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THE USE OF BONE INJECTION GUN IN THE LOADING OF PHENYTOIN
An Experimental study in dogs

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ABSTRACT: Status epilepticus can cause irreversible cerebral injury if it prolongs and it is essential to terminate seizure rapidly. Antiepileptic drugs should be introduced to the patients intravenously (IV), but it is almost impossible to achieve IV access during the seizure. However, intraosseous (IO) route can be accessible easily. Phenytoin was introduced to dogs by IV and IO routes. The levels of phenytoin in the blood were measured and the results were compared. The plasma profile of phenytoin was found to be in the therapeutic level when it was administered by IO route. It was concluded that the IO route can be an alternative route to IV route in the loading of phenytoin.
[Keywords: Phenytoin, bone marrow infusion, intrasseous infusion, bone infusion gun, intravascular access.]

INTRODUCTION

Status epilepticus (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 seizure which persists more than twice its normal duration (1). SE can cause neuronal brain damage. This morbidity is attributable not only to the underlying cause, but also to the duration of the status episode (2). Management of SE requires life support and monitoring measure as well as timely administration of IV antiepileptic drugs to terminate the seizure and reduce the risks of morbidity and mortality.

Phenytoin is one of the antiepileptic drug used frequently. In the absence of acute structural lesions, phenytoin may be the only necessary antiepileptic drug in as much as 80 % of the patients who have generalized convulsive status epilepticus. A usual loading dose is 15 mg/kg, but 20 mg/kg may be reasonable before concluding that phenytoin is insufficient. It should be given intravenously with a maximum dose of 50 mg / min without any concern for cardiac arrhythmias. It may be beneficial before reaching therapeutic level (3,4). IV access, however, is frequently difficult to achieve. In addition, attempts for both IV and IM injections during seizures can pose risks to the patient and the caregivers. For these reasons, an alternative means of delivery of the medication to the patient in seizure is desirable. It has been reported that the IO route is an alternate way to administer fluids and drugs (5).

The purpose of this study was to determine the absorbed phenytoin level after IO administration and whether therapeutically significant plasma concentrations can be obtained.

MATERIAL AND METHODS

Ten adult dogs weighing 8.7-9.8 kg were determined to be normal by physical examination. The dogs were fasted for 12 hours They were anesthetized by chamber induction with isoflorane. After tracheal intubation, anesthesia was maintained with isoflorane. All animals were treated in a humane fashion and recovered with adequate pain control after procedure.

Animals were divided into two groups; IO and IV. They underwent a surgical procedure for placement of a catheter into the right femoral vein. The IV group had a long IV catheter placed next to the other catheter for delivery of phenytoin. Both catheters were secured at their entry site with nylon suture.

IO lines were performed using a automatic device, for insertion of 18-gauge trocar needle (small children's size) into the bone marrow, the bone injection gun (BIG) (Wais Med Ltd. Even Yehuda, Israel). The preferred anatomic point for insertion of the trocar needle was an area 0.5 to 1 cm medial and 1 cm distally to the tibial tuberosity. The BIG were used by the specifically trained ED personnel. The depth of penetration for the trocar needle using the BIG can be adjusted by unscrewing the sleeve from the cylindrical housing, according to the size of cases and the anatomical area chosen for the injection. For this study, to gain IO access in the proximal tibial metaphysis (around the tibial tuberosity), the dept of penetration was adjusted 1cm. The skin area is thoroughly cleaned with an antiseptic. The front part of the BIG is placed in a perpendicular position to the site of injection, holding firmly. The safety pin is pulled out. The BIG is triggered by pressing the rear part against the two shoulders-handles of the housing and the sterile trocar is inserted into the bone at high speed. The BIG is removed and the trocar needle is separated from its housing. The stylet trocar is then manually separated by pulling it from the needle and only the needle cannula remained in the bone. The needle is then connected to a standard IV infusion set. Proper needle placement was confirmed by observing spontaneous blood return from the needle, easy aspiration of blood, and the ability to infuse fluid easily under gravity. The safety latch device is fixed around the needle-skin surface and provided an additional stabilization.

A 15 mg/kg dose of phenytoin was injected over 15 minutes, followed by 5-mL flush of normal saline into each of the IO and IV sites in a predetermined sequence. Two mL blood samples were withdrawn at 0, 5, 10, and 20 mins after injection

Determination of blood pheytoin concentrations:

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 phenytoin were determined using fluorescence polarization immunoassay (FBIA; TDx, Abbott Diagnostics, North Chicago, IL, U.S.A). Serum samples containing only unbound fractions of phenytoin were prepared by ultrafiltration using the Centrifree Micropartition System (no. 4104; Amicon, Danvers, MA, U.S.A. . 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 phenytoin were < 5.0 %.

RESULTS

Five dogs received the bone-marrow infusion procedure. 18 gauge trocar needle used for all dogs. Insertions of the needle using this method were successful in all cases. Correct placements were confirmed by aspiration of marrow content and easy infusion of fluid. The time required to establish the bone-marrow infusion lines was 20 seconds to 1 minute (Median 39 seconds).

In all cases, the trocar needle was inserted into the area of the tibial tuberosity. Intraosseous lines were kept in place for 1 to 3 hours, however the dogs were followed-up for a period of 48 hours and no local or systemic complications from the procedure were observed in this study.

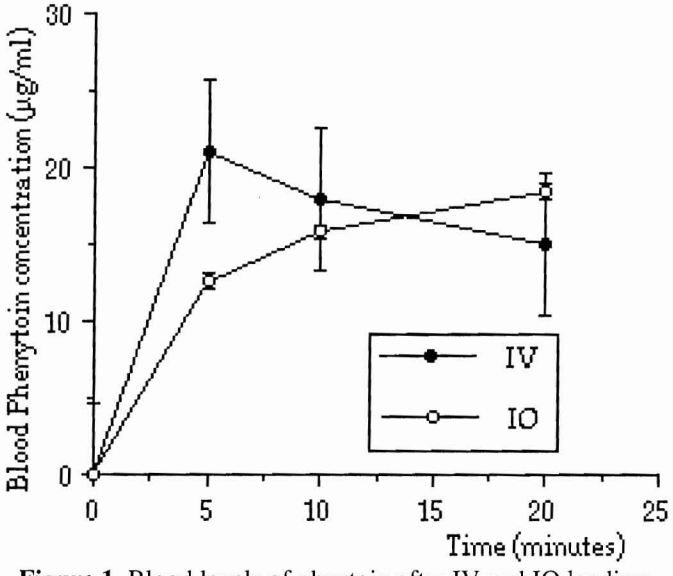

Figure 1. Blood levels of pheytoin after IV and IO loading. (Error bars represent SEM, n=5).

DISCUSSION

The anatomy and physiology of bone-marrow circulation was recognized more than 200 years ago. In 1901, stereophotographs and X-rays demonstrated that there were well defined blood vessels in bone marrow, divided into superior and inferior branches that were part of the general circulation. As IV catheters and techniques developed and improved during the 1950s and 1960s, IO route fell from grace for most part. However, occasional studies continued to appear in the literature; it has been reported a study on 15 patients treated with IO infusions ranging in age from 18 to 86 years. Using a 14-gauge needle placed in the tibial bone marrow, blood, Ringer's lactate, glucose, dexamethasone, atropine, and diazoxide were infused successfully (5,6,7,8). In 1997, BIG was used on fifty adult patients, aged 27 through 78 years, to obtain vascular access through IO lines, which was universally successful. In 76 % of the cases, the needle was inserted into the area of the tibial tuberosity; in the reminder of the cases, the needle was inserted at the distal end of the radial bone and into the lateral or the medial malleolus. The success rate for an adequate insertion was 100 % in this group of patients. No complications from the procedure were observed in this series (9).

In the present study, it has been shown that blood phenytoin levels after IV administration were higher than after IO administration at each time point. But this difference was not statically significant, and therapeutic levels could be maintained.

In a study previously conducted in domestic swine in the literature, it has been shown that the phenytoin levels by IO dosing were subtherapeutic at the ten-, 15, and 30 minute sampling times. In this investigation, a 16-gauge adjustable length aspiration needles were used, and phenytoin was administrated over two minute (10). In another study in pigs, phenytoin dosing were performed over 15 minutes, and the results were similar to our data (11).

In this study, it has been demonstrated that IO route is an effective alternative to IV route in the loading of phenytoin. The use of an impact penetration of a trocar needle into the spongeous bone improved success rate. The drug injected into the bone marrow

disperses via its venous drainage which connects the bone marrow to systemic circulation.

In despite of the fact that the technique of IO access has been very well known for many years, most physicians are unaware of its existence or avoid using it for various reasons. Avoidance of using includes a lack of suitable training and fear of complications such as infection or causing pain during the insertion of the trocar needle. The most frequent complications are osteomyelitis and compartment syndrome. However, these were mainly related to the length of time the infusion was left in place and to poor technique of needle insertion with subsequent leakage of fluid out of the bone into the surrounding tissues. In more than 4.000 cases reviewed, there were 27(0.6%) cases of osteomyelitis, compared with 3.7% of infections related to IV infusions (12). Defects in bone growth after infusions were not demonstrated in the animal models (13,14). The bending of the needle and the trocar have also reported (15). All of the above complications can be avoided by using an automatic device that allows a fast and precise insertion of a trocar needle to a predetermined dept by trained personnel. The BIG's small trocar needle design permitted a high velocity penetration through the bone cortex tightly into the spongeous bone and provided the best stabilization of the needle at the access site, preventing leakage fluids around it.

In conclusion, IO administration of phenytoin by BIG provides safe, rapid and reliable access to the circulation.

REFERENCES

1. Ramsay RE: Treatment of status epilepticus. Epilepsia, 34 (Suppl 1): S71-S81, 1993
2. Dunn DW: Status epilepticus in children: etiology, clinical features, and outcome. J Child Neurol, 3: 167-73, 1988
3. Cranford RE, Leppik IE, Patrick B, et al.: Intravenous phenytoin in acute treatment of seizures. Neurology, 29: 1474-79, 1979
4. Roth HL, Drislane FW: Neurologic emergencies. Seizures. Neurologic Clinics, 16(2): 258-84, 1998
5. Orlowski JP: Emergency alternatives to intravenous access. Pediatrics Clinics of North America, 41 (6): 1183-99, 1994
6. Sawyer RW, Bodai BI, Blaisdell FW, McCourt MM: The current status of intraosseous infusion. J Am Coll Surg, 179(3):353-60, 1994
7. Turkel H: Emergency infusion through the bone. Mil Med, 149(6):349-50, 1984
8. Hodge D: Intraosseous infusions: a review. Pediatr Emerg Care, 1(4):215-8, 1985
9. Waisman M, Waisman D: Bone marrow infusion in adults. J Trauma, 42(2):288-93, 1997
10. Jaimovich DG, Shabino CL, Ringer TV, Peters GR: Comparison of intraosseous and intravenous routes of anticonvulsant administration in a porcine model. Ann Emerg Med, 18: 842-46, 1989.
11. Vinsel PJ, Moore GP, O' Hair KC: Comparison of intraosseous versus intravenous loading of phenytoin in pigs and effect on bone marrow. Am J Emerg Med, 8(3): 181-3, 1990.
12. Rosetti VA, Thompson BM, Miller J, et al.: Intraosseous infusion: an alternative route of pediatric intravascular access. Ann Emerg Med, 14(9):885-8, 1985
13. Bielski RJ, Bassett GS, Fideler B, Tolo VT: Intraosseous infusions: effects on the immature physis--an experimental model in rabbits. J Pediatr Orthop, 13(4):511-5, 1993
14. Brickman KR, Rega P, Koltz M, Guinness M: Analysis of growth plate abnormalities following intraosseous infusion through the proximal tibial epiphysis in pigs. Ann Emerg Med, 17(2):121-3, 1988
15. Glaeser PW, Hellmich TR, Szewczuga D, et al.: Five-year experience in prehospital intraosseous infusions in children and adults. Ann Emerg Med, 22(7):1119-24, 1993

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