced. Fosphenytoin is generally considered more water-soluble and can be efficiently administered intravenously to deliver phenytoin [1]. Intravenously administered fosphenytoin offers several benefits over intravenously administered phenytoin, including a faster infusion rate, decreased pain and irritation at the infusion site, and fewer

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cardiovascular complications [2, 3]. However, the intravenous administration of fosphenytoin may also induce adverse cardiovascular events in some patients [4–6]. Here, we investigated the clinical characteristics of patients who experienced hypotension following an intravenous infusion of a fosphenytoin loading dose. This report may help physicians more aware of fosphenytoin critical adverse effects in the emergency unit or intensive care unit (ICU).

CASE REPORT

A 71-year-old female was admitted to our hospital's emergency department with head trauma. The patient's height and weight were 145 cm and 41.3 kg, respectively. She had no prior history of drug allergies or cardiopulmonary problems. Her initial vital signs were as follows: blood pressure 138/74 mmHg, heart rate 96/min, respiratory rate 18 breaths per minute, and body temperature 36.4°C. Laboratory data were unremarkable except for a serum potassium level of 3.5 mEq/L, calcium level of 7.6 mg/dL, albumin level of 2.6 g/dL, and creatinine level of 0.83 mg/dL. Chest X-ray was unremarkable without cardiomegaly or pneumonia. Computed tomography demonstrated multiple low density area in the brain indicating old cerebral infarction, but no evidence of acute intracranial hemorrhage. The patient was given intravenous fluid hydration with lactate Ringer solution (150 mL/h) and was subsequently admitted to the ICU for further management.

Since the patient had developed a cerebral infarction five years before, she had a history of seizures that were incompletely controlled with carbamazepine 800 mg/day. At day-2 in the ICU, she suddenly presented clonic convulsions and required intravenous fosphenytoin injection (1500 mg phenytoin equivalent unit at 150 PE/min via an infusion pump). Approximately, three minutes into the administration of the intravenous drip-infusion, she developed sudden bradycardia followed by cardiac arrest (Figure 1).

The patient required cardiopulmonary resuscitation for five minutes before becoming hemodynamically stable and undergoing intratracheal intubation.

Figure 1: Electrocardiogram approximately three minutes after the administration of the intravenous drip-infusion of fosphenytoin demonstrated sudden bradycardia followed by cardiac arrest.

Plasma phenytoin concentration measured after resuscitation was 24.2 µg/mL. After the patient was extubated the following day, her clinical course was uneventful with oral sodium valproate administration (800 mg/day).

DISCUSSION

As fosphenytoin has basically the same pharmacological properties as phenytoin, fosphenytoin adverse effects are like those of phenytoin and can be directly explained by an increase in phenytoin concentrations in the blood. These side effects include cardiac arrhythmias, hypotension, dizziness, ataxia, nystagmus, and local dermatological reactions. Purple glove syndrome, an unusual complication of intravenous phenytoin use, normally presents with edema, pain, and injection site discoloration spreading to the distal limb. The syndrome likely occurs with fosphenytoin, but possibly less frequently than with intravenous phenytoin [7, 8]. Fosphenytoin may cause hyperphosphatemia in patients with end-stage renal failure [5]. After intravenous injection, the half-life of conversion of fosphenytoin to phenytoin is 15 minutes. Once released, phenytoin has a long plasma half-life of approximately 12–28.9 hours [1, 2]. Theoretically, fosphenytoin can alter an electrocardiogram via phenytoin's direct effects on cardiac conduction and phosphate calcium binding, which could indirectly change cardiac conduction resulting from hypocalcemia. Our patient's serum calcium, sodium, potassium, and magnesium levels were normal.

Adams et al. [4] found 29 cardiac events related to fosphenytoin infusion, of which 10 resulted in cardiac deaths. Some reports show that manual intravenous push presents a greater possibility of inadvertent overdose during a short time frame, as well as more local symptoms. For indications besides status epilepticus, consideration of intramuscular administration or oral parenteral nutrition loading of fosphenytoin were recommended.

To avoid cardiac complication, an infusion rate below 150 PE/min is recommended. In addition, administration of fosphenytoin through intramuscular route or oral route may be recommended. Blood concentration above 20 µg/mL can be harmful and induce cardiac events [4, 6].

In our patient, an apparently appropriate dose of intravenous phenytoin was initiated via infusion pump, and she was monitored appropriately and given supplemental oxygen. This case shows a patient for whom these recommendations were followed, yet adverse cardiac events still occurred. Baseline electrogram should be obtained for all patients prescribed fosphenytoin to uncover underlying cardiac problems. Many institutions restrict the use of fosphenytoin to emergencies, since fosphenytoin costs more than intravenous phenytoin [9].

CONCLUSION

Clinicians should be aware of the association of fosphenytoin with adverse cardiac events. For patients with known cardiac disease or abnormal preinfusion electrocardiography, emergency physicians should reduce the drug concentration and rate of administration.

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Author Contributions

Kanae Inoue – Substantial contributions to conception and design, Acquisition of data, and interpretation of data, Drafting the article, Revising it critically for important intellectual content,, Final approval of the version to be published

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Hiromichi Naito – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content,, Final approval of the version to be published

Atsunori Nakao – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

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