Comparison of Intravenous and Intraosseous Routes for The Administration of Phenobarbital

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Fenobarbital Uygulamasında Intravenöz ve Intraosseöz Yolların Karşılaştırılması

Özet

Status epileptikus klasik olarak 30 dakikadan uzun süren jenaralize tonik-klonik nöbet olarak tarif edilir. Uzun süren nöbet aktivitesi irreversibl serebral hasar ile sonuçlanabilir. Üstelik, nöbet aktivitesinin uzun sürmesinin kontrol edilebilirliğini azalttığı yönünde kanıtlar vardır. Damar yolunun sağlanması nöbet esnasında sıklıkla zordur. Öte yandan intraosseöz yol (IO) kullanıma hazırdır. Bu çalışmada, 20 mg/kg dozunda fenobarbital IV ve IO yoldan tavşanlara uygulandı. Fenobarbital kan düzeyleri ölçüldü ve sonuçlar karşılaştırıldı. Fenobarbital plazma profilinin IO uygulamada terapötik seviyede olduğu görüldü. IO yolun fenobarbital verilmesinde IV yola alternatif olabileceği sonucuna varıldı.

Anahtar Kelimeler: *Fenobarbital, kemik iliği infüzyonu, intraosseöz infüzyon, intravasküler giriş, status epileptikus*

Abstract

Status epilepticus (SE) is classically defined as a generalized tonic-clonic seizure lasting longer than 30 min. Prolonged seizure activity can result in irreversible cerebral injury. In addition, evidence suggests that the longer the duration of the seizure, the less likely the activity is to be controlled. IV access, however, is frequently difficult to achieve during the seizure. On the other hand, intraosseous (IO) access is available. In this study, phenobarbital was administered to rabbits using both IV and IO lines at the dose of 20 mg/kg. The levels of phenobarbital in the blood were measured and the results were compared. The plasma profile of phenobarbital was found to be in the therapeutic level when it was administered by IO route. It was concluded that the IO line appeared to be an alternative route to IV access in the administration of phenobarbital.

Key Words: *Phenobarbital, bone marrow infusion, intraosseous infusion, intravascular access, status epilepticus*

The intraosseous (IO) route for vascular access is based on the presence of non-collapsible veins that drain the medullary sinuses in the bone marrow. This vascular network empties into the central venous circulation via nutrient and emissary veins. As a result, many drugs, crystalloid solutions, and blood products may be given effectively with almost immediate absorption. Although commonly used in the 1930s and 1940s, the IO route for vascular access has declined with improvements in intravenous (IV) catheters and alternative access techniques. Today, this technique is reserved for acute, life-threatening situations, when standard access methods have failed (1,2). One of these situations is status epilepticus or seizure.

Phenobarbital is one of the major antiepileptic drugs available for intravenous and long-term management. It is frequently avoided for fear of sedation, but levels below 40 mu/mL should not produce pro longed coma. Its advantages include a relative lack of cardiac toxicity at typical doses. A reasonable loading dose is as much as 20 mg/kg at a rate of 100 mg/min. Phenobarbital may help before therapeutic levels are reached. It compared favorable with a combination of diazepam and phenytoin in a prospective trial and produced a faster response (3). High enough doses will control almost all seizures. Very high doses require artificial ventilation and may cause hypotension, but they may be tolerated better than expected (4). IV access, however, is frequently difficult to achieve.

The purpose of this study was to determine if phenobarbital is absorbed after IO administration and whether therapeutically significant plasma

concentrations can be obtained in an experimental model in rabbits.

Materials and Methods

Ten New Zealand White adult rabbits (mean weight, 2.79 kg; range 2.47 to 2.95 kg.) were anesthetized with 80 mg/kg IM ketamine. All animals received repeated doses of anesthetic as needed during the experiment, resulting in a total mean dose of 160 mg/kg (range, 120 to 170 mg/kg). Animals were divided into two groups.

After adequate anesthesia was observed, a 18-gauge Illinois Bone Marrow Aspiration/IO infusion needle (Allegiance Healthcare Corporation, USA) was angled inferiorly (away from the growth plate) on the medial aspect of the proximal tibia, and, was advanced with boring or screwing motions. Entry into the marrow cavity was understood by loss of resistance to the advancing needle. The stylet was withdrawn, and correct placement of the needle was confirmed by free aspiration of blood or marrow and free flow of fluid under gravity. A 24-gauge peripheral intravenous catheter was inserted in an ear vein. Venous drug samples were collected at 10, 30 and 60 minutes after bolus infusion.

After administrations were completed, the line was withdrawn, and pressure was held on the entry site to decrease hematoma formation. Antibiotic ointment was then placed on the entry site. Animals were observed until the effects of sedation had cleared. Within 48 h after investigation, all animals were able to move easily and used the drug administered leg without difficulty. None of animals demonstrated evidence of infection or disability in the days after investigation.

Analysis of Phenobarbital in plasma

Blood was collected in vacutainer tubes (Belliver Industrial Estate, Plymouth, PL6 7BP UK). Serum was separated and frozen immediately at -20°C until analyzed. Total serum and unbound serum concentrations of phenobarbital were determined using fluorescence polarization immunoassay (FBIA; TDx, Abbott Diagnostics, North Chicago, IL, USA). Serum samples containing only unbound fractions of phenobarbital were prepared by ultrafiltration using the Centrifree Micropartition System (no. 4104; Amicon, Danvers, MA, USA) Approximately 1 ml of serum was pipetted into the ultrafiltration device, then centrifuged at 1500g at 25 ± 2°C for 20 min. The within-run coefficients of variation for serum analysis procedures of phenobarbital were<5.0 %.

Results

An intraosseous infusion was successful in 10 cases of 11 attempts (90 %), and all needles were placed in less than 90 seconds. Figure 1 shows the blood phenobarbital concentrations after IV and IO administrations in rabbits.

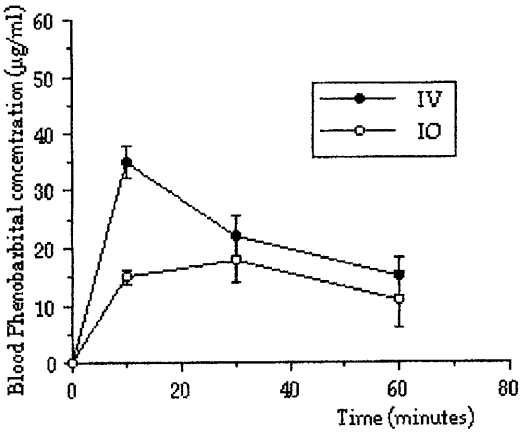

Figure 1. Blood phenobarbital concentrations after IV and IO phenobarbital administrations (Error bars represent SEM, n=10) (Dose was 20 mg/kg for both IV and IO administration).

Discussion

SE is classically defined as a generalized tonic-clonic seizure lasting longer than 30 min. Some investigators have suggested that a better definition would include any seizure that persists for more than twice its normal duration (5). The patients in SE present many challenges to the emergency physician. Prolonged seizure activity can result in irreversible cerebral injury as a result of excessive metabolic demands and nutrient depletion (6). Furthermore, evidence suggests that the longer the duration of the seizure, the less likely the activity is to be controlled (7). IV access, however, is frequently difficult to achieve. It has been reported that peripheral IV access was achieved in only 21 % of children who presented with seizures (8). In addition, attempts at both IV and IM injections during seizures can pose risks to the patient and the caregivers. For these reasons, an alternative means of delivering medication to the patient in seizure is desirable. The intraosseous route offers an effective means of rapidly establishing vascular access and has been used for volume resuscitation as well as for rapid administration of medications (9). The relative ease of application of this technique was shown by

an 80 % success rate for IO infusion achieved by paramedical staff (10).

IM phenobarbital takes approximately 45 minutes to act (11). However, it has been shown that the IO infusion of phenobarbital was to be superior to IV administration in achieving and maintaining serum levels. In this investigation, only phenobarbital levels ten minutes after injection were measured (12).

Multiple IO sites previously suggested includes the proximal tibia, medial malleolus, distal femur, proximal humerus, iliac crests, and sternum. The proximal tibia is generally agreed to be the optimal site for the insertion of the needle in children during emergencies; the use of this site precludes interference with ventilation or chest compressions during placement (13,14). In the present study also, this site is preferred.

Possible complications of the IO administration include, infection, fat emboli, a fracture at the IO entry site, injury to local soft tissues or physes, and compartment syndrome (9,15,16). All these complications have been generally attributed to the technical errors, the duration of the needle in situ and the infusion of hypertonic solutions (9,17,18). and it is possible to avoid them by using the recommended techniques and management.

In the present study, infusion was not successful only in one case due to the penetration to the opposite side of the bone. There were no any other complications, since needle insertion was done under controlled conditions by experienced personnel.

We suggest that the administration of phenobarbital by the IO route is an alternative way during SE, when intravenous access is delayed or not available.

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